**BECOLEX™ MODULITE® 50 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)**

PL 06607/0017

**BECOLEX™ MODULITE® 100 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)**

PL 06607/0018

**BECOLEX™ MODULITE® 200 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)**

PL 06607/0019

**BECOLEX™ MODULITE® 250 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)**

PL 06607/0020

**UKPAR**

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BECOLEX™ MODULITE® PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PL 06607/0017-20

LAY SUMMARY

The MHRA granted Chiesi Farmaceutici SpA Marketing Authorisations (licences) for the medicinal products Becolex™ Modulite® 50 micrograms per actuation pressurised inhalation solution (PL 06607/0017), Becolex™ Modulite® 100 micrograms per actuation pressurised inhalation solution (PL 06607/0018), Becolex™ Modulite® 200 micrograms per actuation pressurised inhalation solution (PL 06607/0019) and Becolex™ Modulite® 250 micrograms per actuation pressurised inhalation solution (PL 06607/0020) on 29th June 2006. This prescription only medicine (POM) is used to help prevent the symptoms of asthma.

Becolex™ Modulite® pressurised inhalation solution contains the active ingredient beclometasone dipropionate, a corticosteroid with an anti-inflammatory action which helps to reduce swelling and irritation in the walls of the small air passages in the lungs, easing breathing problems.

The clinical data presented to the MHRA, pre licensing, demonstrated that Becolex™ Modulite® pressurised inhalation solution helps prevent symptoms of asthma. There were no safety concerns that were considered to be unmanageable and therefore the benefits of taking Becolex™ Modulite® pressurised inhalation solution were judged to outweigh the risk; hence Marketing Authorisations have been granted.
BECOLEX™ MODULITE® PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PL 06607/0017-20

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal product Becolex™ Modulite® 50 micrograms per actuation pressurised inhalation solution (PL 06607/0017), Becolex™ Modulite® 100 micrograms per actuation pressurised inhalation solution (PL 06607/0018), Becolex™ Modulite® 200 micrograms per actuation pressurised inhalation solution (PL 06607/0019) and Becolex™ Modulite® 250 micrograms per actuation pressurised inhalation solution (PL 06607/0020) to Chiesi Farmaceutici SpA on 29th June 2006. The products are prescription only medicines.

The application were submitted as abridged applications according to article 10.1 [formerly 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to Becotide Inhalers (50, 100 & 200mcg) and Becloforte Inhaler (250mcg). These are currently licensed to Glaxo Wellcome Limited (10949/0058-0060, 0065).

The product contains the active ingredient beclometasone dipropionate which is a corticosteroid with anti-inflammatory properties. Beclometasone dipropionate pressurised inhalation solution is indicated for the management of mild, moderate, or severe asthma in adults or children.

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity. Beclometasone dipropionate exerts a topical, anti-inflammatory effect in the lungs and is well established in the prophylactic management of mild, moderate and severe asthma in adults and children.

The same data package has been presented for inhalers by Trinity-Chiesi Pharmaceuticals Ltd PL 08829/0133-0136. Chiesi is the parent company of Trinity-Chiesi, consequently the assessment of the scientific data is identical for all these applications.

The UK Advisory Committee considered the licence applications on several occasions and after assessment of further data received from the applicant, advised that Marketing Authorisations should be granted.
PHARMACEUTICAL ASSESSMENT

Note: This assessment report has been updated to incorporate the information provided by the applicant, in response to queries raised by the assessor and/or the UK Advisory Committee. All queries were answered satisfactorily.

1. INTRODUCTION

These are abridged applications for Marketing Authorisation in the UK submitted under Article 10.1 [formerly article 10(a)(iii)] of Directive 2001/83/EC (as amended) for products claiming essential similarity to Becotide Inhalers (50, 100 & 200mcg) and Becloforte Inhaler (250mcg). These are currently licensed to Glaxo Wellcome Limited (PL 10949/0058-0060, 0065). All the licenses were originally granted to Allen & Hanburys Ltd [Becotide 50 00045/0089 granted 10/10/1972; Becotide 100 00045/0131 granted 23/6/1986; Becotide 200 00045/0152 granted 25/4/1991; Becloforte 00045/0125 granted 12/5/1982].

The inhalers have been developed by Chiesi Farmaceutici SpA to contain a CFC-free propellant, HFA-134a (Norflurane BAN, USAN, rINN). Therefore they will be used as replacements to currently marketed CFC-containing inhalers which are to be removed from the market in the near future due to their ozone-depleting propellants. Norflurane has already been included in other licensed CFC free inhalers..

2. DRUG SUBSTANCE

2.1. General information

2.1.1. Nomenclature

BANM, rINNM: Beclometasone dipropionate

Chemical Name: 9alpha-Chloro-11beta,17alpha,21-trihydroxy-16beta-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

2.1.2. Structure

C_{28}H_{37}ClO_{7}  RMM 521.1

2.1.3. General properties
A white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone, sparingly soluble in alcohol. It melts at about 210°C, with decomposition.

2.2. Manufacture

2.2.1. Manufacturers

Two manufacturers have been proposed.

Both these active manufacturers supply beclometasone dipropionate for use in other currently licensed inhalation products. One of the manufacturer had supplied DMF which then later replaced by a certificate of suitability. The other manufacturer of the active substance submitted a certificate of suitability which was assessed and later withdrawn before approval.

2.3. Control of drug substance

2.3.1. Specification

Beclometasone dipropionate is tested by each active manufacturer to the specifications provided. These are equivalent to those of the Ph. Eur. monograph. The methods used are also identical to the monograph except where indicated. The finished product manufacturer routinely checks the appearance and identity of the drug substance. Periodically they perform the full monograph test using the specified methods except for the assay, which is performed an UV spectrophotometric method.

In the Certificate of Suitability it is stated that the potential residual solvents are adequately controlled by the limit for loss in drying.

2.3.2. Batch analyses

Data for commercial scale batches from each supplier are provided. These demonstrate compliance with the Ph. Eur. monograph.

2.4. Reference standards or materials

Details of the current reference standards in use are provided.

2.5. Stability

A 5 year re-test date is assigned to the beclometasone dipropionate.

3. DRUG PRODUCT

3.1. Composition

Consistent with the other CFC-free inhalers developed using HFA 134a as the propellant the formulation is a solution as opposed to the suspension formulations used in the CFC containing metered dose inhalers. The qualitative composition of the product for all strengths is shown in table 1.
Table 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone dipropionate</td>
<td>active</td>
</tr>
<tr>
<td>Glycerol</td>
<td>non-volatile cosolvent</td>
</tr>
<tr>
<td>Ethanol anhydrous</td>
<td>cosolvent</td>
</tr>
<tr>
<td>HFA-134a (Norflurane)</td>
<td>propellant</td>
</tr>
</tbody>
</table>

The solution is filled into an aluminium alloy can fitted with a metering valve and equipped with an actuator. The labelled doses of 50, 100, 200 and 250µg are the metered doses for the inhalers and these are stated to be equivalent to delivered doses of 46, 93, 187 and 233µg, respectively.

Clinical studies have been performed to evaluate the suitability of the proposed products. The same formulation and primary packaging were used for the clinical batches.

3.2. Pharmaceutical development

A comprehensive discussion with relevant data and published references for the pharmaceutical development of these products is provided. The aim was to formulate an inhaler that could be shown to be clinically and pharmacologically equivalent to the currently marketed products to enable a ‘seamless transition’ from CFC containing MDI’s to the HFA containing MDI’s. The inhalation has been formulated as a solution. Full details of the device have been provided.

3.3. Manufacture

3.3.1. Manufacturer(s)

The manufacturing sites have been named and are acceptable.

3.3.2. Batch formula

The proposed batch sizes have been provided as have the quantities of ingredients required for all inhaler strengths for these batch sizes.

3.3.3. Manufacturing process and process controls

A flow diagram has been included. Appropriate controls have been proposed and are acceptable for this manufacturing process.

3.3.4. Process validation or evaluation

Validation has been performed at the finished product manufacturer for batches of the inhaler over the full range of strengths (50µg/act, 100µg/act, 200µg/act & 250µg/act). All were at the lowest proposed batch size except for the highest strength inhalers where the maximum batch size was manufactured. Active from both sources was used.
The data provided demonstrate that the manufacturing method is adequately validated up to the proposed maximum manufacturing size.

3.4. Control of excipients

3.4.1. Specifications - Pharmacopoeial

Glycerol and ethanol anhydrous comply with the relevant Ph. Eur. monographs. The finished product manufacturer routinely checks the identity of these excipients on receipt of new batches but do not routinely perform the full tests of the Ph. Eur. monograph as they are supplied with a Certificate of Analysis. Representative certificates of analyses for these excipients showing compliance with the Ph. Eur. monographs have been supplied.

It has been confirmed that the glycerol that will be used in the manufacture of commercial batches will be from a vegetable source only. During development of the inhaler however animal derived glycerol was used.

3.4.2. Specification – Non-pharmacopoeial

The propellant, HFA-134a was accepted by the CPMP during the review of non-CFC propellants in 1994. A full technical document relating to this excipient is provided which includes the accepted specifications. Full testing is undertaken by the manufacturer of the pharmaceutical grade propellant and is supplied to the finished product manufacturers with a Certificate of Analysis. Suitable batch analyses have been presented. The finished product manufacturers routinely check the identity of the propellant on receipt and may also carry out additional tests from the specifications on a non-routine basis to confirm the results on the Certificate of Analysis. This is acceptable.

3.5. Control of drug product

3.5.1. Specification

The finished product specifications at release and end of shelf life have been provided.

In general the specifications are in line with the monograph for preparations for inhalation in the Ph. Eur. and the recommendations in the draft CPMP guidelines.

3.5.2. Analytical procedures

Details of the test methods used are provided and are satisfactory.

3.5.3. Validation

HPLC methods have been adequately validated.

3.5.4. Batch analyses

Batch data are provided for batches of varying sizes, although only the 250µg/act has been manufactured at the maximum batch size. Although the active batches used in the production are not specified since the inhalers were prepared over a period of years (1997-
2000) different batches must have been used. The batches have been utilised in the stability and clinical studies.

The data provided indicate there is minimal inter-batch variability. No obvious difference is seen between the batches manufactured at the different proposed manufacturing sites. All the batches satisfy the proposed finished product specifications.

3.6. Container closure system

Diagrammatic representations of the canister, metering valve and actuator are provided. The canister is made of an aluminium alloy whilst the actuator is composed of polypropylene. The individual components of the inhaler are supplied with a Certificate of Analysis. Representative Certificates of Analysis for the packaging components have been provided. The canisters, metering valves and actuator are routinely examined visually for defects and the air-flow in the latter is also checked. Additional tests may also be performed. Batch data showing compliance with these tests are supplied.

The components of the metering valve and the actuator have been evaluated for extractables.

3.7. Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months when stored below 30ºC has been set, which is satisfactory.

3.8. Other information

3.8.1. Bioanalytical methods

Suitable validation has been performed for the analytical methods used to quantify the beclometasone dipropionate and metabolites in plasma during the pharmacokinetic studies.

3.8.2. Bioavailability, bioequivalence

The medical assessor will discuss the clinical studies that have been performed.

3.8.3. Essential similarity

Data are provided comparing the delivered dose and fine particle dose of the proposed CFC-free inhalers with the currently marketed CFC containing inhalers. For the HFA inhalers 2 cans from a single batch were analysed whilst for the CFC inhalers the data are compiled from tests with up to nine cans from three different batches. The batches used in this study are representative of the clinical batches.

The delivered dose for the CFC and HFA inhalers are similar for all inhaler strengths. Overall the data provided suggests that the two formulations are equivalent. Therefore unless the clinical data indicate otherwise it can be considered that essential similarity has been demonstrated.
Data are also provided to compare the 250µg/act inhaler with Qvar 100µg/act, a licensed CFC free inhaler containing beclometasone dipropionate.

3.9 Product Literature

3.9.1 SPC
The SPCs are satisfactory.

3.92 PIL
The PIL is satisfactory

3.93 Labelling
The labelling supplied is satisfactory

4. Administrative

4.1 Comment on Expert report
A recognised expert in this field has written the report and supports the licensing of these inhalers.

4.2 MAA form
The MAA forms are satisfactory

5. CONCLUSIONS AND ADVICE
The data presented to support these applications are very comprehensive. The development of the formulation and the subsequent validation of the method of manufactured is well documented. Suitable stability studies have been performed to confirm the stability of the formulation and demonstrate acceptable product performance throughout the proposed shelf life.
PRECLINICAL ASSESSMENT

Introduction
These are abridged applications for pressurised inhalation solution formulations of beclometasone dipropionate containing the non-chlorofluorinated propellant HFA 134a or norfluorane (BDP HFA). The formulations are available in four-strengths (50, 100, 200 and 250 µg BDP/actuation) via a metered dose inhaler (MDI). HFA 134a has been approved by the CPMP as an alternative to CFCs used in medicinal products. Aerosol formulations containing BDP as active ingredient and HFA 134a as propellant have recently been authorised for marketing.

BDP HFA is indicated for the prophylactic management of mild, moderate or severe asthma in adults or children. It is for oral inhalation use only.

The toxico-pharmacological data and Expert Report supporting the Trinity Pharmaceuticals Applications (PLs 08829/0133-6) are identical to those that have been submitted by the parent company Chiesi Farmaceutici SpA in support of their PLs 06607/0017-20 for BDP HFA formulations. These data have been assessed together.

The present MAA is stated to be essentially similar to the currently marketed BDP MDI formulations. Since the active ingredient is a well known medicinal product, used also in recently authorised HFA 134a formulations, and products containing BDP for inhalation have been on the market for over 10 years in the EU, preclinical studies on the active ingredient have not been conducted. However in order to test the local tolerance and potential systemic effects of the formulation as well as the potential effects of the excipients, inhalational toxicity studies were conducted using the previous CFC formulation as comparator.

The well known properties of BDP and HFA 134a are described in the Expert Report; they will not be re-iterated in this Assessment Report. The Applicant has also submitted a separate Expert Report which is a more detailed evaluation of HFA 134a. This has not been included with this assessment report.

SmPC
Section 5.3 (Preclinical safety Data) is acceptable.

Conclusion
The BDP HFA MDI formulation has been tested in comparison with the CFC formulation in inhalation toxicity studies. No toxicological differences were seen between the two BDP formulations at the highest doses tested (about 27 times the maximum daily dose). There were no overt or histological signs of local toxic effects on the respiratory system.

In conclusion there are no preclinical concerns over these MAAs.
CLINICAL ASSESSMENT

1. INTRODUCTION
For the purposes of this report beclometasone dipropionate formulated in an excipient mix, including HFA-134a as a propellant will be described as BDP HFA (unless describing a specific strength); beclometasone dipropionate as currently formulated in an excipient mix including propellants 11/12 and the brand leader products in the UK, Becotide and Becloforte Inhalers, will be described as BDP CFC (or Becotide/Becloforte CFC); beclometasone dipropionate, the drug substance will be abbreviated simply to BDP. This terminology is in line with that used by the Applicant throughout the dossier presented.

The products to which essential similarity is claimed are metered dose aerosols, containing beclometasone dipropionate formulated in an excipient mix including CFC propellants. The applicant does not hold marketing authorisations for CFC-containing formulations of beclometasone dipropionate and, therefore, if marketing authorisations for the new non-CFC-containing pressurised inhalation solutions are granted, they will be available on the market as new products and not as replacement formulations for CFC-containing inhalers.

Under the terms of the Montreal Protocol, parties to the agreement agreed to phase out the use of CFCs, including use in medicinal products, by end 1999.

Currently, five metered dose inhalers containing the bronchodilator salbutamol (as the sulphate), one containing the corticosteroid beclometasone dipropionate, one containing the corticosteroid fluticasone propionate and one containing the combination of salmeterol and fluticasone propionate have been reformulated in an excipient mix, including the non-CFC propellant, HFA-134a.

2. PHARMACODYNAMICS

The Applicant makes reference to the literature and has submitted one study to assess the systemic pharmacodynamic effects of beclometasone dipropionate (BDP) and its metabolites by measuring effects seen on the hypothalamic pituitary adrenocortical (HPA) axis. Effects on HPA axis function are well accepted as reflective of possible systemic exposure to corticosteroids and including corticosteroids taken via the inhaled route.

2.1 Study SGS B100.524: Open, randomised, two-way cross-over, comparative bioavailability study of two metered dose inhalers of beclometasone dipropionate after single dose in 12 healthy male subjects.

The objectives of this study were two-fold:
- To compare the systemic exposure to BDP and its active metabolite beclometasone 17 monopropionate (B17MP) after inhalation of BDP formulated in an excipient mix, including propellant HFA-134a (BDP HFA) and BDP formulated in an excipient mix including CFC propellants (BDP CFC) (see 3.1 below).
- To assess systemic safety of the two formulations of BDP through evaluation of serum cortisol and urinary cortisol excretion over 24 hours following drug administration.
The study comprised a one week period during which subjects were well trained in inhalation technique, a one-day run-in period which was five days (protocol deviation from two day) prior to the two single dose treatment periods which were separated by a one-week wash-out. The single dose treatment exposures compared the two formulations, CFC-free and CFC-containing, at a dose of BDP 2000µg (8x250µg).

The aim of this study was to test for large differences (>50%) in systemic exposure between the two inhalers, that would be deemed clinically relevant with regard to the safety of the new BDP HFA product, as measured through the area under the plasma concentration versus time curve (AUC) of B17MP. A sample size of 12 subjects had at least an 80% power to detect a variation of 50% in AUC assuming a coefficient of variation of 40% with a 0.05 significance level. (B17MP is the main metabolite of BDP and is associated with most of the pharmacological activity of the drug).

The findings in respect of serum cortisol are shown below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment A: BDP/HFA (test)</th>
<th>Treatment B: BDP/HFA (Becloforte®, reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δmax (ng/mL)</td>
<td>-85 (-106; -68)</td>
<td>-87 (-103; -73)</td>
</tr>
<tr>
<td>tΔmax (h)</td>
<td>6.00 (1.00: 16.05)</td>
<td>6.00 (1.00: 16.00)</td>
</tr>
<tr>
<td>AUC0-24 (h.ng/mL)</td>
<td>1229 (916; 1650)</td>
<td>1294 (1032; 1622)</td>
</tr>
<tr>
<td>AUCΔ (h.ng/mL)</td>
<td>-734 (-1265; -426)</td>
<td>-592 (-1680; -209)</td>
</tr>
</tbody>
</table>

Δmax: maximum deviation from basal level

Summary of the statistical comparison between parameters of cortisol in serum

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV (%)</th>
<th>BDP/HFA vs BDP/CFC*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δmax</td>
<td>10</td>
<td>98 (91; 106)</td>
<td>0.65</td>
</tr>
<tr>
<td>tΔmax</td>
<td>-</td>
<td>0.00 (0.00: 2.00)</td>
<td>0.22</td>
</tr>
<tr>
<td>AUC0-24</td>
<td>22</td>
<td>95 (80; 111)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

p: Probability associated with the hypothesis of no difference between the two treatments (ANOVA, except for tΔmax: Koch’s test);
CV: Residual coefficient of variation derived from the ANOVA;
*: Geometric mean Test/Reference ratio (%) except for tΔmax: median difference (h): point estimate (90% CI).
The changes in urinary cortisol excretion were similar and are shown below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Run-in period</th>
<th>Treatment A: BDP/HFA (test)</th>
<th>Treatment B: BDP/HFA (Becloforte®, reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ae (µg)</td>
<td>71.7 (53.9; 95.4)</td>
<td>39.1 (21.5; 71.1)</td>
<td>38.6 (24.3; 61.5)</td>
</tr>
<tr>
<td>Ae/norm (%)</td>
<td>-</td>
<td>54.6 (33.1; 90.1)</td>
<td>53.9 (38.1; 76.3)</td>
</tr>
<tr>
<td>Ae/Aecreat (µg/g)</td>
<td>43.3 (30.2, 61.9)</td>
<td>22.5 (12.9; 39.1)</td>
<td>24.0 (14.3; 40.4)</td>
</tr>
</tbody>
</table>

Values are geometric means

Ae: 24 hour urinary excretion of cortisol
Ae/norm: 24 hour urinary excretion normalised for excretion obtained during the run-in period, calculated as Ae/Ae run-in
Ae/Aecreat: 24 hour urinary excretion of cortisol normalised for creatinine excretion
Aecreat: 24 hour urinary excretion of creatinine

Summary of the statistical comparison between parameters of cortisol in urine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV (%)</th>
<th>BDP/HFA vs BDP/CFC*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ae</td>
<td>33</td>
<td>104</td>
<td>(81; 133)</td>
</tr>
<tr>
<td>Ae/norm</td>
<td>33</td>
<td>104</td>
<td>(81; 133)</td>
</tr>
<tr>
<td>Ae/Aecreat</td>
<td>30</td>
<td>96</td>
<td>(76; 121)</td>
</tr>
</tbody>
</table>

p: Probability associated with the hypothesis of no difference between the two treatments (ANOVA);
CV: Residual coefficient of variation derived from the ANOVA;
*: Geometric mean Test/Reference ratio (%): point estimate (90% CI).

In conclusion the maximum decrease observed for serum cortisol from the run-in values was similar, for the test and the reference treatments, geometric means of 85 and 87ng/mL respectively, and occurred six hours (median) after administration of the two study medications. The AUC\(_{0-24}\) was slightly, but not statistically significantly lower after administration of the test treatment compared with the reference treatment, geometric means of 1229 and 1294 h.ng/mL, respectively. The reduction in serum cortisol was a 40% decrease from run-in for each of the two treatments.

The average 24 hour urinary excretion of cortisol was 39µg (geometric mean) following both study treatments compared with 72µg during the run-in period. The reduction in urinary cortisol excretion was a 45% decrease from run-in for each of the two treatments.

The 90% confidence intervals for mean test/reference ratios of serum cortisol AUC and urinary cortisol excretion were 80-111% and 76-121%, respectively.

The Applicant concludes that the data presented demonstrate a similar potential for systemic effects across the two formulations of beclometasone dipropionate.

### 2.2 Assessor’s Comment

The findings from this study confirm that inhaled BDP at the maximum recommended total daily dose of 2000µg (administered as a single dose) does have an effect on the HPA axis but that this effect would appear to be the same regardless of whether BDP is formulated with the new non-CFC propellant, HFA-134a or whether formulated as currently available with CFCs as propellants.

The findings suggest that the two formulations of BDP can be deemed comparable with similar potential for systemic exposure following single dose administration.
3. PHARMACOKINETICS
The applicant presented three pharmacokinetic studies.

3.1 Study SGS B100.524: Open, randomised, two-way cross-over, comparative bioavailability study of two metered dose inhalers of beclometasone dipropionate after single dose in 12 healthy male subjects.

This study has been discussed at Paragraph 2.1 above in respect of the assessment of the systemic safety of BDP HFA compared with BDP CFC.

All subjects received a single dose of BDP HFA and BDP CFC in a dose of 2000µg (8x250µg) in the two-way cross-over study. Concentration-time profiles of BDP and the main active metabolite, B17MP in plasma were evaluated over a 24 hour period post inhalation of each study treatment. The majority of the systemic effects seen following the inhalation of BDP are due to the systemic exposure to B17MP, a metabolite with approximately 30 times the potency of the pro-drug. [Minor inactive metabolites, beclometasone-21-monopropionate (B21MP) and beclometasone (B0H) are also products of metabolism of BDP but contribute little to the systemic exposure].

The average B17MP plasma concentration versus time curve is shown below:

The derived pharmacokinetic parameters and the statistical comparisons are shown in the tables below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment A: BDP/HFA</th>
<th>Treatment B: BDP/HFA (Becloforte®, reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (pg/mL)</td>
<td>2656 (1708 – 4128)</td>
<td>1004 (539 – 1873)</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>0.50 (0.17 – 1.00)</td>
<td>0.77 (0.75 – 1.00)</td>
</tr>
<tr>
<td>AUC_t (h.pg/mL)</td>
<td>10537 (6261 – 17735)</td>
<td>4524 (1990 – 10285)</td>
</tr>
<tr>
<td>AUC_{∞} (h.pg/mL)</td>
<td>10850 (6500 – 18112)</td>
<td>4799 (2197 – 10486)</td>
</tr>
<tr>
<td>t_{1/2z} (h)</td>
<td>4.59 (3.84 – 5.48)</td>
<td>4.75* (3.94 – 5.72)</td>
</tr>
</tbody>
</table>

\(t_{max}\) values are median (range). Other values are geometric mean.

N=11, except *: N=10.
C\textsubscript{max}: maximum plasma concentration

\(t_{\text{max}}\): time to maximum plasma concentration

AUC\textsubscript{t}: area under the plasma concentration versus time curve observed from time 0 hours to the last measurable data point

AUC\textsubscript{\infty}: area under the curve extrapolated to infinity

\(t_{\frac{1}{2z}}\): the elimination half life associated with negative terminal slope

### Summary of the statistical comparison of the plasma pharmacokinetic parameters of B17MP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV (%)</th>
<th>BDP/HFA vs BDP/CFC*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>36</td>
<td>263 (200; 346)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(t_{\text{max}})</td>
<td>-</td>
<td>-0.25 (-0.42; -0.01)</td>
<td>0.028</td>
</tr>
<tr>
<td>AUC\textsubscript{t}</td>
<td>43</td>
<td>232 (167; 320)</td>
<td>0.001</td>
</tr>
<tr>
<td>AUC\textsubscript{\infty}</td>
<td>41</td>
<td>225 (165; 306)</td>
<td>0.001</td>
</tr>
<tr>
<td>(t_{\frac{1}{2z}})</td>
<td>14</td>
<td>97 (86; 109)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

\(p\): Probability associated with the hypothesis of no difference between the two treatments (ANOVA, except for \(t_{\text{max}}\): Koch’s test);

CV: Residual coefficient of variation derived from the ANOVA;

*: Geometric mean Test/Reference ratio (%) except for \(t_{\text{max}}\): median difference (h): point estimate (90% CI).

The findings in respect of the pharmacokinetics of BDP were similar with plasma levels of both the pro-drug and the active metabolite markedly higher after administration of BDP HFA than BDP CFC. For BDP plasma concentrations peaked early and fell rapidly and for BDP HFA were all below the limit of quantitation of 20pg/mL from 4 hours post inhalation; this compared with 2 hours post inhalation of the reference treatment, BDP CFC. For B17MP plasma concentrations also peaked early; however 24 hours post inhalation concentrations remained quantifiable in 9 subjects inhaling BDP HFA and in 6 inhaling BPD CFC. The individual plots revealed large inter-subject variability.

When compared with the reference treatment, BDP CFC the bioavailability of both BDP and B17MP was significantly higher with the test treatment, BDP HFA. A >2-fold increase in \(C_{\text{max}}\), AUC\textsubscript{t} and AUC\textsubscript{\infty} was seen for B17MP together with a statistically significantly shortened time to peak effect. For BDP a 2.7-fold increase in \(C_{\text{max}}\) and AUC\textsubscript{t} was seen (AUC\textsubscript{\infty} was not calculated as the elimination phase consisted of no more than 2 or 3 points in several pharmacokinetic profiles) following BDP HFA compared with BDP CFC; however the time to peak effect was not significantly different between the 2 treatments.

The Applicant comments that the difference between BDP HFA and BDP CFC is mainly due to the lower than expected B17MP and BDP plasma levels in 3 subjects (subject nos 2, 3 and 5) following inhalation of BDP CFC. Inhalation technique was poor following inhalation from the BDP CFC inhaler but seemingly much improved when inhaling from the BDP HFA inhaler (increased plasma levels of both B17MP and BDP). The Applicant has reviewed the literature in respect of the systemic exposure following inhalation of BDP CFC and has found it to be greater than seen in the study presented above.

### Summary of literature data for BDP CFC MDI: median values (range)

<table>
<thead>
<tr>
<th></th>
<th>BDP CFC 50 µg (Glaxo) (n=12)</th>
<th>BDP CFC 250 µg (Glaxo) (n=21)</th>
<th>BDP CFC 250 µg (Norton) (n=12)</th>
<th>BDP CFC 250 µg (Norton) (n=10)</th>
<th>BDP CFC 50 µg (Glaxo) (n=8)</th>
</tr>
</thead>
</table>

- 16 -
Becolex™ Modulite® pressurised inhalation solution (beclometasone dipropionate) PL 06607/0017-20

<table>
<thead>
<tr>
<th>B17MP AUC&lt;sub&gt;∞&lt;/sub&gt; (pg/ml*h)</th>
<th>7192&lt;sup&gt;a&lt;/sup&gt;</th>
<th>8217&lt;sup&gt;a&lt;/sup&gt;</th>
<th>7288&lt;sup&gt;a&lt;/sup&gt;</th>
<th>8728&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3590-19285)</td>
<td>(3955-14912)</td>
<td>(4350-14790)</td>
<td>(2635-30810)</td>
</tr>
</tbody>
</table>

a) data scaled to 2000µg dose; b) geometric mean

3.2 Study SGS 198.655: Open, randomised, three-way cross-over, comparative bioavailability study of three metered dose inhalers of beclometasone dipropionate after single dose in 12 healthy male subjects.

This study was of similar design to Study SGS B100.524, described in Paragraphs 2.1 and 3.1 above but compared BDP HFA with BDP CFC (Becloforte) in the lower single dose of 1000µg (4x250µg) administered through the Jet spacer (a Chiesi actuator-spacer device) instead of the standard actuator, and included a comparison with Qvar 1000µg (10x100µg) (beclometasone dipropionate formulated with propellant HFA-134a and a product of 3M Health Care Limited). The objective of the study was to evaluate the systemic exposure to BDP and its metabolites B17MP and beclometasone (BOH).

[The Jet actuator-spacer device is not a subject of these applications but has been used in the supportive efficacy and safety studies, described below in Paragraphs 4.3 and 5].

The findings in respect of the systemic exposure to B17MP are shown in the table below and are compared with the data generated in Study SGS B100.524 (Paragraph 3.1 above); the data presented have been normalised to the 2000µg dose.

### Median (range) B17MP pharmacokinetic parameters in 12 healthy volunteers

<table>
<thead>
<tr>
<th>BDP CFC (Glaxo)</th>
<th>BDP HFA (Chiesi)</th>
<th>HFA 134a BDP (3M)*</th>
<th>BDP CFC Jet* (Chiesi)</th>
<th>BDP HFA Jet* (Chiesi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study SGS B100.524</td>
<td>Study SGS B198.655</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Cmax (pg/mL) | 1180 (353 – 1960) | 3200 (980 – 4440) | 5046.5 (3521.4-9800.2) | 1760 (732.4-2297.4) | 2470.2 (1966.2-4884.4) |
| Tmax (h) | 0.77 (0.75 – 1) | 0.5 (0.17-1) | 0.5 (0.31-1) | 0.5 (0.75-1.5) | 0.5 (0.13-0.75) |
| AUC<sub>∞</sub> (pg/mL*h) | 5750 (1109-11304) | 11659 (3000-17409) | 17894 (12120.4-26346.5) | 3976.6 (3619.6-10733.2) | 9988.4 (6318.3-13975) |
| t½el (h) | 5.04 (3.63-6.05) | 4.36 (3.94-7.20) | 3.12 (2.7-4.97) | 2.99 (2.55-4.81) | 3.29 (2.72-4.9) |

* data normalised to the 2000µg dose

As in the previous study systemic exposure to BDP HFA would appear to be greater than for BDP CFC although the difference when the drugs are administered via the Jet spacer is less than when administered via the metered dose inhaler with standard actuator as in Study SGS B100.524, above. Both C<sub>max</sub> and AUC<sub>∞</sub> after inhalation of BDP HFA-134a/Qvar (3M) were more than double the values seen following BDP CFC (via the Jet spacer).

The Applicant comments that although differences are seen between BDP HFA and BDP CFC, the median values of B17MP AUC for BDP HFA, as given in the table above, do lie within the range of AUCs where 90% of values for BDP CFC would be expected (range 2400-13000pg/mL*h). The median AUC for the 3M product (Qvar) of 17894pg/mL*h is outside the upper limit of this range by some 40%.

The findings in this study might not be unexpected when reviewed alongside the *in vitro* data – in the batches used in this study the mass median aerodynamic diameter (MMAD)
for the reference product, BDP CFC was approximately 4.8µm, for the test product BDP HFA approximately 2.6µm and for the second test product, BDP HFA-134a/Qvar (3M) approximately 1.1µm.

3.3 Study SGS B100.512: Pilot, open, randomised, three-way cross-over, comparative lung absorption study of a BDP CFC free metered dose inhaler (BDP HFA) in six healthy male subjects.

This study was set up to assess the pulmonary absorption of BDP HFA administered via the Jet spacer and via the standard MDI with or without active charcoal block to prevent the gastrointestinal absorption of that part of the inhaled drug which is swallowed.

Each treatment was a single dose of 1600µg (8x200µg) and as previously the pharmacokinetics of BDP and B17MP were determined.

When compared with the inhalation of BDP HFA from the Jet spacer administration of HFA BDP via the standard MDI with or without a charcoal block did not affect plasma levels of BDP which confirms that BDP in the systemic circulation must arise from that absorbed unchanged from the lung. Swallowed BDP is not bioavailable through pre-systemic conversion to B17MP (resulting in absorption of approximately 40% of the swallowed portion as B17MP).

B17MP plasma levels were reduced following inhalation from the standard MDI with charcoal block. C_max was similar for the three treatments but AUC_t and AUC_∞ were reduced by 22% compared with the reference treatment (BDP HFA through the Jet spacer). The apparent elimination half life was reduced by 21% following inhalation via the standard actuator with charcoal block and by 11% after inhalation from the standard actuator without charcoal block compared with the reference treatment. Other differences between test formulations and the reference treatment did not exceed 10% and no differences reached statistical significance.

Graphs which suggest that pulmonary delivery of BDP is similar regardless of whether the drug is inhaled via the standard MDI or the Jet spacer are provided in the Clinical Expert Report.

3.4 Dose Linearity
Bringing together the data generated in the three studies described above shows a linear increase in systemic exposure with increasing doses of inhaled BDP.

3.5 Drug Interactions
No specific interaction studies have been presented.

HFA-134a is chemically inert. Interactions between beclometasone dipropionate formulated with HFA-134a as a propellant and other drugs are not expected to be different from those seen with the current formulations of beclometasone dipropionate formulated with CFCs as propellants.

3.6 Assessor’s Comment
Studies SGS B100.524 and SGS 198.655 both define differences in respect of the systemic exposure. In the first study a >2-fold increase in systemic exposure is seen following BDP
HFA compared with BDP CFC and although this increase is not as marked in the second study (which used the Jet spacer) increased systemic exposure is seen with the BDP HFA formulation. The Applicant raises arguments in an attempt to explain these findings and comments on a lower than expected systemic exposure obtained following inhalation of BDP CFC, particularly in the first study. Comment is also made in respect of the median values of B17MP AUC for the BDP HFA product in the two studies which both lie within the range of AUCs where 90% of the values for BDP CFC would be expected. The second study also compares the pharmacokinetics of these two formulations of BDP with a second active control, the 3M product (Qvar) where the median AUC is outside the upper limit of this range by 40%.

The findings in respect of systemic exposure have been reviewed alongside the in vitro data in respect of the MMAD for the three products; the smaller the MMAD the greater the systemic exposure.

Although there would appear to be a greater systemic exposure when BDP is formulated with HFA-134a this would not appear to be reflected in any effect on the HPA axis (see Paragraph 2, above) where a comparable systemic safety profile is seen.

4. EFFICACY

The clinical efficacy programme submitted with these applications was set up to demonstrate unilateral equivalence (non-inferiority) in the comparison of BDP HFA with BDP CFC within prospectively defined limits and comprised two pivotal multiple dose studies comparing both efficacy and safety of BDP HFA with BDP CFC, either Becotide or Becloforte Inhalers, in adults with mild and mild to moderate asthma, and one pivotal study in children with mild to moderate asthma. In the adult studies the severity of asthma studied permitted assessments of a low dose regimen of BDP HFA, 200\(\mu\)g BD (using the 100\(\mu\)g/actuation inhaler) and a higher dose regimen of 500\(\mu\)g BD (using the 250\(\mu\)g/actuation inhaler). The study in childhood asthma employed a dose regimen of 200\(\mu\)g BD but the design of the study permitted use of both the 50 and 100\(\mu\)g/actuation inhalers in order that a comparison across the two strengths could be made. The study in mild asthmatics also incorporated an assessment of bronchial hyperreactivity in a sub-group through methacholine challenge.

The clinical efficacy programme was completed by the inclusion of two supportive studies in which BDP HFA was inhaled through the Chiesi actuator-spacer device, the Jet spacer and not through the standard MDI actuator. One was a study in mild to moderate asthma with administration of BDP HFA in a dose of 500\(\mu\)g BD (using the 250\(\mu\)g/actuation inhaler); the second study recruited more severe asthmatics and employed dosing with BDP HFA up to 1500\(\mu\)g/day (using the 250\(\mu\)g/actuation inhaler).

The key objectives of the clinical development programme were as follows:

- To confirm that the similar in vitro performance of BDP HFA and BDP CFC MDIs translates into equivalent therapeutic efficacy.
- To assess the local and systemic safety of the BDP HFA product versus BDP CFC in asthma patients after prolonged administration.
- To provide evidence that the risk/benefit ratio of the new BDP HFA formulation is comparable with currently available BDP CFC products.
A total of 1083 patients were entered into the clinical programme, 647 received treatment with BDP HFA and 436 with currently available BDP CFC formulations.

The Clinical Expert describes the key objectives of the clinical programme, the study designs, methods of assessment and statistical methods and tests for equivalence in some detail in the Clinical Expert Report. Therefore in the light of this detail and in the light of full study descriptions given in Paragraph 4.4 Statistical Comments below, further detailed description of the clinical studies will not be given in this section of the Assessment Report.

4.2 Pivotal Efficacy Studies

4.2.1 Study 004/00: Double blind, double dummy multicentre parallel-group design trial of the efficacy and tolerability of beclometasone dipropionate spray aerosol (500µg bid) via metered dose inhaler using HFA-134a or CFC propellant in the 12-week treatment of mild to moderate persistent asthma in adult patients.

Patients entered were not to be receiving inhaled corticosteroids in a daily dose exceeding a dose equivalent to inhaled BDP CFC 1000µg. The table below shows the requirement for inhaled BDP CFC, inhaled budesonide and inhaled fluticasone propionate at the beginning of the study and during the run-in period.

**Number of patients on inhaled steroids at the commencement of the study and during run-in (ITT population)**

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA</th>
<th>BDP CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Number of patients taking</td>
<td>56 (100%)</td>
<td>56 (100%)</td>
</tr>
<tr>
<td>inhaled steroids at the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>entry and during run-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active ingredient:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclometasone dipropionate</td>
<td>50 (89.3%)</td>
<td>49 (87.5%)</td>
</tr>
<tr>
<td>daily dose:</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>1000µg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800µg</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>600µg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>500µg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>400µg</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>300µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>200µg</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>100µg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Budesonide</td>
<td>4 (7.1%)</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>Daily dose:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800µg</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>400µg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>3 (5.4%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Daily dose:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500µg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>100µg</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

At the end of the run-in period patients entering the treatment periods had to show <10% increase in FEV₁ over the two-week period. On entry to the study all patients received a total daily dose of BDP of 500µg BD as either BDP HFA or BDP CFC.
From the table it can be seen that more than 50% of patients in each treatment group were requiring a total daily dose of BDP CFC or equivalent inhaled steroid of 500µg or less; these patients, together with those requiring a >500µg total daily dose then all received BDP 1000µg as a total daily dose for the duration of the study.

The table below summarises the mean morning PEFR values for the ITT population for each two-week period and for the end of study period.

### Mean Morning PEFR (L/min) Measurement for Each 2-week Period (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>HFA-134a (N=56)</th>
<th>CFC (N=56)</th>
<th>Total (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week prior to randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>56</td>
<td>55</td>
<td>111</td>
</tr>
<tr>
<td>Mean</td>
<td>405.69</td>
<td>425.88</td>
<td>415.69</td>
</tr>
<tr>
<td>First 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>56</td>
<td>55</td>
<td>111</td>
</tr>
<tr>
<td>Mean</td>
<td>411.48</td>
<td>423.03</td>
<td>417.20</td>
</tr>
<tr>
<td>Second 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>53</td>
<td>105</td>
</tr>
<tr>
<td>Mean</td>
<td>415.18</td>
<td>422.33</td>
<td>418.79</td>
</tr>
<tr>
<td>Third 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>51</td>
<td>50</td>
<td>101</td>
</tr>
<tr>
<td>Mean</td>
<td>414.82</td>
<td>417.45</td>
<td>416.12</td>
</tr>
<tr>
<td>Fourth 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>48</td>
<td>97</td>
</tr>
<tr>
<td>Mean</td>
<td>417.20</td>
<td>420.04</td>
<td>418.61</td>
</tr>
<tr>
<td>Fifth 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>49</td>
<td>96</td>
</tr>
<tr>
<td>Mean</td>
<td>421.79</td>
<td>423.39</td>
<td>422.61</td>
</tr>
<tr>
<td>Sixth 2-week period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>45</td>
<td>46</td>
<td>91</td>
</tr>
<tr>
<td>Mean</td>
<td>417.45</td>
<td>421.76</td>
<td>419.63</td>
</tr>
<tr>
<td>End of study period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>56</td>
<td>56</td>
<td>112</td>
</tr>
<tr>
<td>Mean</td>
<td>408.90</td>
<td>422.17</td>
<td>415.54</td>
</tr>
</tbody>
</table>

n = total number of patients

The values of morning PEFR were substantially unchanged at the end of study period in both groups. These findings in the ITT population were similar to and consistent with those obtained for the PP population.

For both the ITT population and the PP population statistical analysis showed that BDP HFA was significantly non-inferior to BDP CFC in respect of average morning PEFR. For the two populations the lower limit of the unilateral 95% confidence interval for the treatment difference between the mean morning PEFR values in the two treatment groups was −3.74L/min and −6.32L/min, for the two populations respectively, values which are both greater than the lower limits of the equivalence interval (-10%) of −41.28 and −41.44L/min, for the two populations respectively.

It was also shown for both populations that BDP HFA was equivalent to BDP CFC in terms of average morning PEFR. The bilateral 95% confidence interval for the treatment difference was −5.63 to 17.50L/min and −8.24 to 15.24L/min for the two populations, ITT and PP, respectively each falling entirely within the equivalence interval (±10%) of ±41.28L/min and ±41.44L/min, for the two populations respectively.

When the changes in average morning PEFR at each clinic visit were compared with baseline values for each treatment group the changes in average morning PEFR values were slightly higher in the BDP HFA treatment group than in the BDP CFC group and following the second, third and fourth two-week periods of the study the mean changes were statistically significant. There were no statistically significant differences in the small
change seen in morning PEFR overtime and compared with baseline in the BDP CFC treatment group.

4.2.2 Study 003/00: Double blind, double dummy, parallel-group design trial of the clinical efficacy, activity on bronchial hyperresponsiveness and tolerability of beclometasone dipropionate spray aerosol (200µg bid) via a metered dose inhaler using HFA-134a or CFC propellant in the 6-week treatment of mild persistent asthma in adult patients.

Patients entered were not to be receiving inhaled corticosteroids in a daily dose exceeding a dose equivalent to inhaled BDP CFC 400µg; patients were permitted entry to the study if previously inhaled steroid naïve. The table below shows the requirement for inhaled BDP CFC, inhaled budesonide and inhaled fluticasone propionate at the beginning of the study and during the run-in period.

<table>
<thead>
<tr>
<th>No of patients on inhaled steroids at the commencement of the study and during run-in</th>
<th>BDP HFA</th>
<th>BDP CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Number of patients taking inhaled steroids at study entry and during run-in</td>
<td>73 (84.9%)</td>
<td>70 (81.4%)</td>
</tr>
</tbody>
</table>

Active ingredient:

<table>
<thead>
<tr>
<th>Beclometasone dipropionate daily dose</th>
<th>62 (84.9%)</th>
<th>55 (78.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400µg</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>300µg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>250µg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>200µg</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>100µg</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Budesonide daily dose</th>
<th>9 (12.4%)</th>
<th>13 (18.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400µg</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>300µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>200µg</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluticasone propionate daily dose</th>
<th>2 (2.7%)</th>
<th>2 (2.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200µg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>125µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>100µg</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

At the end of the run-in period patients entering the treatment periods have to show ≤15% increase in FEV₁ over the one-week period. On entry to the study all patients received a total daily dose of BDP of 200µg BD as either BDP HFA or BDP CFC.

Thirty seven patients (including 13 inhaled steroid naïve) out of 86 in the BDP HFA group and 41 (including 16 inhaled steroid naïve) out of 86 in the BDP CFC group were requiring a total daily dose of BDP CFC or equivalent inhaled steroid of less than 400µg; these patients, together with those requiring a total daily dose of 400µg, then all received 400µg as a total daily dose for the duration of the study.

In the analysis of the primary efficacy variable no substantial changes over baseline were seen in either treatment group. The analyses of equivalence in the ITT and PP populations are shown in tables below.
Morning PEFR (L/min): Equivalence between groups in the ITT population

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA</th>
<th>BDP CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean</td>
<td>442.1</td>
<td>447.9</td>
</tr>
<tr>
<td>SE</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>N</td>
<td>85</td>
<td>83</td>
</tr>
</tbody>
</table>

BDP CFC – BDP HFA

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>5.81</td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>5.43</td>
<td></td>
</tr>
<tr>
<td>Unilateral 95% CI</td>
<td>(-3.17 to 14.78)</td>
<td></td>
</tr>
<tr>
<td>Bilateral 95% CI</td>
<td>(-4.91-16.52)</td>
<td></td>
</tr>
</tbody>
</table>

Equivalence limit: (-44.79)

Morning PEFR (L/min): Equivalence between groups in the PP population

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA</th>
<th>BDP CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean</td>
<td>441.8</td>
<td>447.6</td>
</tr>
<tr>
<td>SE</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>N</td>
<td>84</td>
<td>83</td>
</tr>
</tbody>
</table>

BDP CFC – BDP HFA

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>5.78</td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>5.46</td>
<td></td>
</tr>
<tr>
<td>Unilateral 95% CI</td>
<td>(-3.26 to 14.81)</td>
<td></td>
</tr>
<tr>
<td>Bilateral 95% CI</td>
<td>(-5.01-16.56)</td>
<td></td>
</tr>
</tbody>
</table>

Equivalence limit: (-44.76)

SE = Standard error
SED = Standard error of the difference
CI = Confidence interval

The findings are similar to those in the first study described, Study 004/00; conclusions drawn are that BDP HFA is not inferior to BDP CFC and the two treatments can be deemed to be equivalent in respect of efficacy.

The analysis of morning PEFR in the two separate populations of asthmatic patients, those previously requiring inhaled steroids (steroid-dependent) and those not previously taking inhaled steroids (steroid-naïve) showed no significant changes over baseline or between treatment groups.

A sub-group of patients, 34 receiving BDP HFA and 31 receiving BDP CFC underwent methacholine challenge tests at the commencement of and at the end of the six week treatment period. Improvements (increase) over baseline were reported in both treatment groups for both PD20 (provocative dose of methacholine producing a 20% fall in FEV1) and PC20 (provocative concentration of methacholine producing a 20% fall in FEV1). The analysis within treatment showed a statistical significant difference over baseline in the BDP CFC treatment group for PC20; no statistically significant differences were seen between groups, p=0.657 and p=0.990, for the two parameters, respectively. These findings would suggest a slight improvement in bronchial hyperreactivity following six weeks treatment with beclometasone dipropionate.

The assessment of the patient’s own opinion of efficacy is slightly in favour of the BDP CFC treatment group.
4.2.3 Study 005/00: Double blind, double dummy, multicentre parallel-group design trial of the efficacy and tolerability of beclometasone dipropionate spray aerosol (unit dose: 50µg) via a metered dose inhaler using HFA-134a or CFC propellant in the 12-week treatment of mild to moderate persistent asthma in paediatric patients. Comparison with an open control group treated with beclometasone dipropionate (unit dose: 100µg) using HFA –134a propellant at a same daily dose (200µg bd).

Children entered into the study were not to be receiving inhaled corticosteroids in a daily dose exceeding a dose equivalent to inhaled BDP CFC 400µg; patients were permitted entry to the study if previously inhaled steroids naïve. (If patients were inadvertently entered receiving a total daily dose higher than that permitted, and 8 such patients were randomised to treatment, they were excluded from the PP analysis). The table below shows the requirement for inhaled BDP CFC, inhaled budesonide and inhaled fluticasone propionate at the beginning of the study and during the run-in period.

<table>
<thead>
<tr>
<th>Treatment with inhaled steroids at the screening visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Number (%) of patients]</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Number of patients taking inhaled steroids at study entry and during run-in</td>
</tr>
<tr>
<td>Active ingredient:</td>
</tr>
<tr>
<td>BDP</td>
</tr>
<tr>
<td>daily dose:</td>
</tr>
<tr>
<td>800µg</td>
</tr>
<tr>
<td>600µg</td>
</tr>
<tr>
<td>400µg</td>
</tr>
<tr>
<td>200µg</td>
</tr>
<tr>
<td>100µg</td>
</tr>
<tr>
<td>50µg</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>daily dose:</td>
</tr>
<tr>
<td>800µg</td>
</tr>
<tr>
<td>400µg</td>
</tr>
<tr>
<td>200µg</td>
</tr>
<tr>
<td>100µg</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
</tr>
<tr>
<td>daily dose:</td>
</tr>
<tr>
<td>600µg</td>
</tr>
<tr>
<td>375µg</td>
</tr>
<tr>
<td>200µg</td>
</tr>
<tr>
<td>100µg</td>
</tr>
<tr>
<td>Budesonide 200µg → BDP 400µg at Visit 1</td>
</tr>
<tr>
<td>(patients 275, 276 and 284 changed doses and drug at the start of the run-in period)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

As in Study 004/00 patients entering the treatment periods had to show a <10% increase in FEV₁ over the one or two week run-in period and on entry to the study all patients received a total daily dose of BDP of 200µg bd.

As in the previous studies a number of patients (at least 25% in each treatment group) were only using a total daily dose of BDP CFC or equivalent inhaled steroid of 200µg or less during the run-in period and in each treatment group a small number of patients were steroid naïve on entry to the study – three patients who subsequently received BDP HFA 50, 11 who received BDP CFC 50 and 6 who received BDP HFA 100. All patients, including the steroid naïve, those requiring <400µg as a total daily dose and those requiring
400µg (and even more in 8 patients recruited) then all received BDP 400µg (200µg bd) as a total daily dose for the 12 week duration of the study.

In the ITT population no statistically significant differences were observed in baseline morning PEFR between the three treatment groups. A statistically significant increase over baseline was seen in all three treatment groups from weeks 5-6 onwards to the end of the study. No statistically significant pairwise differences were seen between treatment groups in morning PEFR measurements at the end of the study (12 weeks).

### Treatment Comparison of Morning PEFR at the End of Trial Period (ITT population)

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Estimate</th>
<th>SE</th>
<th>Unilateral Lower 95%</th>
<th>Bilateral Lower 95%</th>
<th>Bilateral Upper 95%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP HFA 50 – BDP CFC 50</td>
<td>4.95</td>
<td>7.458</td>
<td>-7.32</td>
<td>-9.67</td>
<td>19.56</td>
<td>0.508</td>
</tr>
<tr>
<td>BDP HFA 100 – BDP HFA 50</td>
<td>-3.76</td>
<td>7.628</td>
<td>-16.31</td>
<td>-18.71</td>
<td>11.18</td>
<td>0.622</td>
</tr>
<tr>
<td>BDP HFA 100 – BDP CFC 50</td>
<td>1.18</td>
<td>7.653</td>
<td>-11.41</td>
<td>-13.82</td>
<td>16.18</td>
<td>0.877</td>
</tr>
</tbody>
</table>

Least square means: BDP HFA 50 = 349.36; BDP CFC 50 = 344.41; BDP HFA 100 = 345.59.

The mean average morning PEFR increased from baseline values of 324.2, 324.2 and 344.0L/min in the three treatment groups, BDP HFA 50, BDP CFC 50, and BDP HFA 100, respectively, to 346.7, 340.7 and 360.6L/min in the three groups, respectively. The unilateral lower CI for each treatment comparison (test -reference) was above −10% of the least square mean for the reference, indicating that BDP HFA 50 and BDP HFA 100 were non-inferior to BDP CFC 50 at that BDP HFA 100 was not inferior to BDP HFA 50. The two-sided CIs (95%) for each treatment comparison were within ±10% of the least square mean for the reference, indicating that BDP HFA 50 and BDP HFA 100 were equivalent to BDP CFC 50 and that BDP HFA 50 and BDP HFA 100 were also equivalent.

For the PP population the findings were similar.

In respect of the secondary end points of function the findings in the analysis of evening PEFR were similar. However for FEV1, statistically significant pairwise differences were observed between BDP HFA 50 and BDP CFC 50 (p=0.031) and between BDP HFA 100 and BDP CFC 50 (p=0.026) at the end of the treatment period. The unilateral lower 95% CI for each treatment comparison (test –reference) was above −10% of the least square mean for the reference which would indicate that BDP HFA 50 and BDP HFA 100 were non-inferior to BDP CFC 50. The bilateral 95% CIs in the comparison between the two BDP HFA treatment groups were within ±10% of the least square mean for reference which would indicate that BDP HFA 50 and BDP HFA 100 were equivalent. However the bilateral 95% CIs in the comparison of the two BDP HFA treatment groups with the BDP CFC group were outside ±10% which would indicate that the two BDP HFA treatment groups were not equivalent to the BDP CFC 50 group.

Statistically significant differences were seen for FVC and FEF25 at the end of the study period, for FVC the findings would suggest that BDP HFA 50 and BDP HFA 100 were not equivalent to BDP CFC 50 and were superior, for FEF25 BDP HFA 100 was shown to be not equivalent and superior to BDP HFA 50 although no statistically significant differences were seen between either BDP HFA group and BDP CFC 50.
4.3 Supportive Studies
The two supportive studies have studied the administration of BDP either formulated with HFA 134a or with CFC propellants (both Chiesi Farmaceutici SpA formulations of BDP) through the Chiesi actuatorspacer device, the Jet spacer-actuator, instead of the standard metered dose actuator. The use of the Jet spacer-actuator is supported through pharmacokinetic studies (see Paragraphs 3.2 and 3.3, above) and by in vitro data generated using an Andersen Cascade Impactor (see Part II, Paragraph 3.2 Pharmaceutical development, seventh bullet point). The in vitro data would suggest that delivery of beclometasone dipropionate to the lungs may be unaffected by the delivering device in the comparison of the Jet spacer-actuator with the standard metered dose actuator.

4.3.1 Study 01/98: Comparison of the efficacy and safety of two formulations of beclometasone dipropionate suspension for oral inhalation in adults with moderate asthma: one propelled by HFA-134a, the other by CFC 11 and 12.

The objective of this study was the demonstration of clinical equivalence (non-inferiority) in respect of the efficacy and safety of the two formulations of BDP, BDP HFA 250 and BDP CFC 250 both inhaled through the Jet spacer (also known as Beclojet). The study was a multicentre, randomised, double blind, parallel group study of six weeks duration, preceded by a one-week run-in period and followed by an eight-week open-label treatment period with BDP HFA 250 Jet only.

Patients recruited were adult males and females with clinically stable (for at least one month) asthma and requiring inhaled corticosteroids, with or without the use of a spacing device and at a daily dose ≤1500µg BDP or equivalent.

At the end of the run-in period patients received study treatment as the same dose of BDP or equivalent as that used prior to entry (and when disease was stable).

The Applicant presents a number of analyses performed on the primary endpoint, including an analysis of morning PEFR as initially defined using non-adjusted raw data and subsequently an analysis of morning PEFR following adjustment for baseline values. This second post-hoc analysis is more appropriate although this was only recognised when the findings of the first analysis failed to demonstrate non-inferiority between the two formulations. The findings are described below, Statistical Comments, Paragraph 4.4.2.1. It is concluded that non-inferiority of BDP HFA 250 to BDP CFC 250 is established. Similar analyses on the PP population confirmed non-inferiority.

Gender may have had an effect on the findings in that the higher proportion of male patients in the BDP CFC 250 group tended to increase the value of the final PEFR in this group.

4.3.2 Study 002/00: A double blind multicentre parallel-group design trial of the efficacy and tolerability of beclometasone dipropionate spray aerosol (500µg bid) via a spacer device using HFA-134a or CFC propellants in the 12-week treatment of mild to moderate persistent asthma in adult patients.

As in the pivotal efficacy studies not all patients recruited to this study were receiving the same dose of inhaled steroid when randomised to treatment and 28.6% of patients in the BDP HFA 250 treatment group and 36.4% in the BDP CFC 250 group were not receiving
inhaled steroids on entry to the study. Of those patients who were receiving inhaled steroids the majority were receiving BDP 1000µg or equivalent inhaled steroid with only 11 patients in the BDP HFA 250 group and 9 patients in the BDP CFC 250 group receiving lower doses. However, as in the pivotal studies all patients, regardless on their prior dose of inhaled corticosteroids, were randomised to receive one or other of the two formulations of BDP at a total dose of 1000µg (500µg bd). Almost 50% of patients in each treatment group were requiring a lower dose of inhaled steroid prior to the study than that which they received during the 12 week study period.

In the analysis of data generated in respect of the primary efficacy variable, morning PEFR measured daily by the patient at home, a progressive increase over baseline was reported in both treatment groups (the mean change from baseline was 21.9L/min in the BDP HFA group and 16.0L/min in the BDP CFC group at the end of the study). The analysis within treatment showed a statistically significant difference over baseline mid study (weeks 5-6) and at the end of the study (weeks 11-12) in both treatment groups. The adjusted mean (last 2-week period) was equal to 437.7L/min in the BDP HFA 250 group compared with 431.7L/min in the BDP CFC 250 group. The limit of the unilateral 95% confidence interval for the difference between the least square means did not exceed -43.17 (-10% of the adjusted mean of the BDP CFC 250 group) which demonstrates that BDP HFA 250 is not inferior to BDP CFC 250; the bilateral 95% CI was within +/-10% of the adjusted mean of the BDP CFC 250 group confirming equivalence. The primary end point was also analysed for the two populations (steroid requiring and steroid naïve) with similar findings.

4.4 Statistical Comments

These applications request approval to market pressurised metered-dose inhaler (MDI) formulations of beclometasone dipropionate (BDP) containing the CFC-free propellant, HFA-134a. This report focuses on three pivotal studies and two supportive studies. In the pivotal studies the CFC containing BDP comparator was Becloforte® Inhaler (Allen and Hanburys). In the supportive studies BDP was administered using a spacer and the BDP-MDI comparator was Beclojet® (Chiesi).

4.4.1 Pivotal Studies

4.4.1.1 Study 004/00

Study 004/00 was a multi-centre, randomised, double-blind, double-dummy, parallel group study designed to assess the efficacy and tolerability of BDP (500µg bid) via a MDI and formulated with HFA-134a or CFCs as propellants for the treatment of mild to moderate persistent asthma in adults. The study was 12 weeks long with a 2-week run-in period. Patients were not enrolled in the study if they were already receiving inhaled corticosteroids at a daily dose exceeding a corresponding dose of 1000µg inhaled BDP given via a MDI formulated with CFC propellants. Eligible patients entered a 2-week run-in period during which any non-permitted medications were withdrawn prior to entry into the study treatment period and inhaled corticosteroids were permitted at the same constant daily dose as at baseline. At the end of the run-in period, patients were not allowed to proceed to the treatment phase of the study if their FEV₁ (L) at the end of the run-in period was ≥ 10% higher than the FEV₁ (L) at baseline. Eligible patients were then randomised to receive either the BDP (Chiesi) spray aerosol and the Allen and Hanburys placebo via MDI, with HFA-134a propellant or BDP (Allen and Hanburys) spray aerosol and the
Becolex™ Modulite® pressurised inhalation solution (beclometasone dipropionate) PL 06607/0017-20

Chiesi placebo via MDI, with CFC propellants. Each actuation of active treatments contained 250µg of active substance. Both BDP formulations were administered in a dosage of 2 actuations (500µg) with 2 actuations of the matched placebo twice daily, at approximately 8am and 8pm. The study was double dummy because it was not possible for a Chiesi MDI to be identical in appearance to the Allen and Hanburys (Becloforte®) MDI.

One hundred and sixteen patients were enrolled and received at least one dose of study treatment and matched placebo. 4 patients (3 from the HFA group and one from the CFC group) were not included in the ITT population because they did not have at least 10 days post-randomisation efficacy data. Therefore the ITT population contained 112 subjects; 56 in each treatment group. The per protocol population contained 106 patients, 54 from the HFA-134a group and 52 from the CFC group.

Comment: The protocol definition of the ITT population was all randomised patients who received at least one dose of study medication and with at least one visit after baseline. Hence the definition of the ITT population used in the study report is slightly different from the original protocol definition of the ITT population. However, as this is an equivalence trial the prime concern will be the per protocol population but similar results should be obtained from both data sets. Only a few patients have been excluded from the pure ITT population and hence the definition of ITT is probably acceptable in this case.

The prior dose of corticosteroids in the ITT population is shown in paragraph 4.2.1 above.

Comment: There is a major flaw in the design of this study. Patients continued to receive their pre-trial dose of inhaled corticosteroids during the 2-week run-in period. At least half of the patients then had their BDP dose at least doubled. If these subjects had become overtreated as a result it is likely that there would be less variability in their lung function parameters than at the end of the run-in period. This would then result in a reduction of the sensitivity of the trial and make it easier to show that the two products were equivalent than if the products had been given at the correct dose for each patient.

The protocol-defined primary efficacy variable was the morning PEFR (L/min) measured daily by patients and recorded on the diary cards. Values from the second week of the run-in period were averaged to assess the baseline level and values were then averaged across each 2-week period; a minimum of 10 measurements was required in each period. Comparisons between treatment groups were made using an ANCOVA model for morning PEFR values at each two-week period. The ANCOVA model included terms for investigator and treatment and the baseline PEFR value was a covariate. A preliminary test for the investigator-by-treatment interaction was performed at the 10% significance level. The equivalence between the two test treatments was evaluated using a 95% confidence interval for the difference in morning PEFR means between the two groups. The two test treatments were defined as equivalent if the confidence limits for the difference fell within ±10% of the least square mean of the BDP CFC group. The primary efficacy endpoint was analysed using the ITT and per protocol populations.

A protocol amendment declared that the test drug was defined as non-inferior to the control one if the lower limit of the unilateral 95% confidence interval for the difference in morning PEFR means between the two groups did not exceed -10%. The reference to this was changed to ICH E9.
Comment: To claim non-inferiority the lower limit of a two-sided 95% confidence interval would have to be greater than the pre-specified non-inferiority margin. Using a one-sided ("unilateral") 95% confidence interval is not appropriate in therapeutic non-inferiority or equivalence trials. The equivalence margins are justified as being similar to those used in previous submissions. A more robust defence of their chosen margins would have been welcomed. To provide robust evidence of efficacy equivalence needs to be confidently demonstrated using both the ITT and per protocol populations.

Secondary endpoints included the evening PEFR (recorded daily on diary cards) and FEV$_1$, FVC, PEFR, MEF$_{50}$, FEF$_{25}$ and the FEV$_1$/FVC ratio (recorded at each clinic visit).

The values of morning PEFR were substantially unchanged at the end-of-study period in both groups. In the ITT population, the mean average morning PEFR during the week prior to randomisation was 405.69 L/min in the HFA group and 425.88 L/min in the CFC group. During the end of study period the mean average morning PEFR was 408.90 L/min in the HFA group and 422.17 L/min in the CFC group. The results obtained in the ITT population were consistent with those obtained from the per protocol population.

Comment: All patients who were randomised also received at least one dose of study medication. Therefore no patients were excluded from entering the double-blind treatment phase because of a significant increase from baseline in FEV$_1$. Therefore, it is reasonable to conclude that their existing medication had stabilised their asthma. Surprisingly, after at least doubling the pre-trial dose in over half of the patients in the study the end-of-study PEFR values were still very similar to those observed at the end of the run-in period. This casts doubt over whether this trial has the sensitivity to observe differences between treatments.

The two-sided 95% confidence interval for the treatment difference between the mean morning PEFR values in the HFA and CFC groups was -5.63 to 17.5 L/min and -8.24 to 15.24 L/min in the ITT and per protocol populations respectively. The ±10% equivalence margins were ±41.28 L/min and ±41.40 L/min for the ITT and per protocol populations. Hence the observed 95% confidence intervals fell well within the prespecified equivalence margins.

Comment: It is not clear whether the predefined ±10% equivalence margins were tight enough. However, the observed limits of the confidence intervals fell within a much more stringent ±5% level. All the secondary endpoints also demonstrated equivalence between the HFA and CFC MDIs.

Statistical Conclusion on study 004/00
This trial does not provide pivotal evidence to satisfactorily conclude that the BDP HFA has comparable efficacy to BDP CFC. The main reason for this is the potential lack of sensitivity of the trial - i.e. lack of ability to detect real differences. By leaving patients on their pre-trial dose of corticosteroid and then increasing the dose at the beginning of the study period it is possible that patients are at the top of their dose response curve for BDP. The fact that the limits of the 95% confidence intervals fell well within the prespecified levels is not convincing because this trial lacks the ability to detect differences between treatments. This is borne out when patients had their dose of BDP increased but their mean morning PEFR value remained fairly constant.
4.4.1.2 Study 003/00

Study 003/00 was a randomised, double-blind, double-dummy, parallel group study designed to assess the efficacy and tolerability of BDP (200 µg bid) via a MDI and formulated with HFA-134a or CFCs as propellants, for the treatment of mild persistent asthma in adults. The study was 6 weeks long with a 1-week run-in period. Patients were not enrolled in the study if they were already receiving inhaled corticosteroids at a daily dose exceeding a corresponding dose of 400 µg inhaled BDP given via a MDI formulated with CFC propellants.

Eligible patients entered a one-week run-in period during which any non-permitted medications were withdrawn prior to entry into the study treatment period and inhaled corticosteroids were permitted at the same constant daily dose as at baseline. At the end of the run-in period, patients were not allowed to proceed to the treatment phase of the study if their FEV₁ (L) at the end of the run-in period was ≥ 15% higher than the FEV₁ (L) at baseline. Eligible patients were then randomised to receive either the BDP (Chiesi) spray aerosol and the Allen and Hanburys placebo via MDI, with HFA-134a propellant or BDP (Allen and Hanburys) spray aerosol and the Chiesi placebo via MDI, with CFC propellants. Each actuation of active treatments contained 100 µg of active substance. Both BDP MDI formulations were administered in a dosage of 2 actuations (200 µg) with 2 actuations of the matched placebo twice daily, at approximately 8am and 8pm. The study was double dummy because it was not possible for a Chiesi MDI to be identical in appearance to the Allen and Hanburys (Becotide®) MDI.

Comment: It is not clear whether the 1-week run-in period or the 6-week treatment period are long enough to adequately evaluate the comparative efficacy of BDP CFC and BDP HFA.

One hundred and eighty-nine patients were recruited into the study; 17 were not randomised because they did not meet the inclusion/exclusion criteria (11 patients), poor co-operation (one patient), adverse events (3 patients), lost to follow-up (1 patient) and one patient was not randomised since the target total number of patients had been reached. Hence 172 patients were randomised; 86 in each treatment group. One patient in the HFA group and three patients in the CFC group either did not meet the inclusion criteria or were lost to follow-up prior to the end of the run-in period. Therefore the ITT population consisted of 85 patients in the HFA group and 83 in the CFC group. There was one major protocol violation in the HFA group. Hence the per protocol population contained 167 patients.

The prior dose of corticosteroids in the ITT population is shown in paragraph 4.2.2 above.

Comment: In this study 25% of patients had their dose of steroid at least doubled at the end of the run-in period. This is about the same percentage as study 005. Therefore there are the same concerns as with study 005 about whether the sensitivity of this trial will be reduced by increasing the dose of BDP at the end of the run-in period. Also, 29 patients had not taken inhaled steroids before. It is open to question whether these patients should have been analysed separately from patients with previous experience of inhaled steroids. The primary and secondary endpoints are the same as in study 004. The only difference is that daily PEFR values have been averaged across each weekly treatment period instead of across each two-week treatment period. As only 1 ITT patient was excluded from the per protocol population only the results from the ITT analyses are presented below.
The mean average morning PEFR values were 441.6 L/min and 447.2 L/min at baseline for the BDP HFA and BDP CFC groups respectively. No substantial changes from the baseline mean morning PEFR levels were seen throughout the 6-week treatment period. The estimated mean difference between mean PEFR values for the two treatment groups (BDP CFC - BDP HFA) was 5.78 L/min with a 95% confidence interval of -4.91 L/min to 16.52 L/min. These limits are well inside the prespecified ±10% levels and are also inside a more stringent ±5% margin.

Similar patterns were seen in the secondary endpoints. An analysis of morning PEFR for steroid-dependant and steroid-naïve patients separately did not show statistically significant changes over baseline in either group. Also a comparison between groups did not show statistically significant differences in either category.

Comment: Although not many steroid naïve patients were included in the study it is surprising that in these patients PEFR levels did not increase when given BDP.

Statistical Conclusion on study 003/00
The fact that morning PEFR levels did not change significantly from baseline levels even though about 25% of patients had had their BDP dose at least doubled suggests that this trial lacks the ability to detect differences. Hence even though the limits of the 95% confidence intervals fell well within the prespecified levels equivalent efficacy between the CFC and HFA formulations has not been satisfactorily demonstrated from this study.

4.4.1.3 Study 005/00
Study 005/00 was a multi-centre, randomised, double-blind, double-dummy, parallel group study designed to assess the efficacy and tolerability of BDP (200µg bid) via a MDI with HFA-134a or with CFC propellants for the treatment of mild to moderate persistent asthma in children. The study was 12 weeks long with a 2-week run-in period. Patients were not enrolled in the study if they were already receiving inhaled corticosteroids at a daily dose exceeding a corresponding dose of 400µg inhaled BDP given via a MDI with CFC propellants. Eligible patients entered a 2-week run-in period during which any non-permitted medications were withdrawn prior to entry into the study treatment period and inhaled corticosteroids were permitted at the same constant daily dose as at baseline. At the end of the run-in period, patients were not allowed to proceed to the treatment phase of the study if their FEV₁ (L) at the end of the run-in period was ≥10% higher than the FEV₁ (L) at baseline. Eligible patients were then randomised to one of three groups. Groups 1 (BDP-HFA 50) and 2 (BDP-HFA 100) received the BDP (Chiesi) spray aerosol and the Allen and Hanburys placebo via MDI with HFA-134a propellant and group 3 (BDP-CFC 50) received the BDP (Allen and Hanburys) spray aerosol and the Chiesi placebo via MDI, with CFC propellants. Group 1 and 3 patients received BDP at unit doses of 50µg (4 actuations bid) and group 2 patients received BDP at unit doses of 100µg (2 actuations bid). Hence all patients received a total daily dose of 400µg. Patients allocated to group 2 were treated in an open fashion; in order to reduce difficulties in managing a whole blinded trial, in terms of both formulation and unit dose. The study was double dummy because it was not possible for a Chiesi MDI to be identical in appearance to the Allen and Hanburys (Becotide®) MDI.

Comment: It is clear that it would be difficult to ensure that patients who received BDP 100µg/actuation were blinded to study treatment. However, it would have been possible
with more placebo inhalers to maintain the double blind design for all groups in the study. It is acknowledged that this would result in a very cumbersome design. It would have been far easier to have a fourth arm in the study in which patients received BDP-CFC 100µg per actuation. This would then permit two blinded comparisons, one between 50µg strength inhalers and one between 100µg strength inhalers. Any comparison made between patients allocated to the open-label group and the other groups will be less secure than comparisons made between patients allocated to the double blind groups. The comparison of primary interest will be the comparison between the BDP-HFA 50 and the BDP-CFC 50 groups. Given the different way in which the same daily dose is given for the BDP-HFA 100 and BDP-CFC 50 groups it is clear that it is not necessary to demonstrate equivalence between these two groups.

Two hundred and ninety-six patients were screened and 218 were randomised to receive study treatment. Eight of these patients did not receive any trial medication. This left 72 patients in the BDP-HFA 50 group, 71 patients in the BDP-CFC 50 group and 67 patients in the BDP-HFA 100 group. 3 patients (1 from the BDP-HFA 50 group and 2 from the BDP-HFA 100 group) were not included in the ITT population because they did not have any post baseline data. Therefore the ITT population contained 207 subjects; 71, 71 and 65 patients in the BDP-HFA 50, BDP-CFC 50 and BDP-CFC 100 groups respectively. The per protocol population contained 182 patients; 62, 64 and 56 in the BDP-HFA 50, BDP-CFC 50 and BDP-HFA 100 groups respectively.

The prior dose of corticosteroids in the ITT population is shown in Paragraph 4.2.3 above.

**Comment:** 5 patients in the BDP-HFA 50 group, 2 in the BDP-CFC 50 group and 1 in the BDP-HFA 100 group were treated with a daily dose higher than permitted in the run-in period. Also, in a further three patients the active ingredient and its dose was changed at the start of the run-in period: all 11 patients were excluded from the per protocol analysis. 25% of patients had their dose of steroid at least doubled at the end of the run-in period. Although, this percentage is much smaller than in study 004/00 it is still a large enough percentage to provide concern over whether this will reduce the sensitivity of the trial. Also note that 20 patients were not taking inhaled steroids to control their asthma at baseline. It is not clear whether these patients should have been included in this trial.

The protocol-defined primary efficacy variable was the morning PEFR (L/min) measured daily by patients and recorded on the diary cards. The same methods and secondary endpoints were defined as in study 004/00.

**Comment:** The comments made on study 004/00 are equally relevant for this study.

The values of morning PEFR at the end of the study increased significantly from baseline in all treatment groups. In the ITT population, the mean average morning PEFR during the week prior to randomisation was 324.2 L/min, 324.2 L/min and 344.0 L/min in the BDP-HFA 50, BDP-CFC 50 and BDP-HFA 100 groups respectively. By the end of the study period the mean average morning PEFR had increased to 346.7 L/min, 340.7 L/min and 360.6 L/min in the 3 groups respectively. Similar results were seen in the per protocol population.

**Comment:** All patients who entered the run-in period were stabilised on their current asthma medication. However, by the end of the treatment period mean morning PEFR
values had significantly increased in all groups. Hence this trial does have the ability to detect differences. There are at least two possible explanations for the increase in lung function parameters during the treatment period. Firstly, patients were not stable on their current medication and the two-week run-in period was not long enough to observe an improvement in their lung function parameters. Alternatively, patients who had the dose of BDP increased at the end of the run-in period were not optimally controlled on their previous therapy and consequentially the lung function improved when their treatment was changed.

The two-sided 95% confidence interval for the treatment difference between the mean morning PEFR values in the HFA 50 and CFC 50 groups was -9.67 to 19.56 L/min and -10.26 to 21.65 L/min in the ITT and per protocol populations respectively. The ±10% equivalence margins were ±32.24 L/min and ±32.19 L/min for the ITT and per protocol populations. Hence the observed 95% confidence intervals fell well within the prespecified equivalence margins.

**Comment:** These confidence intervals are wider than observed in study 004/00 even though this is a larger study. Although, falling well within the prespecified margins the confidence limits are not within a more stringent ±5% margin.

Similar patterns were seen in the evening PEFR endpoint. Similar increases in FEV1 at the end of the study compared with baseline levels to those observed for PEFR values were also observed. However, significant differences between groups were observed for FEV1.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Estimate</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP-HFA 50 - BDP-CFC 50</td>
<td>0.12</td>
<td>0.01, 0.22</td>
<td>0.031</td>
</tr>
<tr>
<td>BDP-HFA 100 - BDP-HFA 50</td>
<td>0.01</td>
<td>-0.10, 0.11</td>
<td>0.911</td>
</tr>
<tr>
<td>BDP-HFA 100 - BDP-CFC 50</td>
<td>0.12</td>
<td>0.02, 0.23</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Note that the least square mean for CFC propellant was 2.12L.

**Comment:** The table above shows that the change from baseline in FEV1 was significantly higher in the HFA 50 group than the CFC 50 group. Also the upper limit of the 95% confidence limit is greater than 10% of the baseline FEV1 value for the CFC 50 group. The same conclusions can be drawn from the comparison between the HFA 100 and CFC 50 groups. It is debated whether FEV1 or PEFR should be the primary endpoint in asthma studies. In this case the results for FEV1 are different to those for PEFR. This trial does provide evidence that the HFA formulation of BDP has significantly greater efficacy than the CFC formulation in terms of increasing FEV1.

**Statistical Conclusion on study 005/00**
Although, this trial suffers from the same design flaw as study 004/00, a higher percentage of patients in this study were already on the study dose of BDP. Due to significant rises in lung function parameters there is evidence that either these patients were not optimally treated on their previous therapy or that they were not stable at baseline. However, the significant increase in lung function parameters does confirm that differences can be detected in this trial. The main concern in this study is the significant difference observed in the change from baseline in FEV1 in the HFA 50 and CFC 50 groups. This provides evidence that the HFA-134a formulation is more potent than the CFC formulation for the
same dose of BDP. Therefore, it would be unwise to conclude that equivalent therapeutic efficacy has been convincingly demonstrated for the CFC and HFA-134a formulations.

4.4.2 Supportive Studies
4.4.2.1 Study 01/98
Study 01/98 was a multi-centre, randomised, double-blind, parallel group study designed to assess the efficacy and tolerability of BDP via the Jet spacer and formulated with HFA-134a or CFCs as propellants for the treatment of mild to severe persistent asthma in adults. The study was 6 weeks long with a 1-week run-in period. Patients were not enrolled in the study if they were already receiving inhaled corticosteroids at a daily dose exceeding a corresponding dose of 1500µg inhaled BDP given via a MDI formulated with CFC propellants. Eligible patients entered a 1-week run-in period during which any non-permitted medications were withdrawn prior to entry into the study treatment period and inhaled corticosteroids were permitted at the same constant daily dose as at baseline. At the end of the run-in period, patients were randomised to receive either BDP HFA 250 or BDP CFC 250 for 6 weeks at the same dose (BDP equivalent) as their previous treatment in a 2:1 ratio. At the end of the treatment period all patients received the BDP HFA 250 for an 8-week open label follow-up period.

Four hundred and seventy-three patients were randomised to receive study treatment. Twenty-four patients did not provide any data during the run-in period and therefore 449 patients received study treatment. Six patients, 4 in the HFA group and 2 in the CFC group, did not provide any post-baseline measurements. Hence 443 patients were included in the ITT population, 293 in the HFA group and 150 in the CFC group. The per protocol analysis was performed on 334 patients: 222 in the HFA group and 112 in the CFC group. All patients had been previously treated with inhaled corticosteroids. 72.7% were receiving BDP, 25.5% budesonide and 1.8% flunisolide. The prior dose of BDP or equivalent in the ITT population is shown below. Only 14.1% of patients had used a spacer prior to receiving study treatment.

<table>
<thead>
<tr>
<th>Dosage (µg)</th>
<th>BDP HFA</th>
<th></th>
<th>BDP CFC</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>250</td>
<td>4</td>
<td>1.4</td>
<td>0</td>
<td>0.0</td>
<td>4</td>
</tr>
<tr>
<td>500</td>
<td>54</td>
<td>18.4</td>
<td>28</td>
<td>18.7</td>
<td>82</td>
</tr>
<tr>
<td>750</td>
<td>6</td>
<td>2.0</td>
<td>6</td>
<td>4.0</td>
<td>12</td>
</tr>
<tr>
<td>1000</td>
<td>201</td>
<td>68.6</td>
<td>101</td>
<td>67.3</td>
<td>302</td>
</tr>
<tr>
<td>1500</td>
<td>28</td>
<td>9.6</td>
<td>15</td>
<td>10.0</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>293</td>
<td>100.0</td>
<td>150</td>
<td>100.0</td>
<td>443</td>
</tr>
</tbody>
</table>

Dosage of previous corticosteroids therapy (BDP or BDP equivalent)

**Comment:** This study has a clear design advantage over the other studies submitted with this application. Patients continued to receive the pre-trial dose of BDP or equivalent during the study. Of course, this is what is likely to happen when patients are switched from BDP CFC to BDP HFA. On the negative side, the six-week double blind treatment period and 1-week run-in period could be viewed as too short to provide robust evidence of comparable efficacy between the two formulations. Also, the fact that only 14% of patients had previously used a spacer may imply that this trial is not representative of patients who currently use a spacer with BDP CFC inhaler and wish to switch to a BDP HFA inhaler.
The protocol-defined primary efficacy variable was the morning PEFR (L/min) recorded using a One Flow Meter (OFM) at the end of the 6-week double blind treatment period (mean of the last 7 values recorded during the last 14 days of double-blind treatment). The protocol-defined definition of non-inferiority was that the lower limit of the 95% “unilateral” Hodges-Lehman confidence interval for the difference between the two treatments (BDP HFA-BDP CFC) should be greater than –25L/min. The 25L/min limit was chosen as it was less than 10% of the mean PEFR observed with BDP CFC in previous studies conducted by Chiesi. A fixed value was defined in order to avoid too wide a range for equivalence being used because of the heterogeneous nature of the patient population recruited to this study.

**Comment:** This study makes the same mistake as the three pivotal studies by defining non-inferiority based on the lower limit of a one-sided 95% confidence interval. Attention will be focused on the lower limit of the two-sided 95% confidence interval. The observed mean PEFR values were not normally distributed. The use of distribution-free methods was predefined in the protocol if mean PEFR values were not normally distributed. This analysis is appropriate. It would be more appropriate to use change from baseline in mean PEFR rather than the observed mean of the final week PEFR values as the primary endpoint. The applicant recognised this after the results of the primary analysis failed to demonstrate non-inferiority between the two formulations. Normally changing the primary analysis in a study is unacceptable. However, in this case the post-hoc analysis is the correct analysis and the findings of the morning PEFR analysis after adjusting for baseline PEFR values are presented below.

The mean morning PEFR values at baseline were 385.30 L/min and 378.51 L/min in the BDP HFA and BDP CFC groups respectively for the ITT population. The corresponding values were 389.82 L/min and 394.30 L/min for the per protocol population. Only 395 out of the 443 ITT patients had PEFR data recorded using the OFM. Mean baseline morning PEFR values were only available in 287 patients for whom a final PEFR was also available. The lower limit of the one-sided 95% Hodges-Lehman confidence interval for the difference in median PEFR values adjusted for baseline PEFR in the ITT population was –5.2 L/min. Therefore, non-inferiority of the HFA MDI to the CFC MDI was deemed to have been established.

**Comment:** The PEFR values have remained fairly similar throughout the study. This is expected as patients have remained on their pre-trial dose of BDP (or equivalent) throughout the whole study period. Although the lower limit of a two-sided 95% confidence interval for the difference in median PEFR values has not been given it is clear from the lower limit of the 90% confidence interval given that the required limit would have been much smaller than the pre-specified 25L/min level. The analysis of the per protocol population gives similar results. Only 43 patients dropped out of the study before the end of the treatment period. It is unclear why only 287 of the 443 patients included in the ITT population had baseline and endpoint PEFR values. Of course, it is possible that very different conclusions would have been drawn if data were available on these missing subjects. However, it is reassuring to note that an analysis of FEV1 values on 392 subjects also demonstrated clinical equivalence between the two treatments. Therefore, overall it is reasonable to conclude that the Chiesi BDP CFC and BDP HFA Jet spacers have been shown to be clinically equivalent.
**Statistical Conclusion on study 01/98**

Study 01/98 investigated the effect of switching patients currently taking CFC inhaled steroids to the equivalent dose of BDP HFA administered via a Jet spacer.

The study was well designed and the results of the primary efficacy analysis provide convincing evidence of the clinical equivalence of the two formulations of BDP.

### 4.4.2.2 Study 002/00

Study 002/00 was a multi-centre, randomised, double-blind, parallel group study designed to assess the efficacy and tolerability of BDP via the Jet spacer formulated with HFA-134a or CFCs as propellants for the treatment of mild to moderate persistent asthma in adults. The study was 12 weeks long with a 2-week run-in period. Patients were not enrolled in the study if they were already receiving inhaled corticosteroids at a daily dose exceeding a corresponding dose of 1000µg inhaled BDP given via a MDI formulated with CFC propellants. Eligible patients entered a 2-week run-in period during which any non-permitted medications were withdrawn prior to entry into the study treatment period and inhaled corticosteroids were permitted at the same constant daily dose as at baseline. At the end of the run-in period eligible patients were randomised into one of two groups, BDP HFA or BDP CFC. The unit dose was 250µg. Each patient took 2 actuations twice a day to give a total daily dose of BDP 1000µg.

**Comment:** This study followed a similar design to the three pivotal efficacy study and similar comments to those made on those studies are equally relevant to this study. The methods of analysis and the predefined primary endpoints were the same as in the pivotal studies.

One hundred and sixty-three patients were screened and 154 were randomised to receive study treatment, 77 were assigned to each treatment group. All 77 patients completed the study in the HFA group and 73 patients completed the study from the CFC group. One patient was withdrawn after 3 days of study treatment and was not included in the ITT population. No major protocol violations were reported and therefore the ITT and per protocol population both included 153 patients.

The prior dose of corticosteroids in the ITT population is shown below.

<table>
<thead>
<tr>
<th>Active Ingredient:</th>
<th>BDP HFA</th>
<th>BDP CFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP daily dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000µg</td>
<td>38 (78.2%)</td>
<td>32 (77.6%)</td>
</tr>
<tr>
<td>750µg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>600µg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>500µg</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>250µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Budesonide daily dose</td>
<td>11 (20.0%)</td>
<td>10 (20.4%)</td>
</tr>
<tr>
<td>800µg</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>600µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>400µg</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>200µg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flunisolide daily dose</td>
<td>1 (1.8%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>1000µg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients not taking inhaled steroids at study entry or during run-in</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>77</td>
</tr>
</tbody>
</table>
Comment: Fortunately, the majority of patients in this study were already receiving a daily dose of 1000µg or a similar slightly lower dose of BDP or equivalent. It is unclear whether the 50 patients who had not received inhaled steroids should have been analysed together with the other patients or whether they should have been included in the study at all. It was not stated how many patients who were taking inhaled steroids at study entry were using a spacer device.

The mean morning PEFR values at baseline were 416.7 L/min and 413.7 L/min in the HFA and CFC groups respectively for the ITT population. A progressive increase in PEFR values over baseline was reported in both groups. A statistically significant increase from baseline at the end of the treatment period was seen in both groups. An analysis of morning PEFR in two separate populations, namely patients taking (steroid-dependant) or not taking (steroid-naïve) inhaled steroids at study entry and during the run-in, showed statistically significant increases over baseline in both groups.

Comment: The increase in PEFR during the study indicates that this study is capable of detecting differences. It also indicates that patients, whether they were steroid-naïve or previous inhaled steroid users, were capable of improving their lung function.

The estimated mean difference between mean PEFR values for the two treatment groups (BDP CFC - BDP HFA) was –6.05 L/min with a 95% confidence interval of –19.7 L/min to 7.6 L/min. These limits are well inside the pre-specified ±10% levels and are also inside a more stringent ±5% margin. This analysis was repeated for the steroid-naïve and previous steroid users subgroups and similar confidence intervals were reported.

Statistical Conclusion on study 002/00
Study 002/00 suffers from the same design flaw as the pivotal efficacy studies. By increasing patients inhaled steroid dose at the end of the run-in period it remains possible that these patients have been over treated and their variability of PEFR values has been reduced. If this were the case it would be easier to show equivalence between BDP CFC and BDP HFA. However, as the majority of patients remained on a similar dose of BDP to their pre-trial BDP dose this study still provides some evidence to support the claim of clinical equivalence between the two formulations. It is questionable whether the results from this study alone are sufficient to conclude that the Chiesi CFC and HFA formulations of BDP administered using a Jet spacer are clinically equivalent.

Overall Statistical Conclusion
Studies 004/00 and 003/00 compared the efficacy of the proposed BDP HFA MDI with BDP CFC MDI (Allen and Hanburys) in adults. Due to the design flaw of increasing patients BDP dose at the end of the run-in period there are doubts over the robustness of the results in both of these studies. It is not clear whether either of these studies had the ability to detect differences between treatments. Note also that these studies only investigated daily doses of BDP of up to 1000µg. The clinical equivalence of the proposed BDP HFA to BDP CFC has not been tested at doses in excess of 1000µg in the pivotal efficacy programme.

Study 005/00 compared the efficacy of the proposed BDP HFA MDI with BDP CFC MDI (Allen and Hanburys) in paediatric patients. In study 005/00 more patients stayed on their pre-trial dose of inhaled steroids during the study period than in Study 004/00 and also the
morning PEFR values increased significantly during the study period. However, although the predefined criteria for clinical equivalence were met for PEFR, the FEV\textsubscript{1} values increased significantly more in the HFA group than the CFC group. If these increases were thought to be clinically relevant, or there were safety concerns that implied that the HFA product was more potent than the CFC formulation, then it would be unwise to conclude that clinically equivalent efficacy had been demonstrated between the HFA and CFC formulations of BDP in paediatric patients. It is of note also that Study 005/00 only investigated a daily dose of BDP of 400µg. The clinical equivalence of the proposed BDP HFA to BDP CFC has not been tested at other doses in paediatric patients.

Studies 01/98 and 002/00 compared the efficacy of the proposed BDP HFA MDI with the Beclojet\textsuperscript{®} CFC containing MDI (Chiesi) in adults. Study 01/98 was well designed and provides convincing evidence of the clinical equivalence of the CFC and the HFA-134a formulations of BDP in adult patients inhaled via a spacing device. Although Study 002/00 suffers from the same design flaw as Studies 003/00, 004/00 and 005/00 when the results are taken together with the results from Study 01/98 there is good evidence of clinical equivalence between the CFC and the HFA-134a formulations in adult patients at daily doses of up to 1500µg using a spacer. However, it is unwise to infer that because the proposed inhaler is clinically equivalent to the Chiesi CFC inhaler that the proposed inhaler is also clinically equivalent to the Allen and Hanburys’ CFC containing formulations of BDP.

4.5 Assessor’s Comment
The Applicant has presented five clinical studies, three pivotal and two supportive in an attempt to show that BDP formulated with the non-CFC propellant, HFA-134a is clinically equivalent to BDP as currently formulated with CFC propellants, Becotide and Becloforte Inhalers, the brand leader products in the UK and the products to which the Applicant is claiming essential similarity.

The three pivotal studies all compared BDP HFA with BDP CFC (either Becloforte or Becotide), two of three studies recruited adult patients with mild to moderate asthma and the third recruited children with mild to moderate asthma. The two adult studies compared the two formulations of BDP at the lower end of the currently accepted dose range for the CFC-containing formulation (200µg BD) and at the mid point of the recognised dose range (500µg BD). No assessment is presented at the top end of the dose range (1000µg BD) within the pivotal programme nor within the supportive programme in respect of a comparison with the product to which essential similarity is claimed. The study in childhood asthma assessed a dose of BDP HFA at the top end of the recognised dose range for use in children (200µg BD) and incorporated within the design an assessment of the two lower inhaler strengths, 50 and 100µg/actuation. This could then permit extrapolation of the findings at the top end of the dose range downwards. A comparative efficacy study at the lower end of the dose range in children (100µg BD) would not necessarily be required.

The three studies in the pivotal programme adopted similar designs, were appropriately sized and assessed efficacy through well accepted primary and secondary end points. However each study was essentially flawed in one aspect of the design raising serious questions over the eventual outcomes in each study.
In each of the three studies patients recruited were requiring a range of doses of inhaled corticosteroids from a protocol defined maximum upper limit equivalent to the dose of inhaled steroid to be studied in the particular study, downwards. In each study patients remained on their pre-study dose of inhaled steroid during the run-in period during which stability of asthma control on that particular dose was demonstrated. At the end of the run-in period all patients were transferred to study treatments, either HFA or CFC containing formulations of BDP. From the tables presented in Paragraphs 4.2.1, 4.2.2 and 4.2.3 it can be seen that in each study a number of patients appeared to require a significantly lower dose of inhaled BDP to effect asthma control than the dose which they subsequently received during the study.

- In Study 004/00, the study of adults with mild to moderate disease and receiving a dose of BDP of 500µg BD for 12 weeks, more than 50% of patients in each treatment group were requiring a total daily dose of BDP CFC or equivalent inhaled steroid of 500µg or less prior to randomisation to study treatments. These patients then received an at least doubling of their total daily dose on receipt of study treatments.

- In Study 003/00 the study in adults with mild asthma and receiving BDP 200µg BD during the six week treatment period, almost 50% of patients entering each treatment group were stable at the end of the run-in on a dose of <200µg BD as a total daily dose and of these 13 patients who went on to receive BDP HFA and 16 who received BDP CFC were steroid naïve asthmatics.

- In the study in childhood asthma, Study 005/00 at least 25% of children recruited to each treatment group were using a total daily dose of BDP CFC or equivalent of 200µg or less and of these 20 children were steroid naïve; all children recruited to the study received a total daily dose of 400µg for the 12 week study.

In the two adult studies the findings were essentially similar and in the analysis of the primary efficacy variable there were no substantial changes seen over baseline at the end of the treatment period in either treatment group. When the population studied in the low dose study was split to steroid dependent and steroid naïve on entry to the study again there were no significant changes seen in either treatment group in either population in morning PEFR at the end of study period compared with baseline or between treatment groups. These findings were similar for both the ITT population and the PP population and were essentially mirrored in the analyses of the secondary efficacy variables.

These findings would suggest that BDP HFA was both non-inferior to and equivalent to BDP formulated with CFCs. However increasing the dose of inhaled steroid required in a large proportion of patients in both of these studies and seeing no change in asthma status over the treatment period raises questions as to whether it would have been possible to pick up differences in the light of substantial over treatment of the disease. This would lead to a reduction in sensitivity of the study such that the study would lack the ability to detect differences. If the patients were truly stable at the end of the run-in the substantial increase in dose of inhaled steroid is likely to ensure that the patient hits the top of their dose response curve with plateauing of pulmonary function. Differences between treatments would then be undetectable. The marked increase in dose of inhaled steroid and the lack of improvement in pulmonary function would suggest that patients were optimally treated on
entry. Therefore the studies presented cannot be accepted as adequate evidence of therapeutic equivalence.

In the study in childhood asthma a statistically significant increase over baseline was seen in all three treatment groups from weeks 5-6 to the end of the study and at the end of 12 weeks no statistically significant pairwise differences were seen between treatment groups. This improvement in pulmonary function would suggest that at least a proportion of patients entered did have room for improvement and that the study does have the ability to detect differences between treatments. The analysis of the primary efficacy variable would suggest that both BDP HFA 50 and BDP HFA 100 are not inferior to BDP CFC 50, that BDP HFA 100 is not inferior to BDP HFA 50 and that all three treatments are equivalent. These findings are supported through the PP population analysis; however the analysis of secondary end points of function and particularly FEV₁ suggest that the two BDP HFA formulations are not equivalent to BDP CFC 50 and are superior. The findings are similar in respect of changes seen in FVC and FEF₂₅.

These findings are worrying in the light of the position that FEV₁ holds in the assessment of pulmonary function in this type of study as some investigators and regulators would use FEV₁ as the primary variable. PEFR is an acceptable primary efficacy variable but in the light of the findings in respect of FEV₁ (and also possibly in respect of the initial design of the study) it is difficult to conclude convincingly that the two formulations of BDP, BDP HFA and BDP CFC are clinically equivalent in this population.

The two supportive studies employ a different comparator product (the Applicant’s own CFC containing formulation of BDP) administered through the Jet actuator-spacer device rather than the standard metered dose actuator. The second of the two supportive studies, Study 002/00 contains the same design flaw as the three pivotal studies but in the light of the majority of patients receiving a similar dose of inhaled steroid prior to study and during the run-in, as subsequently used during the treatment period, and statistically significant increases in pulmonary function over time from baseline in both treatment groups and in both populations (steroid dependent and steroid naïve) it is concluded that this study does provide evidence to support clinical equivalence between the two BDP formulations of the applicant.

The design of the fifth study, also a supportive study, Study 01/98 was more appropriate as patients continued to inhale the same dose of inhaled steroid during the 6 week treatment period as they had received during the run-in whilst stable. This study would suggest that switching patients from their CFC-containing inhaler to the HFA-containing inhaler at the same dose is appropriate as the two formulations appear clinically equivalent. This study has assessed a higher dose, a total daily dose of 1500µg; however the treatment duration is short and the study lacks a comparison with the product to which essential similarity is claimed.

An assessment of bronchial hyperreactivity in a sub-population in Study 003/00 (200µg BD) would suggest slight improvement over six weeks treatment.

5. SAFETY
5.1 Overview/Exposure
A total of 1159 subjects were randomised to and received study treatments in the clinical pharmacology and clinical efficacy and safety studies and of these 519 adults and 139
children with asthma and 34 healthy males received BDP HFA. Of the adults with asthma the majority (n=337) inhaled a total daily dose of BDP HFA 1000µg, only 28 inhaled a dose in excess of 1000µg (1500µg) and the remaining adult patients inhaled total daily doses of BDP HFA of less than 1000µg. All children recruited to Study 005/00 received BDP HFA 400µg as a total daily dose. Twelve healthy male volunteers received single doses of BDP HFA 2000µg.

The duration of treatment ranged from single dose pharmacology studies through to 12 week safety and efficacy studies (Studies 004/00, 005/00 and 002/00). A total of 136 adult patients received BDP HFA in a total daily dose of 1000µg for up to 12 weeks, 28 adults received a total daily dose of 1500µg over a treatment period of up to 6 weeks and 139 children received 400µg as a total daily dose for up to 12 weeks.

The top of the proposed dose range for adults is 2000µg as a total daily dose. This dose was not studied in the clinical safety and efficacy programme.

The evaluation of safety covers children and adolescents aged 6-16 years (Study 005/00) and adults aged between 18 and 75 years. No specific studies were carried out in the 65 years and over age group; however in the adult studies carried out patients up to 75 years of age were recruited.

5.2 Adverse Events
A total of 239 (36%) patients receiving BDP HFA and 189 (43%) patients receiving BDP CFC reported at least one adverse event. Tabulations of the summary of adverse events across clinical trials, adverse events in the respiratory system and oropharyngeal adverse events are presented on page 32 of the Clinical Expert Report.

The general pattern of adverse events was similar across the five clinical studies and between the two formulations of BDP. The most commonly affected body system was the respiratory system and the most commonly reported event was upper respiratory tract infection. Other commonly occurring events included other respiratory events, cough, pharyngitis and rhinitis, and all occurring with similar frequencies across the treatment groups.

An incidence of headache was reported in all studies but again with similar incidence across the two BDP formulations and with the highest incidence seen in Study 004/00 (500µg BD) where a reported incidence of 11.9% and 14.0% was seen in the BDP HFA and BDP CFC treatment groups respectively.

Gastrointestinal events were also reported in all studies, nausea, vomiting, diarrhoea and abdominal pain (nausea and abdominal pain only in the paediatric study), and again with similar incidence across the two BDP formulations, ranging from 1-5% incidence across studies.

Local oropharyngeal events including taste perversion were seen in all studies but the only event where an increased incidence was seen in the BPD HFA treatment groups was moniliasis/oral candidiasis. An increased incidence was seen in four of the five studies with an incidence of 10% compared with 5% in Study 004/00 (500µg BD), 5% compared with 1% in Study 003/00 (200µg BD) and 3% compared with zero in Study 005/00 (200µg BD in children).
Infection (non-specific) was reported with quite marked incidence in Study 004/00 (500µg BD), 15.3% of patients receiving BDP HFA compared with 12.3% receiving BDP CFC.

The majority of adverse events reported were described as mild or moderate in severity with <10% of events across studies described as severe.

Across the five studies a slightly increased incidence of events which in the opinion of the investigator were thought to be related to treatment (described as adverse drug reactions – ADR) was seen in the BDP HFA treatment groups and as might be expected the majority of these were related to events within the respiratory or gastrointestinal systems or headache.

Nasal symptoms were asked after and were recorded on diary cards in Study 003/00 (200µg BD) using a 4-point scale. A progressive decrease from baseline was reported in both BDP treatment groups and with no statistically significant differences between groups, p=0.176.

Vital signs, heart rate and blood pressure, were measured in all five studies. With the exception of heart rate in Study 003/00 (200µg BD) where a statistically significant increase over baseline was reported at the mid-point of the study (three weeks) in the BDP HFA treatment group and either at the three week point or at the final visit in the BDP CFC treatment group, changes which were considered to have no clinical relevance, there were no significant differences between treatments and no relevant changes over time in any treatment group.

5.3 Withdrawals due to Adverse Events
A total of 39 patients were withdrawn from clinical studies and of these 21 had received BDP HFA and 18 BDP CFC. The majority of patients withdrawn reported symptoms referable to the respiratory tract and described as mild to moderate in intensity. Five patients in Study 01/98 (up to 1500µg/day via the Jet spacer) were withdrawn following the development of serious adverse events.

5.4 Serious Adverse Events
A total of 13 serious adverse events were reported across the five clinical studies. Seven of these reported by patients receiving BDP HFA and 6 in patients receiving BDP CFC. None was thought to be causally related to the study treatments.

5.5 Deaths
No deaths were reported during the clinical programme.

5.6 Pregnancies
No pregnancies were reported during the clinical programme.

5.7 Systemic Effects/Hypothalamic Pituitary Adrenocortical Axis
Four of the five clinical studies looked at the effect of BDP formulated with HFA 134a and with CFC propellants on the HPA axis.

In Study 004/00 (500µg BD) changes from baseline in morning serum cortisol were seen in both treatment groups with a decrease from baseline in the BDP HFA treatment group of -10.3nmol/L and an increase in the BDP CFC Becloforte treatment group of 22.7nmol/L.
The analysis of change from baseline in morning serum cortisol demonstrated no significant difference between the two treatment groups with respect to morning serum cortisol levels; the least square treatment mean change from baseline showed a difference (BDP HFA - BDP CFC Becloforte) of -33.0nmol/L, p=0.469.

Five patients in the BDP HFA treatment group had final serum cortisol values below the lower limit of the normal range (one patient had had a baseline value below the lower limit of the normal range) compared with only two patients in the BDP CFC Becloforte treatment group.

In Study 005/00 (200µg bd), the paediatric study the effect on the HPA axis was also assessed through measurement of morning serum cortisol but only in a sub-group (n=93) of children randomised to treatment. The mean change from baseline to visit 6 (end of study) was slightly lower in the BDP HFA 100 treatment group compared with either of the other 2 treatment groups (BDP HFA 50 and BDP CFC Becotide 50); the increase over baseline was statistically significant in the BDP CFC Becotide 50 treatment group only (an increase over baseline was seen in all three treatment groups). No statistically significant pairwise differences in the morning serum cortisol measurements at the end of the study period were seen between any of the treatment groups. Four children in the BDP HFA treatment groups (two receiving BDP HFA 50 and two receiving BDP HFA 100) and one patient in the BDP CFC Becotide 50 group had morning serum cortisol values below the lower limit of the normal range (<119nmol/L) at baseline, three patients in the BDP HFA 100 treatment group and two in the BDP CFC Becotide 50 group had values within the normal range at baseline and outside the normal range at the end of study and of these two, both treated with BDP HFA 100, had serum cortisols below the lower limit of the normal range. The mean duration of exposure to study treatments was similar in the three treatment groups.

In the two clinical studies in which BDP HFA was compared with the Applicant’s own CFC-containing formulation of BDP no statistically significant differences were observed in respect of effects on the HPA axis between the two formulations (urinary free cortisol/urinary creatinine ratio in a sub-set, n=96, 20%, of patients in Study 01/98, up to 1500µg/day) and although morning serum cortisol fell in the second study, Study 002/00 (500µg BD) this fall was not statistically significant either from baseline or in respect of differences seen between treatments.

### 5.8 Other Laboratory Data
Routine laboratory data were collected in only one study in the clinical programme Study 01/98 (up to 1500µg/day) the comparison of BDP HFA with the Applicant’s own CFC-containing formulation of BDP with both drugs inhaled via the Jet spacer. No clinically relevant changes over time or differences between formulations of BDP were seen.

### 5.9 Safety Data Generated in the Clinical Pharmacology Programme
A number of adverse events were reported in the three studies presented, all were mild and with the exception of two reports of headache which were felt to be possibly related to BDP HFA all were considered either not or doubtfully related to study treatments. No clinically relevant changes were seen in vital signs, ECG or laboratory tests.

The effects seen on the HPA axis as measured in the pharmacodynamic study, Study SGS B100.524, are as given at Paragraph 2.1, above.
5.10 Data from ongoing Clinical Studies
A further clinical safety study is planned to assess the effect of BDP HFA in a total daily dose of 2000 µg and administered over time on the HPA axis. No data are available at the present time.

5.11 Post-Marketing Experience
Beclometasone dipropionate formulated with HFA and the subject of these applications has not been marketed in any country to date. BDP HFA 250 µg/actuation inhaled through the Jet actuator-spacer has been available in France since April 2000 using the trade name Beclojet. In the first six months of marketing 44 spontaneous reports were received and of these, three reports (5 events) were considered adverse events related to the use of Beclojet. These events included burning mouth, nausea, vomiting, headache and cough. The majority of the remaining reports were related to the taste or smell of the product. It is estimated that the number of patients exposed to Beclojet in this period was approximately 48,000.

The CPMP Note for Guidance, Appendix IV-2 requests that applications for Marketing Authorisations for metered dose inhalation products containing propellant HFA-134a should include proposals to monitor the introduction of the new non-CFC products in order to identify rare and unexpected adverse events. A method such as the use of record linkage schemes should be considered as these could provide a means for prospectively monitoring the new non-CFC products against historical data relating to the products using CFC propellants.

5.12 Excipients
The excipients in the formulation include glycerol, anhydrous ethanol and the non-chlorofluorocarbon propellant HFA-134a (Norflurane).

Pre-clinical testing of HFA-134a has been carried out through IPACT-I and in November 1993 IPACT-I applied to the CPMP for approval for the use of HFA-134a as an alternative propellant in metered dose inhalers. The conclusions reached by the CPMP are stated at Paragraph 1.2 Background, above.

Study DM/RS/3303/001/98: Double blind randomised crossover design controlled clinical trial of hydrofluoroalkane (HFA-134a) and chlorofluorocarbon (CFC) propellants (single and repeated doses) administered via a metered dose inhaler in healthy human volunteers (n=12).

This study was set up to evaluate the safety of the two formulations but without active drug, a comparison of excipients. The propellants were inhaled over five consecutive days, four actuations twice daily. Pulmonary function tests were carried out before and at repeated intervals after the first and last dose of each treatment cycle, vital signs were measured, adverse events recorded and laboratory safety parameters evaluated. The findings suggest that HFA-134a is as well tolerated as CFC propellants and with the exception of a statistically significant fall in PEFR AUC adjusted for baseline, p<0.05 in the HFA group, which was deemed of no clinical importance by the investigator, no differences were seen between the two study treatments.

The three excipients are addressed in Part II of this Report at Paragraphs 3.1 Composition and 3.4 Control of Excipients.
5.13 Assessor’s Comment
The safety assessment of BDP HFA shows a comparable safety profile to that of BDP CFC in respect of adverse events, both formulations appear well tolerated and no unusual or unexpected adverse events were reported. The slightly increased incidence of oral candidiasis in the treatment groups receiving BDP HFA is noted.

The potential for systemic exposure following administration of BDP HFA was assessed in the Phase 1 study described in Section 2 of this Report and in four of the five clinical efficacy and safety studies. Small changes are seen in the pivotal study in adults when BDP HFA is compared with BDP CFC Becloforte at a total daily dose of 1000µg which might suggest a slightly enhanced systemic effect with BDP HFA. However the only assessment of the systemic effect of BDP HFA at the top of the accepted dose range for BDP and proposed dose range for BDP HFA, a total daily dose of 2000µg, has been carried out in the Phase I study at a single dose level. The effect of BDP HFA at the top of the dose range must be assessed in an appropriate population and in a multiple dose study over time. In the light of the absence of such a study evidence of the systemic safety of BDP formulated with the non-CFC propellant HFA-134a is lacking.

Assessment of systemic effect at a total daily dose of 2000µg administered over time is important particularly in the light of the pharmacokinetic findings described in this Report at Section 3 above, where differences between BDP HFA and BDP CFC in respect of systemic exposure are seen with apparent greater systemic exposure when BDP is formulated with HFA-134a.

6. CLINICAL EXPERT REPORT
The Clinical Expert Report has been written by a Consultant Respiratory Physician.

7. PRODUCT LITERATURE
7.1 Summary of Product Characteristics (SPC)
These are satisfactory.

7.2 Patient Information Leaflet
This is satisfactory

7.3 Labelling
Labelling texts for the four strengths have been submitted and are essentially identical.

7.4 Marketing Authorisation Application Forms
The Marketing Authorisation Application Forms are clinically satisfactory.

8. CONCLUSIONS
8.1 Pharmacodynamics
The Applicant makes reference to the literature and has submitted one study to assess the systemic pharmacodynamic effects of BDP (formulated with HFA-134a or CFC propellants) and its metabolites by measuring effects seen on the HPA axis. When administered in a single dose of 2000µg inhaled BDP does have an effect on the HPA axis but this effect would appear to be the same regardless of the formulation. The findings suggest that two formulations of BDP can be deemed comparable with similar potential for systemic exposure following single dose administration.
8.2 Pharmacokinetics
The Applicant summarises the known pharmacokinetics of BDP and presents three pharmacokinetic studies. Differences are seen in respect of systemic exposure with apparent greater systemic exposure when BDP is formulated with HFA-134a than when formulated with CFC propellants.

The findings in respect of systemic exposure have been reviewed alongside the in vitro data. It is noted that the smaller the MMAD the greater the systemic exposure.

8.3 Safety
The safety assessment of BDP HFA shows a comparable safety profile to that of BDP CFC in respect of adverse events, both formulations appear well tolerated and no unusual or unexpected adverse events were reported.

8.7 Good Clinical Practice
The Clinical Expert states that “all studies in the clinical and clinical pharmacology programme have been undertaken in accordance with standard operating procedures of Chiesi Farmaceutici SpA which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees, informed consent was obtained for all subjects and patients, and the studies were performed in accordance with the Declaration of Helsinki and its subsequent amendments. Where regulatory approval was required, this was obtained from the relevant Health Authority”
The UK advisory committee considered the applications on the 11th June 2001 and wrote to the applicant on the 18th July 2001 stating that the Committee would be unable to advise the licensing authority to grant the applications on grounds relating to safety, efficacy and quality. The main concerns were as follows:

1. **There is inadequate evidence of efficacy and safety in adults, adolescents and children less than 16 years of age as therapeutic equivalence to the product to which essential similarity is claimed has not been demonstrated.**

2. **In the light of concerns regarding greater systemic exposure when beclometasone dipropionate is formulated with HFA-134a, further information on the comparison with the product to which essential similarity is claimed throughout the dose range but particularly at the top of the proposed dose range, is required.**

3. **The design of further studies to assess the efficacy and safety of these products should be such as to encompass an assessment of the changeover from CFC-containing products to the new non-CFC containing products.**

4. **The higher fine particle dose and the different particle size distribution, in particular the larger quantity of particles <1.1μm, of the HFA inhalers compared with the CFC inhalers should be discussed in view of the safety and efficacy issues in relation to the clinical data.**

5. **A favourable risk/benefit ratio has not been demonstrated.**

6. **Data should be presented on the use of a spacing device particularly when the drug is administered at the upper end of the proposed dose range, in order that appropriate information on such use can be included in the product literature.**

   It is required that the product literature should recommend the use of a specific spacing device particularly when inhaled corticosteroids are used in total daily doses of 1000μg or greater. In the absence of appropriate data, a warning should be given in the SPCs to advise against the use of beclometasone dipropionate formulated with propellant HFA-134a in total daily doses in excess of 1000μg.

7. **A definitive proposal for a Phase IV safety study with the identifiable proprietary product according to SMMH Guidelines and compatible with the CFPM Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products III/5378/93 – Final, must be presented and agreed before Marketing Authorisations are granted. The study proposal should be for either an observational cohort study or a blinded trial which has the capability of generating data on the general safety profile of the new product(s). Assessments of the incidence of paradoxical bronchoconstriction, worsening asthma and cough must be incorporated into the design of the study.**

The company appealed against the decision and a 1st Pre-hearing was held on 12 June 2002, following which the Committee remained of the view that on grounds relating to safety, efficacy and quality they would be unable to advise that the Marketing Authorisations applied for should be granted. The Committee felt that in view of the major deficiencies in
these applications with respect of safety and efficacy, the planned hearing should be
cancelled and the applicants would be offered a Clarification Meeting in order to discuss
the outstanding issues. The applicants were informed of these decisions in a letter dated 18
June 2002. The assessment of the applicant’s responses by CSM in 2002 are presented at
the end of this report (please see Annex 1).

Clarification Meeting was held on 25 November 2002 when the applicants met with
members of the CSM, and with external experts in the fields of respiratory medicine in
adults/children and endocrinology. The major outstanding issues on these applications were
discussed and the outcome of the Clarification Meeting was presented to the CSM on
12 February 2003. Issues were raised, which were taken back to the external experts for
further discussion. The applicants were informed of the outcome of the Clarification
Meeting and the further discussions in a letter dated 25 February 2003 and subsequently in
a further meeting with the assessors on 10 April 2003.

Again, the committee was unable to advise that the applications could be granted and
following several clarification meetings with the applicant, further data was supplied,
which was considered at CSM on the 20th October 2004 and 10th November 2004. The
assessment of the additional data supplied in the applicant’s responses and the assessment
of this is presented at the end of this report (please see Annex 2).

Following these hearings, the applicant was informed that the Committee could
recommend the granting of marketing authorisation on the grounds of quality, safety and
efficacy, on condition that recommended changes to the product literature were made and
appropriate amendments were made to the proposal for the safety study. These changes
were as follows:

The Committee considered the company's data and agreed to advise the Licensing
Authority that Marketing Authorisations should be granted but only if the company's are
willing to agree to the following:

1. In the light of the findings in the studies presented in response to Points 1, 2 and 3
of the letter from the CSM dated 25 February 2003 (and in the light of accepted
practice) when beclometasone dipropionate formulated with propellant HFA-134a
is administered to adult patients with asthma in a dose of 1000µg or greater the drug
should be administered via a Volumatic spacing device. Similarly when this same
product, beclometasone dipropionate formulated with propellant HFA-134a is
prescribed for use in children less than 16 years of age administration should always
be via the Volumatic spacing device.

The safety of beclometasone dipropionate formulated with propellant HFA-134a
has only been established in adults in high dose and in children when administered
via the Volumatic spacing device. The in vitro data clearly demonstrate that there are changes to the delivered dose and the fine particle dose when the pressurised metered dose inhaler is used in combination with the Volumatic spacing device and no evidence is provided to demonstrate that other marketed spacing devices produce an equivalent aerodynamic particle size profile and clinical effect.

The ‘Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products (QWP 2845/00)’ states that ‘when a spacer is recommended for a certain product, its use should be evaluated and relevant information given in the Summary of Product Characteristics.’

Therefore the product literature, including the Summaries of Product Characteristics, the Patient Information Leaflets and product labelling should state clearly that the Volumatic spacing device should always be used when beclometasone dipropionate formulated with propellant HFA-134a is prescribed to adults in total daily doses of 1000µg or greater and when prescribed for use in children less than 16 years of age.

2. Different batches of 100µg strength of beclometasone dipropionate formulated with CFCs have been used in the two clinical studies in children. This has resulted in additional variability such that full interpretation of the data generated is difficult. Comment on the use of different batches in this way is requested.

3. Phase IV Safety Study

The following issues with regard to the protocol should be addressed prior to the grant of any Marketing Authorisations:

- The final protocol should make comment on how the three month reference period prior to the new treatment period will be handled, as this will be an unknown mixture of different treatments or no treatment and in the current draft protocol there are no proposals to collect data on prior treatment.

- While not stipulated in the study protocol, it is possible that comparison with other CFC or HFA cohorts may be conducted. These should be made explicit if intended.

- The final protocol should clarify details in causality assessment, reporting of serious adverse drug reactions and provision of interim reports to the MHRA.

- The final protocol must be presented and agreed before Marketing Authorisations are granted.

The applicant accepted the recommendations of the UK Advisory Committee and agreed to submit the necessary documentation to allow the licences to be granted.

Subsequently, due to a potential problem with the continuing supply of the Volumatic™ spacer device, the applicant provided further information to justify the use of alternative devices. This was discussed at CSM on the 21st July 2005 and 12th October 2005, although, ultimately the supply of the Volumatic™ was conserved and no further information was needed in relation to this matter.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Becolex™ Modulite® Pressurised Inhalation Solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
Because the active substance, beclometasone dipropionate, is a well known medicinal product which has been on the market for over 10 years, no new preclinical studies have been performed. Data has been supplied which demonstrates that no toxicological differences were seen between the BDP HFA MDI formulation and the BDP CFC formulation. As such, there are no preclinical issues arising from these applications.

EFFICACY
Beclometasone dipropionate is a well known drug and has been used for the management of asthma for many years. This formulation has been developed to use a CFC-free propellant and has been shown to be efficacious in adults and children.

Clinical data have been provided which demonstrate an adequate level of clinical safety and findings have shown that there are no additional safety concerns caused by the CFC-free formulation.

No clinically significant safety concerns were identified, provided the product is used as intended.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no unmanageable preclinical or clinical safety concerns were identified. Extensive clinical experience with beclometasone dipropionate is considered to have demonstrated the therapeutic value of the compound and a benefit has been shown to be associated with Becolex™ Modulite® Pressurised Inhalation Solution. Clinical data supplied with these applications has demonstrated the safety and efficacy of Becolex™ Modulite® Pressurised Inhalation Solution, when used under conditions specified in the SPC. The risk benefit is therefore considered to be positive.
BECOLEX™ MODULITE® PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PL 06607/0017-20

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 18/12/2000.

2 Following standard checks the MHRA informed the applicant that its application was considered valid on 19/01/2001.

3 The MHRA’s assessment of the submitted data was completed on 31/05/2001.


5 The applicant submitted additional information in support of their applications on 21/03/2002 and 02/08/2004.

6 The applicant was informed that CSM recommended approval of the application subject to the successful resolution of outstanding points and amendments to the product particulars (SPC, PIL and labelling) on 15/11/2004.

7 The applications were further discussed at CSM on the 21/07/2005 and 12/10/2005, in relation to a potential supply problem which was subsequently resolved.

8 The applicant responded to the MHRA and all requested information was supplied by the 23/05/2006.

9 The MHRA completed its assessment of the updated product particulars on 27/06/2006.

10 The application was determined on 29/06/2006.
### STEPS TAKEN AFTER ASSESSMENT

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<th>Date submitted</th>
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<td>IB</td>
<td>Change in shelf-life of the finished product from 2 to 3 years.</td>
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<td>II</td>
<td>Change in batch size of the finished product</td>
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<td>IB</td>
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BECOLEX™ MODULITE® 50 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PL 06607/0017

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Becolex™ Modulite® 50 micrograms per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Beclometasone dipropionate 50 micrograms per metered (ex-valve) dose
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Pressurised inhalation solution
Becolex™ Modulite® contains the new propellant HFA-134a and does not contain any chlorofluorocarbons (CFCs). The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Becolex™ Modulite® is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:

*Mild asthma*: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis

*Moderate asthma*: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone

*Severe asthma*: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms

4.2 Posology and method of administration

**Posology**
Becolex™ Modulite® is for inhalation use only. The Volumatic™ spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath.

The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

*Adults (including the elderly)*: The usual starting dose is 200 micrograms twice daily. In severe cases this may be increased to 600 to 800 micrograms daily. This may then be reduced when the patient’s asthma has stabilised. The total daily dosage should be administered as two to four divided doses.

The Volumatic™ spacer device must always be used when Becolex™ Modulite® is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 micrograms or greater.
**Children:** The usual starting dose is 100 micrograms twice daily. Depending on the severity of asthma, the daily dose may be increased up to 400 micrograms administered in two to four divided doses.

Becolex™ Modulite® must always be used with the Volumatic™ spacer device when administered to children and adolescents 15 years of age and under, whatever dose has been prescribed.

**Patients with hepatic or renal impairment:** No dosage adjustment is needed in patients with hepatic or renal impairment.

**Method of Administration**

The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use Becolex™ Modulite® correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.

**Instructions for Use**

If the inhaler is new or has not been used for three days or more, one puff should be released into the air. It is not necessary to shake the inhaler before use because this is a solution aerosol.

Instruct the patient to remove the mouthpiece cover and check that it is clean and free from foreign objects. The patient should then be instructed to breathe out before placing the inhaler into their mouth. They should then close their lips around the mouthpiece and breathe in steadily and deeply. They must not bite the mouthpiece. After starting to breathe in through the mouth, the top of the inhaler should be pressed down. Whilst the patient is still breathing in, the patient should then remove the inhaler from their mouth and hold their breath for about 5 to 10 seconds, or as long as is comfortable, and then breathe out slowly. The patient must not breathe out into the inhaler. If another dose is required the patient should be advised to wait 30 seconds before repeating the procedure just described. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient should be told not to rush the procedure described. It is important that the patient breathes in as slowly as possible prior to actuation. Inform the patient that if a mist appears on inhalation, the procedure should be repeated.

It may be helpful to advise children and patients with weak hands to hold the inhaler with two hands, by placing both forefingers on top of the inhaler and both thumbs at the bottom of the device.

Patients who find it difficult to co-ordinate actuation with inspiration of breath should be told to use a Volumatic™ spacer device to ensure proper administration of the product.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with the Volumatic™ spacer device with a face mask may help in children under 5 years.

Advise the patient to thoroughly rinse the mouth or gargle with water or brush the teeth immediately after using the inhaler.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.

The patient should be told also to refer to the Patient Information Leaflet accompanying the Volumatic™ spacer device for the correct instructions on its use and cleaning.

**4.3 Contraindications**

Hypersensitivity to any of the components.

**4.4 Special warnings and precautions for use**
Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. Patients should also be informed that Becole™ Modulite® should be used on a regular basis, even when they are asymptomatic.

Becole™ Modulite® does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, i.e. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and/or an appropriate antibiotic if there is an infection, together with β-agonist therapy.

Treatment with Becole™ Modulite® should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to Becole™ Modulite® of patients who have been treated with systemic steroids for long periods of time or at high doses, needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with Becole™ Modulite®. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled beclometasone dipropionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.
Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Patients should be advised that this product contains small amounts of ethanol (approximately 9 mg per actuation) and glycerol. At the normal doses, the amounts of ethanol and glycerol are negligible and do not pose a risk to patients (see section 4.5, Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction
Becolex™ Modulite® contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 Pregnancy and lactation
There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of beclometasone dipropionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed. It is reasonable to assume that beclometasone dipropionate is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines
None reported

4.8 Undesirable effects
Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Becolex™ Modulite® should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat, have been reported.

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 micrograms beclometasone dipropionate per day. Patients with high blood levels of Candida precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic
oral candidiasis can be treated with topical antifungal therapy while continuing with Becolex™ Modulite®.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered.

4.9 Overdose

*Acute:* Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

*Chronic:* Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glucocorticoid
ATC Code: R03B A01

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity.

5.2 Pharmacokinetic properties

*Absorption when administered via inhalation by a MDI*

Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36 %) and oral absorption of the swallowed dose (26 %). The absolute bioavailability following inhalation is approximately 2 % and 62 % of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (tmax) at 0.3 hour. B-17-MP appears more slowly with a tmax of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41 % of the dose being absorbed as B-17-MP.

*Distribution*

The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87 %).

*Biotransformation*

BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

*Elimination*

The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 hour and 2.7 hour. Following oral administration of tritiated BDP, approximately 60 % of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12 % of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.
5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation.

The non-CFC propellant HFA-134a has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HFA-134a
Ethanol
Glycerol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30 °C.

As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold.

Protect from frost and direct sunlight.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.

6.5 Nature and contents of container

Becolex™ Modulite® 50 is supplied in an aluminium canister fitted with a metering valve, actuator and dust cap.
Each inhaler delivers 200 actuations.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici SpA
26/A Via Palermo
43100 Parma
Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 06607/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/06/2006

10 DATE OF REVISION OF THE TEXT

29/06/2006
BECOLEX™ MODULITE® 100 MICROGRAM PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PL 06607/0018

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Becolex™ Modulite® ▼ 100 micrograms per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Beclometasone dipropionate 100 micrograms per metered (ex-valve) dose
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Pressurised inhalation solution
Becolex™ Modulite® contains the new propellant HFA-134a and does not contain any chlorofluorocarbons (CFCs). The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Becolex™ Modulite® is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:
Mild asthma: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis
Moderate asthma: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone
Severe asthma: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms

4.2 Posology and method of administration
Posology
Becolex™ Modulite® is for inhalation use only. The Volumatic™ spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath. The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly): The usual starting dose is 200 micrograms twice daily. In severe cases this may be increased to 600 to 800 micrograms daily. This may then be reduced when the patient’s asthma has stabilised. The total daily dosage should be administered as two to four divided doses. The Volumatic™ spacer device must always be used when Becolex™ Modulite® is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 micrograms or greater.

Children: The usual starting dose is 100 micrograms twice daily. Depending on the severity of asthma, the daily dose may be increased up to 400 micrograms administered in two to four divided doses.

Becolex™ Modulite® must always be used with the Volumatic™ spacer device when administered to children and adolescents 15 years of age and under, whatever dose has been prescribed.
Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration
The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use Becolex™ Modulite® correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.

Instructions for Use
If the inhaler is new or has not been used for three days or more, one puff should be released into the air. It is not necessary to shake the inhaler before use because this is a solution aerosol.

Instruct the patient to remove the mouthpiece cover and check that it is clean and free from foreign objects. The patient should then be instructed to breathe out before placing the inhaler into their mouth. They should then close their lips around the mouthpiece and breathe in steadily and deeply. They must not bite the mouthpiece. After starting to breathe in through the mouth, the top of the inhaler should be pressed down. Whilst the patient is still breathing in, the patient should then remove the inhaler from their mouth and hold their breath for about 5 to 10 seconds, or as long as is comfortable, and then breathe out slowly. The patient must not breathe out into the inhaler. If another dose is required the patient should be advised to wait 30 seconds before repeating the procedure just described. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient should be told not to rush the procedure described. It is important that the patient breathes in as slowly as possible prior to actuation. Inform the patient that if a mist appears on inhalation, the procedure should be repeated.

It may be helpful to advise children and patients with weak hands to hold the inhaler with two hands, by placing both forefingers on top of the inhaler and both thumbs at the bottom of the device.

Patients who find it difficult to co-ordinate actuation with inspiration of breath should be told to use a Volumatic™ spacer device to ensure proper administration of the product.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with the Volumatic™ spacer device with a face mask may help in children under 5 years.

Advise the patient to thoroughly rinse the mouth or gargle with water or brush the teeth immediately after using the inhaler.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.

The patient should be told also to refer to the Patient Information Leaflet accompanying the Volumatic™ spacer device for the correct instructions on its use and cleaning.

4.3 Contraindications
Hypersensitivity to any of the components.

4.4 Special warnings and precautions for use
Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. Patients should also be informed that Becolex™ Modulite® should be used on a regular basis, even when they are asymptomatic.

Becolex™ Modulite® does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are
required as this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, ie. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and / or an appropriate antibiotic if there is an infection, together with β-agonist therapy.

Treatment with Becolex™ Modulite® should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to Becolex™ Modulite® of patients who have been treated with systemic steroids for long periods of time or at high doses, needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with Becolex™ Modulite®. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled beclometasone dipropionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc. Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and / or topical preparations, including topical steroids.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Patients should be advised that this product contains small amounts of ethanol (approximately 9 mg per actuation) and glycerol. At the normal doses, the amounts of ethanol and glycerol are negligible and do not pose a risk to patients (see section 4.5, Interaction with other medicinal products and other forms of interaction).
4.5 Interaction with other medicinal products and other forms of interaction

Becolex™ Modulite® contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 Pregnancy and lactation

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of beclometasone dipropionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed. It is reasonable to assume that beclometasone dipropionate is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Becolex™ Modulite® should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat, have been reported.

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 micrograms beclometasone dipropionate per day. Patients with high blood levels of Candida precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Becolex™ Modulite®.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered.

4.9 Overdose

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.
Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Glucocorticoid
ATC Code: R03B A01

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity.

5.2 Pharmacokinetic properties
Absorption when administered via inhalation by a MDI
Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36 %) and oral absorption of the swallowed dose (26 %). The absolute bioavailability following inhalation is approximately 2 % and 62 % of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (tmax) at 0.3 hour. B-17-MP appears more slowly with a tmax of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41 % of the dose being absorbed as B-17-MP.

Distribution
The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87 %).

Biotransformation
BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination
The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 hour and 2.7 hour. Following oral administration of tritiated BDP, approximately 60 % of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12 % of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

5.3 Preclinical safety data
Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation. The non-CFC propellant HFA-134a has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
HFA-134a
Ethanol
Glycerol

6.2 Incompatibilities
6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30 °C.

As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold.

Protect from frost and direct sunlight.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.

6.5 Nature and contents of container
Becolex™ Modulite® 100 is supplied in an aluminium canister fitted with a metering valve, actuator and dust cap.
Each inhaler delivers 200 actuations.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Chiesi Farmaceutici SpA
26/A Via Palermo
43100 Parma
Italy

8 MARKETING AUTHORISATION NUMBER(S)
PL 06607/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/06/2006

10 DATE OF REVISION OF THE TEXT
29/06/2006
BECOLEX™ MODULITE® 200 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Becolex™ Modulite® ▼ 200 micrograms per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Beclometasone dipropionate 200 micrograms per metered (ex-valve) dose
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Pressurised inhalation solution
Becolex™ Modulite® contains the new propellant HFA-134a and does not contain any chlorofluorocarbons (CFCs). The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Becolex™ Modulite® is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:

Mild asthma: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis

Moderate asthma: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone

Severe asthma: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms

4.2 Posology and method of administration

Posology
Becolex™ Modulite® is for inhalation use only. The Volumatic™ spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath. The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly): The usual starting dose is 200 micrograms twice daily. In severe cases this may be increased to 600 to 800 micrograms daily. This may then be reduced when the patient’s asthma has stabilised. The total daily dosage should be administered as two to four divided doses. The Volumatic™ spacer device must always be used when Becolex™ Modulite® is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 micrograms or greater.

Children: Becolex™ Modulite® 200 is not recommended for children.

Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration
The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use Becolex™ Modulite® correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.
Instructions for Use

If the inhaler is new or has not been used for three days or more, one puff should be released into the air. It is not necessary to shake the inhaler before use because this is a solution aerosol.

Instruct the patient to remove the mouthpiece cover and check that it is clean and free from foreign objects. The patient should then be instructed to breathe out before placing the inhaler into their mouth. They should then close their lips around the mouthpiece and breathe in steadily and deeply. They must not bite the mouthpiece. After starting to breathe in through the mouth, the top of the inhaler should be pressed down. Whilst the patient is still breathing in, the patient should then remove the inhaler from their mouth and hold their breath for about 5 to 10 seconds, or as long as is comfortable, and then breathe out slowly. The patient must not breathe out into the inhaler. If another dose is required the patient should be advised to wait 30 seconds before repeating the procedure just described. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient should be told not to rush the procedure described. It is important that the patient breathes in as slowly as possible prior to actuation. Inform the patient that if a mist appears on inhalation, the procedure should be repeated.

It may be helpful to advise children and patients with weak hands to hold the inhaler with two hands, by placing both forefingers on top of the inhaler and both thumbs at the bottom of the device.

Patients who find it difficult to co-ordinate actuation with inspiration of breath should be told to use a Volumatic™ spacer device to ensure proper administration of the product.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with the Volumatic™ spacer device with a face mask may help in children under 5 years.

Advise the patient to thoroughly rinse the mouth or gargle with water or brush the teeth immediately after using the inhaler.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.

The patient should be told also to refer to the Patient Information Leaflet accompanying the Volumatic™ spacer device for the correct instructions on its use and cleaning.

4.3 Contraindications

Hypersensitivity to any of the components.

4.4 Special warnings and precautions for use

Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. Patients should also be informed that Becolex™ Modulite® should be used on a regular basis, even when they are asymptomatic.

Becolex™ Modulite® does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, i.e. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and / or an appropriate antibiotic if there is an infection, together with β-agonist therapy.
Treatment with Becolex™ Modulite® should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to Becolex™ Modulite® of patients who have been treated with systemic steroids for long periods of time or at high doses, needs special care, since recovery from possible adrenocortical suppression may take considerable time.

Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with Becolex™ Modulite®. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled beclometasone dipropionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and / or topical preparations, including topical steroids.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Patients should be advised that this product contains small amounts of ethanol (approximately 9 mg per actuation) and glycerol. At the normal doses, the amounts of ethanol and glycerol are negligible and do not pose a risk to patients (see section 4.5, Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction
Becolex™ Modulite® contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.
4.6 Pregnancy and lactation

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of beclometasone dipropionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed. It is reasonable to assume that beclometasone dipropionate is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Becolex™ Modulite® should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat, have been reported.

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 micrograms beclometasone dipropionate per day. Patients with high blood levels of Candida precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Becolex™ Modulite®.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered.

4.9 Overdose

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glucocorticoid
Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption when administered via inhalation by a MDI
Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36 %) and oral absorption of the swallowed dose (26 %). The absolute bioavailability following inhalation is approximately 2 % and 62 % of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (tmax) at 0.3 hour. B-17-MP appears more slowly with a tmax of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41 % of the dose being absorbed as B-17-MP.

Distribution
The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87 %).

Biotransformation
BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination
The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 hour and 2.7 hour. Following oral administration of tritiated BDP, approximately 60 % of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12 % of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

5.3 Preclinical safety data
Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation. The non-CFC propellant HFA-134a has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
HFA-134a
Ethanol
Glycerol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30 °C.
As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.

6.5 Nature and contents of container
Becolex™ Modulite® 200 is supplied in an aluminium canister fitted with a metering valve, actuator and dust cap.

Each inhaler delivers 200 actuations.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
Chiesi Farmaceutici SpA
26/A Via Palermo
43100 Parma
Italy

8 MARKETING AUTHORISATION NUMBER(S)
PL 06607/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/06/2006

10 DATE OF REVISION OF THE TEXT
29/06/2006
**NAME OF THE MEDICINAL PRODUCT**
Becolex™ Modulite® 250 micrograms per actuation pressurised inhalation solution

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Beclometasone dipropionate 250 micrograms per metered (ex-valve) dose

For excipients, see 6.1

**PHARMACEUTICAL FORM**
Pressurised inhalation solution

Becolex™ Modulite® contains the new propellant HFA-134a and does not contain any chlorofluorocarbons (CFCs). The solution is clear and colourless.

**CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
Becolex™ Modulite® is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:

- **Mild asthma**: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis
- **Moderate asthma**: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone
- **Severe asthma**: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms

4.2 **Posology and method of administration**

**Posology**
Becolex™ Modulite® is for inhalation use only. The Volumatic™ spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath.

The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

- **Adults (including the elderly)**: Usually 1000 micrograms daily, which may be increased to 2000 micrograms daily. This may then be reduced when the patient’s asthma has stabilised. The total daily dosage should be administered as two to four divided doses.

- **Children**: Becolex™ Modulite® 250 is not recommended for children.
Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration
The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use Becolex™ Modulite® correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.

Instructions for Use
If the inhaler is new or has not been used for three days or more, one puff should be released into the air. It is not necessary to shake the inhaler before use because this is a solution aerosol.

Instruct the patient to remove the mouthpiece cover and check that it is clean and free from foreign objects. The patient should then be instructed to breathe out before placing the inhaler into their mouth. They should then close their lips around the mouthpiece and breathe in steadily and deeply. They must not bite the mouthpiece. After starting to breathe in through the mouth, the top of the inhaler should be pressed down. Whilst the patient is still breathing in, the patient should then remove the inhaler from their mouth and hold their breath for about 5 to 10 seconds, or as long as is comfortable, and then breathe out slowly. The patient must not breathe out into the inhaler. If another dose is required the patient should be advised to wait 30 seconds before repeating the procedure just described. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient should be told not to rush the procedure described. It is important that the patient breathes in as slowly as possible prior to actuation. Inform the patient that if a mist appears on inhalation, the procedure should be repeated.

It may be helpful to advise children and patients with weak hands to hold the inhaler with two hands, by placing both forefingers on top of the inhaler and both thumbs at the bottom of the device.

Patients who find it difficult to co-ordinate actuation with inspiration of breath should be told to use a Volumatic™ spacer device to ensure proper administration of the product.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with the Volumatic™ spacer device with a face mask may help in children under 5 years.

Advise the patient to thoroughly rinse the mouth or gargle with water or brush the teeth immediately after using the inhaler.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.

The patient should be told also to refer to the Patient Information Leaflet accompanying the Volumatic™ spacer device for the correct instructions on its use and cleaning.

4.3 Contraindications
Hypersensitivity to any of the components.

4.4 Special warnings and precautions for use
Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. Patients should also be informed that Becolex™ Modulite® should be used on a regular basis, even when they are asymptomatic.

Becolex™ Modulite® does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients should be
assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe exacerbations of asthma must be treated in the usual way, ie. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and / or an appropriate antibiotic if there is an infection, together with β-agonist therapy.

Treatment with Becolex™ Modulite® should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The transfer to Becolex™ Modulite® of patients who have been treated with systemic steroids for long periods of time or at high doses, needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with Becolex™ Modulite®. The size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled beclometasone dipropionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and / or topical preparations, including topical steroids.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Patients should be advised that this product contains small amounts of ethanol (approximately 9 mg per actuation) and glycerol. At the normal doses, the amounts of ethanol and glycerol are negligible and do not pose a risk to patients (see section 4.5, Interaction with other medicinal products and other forms of interaction).
4.5 Interaction with other medicinal products and other forms of interaction

Becolex™ Modulite® contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 Pregnancy and lactation

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of beclometasone dipropionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed. It is reasonable to assume that beclometasone dipropionate is secreted in milk, but at the dosages used for direct inhalation there is low potential for significant levels in breast milk.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

None reported

4.8 Undesirable effects

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Becolex™ Modulite® should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat, have been reported.

Candidiasis of the mouth and throat occurs in some patients, the incidence increasing with doses greater than 400 micrograms beclometasone dipropionate per day. Patients with high blood levels of Candida precipitins, indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Becolex™ Modulite®.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered.

4.9 Overdose

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glucocorticoid
Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone-17-monopropionate (B-17-MP), which has potent topical anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption when administered via inhalation by a MDI

Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. The systemic absorption of B-17-MP arises from both lung deposition (36%) and oral absorption of the swallowed dose (26%). The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged BDP and B-17-MP, respectively. BDP is absorbed rapidly with peak plasma concentrations observed (t_{max}) at 0.3 hour. B-17-MP appears more slowly with a t_{max} of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41% of the dose being absorbed as B-17-MP.

Distribution
The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B-17-MP (424 L). Plasma protein binding is moderately high (87%).

Biotransformation

BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination

The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of 0.5 hour and 2.7 hour. Following oral administration of tritiated BDP, approximately 60% of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation. The non-CFC propellant HFA-134a has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
HFA-134a
Ethanol
Glycerol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30 °C.
As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold. Protect from frost and direct sunlight. The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.

6.5 Nature and contents of container
Becolex™ Modulite® 250 is supplied in an aluminium canister fitted with a metering valve, actuator and dust cap. Each inhaler delivers 200 actuations.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORITY HOLDER
Chiesi Farmaceutici SpA
26/A Via Palermo
43100 Parma
Italy

8 MARKETING AUTHORITY NUMBER(S)
PL 06607/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
29/06/2006

10 DATE OF REVISION OF THE TEXT
29/06/2006
BECOLEX™ MODULITE® PRESSURISED INHALATION SOLUTION (BECLOMETASONE DIPROPIONATE)

PRODUCT INFORMATION LEAFLET

What is Becolex™ Modulite®?
Becolex™ Modulite® is a pressurised inhalation solution containing the active ingredient beclometasone dipropionate which is delivered directly into your lungs. Each actuation (puff) contains 50, 100, 200 or 250 micrograms of beclometasone dipropionate.

To help protect the environment, the inhaler contains the new CFC-FREE PROPELLANT HFA-134a, WHICH REPLACES COMPLETELY THE CHLOROFLUOROCARBON (CFC) PROPELLANTS and appears to have a less damaging effect on the ozone layer. It also contains glycerol and ethanol. The only differences you might notice from your previous CFC-containing inhaler are the taste and the feel of the spray in your mouth. Each canister contains 200 actuations (200 puffs).

Who makes your medicine?
The marketing authorization holder and manufacturer of Becolex™ Modulite® is C.H.eel Farmaciologia SRL, 26 A Via Palermo, 43100 Parma, Italy.

How your medicine works
Becolex™ Modulite® pressurised inhalation solution is used to help prevent the symptoms of asthma. The active ingredient beclometasone dipropionate is one of a group of medicines called corticosteroids which are often referred to simply as steroids. Steroids have an anti-inflammatory action reducing the swelling and irritation in the walls of the small air passages in the lungs, and so ease breathing problems.

Before using Becolex™ Modulite®
Tell your doctor before starting to take this medicine:
• if you are or intend to become pregnant, think you might be pregnant or are breast feeding.
• if you are allergic to any of the ingredients in this medicine or to any other medicines used to treat asthma.
• if you are being, or have ever been, treated for tuberculosis (TB).
• if you are taking any other medicines, including any medicines you have bought from the chemist without a prescription or any other inhalers. Remember to take these medicines and your inhalers with you if you have to go into hospital.
• if you must avoid alcohol because you suffer from any of the following diseases or conditions: liver disease, alcoholism, epilepsy, any brain injury or disease. Each puff of your inhaler contains about 9 mg of alcohol.

If you are taking Becolex™ Modulite® instead of, or as well as, taking steroid tablets, or if your doctor is trying to reduce the dose of your steroid tablets, you should carry a steroid warning card to inform that you may need to take a course of steroid tablets during periods of stress, for example, if your asthma is getting worse. If you have a chest infection or other illnesses, if you need an operation or if you are in an accident.

Do NOT use this medicine to treat a sudden attack of breathlessness - it will not help you. You should use a quick-acting reliever inhaler for this purpose and carry it with you at all times.

Taking your medicine
The starting dose will depend on how severe your asthma is and will be decided by your doctor. It may be higher than the doses given below. Your doctor will prescribe the lowest dose of Becolex™ Modulite® pressurised inhalation solution that will control your symptoms.
A device called a Volumatic® spacer should always be used with Becolex™ Modulite® when adults, the elderly and adolescents 16 years of age and older are taking total daily doses of Becolex™ Modulite® of 1000 micrograms or more, and must always be used by children and adolescents 15 years of age and under whatever dose has been prescribed.

**Becolex™ Modulite® 50 micrograms**
The common starting dose is:
- Adults and the elderly: 200 micrograms (4 puffs) twice a day
- Children: 100 micrograms (2 puffs) twice a day

Usually the most you would take in a day is:
- Adults and the elderly: 800 micrograms (16 puffs)
- Children: 400 micrograms (8 puffs)

The total daily dose may be divided into two, three or four doses per day.

**Becolex™ Modulite® 100 micrograms**
The common starting dose is:
- Adults and the elderly: 200 micrograms (2 puffs) twice a day
- Children: 100 micrograms (1 puff) twice a day

Usually the most you would take in a day is:
- Adults and the elderly: 800 micrograms (8 puffs)
- Children: 400 micrograms (4 puffs)

The total daily dose may be divided into two, three or four doses per day.

**Becolex™ Modulite® 200 micrograms**
The common starting dose is:
- Adults and the elderly only: 200 micrograms (1 puff) twice a day

Usually the most you would take in a day is: 800 micrograms (4 puffs)

The total daily dose may be divided into two, three or four doses per day.

**THIS PRODUCT IS NOT SUITABLE FOR CHILDREN**

**Becolex™ Modulite® 250 micrograms**
The common starting dose is:
- Adults and the elderly only: 500 micrograms (2 puffs) twice a day

Usually the most you would take in a day is: 2000 micrograms (8 puffs)

The total daily dose may be divided into two, three or four doses per day.

**THIS PRODUCT IS NOT SUITABLE FOR CHILDREN**

Do not take more puffs than you were told to take.

It takes a few days for this medicine to work. It is very important that you use it regularly.

Do not stop treatment even if you feel better unless told to do so by your doctor. Do not stop using your inhaler abruptly.

If you miss a dose just take the next dose when it is due.

If you take too much tell your doctor as soon as possible. Your doctor may want to check the cortisol levels in your blood and therefore, may need to take a blood sample (cortisol is a steroid hormone which occurs naturally in the body).

**After taking Becolex™ Modulite®**

While you are taking Becolex™ Modulite® your doctor will want to check your asthma regularly by carrying out simple breathing tests and may need to carry out blood tests from time to time. If your asthma seems to be getting worse, perhaps you are more wheezy and short of breath than usual or if your reliever inhaler seems to be less effective, or you require more puffs from your reliever inhaler than usual, or you do not seem to be getting better tell your doctor as soon as possible. Your doctor may need to increase the dose of your steroid inhaler or may give you a course of steroid tablets, or your doctor may wish to change your treatment altogether. If you have an infection in your chest your doctor may prescribe a course of antibiotics.

If you are transferring from steroid tablets to an inhaler you may find that, even if your chest is getting better you feel a bit poorly or generally unwell or you may develop a rash, eczema or a runny nose and sneezing (influenza). Discuss this with your doctor who may want to treat these symptoms, but do not stop treatment with Becolex™ Modulite® unless your doctor tells you to.

Particularly if you have been treated for a long time with high doses of inhaled steroid, you may require a course of steroid tablets or possibly a steroid injection in times of stress, for example, during admission to hospital after a serious accident or injury, or before an operation, during an acute attack of asthma or if you have a chest infection or other serious illness. Your doctor will decide if you need any extra steroid treatment and will also advise you as to how long you need to take the course of steroid tablets and how you should reduce these as you get better.

Please read back of leaflet
Possible side effects

Most people do not have any problems when taking this medicine.

- If your breathing or wheezing gets worse straight after using your inhaler, STOP using Becolex™ Modulite® and use a quick-acting ‘reliever’ inhaler immediately. Contact your doctor STRAIGHTAWAY. Your doctor will review your asthma and may change your treatment and may prescribe a different inhaler to treat your asthma.

- Very rarely Becolex™ Modulite® may cause allergic reactions including skin rash, hives, itching or redness, or swelling of the face, eyes, lips and throat. Worsening of shortness of breath or wheezing may also be symptoms of an allergic reaction. You may need to use your quick-acting ‘reliever’ inhaler immediately to treat the wheezing and shortness of breath. If you experience any of these reactions, STOP taking this medicine immediately. Tell your doctor as soon as possible or go immediately to the Accident and Emergency Department of your nearest hospital and tell them you have experienced an allergic reaction whilst using Becolex™ Modulite®.

- Some people occasionally develop thrush (Candida infection), in their mouth and throat after inhaling this medicine, which is more likely if the daily dose taken is greater than 400 micrograms. Thrush in the mouth and throat can be treated with anti-fungal medicines whilst you continue to use Becolex™ Modulite®. Some patients may suffer from a hoarse voice or find their throat or tongue becomes sore. Brushing your teeth, or thoroughly rinsing your mouth or gargling with water and spitting it out immediately after each dose may help. Use of the Voludilat® spacer device may also be helpful. Tell your doctor as soon as possible if you suffer from any of these side effects but do not stop treatment unless told to do so.

- In very rare instances, treatment with Becolex™ Modulite®, particularly over a long period of time, may affect the normal production of steroids in the body. Your doctor may want to carry out some blood tests to monitor the levels of steroids in your body from time to time. If you become unwell or develop symptoms such as anorexia (loss of appetite), abdominal pain, weight loss, tiredness, nausea (feeling sick), vomiting (being sick), feeling faint, swelling and possible convulsions (fits), you should consult your doctor. This is particularly important if you have been exposed to stress such as surgery, infection, an acute attack of asthma, or other serious illness, etc. One of the rare effects of Becolex™ Modulite®, particularly if taken over a long period of time or in a high dose, is that children and adolescents may grow more slowly, so they may need to have their height checked regularly by their doctor. If growth is slowed, the child or teenager may be referred to a specialist in the treatment of asthma in children. Other side effects, which might be seen, include a decrease in bone mineral density (thinning) and weakening of the bones, and eye problems which include the formation of cataracts and glaucoma (increased pressure in the eye). Your doctor will try to prevent these effects by prescribing Becolex™ Modulite® in the lowest dose possible to control your asthma.

- Sometimes the replacement of oral steroid treatment with inhaled steroid treatment unmask allergies such as allergic rhinitis (a congested and runny nose) or eczema (a rash) previously controlled by the oral steroid tablets. Your doctor may need to prescribe an alternative treatment for these allergies, so you should see your doctor as soon as possible.

- Sometimes you can feel unwell whilst withdrawing oral steroid tablets even though the symptoms of asthma are reduced. You should continue taking Becolex™ Modulite® and see your doctor as soon as possible.

If you feel unwell or notice anything unusual or which you do not understand, tell your doctor as soon as possible.

How to use your inhaler

It is important that you know how to use your inhaler properly. Your doctor, nurse or pharmacist will show you how to use your inhaler correctly and will check regularly that you are using your inhaler correctly. You must follow their instructions carefully so that you know how, when and how many puffs to inhale and how often you must use your Becolex™ Modulite® pressurised inhalation solution. The instructions should be on the pharmacist’s label and are given in this leaflet. If you are not sure what to do or have problems in inhaling then ask your doctor, nurse or pharmacist for advice.

1. To remove the mouthpiece cover, hold between the thumb and forefinger, squeeze gently and pull apart as shown. Check inside and outside to make sure that the mouthpiece is clean, and that there are no foreign objects.
Testing Your Inhaler

If the inhaler is new or if it has not been used for three days or more, one puff should be released into the air to make sure that it works.

2. Hold the inhaler upright as shown, with your thumb on the base, below the mouthpiece.

3. Breathe out as far as is comfortable, place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.

4. Just after starting to breathe in through your mouth press down on the top of the inhaler to release a puff while still breathing in steadily and deeply.

5. Hold your breath; take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds or as long as is comfortable. Breathe out slowly.

6. If you are to take another puff, keep the inhaler upright and wait about half a minute before repeating steps 2 to 5.

7. After use always replace the mouthpiece cover to keep out dust and fluff. REPLACE FIRMLY AND SNAP INTO POSITION.

Important: Do not rush steps 2, 3, 4 and 5.

It is important that you start to breathe in as slowly as possible just before operating the inhaler. Practice in front of a mirror for the first few times. If you see "mist" coming from the top of the inhaler or the sides of your mouth you should start again from Step 2.

People with weak hands or children may find it easier to hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the bottom below the mouthpiece.

If you find it difficult to operate the inhaler while starting to breathe in you may use the Volumatic™ spacer device. Ask your doctor, pharmacist or a nurse about this device. However, the Volumatic™ spacer device must always be used if you are an adult, elderly or an adolescent 15 years of age and older and are taking total daily doses of Becolex™ Modulite® of 1000 micrograms or more, and the Volumatic™ spacer device must always be used when these inhalers are used by children and adolescents 15 years of age and younger, whatever dose has been prescribed.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with the Volumatic™ spacer device with a face mask may help in children under 5 years. Tell your doctor, nurse or pharmacist if you have any difficulties.

Cleaning

It is important to clean your inhaler at least once a week to stop it blocking up.

- Pull the metal canister out of the plastic case of the inhaler and remove the mouthpiece cover.
- Rinse the plastic case and the mouthpiece cover in warm water. If you use a mild liquid detergent, rinse carefully with clean water before drying. Do not put the metal canister into water.
- Leave to dry thoroughly in a warm place. Avoid excessive heat.
- Replace the canister and mouthpiece cover.

It is important that you also read the Patient Information Leaflet which is supplied with your Volumatic™ spacer device and that you follow the instructions on how to use the Volumatic™ and on how to clean it carefully.

Storing your medicine

- Keep your inhaler in a safe place.
- Keep out of the reach and sight of children.
- Do not store the inhaler above 30 °C (86 °F). Protect from frost and direct sunlight.
- If the inhaler gets very cold, take the metal canister out of the plastic case and warm it IN YOUR HANDS for a few minutes before use. NEVER use anything else to warm it up.
- WARNING: The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.
- Do not use after the expiry date shown on the carton and label.
- If you are told to stop taking this medicine, return the Becolex™ Modulite® inhaler to your pharmacist to be destroyed.

Date of Preparation: December 2005

Volumatic™ is a registered trademark of the GlaxoSmithKline Group of Companies.
BECOLEX™ MODULITE® 50 MICROGRAMS PER ACTUATION PRESSURISED INHALATION SOLUTION (BECLOMETHASONE DIPROPIONATE)

PL 06607/0017

LABELLING

CARTON
**CANISTER**

**Becolex™ Modulite® 50**

Micrograms per actuation pressurised inhalation solution

**Beclometasone dipropionate**

50 micrograms per actuation (metered [ex-valve] dose)

Also contains: HFA-134a (a NEW propellant), ethanol (13 vol %) and glycerol.

PREVENTER

200 actuations. For inhalation use.

Use only as directed by your doctor.

Do not exceed the recommended dose. Use regularly.

Keep out of the reach and sight of children.

Do not store above 30 °C. Protect from frost and direct sunlight.

This canister contains a pressurised liquid.

Do not expose to temperatures higher than 50 °C.

Do not pierce the canister.

MA Holder: Chiesi Farmaceutici S.p.A., Italy.
Distributor: Zurich Pharmaceuticals

Cheadle SK8 3GY, UK.

PL 06607/0017

**ZURICH**

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**ACTUATOR**

**Becolex Modulite** 50 mcg Inhaler
PREVENTER
CANISTER

Beclex™ Modulite® 100 micrograms per actuation pressurised inhalation solution
Beclometasone dipropionate 100 micrograms per actuation (metered [ex-valve] dose)
Also contains: HFA 134a (a NEW propellant), ethanol (13 vol %) and glycerol.
PREVENTER
200 actuations. For inhalation use.
Use only as directed by your doctor.
Do not exceed the recommended dose. Use regularly.
Keep out of the reach and sight of children.
Do not store above 30 °C. Protect from frost and direct sunlight.
This canister contains a pressurised liquid.
Do not expose to temperatures higher than 50 °C.
Do not pierce the canister.

ZURICH

MA Holder: Chiari Farmaceutici S.p.A, Italy.
Distributor: Zurich Pharmaceuticals
Chandos SK8 3GY, UK
PL 06607/0018

ACTUATOR

Beclex
Modulite
100 mcg
Inhaler
PREVENTER
Becolex™ Modulite® pressurised inhalation solution (beclometasone dipropionate) PL 06607/0017-20

CANISTER

Lot No.

Use by: mm/yyyy

Becolex™ Modulite® 200 micrograms per actuation pressurised inhalation solution
Beclometasone dipropionate
200 micrograms per actuation (metered [ex-valve] dose)
Also contains: HFA-134a (a NEW propellant), ethanol (13 vol %) and glycerol.
PREVENTER
200 actuations. For inhalation use.
Use only as directed by your doctor.
Do not exceed the recommended dose. Use regularly.
Keep out of the reach and sight of children.
Do not store above 30 °C. Protect from frost and direct sunlight.
This canister contains a pressurised liquid.
Do not expose to temperatures higher than 50 °C.
Do not pierce the canister.

MA Holder: Chiesi Farmaceutici S.p.A., Italy.
Distributor: Zurich Pharmaceuticals
Cheadle SK8 3GY, UK.
PL 06607/0019

ACTUATOR

Becolex Modulite
200 mcg
Inhaler
PREVENTER
CANISTER

Becolex™ Modulite® 250 micrograms per actuation pressurised inhalation solution
Beclometasone dipropionate 250 micrograms per actuation (metered [ex-valve] dose)
Also contains: HFA-134a (a NEW propellant), ethanol (13 vol %) and glycerol.
PREVENTER
200 actuations. For inhalation use. Use only as directed by your doctor. Do not exceed the recommended dose. Use regularly. Keep out of the reach and sight of children. Do not store above 30 °C. Protect from frost and direct sunlight. This canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister.
Lot No: Z100091
Use by: mm/yy

ACTUATOR

Becolex Modulite 250 mcg Inhaler PREVENTER
ANNEX 1: ASSESSMENT OF THE APPLICANT’S RESPONSES BY CSM IN 2002

5.1 POINT 1. There is inadequate evidence of efficacy and safety in adults, adolescents and children less than 16 years of age as therapeutic equivalence to the product to which essential similarity is claimed has not been demonstrated.

5.1.1 Company Response

The Applicant has undertaken a detailed review of the MCA Assessment Report in an attempt to define the issues raised by the MCA Assessors which led to the provisional opinion that there was inadequate evidence of efficacy and safety of these products across the entire age range. The following issues have been highlighted by the Applicant and the Applicant’s response to each issue is attached at Appendix 5-2:
1. **Over-treatment of patients in studies 004/00, 005/00, 003/00 and study 002/00**

In each of the four studies listed above, the three pivotal studies, studies 004/00, 005/00 and 003/00 and one of two supportive studies, study 002/00, the design of each study was such that in each study a number of patients appeared to require a significantly lower dose of inhaled beclometasone dipropionate (BDP) to effect asthma control than the dose which they subsequently received during the study treatment period. Such over-treatment in a substantial number of patients in each study was felt to reduce the sensitivity of the study such that the study would then lack the ability to detect differences between treatments.

To address this point the Applicant has re-analysed the data and has presented sub-group analyses stratified by dose required to effect asthma control at the end of the run-in period. The primary objective behind these analyses was to demonstrate that if patients in whom the dose of inhaled BDP was increased at the end of the run-in are removed from the study population, the CFC-free formulation of BDP will be shown to be equivalent to the CFC-containing formulation in those patients in whom the dose was not increased at the end of the run-in and in whom asthma was previously controlled. This smaller population would represent a sub-group who were deemed not to have been over-treated.

With the exception of FEV1 for the total population in study 005/00, all confidence intervals for treatment comparisons over-lapped zero. For total populations these intervals were always within ±7%; for the sub-group in whom the dose of inhaled BDP was unchanged at the end of the run-in period the confidence intervals were wider assumed to be due to the smaller sample size, but were always within ±9.6%. In order to confirm that the wider confidence intervals in this sub-group are a manifestation of sample size rather than due to a treatment difference, a meta-analysis was undertaken combining data from all four studies.

**Statistical Assessor’s Comment**

To investigate whether patients in studies 004/00, 005/00, 003/00 and study 002/00 were over-treated the Applicant has re-analysed the lung function data in these studies. Two sub-groups have been analysed; patients who had their dose increased at randomisation and patients whose dose was unchanged at randomisation. The Applicant claims that the latter group represents the majority of those enrolled in the studies and that these patients were not subject to any ‘over-treatment’. The majority of patients in these four studies combined did not have their dose increased. However, in study 004/00 at least half of the patients had their dose of BDP at least doubled at randomisation, the figure in studies 003/00 and 005/00 was around 25%. Hence a large number of patients did have their dose increased substantially at the start of the study and these patients may have been over-treated as a result.
The Applicant has presented the results of the two sub-groups for each of the four studies. The results for morning and evening PEFR and FEV₁ for the ITT and PP populations are shown pictorially as Figures 1-5 of the Company’s response (Appendix 5-9). The Applicant does not explain why a graph of the morning PEFR values for the PP population has not been included in the response. It may be that the ITT and PP populations were the same for this variable. If not, an analysis using the PP population should be provided to confirm the results are consistent with those presented for the ITT population. The Applicant states that for the total population the 95% confidence intervals for morning and evening PEFR and FEV₁ were all within ±7% of the reference baseline mean. For the unchanged dose sub-group the confidence intervals were all within ±9.6%.

These subgroup analyses provide limited reassurance on the matter of overall treatment. The results in the subgroup of patients who did not have their dose increased are similar to the overall results. However, due to the smaller sample sizes involved the confidence intervals in the subgroups are wider and do not fall within ±5% of the reference baseline mean. If a wider equivalence margin of ±10% is used it would appear as if therapeutic equivalence has been demonstrated. However, that conclusion relies on the assumption that these studies have the ability to detect differences between treatments. The validity of that assumption is discussed in the comments to the next point.

In order to show that the wider confidence intervals observed for the unchanged dose subgroup were due to reduced sample size rather than a difference in treatment effect the Applicant has presented a meta-analysis across all four studies for morning PEFR and FEV₁. The 95% confidence intervals for the treatment difference for both endpoints in both the ITT and PP populations were contained within an equivalence margin of ±5%. The Applicant therefore states that a conclusion of no difference between the treatments can be made with confidence. However, there are many differences between the baseline characteristics of patients included in these studies. For example, patients included in these studies have different levels of asthma severity and hence are receiving different doses of BDP. Therefore it is not clear whether it is appropriate to perform a meta-analysis of these four trials. Even if such an approach is deemed warranted the validity of the assumption that these studies have the ability to detect differences is still key to establishing whether these studies have demonstrated therapeutic equivalence of BDP formulated with CFCs (as in Bectide Inhaler and Bectoforte Inhaler) and the Applicant’s CFC-free formulation (BDP HFA-134a).

II. Fairly small response to treatment in studies 063/00 and 064/00

The Applicant has re-examined the pivotal and supportive efficacy studies but more particularly the two pivotal adult studies in order to show evidence of a response to treatment. In the original submission evidence of a response to treatment was seen in the study in children, study 005/00 and in the adult supportive study, study 002/00.
In revisiting the pivotal adult studies the Applicant has undertaken two further analyses of pulmonary function data comprising an analysis of the response to treatment in patients in whom lung function was less than 85% of predicted at study entry in an attempt to isolate the least stable patients recruited to these studies and who might show a response to treatment, and an analysis of the numbers of patients showing particular changes in pulmonary function in an attempt to show that there is a response to treatment in individual patients which might be masked in the analyses of the total population entered. The Applicant has also re-examined the data generated in respect of the secondary symptombased endpoints of symptom scores and use of rescue medication (in the light of the recommendation made in the draft CPMP Notes for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma (CPMP/EWP/29922/00) currently out on consultation, that equal emphasis should be placed on lung function and symptom-based endpoints).

The Applicant discusses the sensitivity of non-inferiority studies in stable asthmatics and the issues surrounding studies carried out in patients with unstable asthma versus those in patients with stable asthma.

Statistical Assessor's Comment

The Applicant has re-examined studies 003/00 and 004/00 in order to show evidence of a response to treatment. Changes in salbutamol consumption and asthma symptoms have been analysed in both studies. During the studies patients' salbutamol consumption reduces slightly in both treatment groups and asthma symptoms also show a slight improvement in both treatment groups. These analyses do not show that these studies have the ability to detect differences in lung function parameters such as morning and evening PEFR and FEV₁.

The Applicant has also presented a subgroup analysis for patients with an entry FEV₁ percent predicted of less than 85% in studies 003/00 and 004/00. The results for study 003/00 are shown in Table 1-5 of the Applicant's response (Appendix 5-2). These results show significant improvements in morning PEFR in the CFC BDP group and FEV₁ in the BDP HFA group. The Applicant states that this suggests that the more severe patients enrolled in this study were not at the plateau of their dose response curve and that this trial had sufficient sensitivity to detect differences between treatments in these patients. Of course this is an example of regression to the mean. It does not provide evidence that the study as a whole has the ability to detect differences between treatments in lung function parameters.

When the analysis is repeated in study 004/00 (the higher dose study in adults) the changes in morning PEFR and FEV₁ are not statistically significant. The Applicant quotes a recent Cochrane review by Adams et al which suggests that relatively small increases in lung function would be expected in this population (as low as 11L/min for PEFR and 9mL on FEV₁ for a doubling of dose from 400µg to 800µg per day). Hence the Applicant states that it is expected that changes seen at lower doses are much greater and this explains why an effect is seen in study 003/00 but not in 004/00. The total daily dose of BDP was 1000µg in study 004/00 and 400µg in studies 003/00 and 005/00.
The results of the Cochrane review have major implications for establishing therapeutic equivalence for this product. Imagine that the HFA formulation was delivering twice the amount of BDP than the CFC formulation. If the results from the Cochrane review are to be believed then the PEFR in patients randomized to receive the HFA-134a formulation would only rise by around 11 L/min compared with the PEFR in patients who remain on the CFC formulation. 11 L/min is included within the 95% confidence intervals for change from baseline in PEFR in studies 004/00 and 005/00. Therefore it remains possible that the HFA-134a formulation of BDP is more potent than the CFC formulation. Note that if the HFA-134a formulation was less potent it is likely that these studies would have been able to detect such a difference. Therefore these studies provide good evidence that the efficacy of the HFA-134a formulation is non-inferior to the CFC formulation in terms of FEV$_1$ and PEFR. There is a concern that the pivotal studies were unlikely to be able to detect whether the new formulation was more potent than the original formulation due to subjects included in the studies being at the top of the dose response curve for BDP. It remains to be established whether any superior efficacy that the HFA-134a formulation may have, introduces any safety concerns.

The Applicant states that performing new studies in this area is unlikely to lead to any different conclusions regarding therapeutic equivalence in respect of efficacy between the new product and existing CFC formulations. At doses of 400 µg/day and higher it appears that it would be very difficult to perform a satisfactory therapeutic equivalence study in patients with asthma receiving BDP. Such trials are unlikely to be sensitive to treatment differences and hence are of little value in establishing the equivalence of two formulations. However, a study at a much lower dose, say 50 or 100 µg/day of BDP in which patients are randomised to received the low dose of the CFC or HFA formulation or a higher dose (say 200 µg/day) of BDP CFC is feasible. Such a study may be able to show superior efficacy for the 200 µg/day dose and hence establish that the study has the ability to detect differences between treatments and also be able to establish therapeutic equivalence between the CFC and HFA formulations.

**Clinical Assessor's Comment**

Points are raised by the Applicant which would suggest some misinterpretation of comments made in the MCA Assessment Report and in discussions between the Applicant and the MCA following receipt by the Applicant of the letter from the CSM dated 18 July 2001. These points comprise the following:

- **Study design.** The Applicant claims that the design of study 001/00, the pivotal efficacy study in adults with mild asthma and receiving beclometasone dipropionate (BDP) 200 µg bd over a six week treatment period was agreed with the MCA prior to its inception. This statement is inaccurate in that any agreement of the study design was an agreement of the broad principles of the design and not the specific details.
The design of this study, together with that of the other two pivotal studies, study 004/00 (the efficacy study in adults with mild to moderate persistent asthma and receiving a dose of BDP 500µg bd for 12 weeks) and study 005/00 (the efficacy study in childhood asthma) and the supportive study, study 002/00 (a study also carried out in adult patients with mild to moderate disease and receiving a dose of BDP 500µg bd for 12 weeks, but not a comparison with the product to which essential similarity was claimed) was essentially flawed in one aspect of the design which raised serious questions over the eventual outcomes. In each study patients recruited were requiring a range of doses of inhaled corticosteroids from a protocol defined maximum upper limit equivalent to the dose of inhaled steroid to be studied in the particular study, downwards. In each study patients remained on their pre-study dose of inhaled steroids during the run-in period during which stability of asthma control on that particular dose was demonstrated, and at the end of run-in period all patients were transferred to study treatments, either HFA or CFC containing formulations of BDP. In each study a number of patients appeared to require a significantly lower dose of inhaled BDP to effect asthma control than the dose which they subsequently received during the study period. In the two pivotal studies in adults this design flaw coupled with no substantial change seen over baseline at the end of the treatment period in either treatment group raised questions as to whether it would have been possible to detect differences in the light of possible substantial over-treatment of the disease. This over-treatment would result in reduced sensitivity such that the studies lacked the ability to detect differences. It is this flaw in the design which was not agreed with the Applicant prior to running the efficacy programme.

• Stable versus unstable disease. Studies in patients with unstable asthma are not preferred over studies in patients with stable asthma and the practical and ethical difficulties in studying patients with unstable disease are appreciated. The CMAFP Note for Guidance replacement of chlorofluorocarbons (CFCs) in metered dose inhalation products — III/537/83 — Final does give a preference to comparing CFC-free with CFC-containing formulations of BDP in steroid-naive patients with asthma where a response to treatment can be seen and hence determination of equivalence becomes easier. However the Note for Guidance does not suggest that equivalence studies should be carried out in patients who have unstable disease or that patients with stable disease should have their medication reduced in order to produce symptoms and hence unstable or less stable disease. The more appropriate study design if looking to show therapeutic equivalence would be the one which takes the patient with asthma and whose disease is controlled, but not over-treated, enters them into a run-in period to define the baseline in terms of pulmonary function, symptoms and requirement for inhaled β2 agonist therapy as relief medication, and then randomises the patient to receive either a CFC-free or CFC-containing formulation of BDP at the same dose which as been deemed appropriate to control asthma in that patient population. Changes over the treatment period would then be compared with baseline and between treatments.
Re-analysis of data generated in respect of the secondary endpoints pertaining to symptoms of asthma and use of relief β₂ agonist therapy from studies 003/00 and 004/00 (pivotal efficacy studies in adult patients).

The draft CPMP Notes for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma to which the Applicant refers in respect of co-primary endpoints, comprising a primary endpoint of pulmonary function and a primary endpoint in respect of symptoms/β₂ agonist use, is essentially a document providing guidance on the clinical investigation of new products in the treatment of asthma. In a study designed to show therapeutic equivalence, though it would be equally acceptable to employ co-primary endpoints as described, the demonstration of therapeutic equivalence would not be based solely on the findings in respect of symptoms/β₂ agonist use in a programme of studies where adequate evidence of therapeutic equivalence cannot be demonstrated through measures of pulmonary function. In the studies presented in the efficacy programme the findings in respect of changes in symptomology and use of β₂ agonists would support the primary endpoint of function but are not measures which are robust enough on their own to be accepted as adequate evidence of therapeutic equivalence when this is not demonstrated through endpoints of pulmonary function.

An analysis of the response to treatment in patients in whom pulmonary function was <85% of predicted at study entry.

In the two efficacy studies in adult patients, studies 003/00 and 004/00, the Applicant presents the analysis of changes compared with baseline in morning PEFR and FEV₁ in the sub-group of patients enrolled into these two studies in whom pulmonary function at entry was <85% of predicted in an attempt to pick out the least stable patients recruited to these two studies and who might show a response to treatment.

The findings in the low dose study, study 003/00 might suggest that those patients who on entry were more severe were not at the plateau of their dose-response curve and that the trial had sufficient sensitivity to detect differences between treatments. In the analysis of equivalence the findings mirrored those seen in the total population with the bilateral 55% confidence interval for the treatment difference for both PEFR and FEV₁ failing within the equivalence interval of ±10%. However, these findings only represent a regression to the mean and do not provide evidence that the study has the ability to detect differences between treatments.

In study 004/00 the changes in morning PEFR and FEV₁ over baseline in this sub-group of less stable asthmatics were smaller and were not statistically significant.
This latter finding is discussed by the Applicant. A recent review of the literature from Adams, Bestall and Jones Inhaled beclomethasone at different doses for long-term asthma – The Cochrane Library 2001:3 suggests that relatively small increases in lung function would be expected in a population such as that studied in study 004/00, as low as 11 L/min for PEFR and 2s for FEV1, for a doubling of dose from 400 μg to 800 μg/day. If the patient’s pulmonary function is near to the plateau of their dose-response curve then a doubling of dose would indeed produce a very minimal increase in pulmonary function. Therefore if the patient receives a dose of inhaled steroid which ensures their pulmonary function reaches the plateau of their dose-response the demonstration of equivalent efficacy between two doses becomes impossible and an equivalent effect or otherwise would have to rest on measures of systemic absorption/systemic safety.

These further analyses of pulmonary function data in the sub-group of less stable asthmatics add little to the original conclusions.

Further analysis of morning PEFR changes from baseline

The Applicant has attempted to look at the data generated in individual patients to show that any one individual patient may respond to treatment whereas another may not and that these increases and decreases in pulmonary function may cancel each other out such that the change seen in the overall population is then relatively small and not significant. The Applicant looks at each of the efficacy studies in turn and at the pooled data derived from the three pivotal studies and the supportive study, study 002/00 and concludes that the findings suggest a degree of sensitivity to treatment amongst the patients studied.

These further analyses of pulmonary function data add nothing to the original conclusions.

III. Relevance of the non-pivotal studies 002/00 and 01/98

The two supportive/non-pivotal studies, studies 002/00 and 01/98 studied the administration of BDP either formulated with HFA-134a or CFC propellants (both Chiesi Farmaceutici SpA formulations of BDP) administered through the Chiesi actuatorspacer device, the Jet actuator-spacer, instead of the standard actuator/metered dose inhaler. The studies were presented as supportive studies as neither study included a comparison of BDP formulated with HFA-134a with any of the products to which essential similarity is claimed, ie the products of Allen & Hanburys Limited, subsequently licensed to Glaxo Wellcome UK Limited, Becotide 50, Becotide 100 and Becotide 200 inhalers and Becloforte Inhaler, all brand leader products. The Jet actuator-spacer device is not available in the UK but its use in these studies would be supported through pharmacokinetic studies and by in vitro data generated using an Andersen Cascade Impactor.

To enhance the relevance of the supportive studies the Applicant has submitted both in vitro and clinical data comparing the performance of BDP formulated with CFCs and administered via a metered dose inhaler with standard actuator and via the Jet actuator-spacer and comparing both these Chiesi formulations with the brand leader product and the product to which essential similarity is claimed, Becloforte Inhaler (formulated with CFCs).
The Applicant also presents data to support drug delivery via the Jet actuator-spacer in the supportive studies in preference to the MDI with standard actuator as proposed for marketing, although the use of the Jet actuator-spacer was supported, as described above in the original submission. The *in vitro* data presented in the original submission suggested that the delivery of beclometasone dipropionate to the lungs may be unaffected by the delivering device in the comparison of the Jet actuator-spacer with the standard metered dose actuator. In this Appeal Dossier the Applicant presents *in vitro* deposition data, as previously and refer to pharmacokinetic data presented in the original submission.

**Pharmaceutical Assessor’s Comment**

Data from studies using the Andersen Cascade Impactor and a twin stage impinger are presented comparing the Chiesi BDP 250µg CFC inhaler with the innovator product to which essential similarity is claimed (Becloforte CFC [250µg]). For the purposes of the clinical studies the dose was administered via a Jet™ Spacer device and thus data are provided for the Chiesi BDP CFC inhaler with and without this device. From the ACI data the delivered doses and fine particle doses (<4.7 µm) were comparable for the two inhalers using their standard actuator (Chiesi BDP CFC cf Becloforte CFC, Delivered dose: 229µg cf 214.2µg, FPD: 45.9µg cf 45.1µg). On using the Jet™ Spacer the delivered dose was halved (104.7µg) but the FPD was consistent with that administered without the spacer device (43.6µg). The twin stage impinger data are also supportive of these data demonstrating that the respiratory fraction was comparable for Chiesi BDP CFC and Becloforte CFC. These data confirm that Chiesi BDP CFC can be considered a suitable comparator product in these studies as it is representative of Becloforte CFC.

Comparative ACI data are also provided for the BDP HFA inhaler with and without the Jet™ Spacer. As with the CFC inhaler there was no change to the FPD with or without the device. It can be concluded from these data that the subjects in the clinical studies would have received the same respiratory fraction if the standard actuator had been used rather than the Jet™ Spacer.

**Clinical Assessor’s Comment**

The Applicant presents two small clinical studies in which the Chiesi formulation of BDP (CFC-containing) 250µg/actuation (in one study, study 14.01/CT/04/91 administered via the standard metered dose actuator and in the second study, study 63.01/CT/03/92 administered via the Jet actuator-spacer (Beclojet)) was compared with the Gino formulation of BDP (CFC containing) 250µg/actuation (as marketed in Germany and France). With the exception of some minor differences seen between treatments in the first, and smaller study (*n*=56) there would appear to be no importance statistically significant differences between treatments.
It is noted however that these studies are small (n=36 and n=82, respectively) and although extrapolations can be made from these studies to the supportive studies presented in the original dossier (where the two Chiesi formulations of BDP, one formulated with CFCs and the other with HFA-134a are compared), they do not provide a comparison of the HFA-134a containing formulation of BDP with the product to which essential similarity is claimed and therefore can only be described as further supportive studies.

The in vitro data comparing the Chiesi formulations of BDP HFA-134a 250μg delivered via the Jet actuator-spacer and via the standard metered dose actuator suggest that the Jet actuator-spacer does not significantly affect the deposition of BDP within the respirable range below 5.8 microns. The fraction of the fine particle dose below 1.1 microns was also comparable for the two actuators.

The Applicant references the pharmacokinetic study presented in the original dossier and described in Part IV – page 14 of the original report, study SGS, B109.512. The findings from this study suggest that the pulmonary delivery of BDP is similar regardless of whether the drug is inhaled via the standard metered dose actuator or the Jet actuator-spacer.

The conclusions drawn by the Applicant in respect of therapeutic equivalence between the Chiesi CFC-containing formulation of BDP and the product to which essential similarity is claimed in these applications, is the Glaxo Wellcome UK Limited CFC-containing formulation of BDP, and the claim that the use of the Jet actuator-spacer does not significantly affect the pulmonary deposition of the drug when compared with the standard metered dose actuator are accepted. They provide data which will support the two studies described as supportive/non-pivotal studies in these applications, studies 062/00 and 01/98 but do not provide any further comparisons of the Chiesi BDP HFA-134a formulation with the product to which essential similarity is claimed. The comparisons presented provide a link between the Chiesi BDP HFA-134a formulation and the essentially similar product.

Statistical Assessor’s Comment

Although the efficacy and safety of the Chiesi BDP CFC MDI is similar to Becloforte it is still unwise to use comparisons between the Chiesi CFC product and the HFA-134a formulation to establish therapeutic equivalence between Becloforte and the HFA-134a formulation. If A and B are equivalent and B and C are equivalent this does not necessarily imply that A and C are equivalent. This highlights one of the reasons why therapeutic equivalence to the product to which essential similarity is claimed must be established. Therefore studies 062/00 and 01/98 can only be considered supportive studies for these applications.
IV. **FEV<sub>1</sub> data from paediatric study 005/00**

Concerns are raised in the MCA Assessment Report in the analysis of the important secondary endpoint of function, FEV<sub>1</sub>, in the study in childhood asthma where it appears that at the end of the 12-week treatment period the two strengths of the BDP HFA formulations are not equivalent to BDP CFC 50 and are superior, findings which are mirrored in the changes seen in FVC and FEF<sub>25</sub>. This finding, coupled with the flawed design of the study (described in I and II above, which made it difficult for convincing conclusions to be drawn that the two formulations of BDP, BDP HFA and BDP CFC were clinically equivalent in this young population), has led the Applicant to present the FEV<sub>1</sub> data generated in this study in more detail than in the original dossier. The Applicant's additional comments in respect of the FEV<sub>1</sub> data are presented in Appendix 5-2, page 51-53.

**Statistical Assessor's Comment**

In study 005/00 a significant difference was observed in the change from baseline in FEV<sub>1</sub> in the HFA 50 group and the CFC 50 group, and the upper limit of the 95% confidence interval was greater than 10% of the baseline FEV<sub>1</sub> value for the CFC 50 group. The Applicant has provided more analyses from study 005/00. In Table 1-0 of the Company Response (Appendix 5-2) it is clear that a significant difference between treatments is only seen at the last clinic visit. The Applicant states this is likely to be a chance finding. The Applicant also states that the lower limit of the confidence intervals is above the more stringent measure of -5% of the reference mean. Also the upper limit of the confidence intervals were only just above +10% of the reference mean. The Applicant also states that equivalence was obtained on the PEFR endpoint. Finally the Applicant concludes that concern over BDP HFA performing better than BDP CFC should only arise if there is clear evidence that BDP HFA is substantially more effective than BDP CFC with respect to lung function which does not appear to be true in this study.

The extra information for study 005/00 does not remove the concerns over therapeutic equivalence being established. It is clear from the earlier discussion that giving twice the dose of BDP in these patients is unlikely to increase their lung function parameters significantly. Therefore it remains possible that the HFA-134a formulation is more potent than Beclofene.

**Clinical Assessor's Comment**

The further discussion provided regarding the suggestion that BDP formulated with HFA-134a is superior in respect of efficacy to BDP formulated with CFCs (the essentially similar product) when assessed through the secondary endpoint of function, FEV<sub>1</sub> at the end of 12 weeks treatment, does not negate the concerns raised in the original assessment.

However the data generated in respect of the primary efficacy variable (morning PEFR), other endpoints of function and the secondary efficacy variables in respect of symptoms and daily use of inhaler salbutamol do suggest that the two strengths of BDP HFA, 50 and 100 are not inferior to BDP CFC 50 when the three treatments are administered. At a dose of 200μg BD, that BDP HFA 100 is not inferior to BDP HFA 50 and that all three treatments are clinically equivalent.
The study is of flawed design although an improvement in pulmonary function is seen over baseline from weeks 5-6 to the end of the study (12 weeks) which would suggest that at least a proportion of patients entered were not optimally treated and had room for improvement and that the study did have the ability to detect differences between treatments.

Therefore if the two formulations of BDP, CFC containing and HFA-134a containing can be deemed to be equivalent in the management of asthma in adults, equivalence in childhood asthma can be accepted as proven.

V. Additional statistical points

The Applicant provides responses to statistical points raised following their interpretation of the MCA Assessment Report, as follows:

- That the non-inferiority hypothesis is based on a one sided 95% confidence interval rather than a two sided 95% confidence interval.
- That the defence of the equivalence interval is not overly robust.
- That equivalence should be demonstrated for both ITT and PP populations.

The Applicant’s responses to the issues raised can be found at Section V on page 54 of Appendix 5-2.

Statistical Assessor’s Comment

The Applicant has now provided two-sided 95% confidence intervals for all the relevant analytes for all the clinical studies. The Applicant also discusses the appropriate equivalence margins for these studies. However, whether ±5% or ±10% is used as an equivalence margin it still remains to establish trial sensitivity for the clinical studies used in these applications.

Overall Statistical Conclusion on Efficacy

The key remaining issue is whether the pivotal therapeutic efficacy studies have the ability to detect differences between treatments in lung function parameters. It is likely that the studies would have the ability to detect inferior efficacy of the HFA-134a formulation. However, due to the similar effect that a daily dose of BDP of 800μg and a daily dose of 400μg has on FEV1 and PEFR it is unlikely that these studies have the ability to detect if the HFA-134a formulation is more potent than the CFC formulation. This of course could have an impact on the safety of the HFA-134a formulation. Therefore it is only if there is very good evidence that the safety of the HFA-134a formulation is comparable to that of the CFC formulation that it would be reasonable to conclude that therapeutic equivalence of BDP formulated with HFA-134a and BDP formulated with CFCs has been demonstrated.
Overall Clinical Conclusion on Efficacy

The further analysis of the data generated in the studies presented in the original submission do not provide any convincing evidence that the two formulations of BDP, BDP formulated with HFA-134a and BDP formulated with chlorofluorocarbon propellants (as in Becotide 50, 100 and 200 Inhalers and Becloforte Inhalers, the products to which essential similarity is claimed) are therapeutically equivalent (at any point in the accepted dose range from 200 µg twice daily in adult patients with mild asthma to 1000 µg twice daily in adult patients with severe asthma). In the initial assessment of these applications the conclusions drawn in respect of efficacy, ie the lack of adequate evidence of therapeutic equivalence to the product to which essential similarity is claimed and the suggestion of greater systemic exposure seen when BDP is formulated with HFA-134a than when formulated with CFCs, led to the conclusion that further clinical studies were required to determine therapeutically equivalent dose regimens prior to the grant of any Marketing Authorisations. The Applicant has chosen not to carry out further studies in respect of efficacy and therefore without such studies the decision to grant Marketing Authorisations can only be based on good evidence of the safety of the new formulation of BDP, BDP HFA-134a, at the top of the dose range (1000 µg twice daily). The Applicant has carried out a study to look specifically at systemic safety at the top of the dose range and this study is presented at Point 5.2, below.

VI. The safety data presented in respect of systemic exposure are inadequate such that conclusions cannot be drawn regarding the safety of BDP formulated with HFA-134a, particularly at the top end of the dose range.

The Applicant's response to the point raised in respect of inadequate evidence of safety is essentially based on the submission of a new high dose safety study which is discussed and commented on in detail at Point 5.2, below.

To complete their response in respect of the point raised regarding inadequate evidence of safety the Applicant also reviews the clinical programme as submitted with the original submission in respect of systemic effects. This review is presented in Appendix 5-2, pages 57-60.

Clinical Assessor's Comment

The Assessor's comment on clinical safety can be found at Point 5.2, below.
VII. The higher fine particle dose and the different particle size distribution, in particular the large quantity of particles <1.1 μm, of the HFA inhalers compared with the CFC inhalers should be discussed in view of the safety and efficacy issues in relation to the clinical data.

The Applicant discusses these issues in their response to Point 4 of the letter from the CSM dated 18 July 2001. This response and the Pharmaceutical Assessor's comments can be found at Point 3.1 above.

Point 1 is considered unresolved (in respect of efficacy).

5.2 POINT 2. In the light of concerns regarding greater systemic exposure when beclometasone dipropionate is formulated with HFA-134a, further information of the comparison with the product to which essential similarity is claimed throughout the dose range but particularly at the top of the proposed dose range is required.

5.2.1 Company Response

The Applicant has submitted new safety data presented in adult patients with asthma following inhalation of beclometasone dipropionate, formulated with propellant HFA-134a or with chlorofluorocarbon propellants and administered in a dose of 1mg bd. This dose is the maximum dose of inhaled beclometasone dipropionate permitted in the Marketing Authorisation for the product to which essential is claimed, Becloforte Inhaler, PL 10940/0065, authorised to Glaxo Wellcome UK Limited.

The Applicant's response to Point 2 of the CSM letter dated 18 July 2001 and the tabular summary of the new high-dose safety study are attached at Appendices 5-3 and 5-4, respectively.

Protocol No: DM073/930/002/89
Double blind, double dummy, parallel-group design trial of the systemic and local safety of high-dose beclometasone dipropionate aerosol spray (1000μg bid) via a metered dose inhaler using HFA-134a or CFC propellant in the six-week treatment of high-dose inhaled steroids-dependent adult patients.

The objective of this study carried out in a single centre in the United Kingdom (principal investigator and author of the Clinical Expert Statement which accompanies the Appeal Dossier for these applications, Professor A A Woodcock, North West Lung Centre, Wythenshawe Hospital, Manchester, UK) was to demonstrate that BDP formulated with HFA-134a and administered via a metered dose inhaler with spacer device (Volumatic, Allen & Hanburys Limited, UK) in a unit strength of 250μg/actuation was not inferior in terms of systemic and local safety to BDP formulated with CFC propellants (Becloforte Inhaler) and administered via a metered dose inhaler with spacer device (Volumatic) in a unit dose of 250μg/actuation, when administered in a total daily dose of 2000μg (1000μg bid) in adult patients with moderate to severe persistent asthma and previously well controlled with high-dose inhaled steroids (BDP CFC in a total daily dose ≥1500μg and ≤2000μg) over a six-week treatment period.
The study comprised a four-week run-in period during which time all eligible patients (n=94) were assigned to treatment with BDP formulated with CFC propellants in a dose of 2000μg/day and any non-permitted medications were withdrawn prior to entry into the study treatment period. (Throughout the run-in period BDP CFC was administered via a metered dose inhaler with Volumatic spacer device). Following the run-in patients (n=83) were randomised to study medication to be continued throughout the six-week treatment period. The total daily dose of BDP (either BDP HFA or BDP CFC) comprised four actuations/puffs (4 x 250μg) twice daily providing a total daily dose of 2000μg/day. (It is noted in the Study Report that the dose is described two puffs twice daily (2000μg/day); this presumed error will be discussed with the Applicant. In the Clinical Study synopsis (tabular summary) the dose is described as four puffs twice daily (2000μg/day) and elsewhere in the Appeal Document the dose is described as either 1000μg bid or 2000μg daily).

The primary safety variable was morning serum cortisol measured at the start and end of the treatment period and between 08.00 and 10.00 hours; secondary safety variables included the 12-hour (overnight) urinary cortisol/creatinine ratio, 12 hour (overnight) urinary creatinine, the incidence of adverse events (any untoward medical occurrence) and adverse drug reactions (any noxious and unintended response with an implied causal relationship between study treatment and the adverse event) and vital signs.

A subgroup of patients (n=32) also participated in a pharmacokinetic assessment to compare the systemic exposure to BDP and to the active metabolite beclomethasone-17-monopropionate (B17MP) following repeated administration of BDP HFA and BDP CFC in a dose of 1000μg bid over the treatment period of 6 weeks. Twenty-eight patients completed this part of the study.

Clinical Study

A total of 94 patients were recruited into the study, 11 were withdrawn prior to randomisation and the intention-to-treat (ITT) population was based on 83 patients, 42 receiving BDP HFA and 41 receiving BDP CFC. Six patients randomised to treatment were withdrawn prior to the last study visit (one in the BDP HFA group and five in the BDP CFC group) and were therefore excluded from the completing ITT population. It is randomised patients who had received at least one dose of study medication and had completed the six-week period. The analysis of the primary endpoint, morning serum cortisol and the urinary cortisol/creatinine ratio was carried out on this completing ITT population; the analysis of adverse events also included all those who had withdrawn from the study. The analysis of the primary endpoint was also carried out on the per protocol (PP) population, all other safety parameters were only analysed for the ITT population. There were no major protocol violations and therefore the PP population equaled the completing ITT population – 41 patients receiving BDP HFA and 36 receiving BDP CFC.

The withdrawals included adverse events (3 patients including the one patient receiving BDP HFA), changes in concomitant medication (2 patients) and other reasons (2 patients).
The findings in respect of the primary safety variable, morning serum cortisol are presented in both tabular and graphical form in Appendix 5-3.

Despite the 4-week run-in period serum cortisol significantly increased in both treatment groups during the 6-week treatment period, an increase which was slightly greater in the BDP HFA treatment group than in the BDP CFC treatment group - mean change from baseline on BDP HFA was 93.85 nmol/L compared with 82.34 nmol/L on BDP CFC. The change from baseline was statistically significant in each treatment group; the comparison between the two treatment groups was not statistically significant, p=0.0679.

The log transformed morning serum cortisol significantly increased in both treatment groups, with the increase slightly greater in the BDP HFA group compared with the BDP CFC group, 0.29 compared with 0.20. The analysis of non-inferiority of the log transformed morning serum cortisol showed that the difference between the adjusted means at week 6 was equal to 0. The bilateral 95% confidence interval for the difference between the least square means in the analysis of covariance model was -0.18 to 0.18 nmol/L and the back transformed 95% CI for the ratio of the means was 0.83 to 1.20. This lower limit of 0.83 is slightly below the pre-specified limit for non-inferiority of 0.85, a finding which, according to the Applicant reflects a slightly greater variability in the data than was accounted for in the power calculation. (For the study to have a power of at least 80% to demonstrate non-inferiority, the lower confidence limit of the ratio of treatment means should be not less than 0.85 (15% reduction) using a one-sided 2.5% significance level and a total of 33 patients per group would be required - based on data generated in previous studies).

Seven patients had serum cortisol determinations which fell outside the normal range but in only one patient, a patient receiving BDP HFA, was a fall seen from normal at baseline to low at the end of the treatment period (a fall from 698.4 nmol/L to 96.6 nmol/L – normal range 165-786 nmol/L). The Applicant discusses travel in the Southern hemisphere and disruption of diurnal rhythm as possible causes.

In the analysis of the secondary safety variables a small decrease in the 12-hour urinary cortisol/creatinine ratio was seen in the BDP HFA treatment group compared with a small increase in the BDP CFC group; however the analysis of changes from baseline showed no statistically significant differences in the two treatment groups and there were no statistically significant differences in the comparison between the treatment groups, p=0.360. The findings in respect of the 12-hour urinary creatinine showed no significant differences between treatment groups, p=0.543; however, changes from baseline (decrease) showed a statistically significant difference in the BDP HFA treatment group.

A number of patients failed to comply with the protocol in the collection of 12-hour urine samples with a resultant decrease in the sample size from 41 to 35 patients receiving BDP HFA and 36 to 29 patients receiving BDP CFC.
The breakdown of adverse events is presented in text format in Appendix 5:1 and 5:4 and no real differences were seen between treatment groups. A total of 53 events were reported of which 35 were deemed to be drug-related - 19 reports in 15 patients receiving BDP HFA (35.7%) and 16 reports in 12 patients receiving BDP CFC (29.3%). The respiratory and central nervous systems were the most commonly affected body systems and most of the thought to be drug-related adverse events were local or pulmonary events possibly related to the use of high-dose inhaled corticosteroids. Oral candidiasis was reported by one patient in both treatment groups. Cough post-inhalation was reported by one patient receiving BDP HFA and sore throat was reported by three patients in both treatment groups. Three patients withdrew due to adverse events during the course of the study, one receiving BDP HFA (asthma exacerbation possibly related to study drug) and two receiving BDP CFC (nausea with doubtful relationship to study drug and right lung pain unrelated). There were no deaths and only one serious adverse event which occurred during the run-in period. There were no statistically significant changes either within or between treatment groups in vital signs.

**Pharmacokinetic Findings**

An investigation of the pharmacokinetics of BDP, a pro-drug and its active metabolite B17MP was carried out in a subgroup of 32 (n=28 completed) patients who took part in the high-dose safety study on the last day of the six-week treatment period. Blood samples were taken pre-dose and at 15 and 30 minutes and 1, 2, 4, 6, 8, 10 and 12 hours after inhalation of study treatments on the last morning of the study.

Unchanged BDP plasma levels were low and variable, there were only few samples with measurable BDP concentrations and in some patients concentrations in all samples were below the lower limit of quantification. This finding is in keeping with previous findings in healthy volunteers. Therefore no pharmacokinetic analysis was performed.

The pharmacokinetic parameters in respect of B17MP are shown in tabular and graphical form in Appendix 5:3. B17MP plasma levels peaked rapidly after inhalation of both formulations, higher peak concentration (C_{max}) and an earlier time to C_{max} (T_{max}) were seen with BDP HFA than with BDP CFC. C_{max} was approximately 35% higher and T_{max} 0.25h earlier with BDP HFA compared with BDP CFC. However total systemic exposure as measured by area under the curve over the time period of measurements (AUC_{0-12}) was more comparable - 2247pg · h/mL *h on BDP HFA compared with 2484 pg/mL *h on BDP CFC. The 90% CI are wide, 63.6-128.7 with a point estimate of 0.90.

Analysis of individual plasma profiles for B17MP showed two outliers, one in each treatment group, and these can also be seen in Appendix 5:3 – individual plasma profiles and AUC_{0-12} scatter plots. The pharmacokinetic analyses were repeated excluding the two outliers and although the higher C_{max} and earlier T_{max} were reproduced, the systemic exposure as measured by AUC_{0-12} confirmed that systemic exposure in this reduced population was comparable across the two products – AUC_{0-12} in the BDP HFA treatment group was 2124pg/mL *h compared with 2160pg/mL *h in the BDP CFC treatment group.
The 90% CIs for $\text{AUC}_0\text{t}$ were again slightly wide, 73.3 – 132.0 with a point estimate of 0.98. One outlier treated with BDP CFC showed B17MP plasma levels approximately 6 times higher than the mean levels in other patients and one patient receiving BDP HFA had an abnormal plasma profile for B17MP with a plasma peak concentration at 4 hours post inhalation – usually around 30 minutes).

The Applicant compares the data with data generated in previous studies in healthy volunteers and systemic exposure to B17MP appeared lower in the current study in patients with asthma with both inhalers. It is postulated that the narrower airway in the asthmatic might produce a more central deposition and as a consequence reduced systemic exposure. This pattern has been seen with other inhaled corticosteroids. The Applicant discusses the possible reasons behind the earlier and higher absorption rate for B17MP following BDP HFA inhalation. This would appear to be due to earlier and faster absorption from the lung rather than any difference in pulmonary deposition in the light of comparable plasma $\text{AUC}$ values ($\text{AUC}_0\text{t} = 0.98$ when outliers are excluded). The Applicant also argues that the higher $\text{C}_{\text{max}}$ is unlikely to result in any difference in pharmacological effect as systemic effects seen following the inhalation of corticosteroids are correlated with total systemic exposure rather than peak concentrations.

The Applicant concludes that the potential risk of increased systemic exposure (as measured through the plasma $\text{AUC}$) when switching from BDP formulated with CFCs to BDP formulated with HFA-134a can be excluded.

5.2.2 Assessor's Comment

Point 2 of the CSM letter of 18 July 2001 was raised following the original assessment of these applications in the light of a lack of safety data particularly in respect of systemic exposure at the top of the dose range. Such that conclusions regarding the safety of BDP formulated with HFA-134a could not be reached. The need to demonstrate safety at the top of the dose range following administration of a total daily dose of 200µg (administered over time) became even more important in the light of the pharmacokinetic findings presented in the original applications where differences between BDP HFA and BDP CFC in respect of systemic exposure are seen with apparent greater systemic exposure when BDP is formulated with HFA-134a.

The study presented by the Applicant is an appropriate study to assess systemic safety at the top of the dose range for inhaled corticosteroids although some of the finer details in the design of the study appear to have been overlooked and the choice of endpoints does raise some important issues. The findings in respect of effects on the hypothalamic pituitary adrenocortical axis would appear to suggest that BDP whether formulated with HFA-134a or with CFC propellants has no adverse effect on the HPA axis as measured by morning serum cortisol determination in the population studied. The increase in the mean morning serum cortisol from baseline (end of the run-in) to end of the 6-week treatment period seen in both treatment groups is interesting and somewhat difficult to explain but in the light of there being no overall fall in serum cortisol and no real differences between the two treatments, should not be of concern.
However it should be commented on that a fall in serum cortisol following six weeks treatment with inhaled BDP in a total daily dose of 2000μg would not have been unexpected. The inclusion of endpoint measurements/assessments at the commencement of the 4-week run-in period would have been appropriate and might have provided a clearer picture of HPA axis effects.

The choice of primary safety variable could be questioned and a more robust primary variable would have been the 24-hour (or even the 12-hour overnight) urinary cortisol measurement although it is accepted that these measurements are never easy as urine collections and particularly the 24-hour collections are renowned for being incomplete and therefore ultimately of little use in the assessment of effects on the HPA axis.

Statistical analyses have not been carried out on the urinary cortisol data per se but review of the individual patient data listings in respect of the urinary cortisol measurements show a high degree of variability. This variability is also seen, although less marked in the measurements of urinary creatinine and these variations are reflected in the urinary cortisol/creatinine ratio. It is also noted that 6 patients in the BDP HFA treatment group and 7 patients in the BDP CFC treatment group failed to collect either one or both of the 12-hour overnight collections. Failed collections decreased the sample size and this also increased the variability in the endpoint. The 12-hour collection of urine had been chosen in preference to the 24-hour collection in an attempt to enhance patient compliance and to ensure a more complete collection.

There would appear to be less variability in the individual patient morning serum cortisol data and with the exception of the one patient described above (Point 5.2.1) where a fall in serum cortisol from high normal at baseline to low and outside the lower limit of the normal range at the end of the treatment period, changes seen were mainly within the normal range or from low at baseline to within the normal range in the BDP HFA treatment group. In the BDP CFC treatment group changes were similar although there were three patients in whom the serum cortisol rose from within the normal range to outside the upper limit of normal, in one patient both serum cortisol measurements were below the lower limit of the normal range and one patient demonstrated a fall from well outside the upper limit of the normal range towards the upper limit of the normal range following six weeks of treatment. What is unknown in respect of the serum cortisol measurements is the precise timing. A window is stated for measurements between 08.00 and 10.00 hours at the start and end of the treatment period. However there would appear to be no information presented in respect of whether the samples were taken at the same time on each occasion in individual patients or whether they were taken before or after inhalation of the morning dose of study treatment.
As stated above the bilateral 95% confidence interval for the difference between the least square means in the analysis of covariance model was -0.18 to 0.18 mmol/L and the back transformed 95% CI for the ratio of the means was 0.83 to 1.20. The lower limit of 0.83 is slightly below the pre-specified limit for non-inferiority of 0.85 and the Applicant appears to accept that this finding reflects a slightly greater variability in the data than was accounted for in the power calculation. There is no discussion that this finding might represent a true lack of equivalence. Even if the data are felt to demonstrate equivalence this point should be raised and discussed and not simply dismissed.

The Applicant also presents an investigation of the pharmacokinetics of BDP and the main product of metabolism, the active metabolite B17MP in support of the findings in respect of systemic safety at the top of the dose range. Systemic exposure to B17MP at steady state in this population of patients with moderate to severe asthma was more or less comparable following inhalation of BDP formulated with HFA-134a and BDP formulated with CFCs in respect of the area under the curve, and more particularly so when two outliers were excluded. The differing shapes of the plasma concentration-time profiles for the two formulations of BDP would appear to be due to an earlier absorption and a higher peak following inhalation of BDP HFA than with BDP CFC. The arguments that the earlier and higher peak seen with BDP HFA are likely to be due to the initial absorption rate from the lung rather than any difference in pulmonary deposition are borne out by comparable plasma AUC values between the two formulations. The higher peak is unlikely to result in any difference in pharmacodynamic effect which over the 6-week treatment period would appear to be confirmed by the findings in respect of the morning serum cortisol measurements as described above. The earlier and higher $C_{\text{max}}$ is likely to be the result of the particle size difference with a higher percentage of the fine particle dose below 1.1 mm following inhalation of BDP HFA than BDP CFC and it is not entirely clear what effect, if any, this increase in $C_{\text{max}}$ would have on the HPA axis.

This study provides data in respect of safety at the top of the dose range through assessment of effects on the HPA axis as measured by morning serum cortisol and confirmed through pharmacokinetic parameters. The findings may not be particularly robust but with the methods available in respect of the assessment of effects on the HPA axis, the study presented is an appropriate study to assess systemic safety of these inhaled drugs. The weaknesses of this study both in the design and in the endpoints have been discussed and accepting the difficulty in the collection of 24-hour urine there is little choice other than to base effects on the HPA axis on the changes seen in the measurements of morning serum cortisol. Cortisol stimulation tests could have been considered and may be felt to provide a more meaningful assessment of HPA axis function; however these tests are not necessarily appropriate for large studies such as this. Other ways of assessing the systemic effects of inhaled corticosteroids, looking for effects on bone or growth, etc would generally form part of further development post-authorisation.
The question which remains unanswered is whether this study allows the conclusion to be drawn that there is no increased systemic exposure following the inhalation of BEP when formulated with HFA-134a than when formulated with chlorofluorocarbon propellants. If it is felt that the findings of this study do lead to this conclusion, is this study alone sufficient to permit the grant of Marketing Authorisations for these products when equivalent efficacy to the products to which essential similarity is claimed has not been demonstrated?

Also the study provides data on the use of the Volumatic spacing device. It is required that product literature should recommend the use of a specific spacing device particularly when inhaled corticosteroids are used in total daily doses of 1000µg or greater. Therefore it is appropriate that the product literature should recommend the use of the Volumatic spacing device when such doses are prescribed.

Point 2 may be considered partially resolved.

5.3 POINT 3. The design of further studies to assess the efficacy and safety of these products should be such as to encompass an assessment of the changeover from CFC-containing products to the new non-CFC containing products.

5.3.1 Company Response

The Applicant has combined data from the three pivotal studies and one supportive study, study 002/00 and has looked at those patients who were maintained on their run-in dose of EDP during the treatment periods as either BDP formulated with HFA-134a or formulated CFCS. The analysis carried out has combined the data generated in this sub-population from each of the four studies and treatment comparisons are presented for the effect on morning and evening peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV1) and serum cortisol measurements.

The Applicant’s response to Point 3 of the CSM letter dated 18 July 2001 is attached at Appendix 5-5.
5.3.2 Assessor’s Comment

The Applicant has attempted to argue the need for an assessment of the changeover from CFC-containing products to the new non-CFC containing products by looking at sub-populations within the clinical programme presented. If adequate evidence of efficacy and safety in adults, adolescents and children less than 16 years of age is demonstrated further studies would not be required and the data presented in the original application and in this Appeal Dossier in respect of the changeover will be accepted. However, if adequate evidence of efficacy and safety is not demonstrated the design of any further studies to assess efficacy and safety of these products should be such as to encompass an assessment of the changeover from CFC-containing products to the new non-CFC containing products.

Point 3 may be considered partially resolved and dependant on the acceptable resolution of Points 1 and 2 above.

5.4 POINT 5. A favourable risk/benefit ratio has not been demonstrated.

5.4.1 Company Response

The Applicant has reviewed the study programme as presented in the original submission and includes the new high-dose safety study presented in the Appeal Dossier. The Applicant argues that although some of the data have been criticised, there is a substantial body of evidence from the clinical development programme of BDP HFA to indicate that the efficacy of BDP HFA is not inferior to that of CFC BDP.

The efficacy analyses were performed using two-sided tests in an effort to demonstrate absence of superiority as well as non-inferiority. However this is not a particularly sensitive analysis and any concern relevant to a potential superiority over the CFC must be assessed on the basis of the safety data.

...in asthmatic patients after multiple dosing of BDP of 1000µg bd via a spacer, comparable exposures to BIDMP were seen with the HFA and CFC products and equivalence was essentially demonstrated between treatments in terms of morning serum cortisol.

The Applicant’s response to Point 5 of the CSM letter dated 18 July 2001 is attached at Appendix 5-6.

5.4.2 Assessor’s Comment

Point 5 can only be deemed to have been resolved if the responses to Points 1 and 2, above are felt to provide conclusive evidence of efficacy and safety of BDP formulated with HFA-134a in adults, adolescents and children less than 16 years of age. The issues raised in respect of efficacy are considered unresolved, and in respect of safety, possibly only partially resolved — see Point 5.1 and 5.2 above.

Point 5 may be considered unresolved.
5.5 **POINT 6.** Data should be presented on the use of a spacing device particularly when the drug is administered at the upper end of the proposed dose range, in order that appropriate information on such use can be included in the product literature.

It is required that the product literature should recommend the use of a specific spacing device particularly when inhaled corticosteroids are used in total daily doses of 1000μg or greater. In the absence of appropriate data, a warning should be given in the SPCs to advise against the use of beclometasone dipropionate formulated with propellant HFA-134a in total daily doses in excess of 1000μg.

5.5.1 **Company Response**

The Applicant has presented comparative particle size distribution data for BDP HFA and BDP CFC (Becotide Inhaler/Becloforte Inhaler) delivered without a spacing device and delivered through both the Volumatic and the Babyhaler. The Applicant’s response to Point 6 of the CSM letter dated 18 July 2001 is attached at Appendix 5-7.

5.5.2 **Assessor’s Comment**

The pharmaceutical comment on the particle size distribution data presented is to be found at Point 3.11, above and comments on particle size and fine particle dose as discussed by the Pharmaceutical Assessor will not be re-discussed in any detail.

The fine particle dose in the range from 5.8μm down to 1.1μm is increased by a greater amount when the Volumatic spacer device or the Babyhaler device are used in the delivery of BDP HFA as compared with BDP CFC. There does not appear to be any marked difference clinically when the high-dose of 1000μg bd as either BDP HFA or BDP CFC is inhaled over a 6-week treatment period as in the study presented in response to Point 2 of the CSM letter dated 18 July 2001 and discussed above at Point 5.2. The conclusions reached by the Pharmaceutical Assessor in the response to Point 13.2 of the CSM letter dated 18 July 2001 are endorsed - although the fine particle dose would appear to be increased *in vitro* when the Volumatic is used with BDP HFA as compared with BDP CFC, this does not appear to produce an enhanced systemic effect *in vivo*.

The product literature (SPCs and Patient Information Leaflet) should recommend the use of these spacing devices (Volumatic and Babyhaler) and particularly the Volumatic when beclometasone dipropionate formulated with propellant HFA-134a is inhaled in total daily doses of 1000μg or greater.

Point 6 may be considered partially resolved.
5.6 **POINT 7. A definitive proposal for a Phase IV safety study with the identifiable proprietary product according to SMMG Guidelines and compatible with the CPMP Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products III/537/93 – Final, must be presented and agreed before Marketing Authorisations are granted. The study proposal should be for either an observational cohort study or a blinded trial which has the capability of generating data on the general safety profile of the new product(s). Assessments of the incidence of paradoxical bronchospasm, worsening asthma and cough must be incorporated into the design of the study.**

5.6.1 **Company Response**

The company has supplied a proposed protocol for a prescription event monitoring (PESM) study to assess the safety of the products for which Marketing Authorisations are currently sought, once marketed.

The study aims to determine first time users of these products using product-specific data supplied by the Prescription Pricing Authority. A sample of first time users in each month will be selected such that adverse event data is followed up from the patients' general practitioners. It is aimed to request data on 15,000 patients. This should generate adverse event data on a cohort of 15,000 patients given a GP response rate of 70%. The data requested from GPs will be returned, anonymised, covering details of adverse events in a 3-month reference period prior to starting the new product and the first 3 months of new product exposure. This sample size will detect a risk difference of 2/1000, with 95% significance and power 80%. Additional data will be collected of demographics, current smoking status, indication for treatment, severity of asthma, concurrent respiratory medication, use of short course steroid treatment, use of spacer, immediate events (<1 hour following treatment), reasons for stopping, any deaths and causes of death. It is estimated that a third of the cohort will be aged <16 years. Interim reports are planned.

5.6.2 **Assessor's Comment**

PESM studies are recognised methods for signal generation for unexpected adverse effects on novel products. There are known general strengths and weaknesses in this study methodology and some specific to adverse event detection in this situation.
The analysis can attempt to stratify factors such as severity of asthma but this is a very crude grading system. While smoking and indication will be collected on all subjects, detailed risk factors will only be collected on follow-up cases. Patients at increased risk of adverse events may be preferentially prescribed the new product because of non-response or intolerance to prior treatment. This can serve to heighten the signal ratio but further testing of specific hypotheses using other studies would be needed. While seasonal factors may influence asthma morbidity, the study data will be collected over protracted and varied time periods and such effect of seasonality should not confound results. The company acknowledges that this study design is not an ideal method to study paradoxical bronchospasm; however, the collection of data on the immediate event is a crude attempt to measure this but is acceptable if this is no longer a major concern.

It must be noted that the reference period in this study is a period prior to new treatment: this will be an unknown mixture of different treatments or no treatment as it is not proposed to collect data on prior treatment. The final protocol should comment on this issue. While not stipulated in the study protocol, it is possible that comparison with other CFC or HFA cohorts may be conducted. These should be made explicit if intended. A response rate of 70% may be optimistic.

The PEM study is pragmatic way of collecting information on a large cohort of patients quickly in real life, on a rational scale without dependence on suspecting causality for ADRs. The unit has previous experience in conducting these studies including those on previous evohalers.

The final protocol should clarify details on causality assessment, reporting of serious adverse drug reactions and provision of interim reports to the MCA.

Conclusion

This design in prospective surveillance is acceptable (with modification as stated) as the primary concern is signal generation rather than specific hypothesis testing.

The following issues with regard to the protocol should be addressed:

- The final protocol should make comment on how the three-month reference period prior to the new treatment period will be handled, as this will be an unknown mixture of different treatments or no treatment and in the current draft protocol there are no proposals to collect data on prior treatment.

- While not stipulated in the study protocol, it is possible that comparison with other CFC or HFA cohorts may be conducted. These should be made explicit if intended.

- The final protocol should clarify details in causality assessment, reporting of serious adverse drug reactions and provision of interim reports to the MCA.

- The final protocol must be presented and agreed before Marketing Authorisations are granted.

Point 7 may be considered partially resolved.
ANNEX 2: ASSESSMENT OF THE APPLICANT’S RESPONSES BY CSM IN 2004

5.1 POINTS 1 AND 2

1. There is inadequate evidence of efficacy and safety in adults, adolescents and children less than 16 years of age as therapeutic equivalence to the product to which essential similarity is claimed has not been demonstrated.

2. In the light of concerns regarding greater systemic exposure when beclometasone dipropionate is formulated with HFA-134a further information on the comparison with the product to which essential similarity is claimed in respect of safety is required and it is proposed that a further study should be carried out. This study should recruit normal volunteers who would inhale a total daily dose of beclometasone dipropionate of 2000µg over a treatment period of 4-6 weeks. Systemic effects would be assessed through effects on the hypothalamic pituitary adrenocortical axis using the short Synacthen test as a measure of HPA axis function.

If the findings of a further safety study provide reassurance in respect of safety this would enable the grant of Marketing Authorisations despite the lack of adequate demonstration of equivalent efficacy to the product to which essential similarity is claimed.

If the proposed further study does not provide adequate reassurance in respect of safety an appropriate dose-defining programme of clinical studies will be required.

5.1.1 Company Response

The Applicants have submitted the following study in response to Points 1 and 2, above:

Protocol Number: SGS Biopharma B103543

Open, randomised, parallel group, evaluation of the HPA function using ACTH 250µg short stimulation test (Synacthen™) in healthy volunteers treated for 4 (four) consecutive weeks with CFC-BDP or HFA-BDP at 1000µg bd (daily dose 2000µg).

A tabular summary of this study is presented in Appendix 5-5 and the study is described and discussed in Appendices 5-1 and 5-2.

The study report includes the following statement:

This study was performed in compliance with the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and with the OECD Good Laboratory Practices (GLP) including the archiving of essential documents.
This study was designed to evaluate the systemic effects of treatment over a four week period with inhaled beclometasone dipropionate (BDP) formulated in an excipient mix including the hydrofluoroalkane propellant HFA-134a, a non-chlorofluorocarbon propellant (BDP HFA) with beclometasone dipropionate as originally formulated in an excipient mix including propellants 11/12 (BDP CFC). The comparator or reference product, BDP CFC is the brand leader product in the UK: Becloforte Inhaler. Systemic effects were assessed by measuring effects on the hypothalamic pituitary adrenocortical (HPA) axis using the adrenocorticotropic hormone (ACTH) short stimulation test (SST). The aim of the study was to compare the response to ACTH in healthy volunteers following treatment with either BDP HFA or BDP CFC each administered at the maximum recommended total daily dose of 2000μg (1000μg twice daily) when prescribed to adult patients with asthma. As the primary objective of the study was to compare the response to ACTH in healthy volunteers in the two treatment groups and not to define a normal clinical response, the peak or maximum serum cortisol concentration after ACTH 250μg (Synacthen) stimulation (Cmax) was taken as the primary variable with the early morning (09:00) serum cortisol concentration pre-ACTH stimulation and the increase in serum cortisol post-ACTH stimulation as secondary variables.

The study was carried out in normal volunteers as the administration of Synacthen (tetracosactrin acetate) is contraindicated in patients with asthma, and as the response to the SST appears to be gender dependent (The short Synacthen test: is less best? Stewart FM, Clark P, Clinical Endocrinology 1999; 50:151-152) only male volunteers were recruited in order to reduce the inter-subject variability. Subjects were treated with a total daily dose of 2000μg over a treatment period of four consecutive weeks; a four-week treatment period was deemed long enough to evaluate systemic effects of corticosteroids (Systemic effect comparisons of six inhaled corticosteroid preparations. Martin R J et al, American Journal of Respiratory Critical Care Medicine 2002; 165:1377-1383). It was also felt to be unethical to treat normal volunteers with such a high dose of inhaled BDP for longer than four weeks. All subject volunteers inhaled the study treatments through a spacing device (the Volumatic) in order that the drugs were used in accordance with advice given in the proposed Summary of Product Characteristics.

The ACTH short stimulation test used to assess adrenal reserve was carried out prior to the four-week treatment period and then again on Day 29 immediately post the four-week treatment period. On each occasion cortisol concentrations in serum were measured prior to the intravenous administration of Synacthen and then at 30 and 60 minutes post-administration. Male subjects recruited were aged between 19 and 56 years (mean ± SD = 38.6 ± 11.1 years), an age range when adrenal cortical size and function are stable, and each was required to demonstrate a normal response to the ACTH short stimulation test defined as:

- a normal basal cortisol of >140nmol/L and a normal response to ACTH stimulation, the latter defined as a peak serum cortisol post-ACTH >550nmol/L and an increase in serum cortisol post-ACTH of >200nmol/L.
[Whether the peak serum cortisol post-ACTH and/or the increase in serum cortisol from baseline post-ACTH should be used to define the normal response, together with differing threshold values for normality depending on analytical methods used for cortisol assay, have been the subjects of much debate. (A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Stewart W et al, The Lancet 1988, May 28 – Role of biochemical assessment in management of corticosteroid withdrawal. Walsh J et al, Annals of Clinical Biochemistry 2000; 37:279-288)]

The assignment of volunteers to treatment groups was according to the peak/maximum serum cortisol concentration ($C_{\text{max}}$) during screening and this ensured two equal treatment groups with $C_{\text{max}}$ between 660 and 1400 nmol/L.

All volunteers were appropriately trained in inhaler technique and compliance was checked regularly. Compliance was measured by recording administration of inhaled BDP/study treatments in the diary card, confirmatory telephone calls, through the measurement of plasma concentrations of beclometasone 17 monopropionate (B17MP) in plasma samples taken in the morning on Days 1, 8, 15, 22 and 28 of the four-week treatment period and by weighing inhalers.

The sample size was determined following a literature review. The inter-subject coefficient of variation of the peak cortisol response following ACTH is 27.3% and assuming this coefficient of variation 32 subjects per treatment group were required to demonstrate with 90% power that the lower limit of the 95% confidence interval, the lower limit of non-inferiority, for the ratio of cortisol $C_{\text{max}}$ following the ACTH SST for BDP-HFA compared with BDP-CFC was >0.80. A lower limit of non-inferiority of 0.80 was justified in order to define non-inferiority of the test treatment based on the following:

- In accordance with the criteria defining a normal response to the ACTH SST a normal response was accepted if a peak serum cortisol response of at least 550 nmol/L (criterion 1) or an increase in serum cortisol of at least 200 nmol/L (criterion 2) was demonstrated. Therefore for a subject with a baseline serum cortisol of 200 nmol/L, according to criterion 2 the peak serum cortisol considered to represent a normal response would be around 400 nmol/L, whilst in accordance with criterion 1 the peak serum cortisol considered a normal response would be >550 nmol/L. Accepting the criteria for a normal response a difference of up to 27% in maximum cortisol concentrations would then be acceptable in the definition of a normal response. Furthermore the peak serum cortisol may range from 400-700 nmol/L (Short Synacthen Tests – the need for rationalisation. Wood P J, Clinical Endocrinology 1998; 49:283) and therefore a mean cortisol response of 550 nmol/L ± 27% may be considered as a normal response.

- The accuracy and precision of the analytical method is 15% over the entire range and 20% at the lower limit of quantification (10 ng/ml, ie 27.6 nmol/L).

- The 0.80 lower limit is the standard accepted in a bioequivalence study and may be applicable in the study presented.
Seventy-two subjects were randomised to treatments (36 in each treatment group) and all were included in the safety analysis. Three subjects failed to complete the study, one in the BDP HFA treatment group (poor compliance) and two in the BDP CFC treatment group (adverse events). Further to these three subjects a fourth was excluded from the per protocol population, considered a major protocol violator. Therefore the per protocol population (the population used for the primary statistical analysis) included 68 subjects, of whom 35 received BDP HFA and 33 BDP CFC.

The findings were as follows:

No analysis was carried out on the values recorded at screening; these data were collected for determination of eligibility for study entry and for allocation to treatment groups.

The serum cortisol concentrations and parameters derived following an ACTH SST carried out after four weeks of treatment with either BDP HFA or BDP CFC and the statistical comparison between the two study treatments are summarised in the table below:

<table>
<thead>
<tr>
<th>Serum cortisol Parameter</th>
<th>BDP HFA (n=35)</th>
<th>BDP CFC (n=33)</th>
<th>CV (%)</th>
<th>p</th>
<th>PE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀ (nmol/L)</td>
<td>303±166</td>
<td>477±147</td>
<td>25.1</td>
<td>0.24</td>
<td>106.2</td>
<td>93.4 - 119.0</td>
</tr>
<tr>
<td>C₃₀ (nmol/L)</td>
<td>897±142</td>
<td>783±150</td>
<td>17.2</td>
<td>0.37</td>
<td>109.9</td>
<td>95.2 - 112.5</td>
</tr>
<tr>
<td>C₉₀ (nmol/L)</td>
<td>874±127</td>
<td>854±135</td>
<td>13.9</td>
<td>0.48</td>
<td>102.5</td>
<td>95.6 - 109.3</td>
</tr>
<tr>
<td>C₃₉₀ (nmol/L)</td>
<td>890±123</td>
<td>867±142</td>
<td>14.4</td>
<td>0.43</td>
<td>102.8</td>
<td>95.7 - 109.9</td>
</tr>
<tr>
<td>Δₙ₉₀ (nmol/L)</td>
<td>387±124</td>
<td>390±175</td>
<td>41.1</td>
<td>0.90</td>
<td>98.8</td>
<td>79.1 - 118.5</td>
</tr>
</tbody>
</table>

Values are arithmetic mean ± SD; CV: Residual (inter-subject) coefficient of variation, derived from the Analysis of Variance (ANOVA); p: probability of no difference between the two treatments (ANOVA); Point estimate (PE) and 95% confidence interval (95% CI) for the HFA/CFC ratio were derived from the ANOVA.

The figure below illustrates the serum cortisol concentrations at baseline and at 30 and 60 minutes post-ACTH SST, C₉₀ and change from baseline (Δ₉₀₀).
Figure 11.4.1: Individual and average serum cortisol concentrations and parameters following a short stimulation test (Sprinten™) performed after four weeks of treatments with CFC-BDP or HFA-BDP (1000 μg twice daily)

Small symbols are individual data, large symbols are arithmetic means;
Error bars are SD (downwards: CFC-BDP, upwards: HFA-BDP);
Dashed lines indicate the lower limit for a normal cortisol response.

After four weeks of treatment serum cortisol levels were within the normal range (baseline >140nmol/L, peak post-ACTH >550nmol/L and maximum increase from baseline post-ACTH >200nmol/L) in 33/35 subjects (94%) following BDP HFA and in 29/33 subjects (88%) following BDP CFC. In the BDP HFA treatment group one subject recorded a cortisol Cmax of 538nmol/L and a maximum increase in cortisol from baseline of 109nmol/L and one subject showed a maximum increase in cortisol from baseline of 171nmol/L; in the BDP CFC treatment group one subject had a baseline cortisol of only 112nmol/L and three subjects had maximum increases in serum cortisol from baseline of only 185, 44 and 19nmol/L.

This study shows that the peak serum cortisol concentration following the ACTH 250μg SST was not lower after four weeks of treatment with BDP HFA compared with four weeks of treatment with BDP CFC in healthy volunteers, with a lower limit of the 95% confidence intervals for the ratio of BDP HFA to BDP CFC above the predefined non-inferiority level of 0.80 (95% CI for Cmax 95.7-109.9). The baseline morning serum cortisol levels were not statistically significantly different in the two treatment groups and the mean was not lower in the BDP HFA treatment group than in the BDP CFC treatment group. The maximum increases over baseline seen in the two treatment groups were not statistically significantly different.
In the evaluation of safety the overall incidence of treatment-emergent adverse events was higher in the BDP CFC treatment group (61%) than in the BDP HFA treatment group (47%) and two subjects in the BDP CFC treatment group were withdrawn from the study (one with a serious and severe event (tuberculosis) deemed to be not related to study medication and one with a moderate adverse event (gingivitis) deemed to be possibly related to study medication). The most frequently reported treatment-emergent adverse events were headache (12 reports, six in each treatment group) and pharyngolaryngeal pain (nine reports, three in the BDP HFA treatment group and six in the BDP CFC treatment group). Other treatment-emergent adverse events were experienced at most by three subjects.

Four adverse events were deemed to be probably/likely related to the study drug, two following BDP HFA (throat pain and sore throat in one subject) and two following BDP CFC (throat irritation and hoarseness). Generally the severity of adverse events reported appeared to be more mild in the treatment group receiving BDP HFA; only one event reported was described as severe in a patient receiving BDP CFC (patient withdrawn – tuberculosis).

In the measurement of laboratory parameters there were some isolated abnormal values, some of which were repeated but none of which were considered by the investigator to be clinically significant. It was noted that hepatic enzymes particularly AST and ALT showed an overall decrease with a markedly higher proportion of values below the lower limit of the normal range on discharge and a high proportion of subjects at screening (65%) which had increased on discharge (93%) presented with red blood cells in the urine. The incidence of these findings in respect of hepatic enzymes and haematuria was similar in both treatment groups.

The proportion of subjects with abnormal electrocardiograms was slightly higher at discharge, 39% compared with 31% at screening and these were seen more frequently in the BDP HFA treatment group than in the BDP CFC treatment group, 44% compared with 25%. However all isolated abnormalities observed during the clinical examination (including physical examination, vital signs and ECGs) were deemed by the investigator as minor and without clinical significance.

5.1.2 Pharmaceutical Assessor’s Comment

250 microgram/actuation – Study SGS B103543

The mean delivered dose and mean fine particle dose for the HFA and CFC-containing batches used in study SGS B103543 when measured with and without the spacing device (Volumatic) are shown in the table below:
Mean delivered and fine particle doses for batches used in Study SGS B103543 determined with and without a Volumatic spacing device

<table>
<thead>
<tr>
<th></th>
<th>without spacer</th>
<th>with spacer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DD</td>
<td>FPD</td>
</tr>
<tr>
<td>HFA 250 (D22505)</td>
<td>214.50</td>
<td>49.23</td>
</tr>
<tr>
<td>CFC 250 (D038031A)</td>
<td>199.38</td>
<td>39.50</td>
</tr>
</tbody>
</table>

DD = mean delivered dose
FPD = mean fine particle dose (particles ≤4.7μm)

As expected the use of the spacing device lowers the delivered dose for both the HFA and CFC-containing products. From these data the HFA-containing product had a greater reduction to the delivered dose (2.5 times) compared with the CFC-containing product (1.8 times). Further, consistent with previous in vitro studies (see response to Point 13.2 of the CSM letter dated 18 July 2001 - Appendix 1) this spacing device increases the fine particle dose, in these cases the percentage enhancement being greater for the HFA-containing product (~25%) compared with the CFC-containing product (~10%). The percentage increases to the fine particle dose on using a spacer however were not as large as seen for previous batches tested in vitro, where mean fine particle doses for the 250μg batches of HFA and CFC-containing products showed 34-57% and 41-50% increases, respectively (data provided in the first response to the CSM letter dated 18 July 2001). This resulted in fine particle doses of up to 98μg. Notably the CFC-containing product used in this clinical study would not satisfy the proposed mean fine particle dose lower limit (46μg) for this inhaler strength of the HFA-containing product both with and without the spacer attached, whilst the HFA-containing product was at the lower end of the specification. This is unfortunate in view of the previous in vitro data from other batches as clearly neither the HFA or CFC-containing products used for this clinical study were at the extreme of their specification. These data would however suggest that for this study the 250μg strength HFA-containing inhaler potentially delivered a higher drug load to the lungs compared with the representative CFC-containing product, particularly with the Volumatic incorporated. However the delivered dose data with the spacer indicates that there could potentially be less deposition in throat from the HFA-containing device compared with the CFC-containing device. Overall the data support the use of this spacer for reducing the amount of drug in the particle size range that would be likely to impact in a patient’s mouth (and be potentially swallowed and absorbed) whether the CFC-containing formulation or HFA-containing formulation was administered.
5.1.3 Statistical Assessor’s Comment

The design and analysis of study SGS Biopharma B103543 is thoroughly described in Section 5.1.1. The pharmaceutical and clinical assessors’ comments on this study given in Sections 5.1.2 and 5.1.4 respectively are fully supported. This study compared the peak cortisol response following ACTH in healthy volunteers taking BDP HFA or BDP CFC. Non-inferiority was deemed to have been established if the lower limits of the 95% confidence interval for the ratio of cortisol Cmax following the ACTH SST for BDP HFA compared with BDP CFC was > 0.8. The Applicant justifies this choice by stating that if a typical normal peak cortisol was observed a difference of up to 27% would be contained in the normal range. This is a convincing argument for choosing a non-inferiority margin of 0.8. The other two arguments for choosing this margin are less convincing; although 0.8 is the standard lower limit in bioequivalence studies this is not a standard bioequivalence study and the accuracy and precision of the method should not be used to justify the margin (see Section 5.1.1).

The 95% confidence interval for the ratio of Cmax was 0.96-1.1. Therefore this study provides convincing evidence that BDP HFA is not less safe than the BDP CFC formulation. Further reassurance is provided by the fact that 94% (33/35 subjects) of patients on BDP HFA had serum cortisols within the normal range compared with 88% (29/33) on BDP CFC. It should be noted that this study does not show that the two formulations have a 1:1 potency ratio. It remains possible that the potency ratio is not 1:1 but that any difference in potency does not impact on the systemic safety at the top dose when given to healthy volunteers. It is therefore considered unlikely that any difference in potency will have any detrimental effect on systemic safety when BDP HFA is given to patients in a dose at the top of the dose range.

5.1.4 Clinical Assessor’s Comment

The study presented and discussed above is the study which was felt to provide the most appropriate way forward following the discussion of the major outstanding issues on these applications at the Clarification Meeting held in November 2002. At the Clarification Meeting it was proposed that the Applicants should conduct a further study (appropriately powered and sized) in normal volunteers in which beclometasone dipropionate formulated with HFA-134a would be compared with beclometasone dipropionate formulated with CFC propellants in a total daily dose of 2000μg (ie 1000μg bd, this dose being the upper limit of the currently authorised dose range for inhaled beclometasone dipropionate when used in the management of asthma in adults) over a treatment period of 4-6 weeks. The short Synacthen test, a test which is well published and clearly validated, would be performed at baseline and at the end of treatment. It was stressed that the Applicants would have to seek advice through the literature and through experts in the field to justify the study size and to ensure that the study would be adequately powered to assess safety.
The study described above was required to confirm the lack of systemic effects (or no enhancement of systemic effects). It was agreed that the study should recruit normal volunteers and not asthmatic patients as the recruitment of the latter would only serve to confuse in that patients entering the study would be receiving high dose inhaled corticosteroids which would make any effects of the HPA axis due to study treatments difficult to interpret.

The study presented is appropriately designed, analysed and demonstrates no difference between the two formulations of beclometasone dipropionate, one formulated with propellant HFA-134a and the other with CFC propellants, following four weeks of treatment at a total daily dose of 2000μg (1000μg bd), in respect of adrenal reserve as measured by the response of the adrenal cortex to ACTH stimulation. Following four weeks of treatment the baseline serum cortisol concentration was not lower in the BDP HFA treatment group compared with the BDP CFC treatment group, there was no statistically significant difference between treatments in the increase seen in serum cortisol following ACTH stimulation of the adrenal cortex and the peak serum cortisol concentration (C\text{max}) following ACTH stimulation, the primary variable in this study was not lower following four weeks of treatment with BDP HFA when compared with the peak serum cortisol concentration following four weeks of treatment with BDP CFC.

The findings from this study would suggest that beclometasone dipropionate formulated with HFA-134a has no greater systemic effect as measured through the assessment of the response of the adrenal cortex to ACTH stimulation than beclometasone dipropionate formulated with CFC propellants when administered via a Volumatic spacing device in a total daily dose of 2000μg, the upper limit of the currently authorised dose range for inhaled beclometasone dipropionate when used in the management of asthma in adults in adults.

In conclusion this study demonstrates that there is no difference in the systemic exposure to beclometasone dipropionate when formulated in an excipient mix including propellant HFA-134a or when formulated with CFC propellants. At the Clarification Meeting it was felt that if the findings of a further safety study provided reassurance in respect of safety when this inhaled glucocorticosteroid, formulated with HFA-134a is administered in a dose at the upper limit of the currently authorised dose range, such a study would enable the grant of Marketing Authorisations despite the lack of adequate demonstration of equivalent efficacy to the product to which essential similarity is claimed.

Therefore Point 1 in respect of efficacy and safety in adults and adolescents and Point 2 may be considered resolved.

5.2 POINTS 1 AND 3

1. There is inadequate evidence of efficacy and safety in adults, adolescents and children less than 16 years of age as therapeutic equivalence to the product to which essential similarity is claimed has not been demonstrated.
3. **Further clinical safety data are required in children and in the light of accepted difficulties in the assessment of the HPA axis in this age group it is proposed that systemic effects should be assessed primarily through short-term measures of bone growth rate through knemometry. It is also proposed that the systemic effects seen in children should be assessed through measurement of the urinary cortisol/creatinine ratio. This further assessment of systemic effects in children should be carried out both with and without the Volumatic Spacing Device.**

Reassurance in respect of systemic safety in children would provide reassurance in respect of efficacy. However if the safety study suggests a difference between the two formulations dose-defining studies will be required.

5.2.1 **Company Response**

The Applicants have submitted the following studies in response to Points 1 and 3, above:

**Study Code: DM/PR/3303/004/03**

*A single centre double blind, double dummy, randomised 3x3 way crossover study to compare safety assessed by knemometry and urinary cortisol measurements of beclometasone dipropionate HFA (metered dose inhaler) 100µg bd and beclometasone dipropionate CFC MDI (metered dose inhaler) 100µg bd and 200µg bd in children with mild asthma during a 2-week treatment period.*

and

**Study Code: DM/PR/3303/005/03**

*A single centre double blind, double dummy, randomised 3x3 way crossover study to compare safety assessed by knemometry and urinary cortisol measurements of beclometasone dipropionate HFA MDI 100µg bd using Volumatic Spacer Device and beclometasone dipropionate CFC MDI 100µg bd and 200µg bd using Volumatic Spacer Device in children with mild asthma during a 2-week treatment period.*

Tabular summaries of these studies are presented in Appendix 5-6 and the studies are described and discussed in Appendices 5-3 and 5-4.

The study reports include the following statement:

*This study conformed to the standards of conduct of clinical studies as set forth in the Declaration of Helsinki and the legal regulations in Denmark. International Conference on Harmonisation for Good Clinical Practice (ICH/GCP) Guidelines for clinical studies were followed.*
These studies were designed to evaluate the systemic effects of regular treatment over time with inhaled beclometasone dipropionate formulated with the hydrofluoroalkane propellant HFA-134a (BDP HFA) with beclometasone dipropionate as originally formulated with CFC propellants (BDP CFC). The comparator or reference product BDP CFC is the brand leader product in the UK, Becotide Inhaler administered in two strengths, 50μg and 100μg. The two studies are essentially identical, the only difference being the use of the Volumatic spacing device in the second study (Study Code: DM/PR/3303/005/03) for administration of study treatments.

The primary objective in both studies was to demonstrate that BDP HFA in a dose of 100μg twice daily is non-inferior to BDP CFC administered in a dose of 100μg twice daily in respect of systemic safety as assessed through short-term measures of bone growth rate through knemometry. Knemometry which measures accurately the height from the bottom of the heel to the top of the knee when the lower limb is flexed at the knee joint to 90°, will pick up immediate effects in lower leg growth rate (LLGR), trends in growth rate and normalisation of growth rate. Knemometry is a reproducible method of assessing systemic activity of inhaled glucocorticosteroids and studies with two or three active treatment periods and wash-out periods in between treatments have shown consistent results. Studies looking at individual growth patterns as well as group based mean growth rates have documented that reduced growth rates caused by inhaled corticosteroids normalise within 3-7 days and that wash-out periods of one week therefore can be used in clinical studies. The Clinical Expert Statement in Appendix 5-3 includes a number of references (references 1-8, Page 21 of the Statement) which describe the use of knemometry in clinical studies.

The primary variable in both of the above studies was the LLGR during the 2-week treatment period.

Secondary objectives in respect of safety were as follows:

- To compare rate of change in lower leg length, measured by knemometry, over a 2-week treatment period - BDP HFA 100μg twice daily (bd) versus BDP CFC 200μg bd.
- To compare lower leg growth rate over a 2-week treatment period - BDP HFA 100μg bd versus the placebo run-in period.
- To compare LLGR over a 2-week treatment period - BDP CFC in doses of 100μg bd and 200μg bd versus the placebo run-in period.
- To compare LLGR over a 2-week treatment period - BDP CFC 100μg bd versus BDP CFC 200μg bd.
- To compare 24-hour total cortisol metabolite (TCM) excretion, corrected for creatinine after 2 weeks of treatment - BDP HFA 100μg bd versus BDP CFC at doses of 100μg bd and 200μg bd.
- To compare 24-hour urinary free cortisol (UFC) excretion, corrected for creatinine after 2 weeks of treatment - BDP HFA 100μg bd versus BDP CFC at doses of 100μg bd and 200μg bd.
- To evaluate the treatments with respect to the incidence of adverse events.
Secondary objectives in respect of efficacy included:

- The comparison of peak expiratory flow rate (PEFR) as recorded in diary cards across the treatment groups.
- Comparison of asthma symptom scores as recorded in diary cards across the treatment groups.
- Comparison of the use of rescue medication as recorded in diary cards across the treatment groups.

In addition to the objectives defined in the study protocols, safety was also evaluated by comparing the excretion of androgen steroids and cortisol metabolites after 2 weeks of treatment with BDP HFA 100µg bd or BDP CFC administered in dose regimens of 100µg bd and 200µg bd.

The studies were carried out on pre-pubertal boys and girls aged between 6 and 14 years with a clinical diagnosis of mild asthma and with a PEFR and forced expiratory volume in one second (FEV₁) >85% of predicted values measured at the screening visit and prior to the run-in period. Treatment prior to study entry comprised inhaled beta₂ agonists as required and/or inhaled budesonide (as a dry powder) in a dose of up to 400µg daily or equivalent other inhaled corticosteroid therapy. Children with known endocrinological diseases including growth impairment or other chronic diseases and any disease requiring additional treatment with topical or systemic glucocorticosteroids were excluded from the study.

The study was a 3x3 way crossover study including a 2-week single blind placebo run-in period followed by three 2-week randomised double blind treatment periods each separated from the next by a 2-week wash-out placebo period. A treatment period of 2 weeks was chosen following review of the literature where it has been shown that treatment with inhaled glucocorticosteroids over a two-week treatment period provides reliable measurements on which conclusions can be drawn in respect of the influence of these drugs on the LLGR in children (Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. Lipworth BJ, Seckl JR, Thorax 1997; 50:476).

The crossover design was chosen for this study, rather than a parallel group design, as the inter-variability in LLGR in children is considered to be markedly higher than the intra-variability of LLGR and hence the comparison of growth rate after two different treatments in the same patient will be less affected by fluctuations unrelated to therapy than the comparison of two different patients receiving two different treatments.

Compliance was assessed through study centre records, by recording administration of inhaled BDP/study treatments in patient diary cards and by weight differences in the canisters calculated from start and end weights in the active treatment periods.

The sample size calculations were based on previously published studies. If a standard deviation of 0.20mm/week was assumed 21 patients were required to demonstrate with 90% power that the lower end of the one-sided 97.5% confidence interval for the difference in lower leg growth following inhalation of BDP HFA 100µg bd relative to inhalation of BDP CFC 100µg bd was above -0.20mm/wk.
In the first of the two studies described above, Study Code: ...004/03, the study carried out without the use of a spacing device 25 children were screened and 24 randomised to treatments. One child withdrew during the initial placebo run-in period and three further children withdrew during the first treatment period (2 receiving BDP HFA 100μg bd and one receiving BDP CFC 200μg bd). The intention-to-treat (ITT) population included the 24 children randomised to study treatments and of these 22 completed the BDP HFA 100μg bd treatment period, 20 completed the BDP CFC 100μg bd treatment period and 21 completed the BDP CFC 200μg bd treatment period. Twenty children met the inclusion and exclusion criteria fully and without protocol violations and therefore these 20 children made up the per protocol (PP) population receiving all three treatments.

In the second study described above, Study Code: ...005/03, the study in which all children used the Volumatic spacing device, a total of 30 children were screened for entry and all 30 were randomised to study treatments. Two children withdrew during the placebo run-in period one child withdrew during the first treatment period and one during the first wash-out period. Both of the withdrawals following the commencement of the first treatment period were children receiving or having received BDP CFC 200μg bd. The ITT population consisted of all 30 children randomised to study treatments. Of these 26 children completed the BDP HFA 100μg bd treatment period, 26 completed the BDP CFC 100μg bd treatment period and 28 completed the BDP CFC 200μg bd treatment period. Twenty-six children met the inclusion and exclusion criteria fully and without protocol violations and therefore these 26 children comprised the PP population, receiving all three treatments.

Three data sets were defined:

- All children enrolled into the study
- The intention-to-treat (ITT) analysis set – consisting of data from all children enrolled into the study, who were randomised to study treatment and who were exposed to at least one dose of study treatment in the first treatment period.
- The per protocol (PP) analysis set – defined as data from all subjects from the ITT analysis set who completed the study, who fulfilled the inclusion and exclusion criteria and who did not violate the protocol in a manner which would affect the efficacy assessments. The analysis of the primary safety endpoint was carried out on both the ITT and PP analysis sets and only if both analyses supported non-inferiority was the result considered to be positive. Unless the two analysis sets differed substantially in size all analyses of secondary endpoints were performed on the ITT analysis set only (unless specified).

The findings were as follows:
Study Code: ...004/03 – study carried out without the Volumatic spacing device

In the assessment of the primary endpoint (safety), LLGR measured by knemometry after a two-week treatment period, the mean difference between the treatments BDP HFA 100μg bd and BDP CFC 100μg bd was -0.02mm/week with a one-sided confidence interval of [-0.24; in the analysis of the ITT population and a mean difference between the treatments of -0.00mm/week with a one-sided confidence interval of [-0.22; for the PP population. The lower end of the confidence interval was slightly below the predefined limit of -0.20mm/week for both analysis sets.

Comparison of LLGR between BDP HFA 100μg bd and BDP CFC 100μg bd, ITT Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA 100</th>
<th>BDP CFC 100</th>
<th>HFA 100 – CFC 100</th>
<th>97.5% one-sided Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate (mm/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value</td>
<td>0.09</td>
<td>0.11</td>
<td>-0.02</td>
<td>[-0.24;</td>
</tr>
<tr>
<td>Only subjects having both treatments are included in the model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of LLGR between BDP HFA 100μg bd and BDP CFC 100μg bd, PP Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA 100</th>
<th>BDP CFC 100</th>
<th>HFA 100 – CFC 100</th>
<th>97.5% one-sided Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate (mm/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean value</td>
<td>0.11</td>
<td>0.11</td>
<td>0.00</td>
<td>[-0.22;</td>
</tr>
<tr>
<td>Only subjects having both treatments are included in the model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The summary of knemometry measurements per treatment is shown in the table below for the ITT population:

Summary of LLGR: ITT Analysis Set

<table>
<thead>
<tr>
<th>Run-in**</th>
<th>BDP HFA 100 N (%)</th>
<th>Wash-out following BDP HFA 100 N (%)</th>
<th>BDP CFC 100 N (%)</th>
<th>Wash-out following BDP CFC 100 N (%)</th>
<th>BDP CFC 200 N (%)</th>
<th>Wash-out following BDP CFC 200 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>RUN-IN**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>24 (100%)</td>
<td>22 (100%)</td>
<td>21 (100%)</td>
<td>20 (100%)</td>
<td>21 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Growth Rate (mm/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.63 (0.23)</td>
<td>0.65 (0.29)</td>
<td>0.37 (0.25)</td>
<td>0.10 (0.45)</td>
<td>0.44 (0.15)</td>
<td>0.08 (0.27)</td>
</tr>
<tr>
<td>Median</td>
<td>0.40</td>
<td>0.04</td>
<td>0.52</td>
<td>0.01</td>
<td>0.45</td>
<td>0.63</td>
</tr>
<tr>
<td>5th-95th Percentile</td>
<td>0.07-0.78</td>
<td>-3.4-0.76</td>
<td>-0.3-0.92</td>
<td>-0.83-0.77</td>
<td>0.13-0.73</td>
<td>-38.0-5.29</td>
</tr>
<tr>
<td>Min - Max</td>
<td>0.05-0.86</td>
<td>-3.4-0.72</td>
<td>-0.3-0.92</td>
<td>-1.0-0.92</td>
<td>0.13-0.73</td>
<td>-49.0-6.62</td>
</tr>
</tbody>
</table>

**The column Run-in represents the baseline growth rate.
There was no measurement of growth rate after the third active treatment period. Therefore the number of subjects in the wash-out periods are not the same as in the active treatment periods.

With the exception of the mean growth rates in the BDP HFA 100μg bd and the placebo treatment following BDP HFA 100μg bd where the mean (SD) growth rates were 0.11 (0.29) and 0.34 (0.23), respectively, the mean growth rates in the PP population were identical across the remaining study periods, in the two treatment periods with BDP CFC 100μg bd and BDP CFC 200μg bd and in the two wash-out periods following these two active treatment periods. There was no influence on the sequence in which treatment was given, no effect on period and no overall difference across active treatments.
### Pairwise comparison of LLGR between active treatments and run-in placebo – a secondary endpoint

<table>
<thead>
<tr>
<th>Mean value BDP HFA 100 and placebo</th>
<th>Active</th>
<th>Placebo</th>
<th>Active-Placebo Difference</th>
<th>95% two-sided Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.09</td>
<td>0.43</td>
<td>-0.34</td>
<td></td>
<td>(-0.53; -0.15)</td>
</tr>
<tr>
<td>Mean value BDP CFC 100 and placebo</td>
<td>0.10</td>
<td>0.42</td>
<td>-0.33</td>
<td>(-0.52; -0.13)</td>
</tr>
<tr>
<td>Mean value BDP CFC 200 and placebo</td>
<td>0.08</td>
<td>0.43</td>
<td>-0.35</td>
<td>(-0.54; -0.16)</td>
</tr>
</tbody>
</table>

*Placebo represents the run-in placebo period.*

Individual growth rates for all active and placebo treatments together with individual and mean LLGRs per treatment group are presented graphically in Appendix 5-7. The pairwise comparisons of LLGR between active treatments and run-in placebo and the mean growth rate following each active treatment period, each wash-out period and the run-in as presented in the two preceding tables and together with the graphical presentations of individual growth rates would indicate that there are no obvious differences between treatments in growth rate but that there is a tendency towards a higher growth rate following placebo treatments when compared with growth rates following active treatments. Growth rates were similar during each of the three active treatment periods and were similar during the run-in and wash-out periods and during these latter periods the LLGRs were higher than during the active treatment periods.

No differences were seen in LLGR between treatments in the comparisons of BDP HFA 100μg bd with BDP CFC 200μg bd and BDP CFC 100μg bd with BDP CFC 200μg bd, with 95% 2-sided confidence intervals -0.20; 0.23 and -0.19; 0.25, respectively.

In the comparisons across treatments in respect of 24 hour total cortisol metabolite (TCM) excretion and 24 hour urinary free cortisol (UFC), each corrected for creatinine no differences were seen between treatment groups when comparing treatments two by two, ie BDP HFA 100μg bd compared with BDP CFC 100μg bd, BDP HFA 100μg bd compared with BDP CFC 200μg bd and BDP CFC 100μg bd compared with BDP CFC 200μg bd. The pairwise comparisons of TCM/creatinine and UFC/creatinine between all active treatments are presented in the Clinical Expert Statement in Appendix 5-3 (Page 6 of the Statement).

A slightly suppressive effect for TCM/creatinine and UFC/creatinine was seen following all three active treatments, but deemed to be of no clinical significance (see the Clinical Expert Statement in Appendix 5-3, Appendix 1, Figures 3 and 5).

Additional analyses were carried out comparing steroid and cortisol metabolites across treatment groups and with the exception of androsterone where a higher value was observed following treatment with BDP HFA 100μg bd compared with BDP CFC 200μg bd (95% confidence interval [1.04; 1.90]), pairwise comparisons of the active treatments demonstrated no other differences for any parameters. Pairwise comparisons of the treatments to the placebo run-in were also performed; no differences were seen between any of the three active treatments and the baseline values. Twenty-four hour UFC was lower following treatment with BDP CFC 200μg bd compared with baseline; no differences were observed in the comparisons of BDP HFA 100μg bd and BDP CFC 100μg bd with baseline; when corrected for creatinine a trend was seen in favour of BDP HFA 100μg bd over BDP CFC 200μg bd.
In the analysis of the efficacy data (also secondary endpoints) and which included comparisons across treatments in respect of pulmonary function (PEFR), asthma symptoms and use of rescue medication, each recorded by the patient in diary cards at home, there were no differences apparent between any of the three active treatments.

In the assessment of adverse events reported a total of 19 adverse events occurred during the trial of which three occurred during the placebo run-in period, six occurred during the BDP CFC 200µg bd treatment period and the remainder were evenly distributed across the remaining two treatment groups and the three wash-out periods. The most frequent events were influenza (n=4) and viral upper respiratory tract infection (n=4) observed during both placebo and active treatments. Only one child was withdrawn with an adverse event (receiving BDP CFC 200µg bd), the majority of events were described as mild (including both the events reported from the BDP HFA 100µg bd treatment group), none were considered related to study treatments and there was only one report of a serious adverse event (appendicitis) during treatment with BDP CFC 100µg bd. There were no deaths reported during the study period.

Conclusions

The Applicant concludes that though mean growth rates in the BDP HFA 100µg bd and BDP CFC 100µg bd treatment groups were almost identical it was not possible to show non-inferiority for the BDP HFA 100µg bd treatment compared with BDP CFC 100µg bd for either the ITT or the PP analysis sets. In each analysis set the lower limit of the one-sided 97.5% confidence interval was slightly below the predefined level of -0.20mm/week.

In respect of the secondary safety endpoints no differences were seen between the treatments compared and lower leg growth rate was decreased for all active treatments when compared with baseline.

Study Code: ...005/03 – study carried out with the Volumatic spacing device

The only important difference in the findings in this second study where study treatments were administered via the Volumatic spacing device and the previous study where study treatments were administered without the Volumatic spacing device, was in respect of the primary objective, the comparison of lower leg growth rate as measured by knemometry over the two-week treatment period with BDP HFA 100µg bd with lower leg growth rate following treatment over a similar period with BDP CFC 100µg bd. The mean difference between treatments in both the ITT and the PP analysis data sets was -0.02mm/week with a one-sided confidence interval of [-0.15. The lower end of the confidence interval was above the predefined limit of -0.20mm/week which might indicate that BDP HFA 100µg bd was non-inferior to BDP CFC 100µg bd.
Comparison of LLGR between BDP HFA 100μg bd and BDP CFC 100μg bd. ITT and PP Analysis Sets

<table>
<thead>
<tr>
<th></th>
<th>BDP HFA 100</th>
<th>BDP CFC 100</th>
<th>HFA 100-CFC 100</th>
<th>97.5% one-sided Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate (mm/week) Mean value</td>
<td>0.30</td>
<td>0.32</td>
<td>-0.02</td>
<td>-0.15;</td>
</tr>
</tbody>
</table>

Analysis of Covariance - ANCOVA.

ANCOVA model with treatment and period as fixed effects, subject as random effect and baseline growth rate as covariate. Means are LSmeans from the ANCOVA model. Only subjects having both treatments are included in the model.

Individual growth rates for all active and placebo treatments together with individual and mean LLGRs per treatment group are presented graphically in Appendix 5-8.

Growth rates were similar during each of the three active treatment periods and were similar during the wash-out periods and during the wash-out periods the LLGRs were slightly higher than during the active treatment periods.

TCM excretion corrected for creatinine during treatment with BDP CFC 100μg bd was significantly higher than during the run-in period, mean (SD) 404.8 (163.1)μg/mmol compared with 358.2 (158.2)μg/mmol. In the pairwise comparisons between all active treatments, treatment with BDP HFA 100μg bd and BDP CFC 200μg bd resulted in lower values of TCM excretion corrected for creatinine than following treatment with BDP CFC 100μg bd and with no difference in excretion between BDP HFA 100μg bd and BDP CFC 200μg bd.

In the additional analysis of steroid and cortisol metabolites pairwise comparison of the active treatments did not demonstrate any differences for any of the parameters analysed apart from comparisons for beta-cortolone + beta-cortol and C21 cortisol. Values were lower for both parameters following treatment with BDP CFC 200μg bd when compared with treatment with BDP CFC 100μg bd; no parameters were lower following treatment with BDP HFA 100μg bd when compared with treatment at either dose level of BDP CFC. (See Clinical Expert Statement in Appendix 5-3, Appendix 1, Figure 4).

A total of 48 adverse events were reported, 15 of which occurred during the placebo run-in period, 21 during the active treatment periods and 12 during the wash-out periods. All adverse events were described as unrelated to study treatments, three children were withdrawn following adverse events, one during the run-in period, one during the BDP CFC 200μg bd treatment period and one in the wash-out following this treatment period, only one adverse event was described as severe (on BDP CFC 200μg bd) and the majority (61%) were described as mild. More adverse events were reported on treatment with BDP HFA 100μg bd (12 events reported from 6 patients) than on the other two active treatments, 4 events from 4 patients and 5 events from 5 patients reported during treatment with BDP CFC 100μg bd and BDP CFC 200μg bd, respectively. The most frequent adverse events were nasopharyngitis (n=9), asthma (n=7) and cough (n=4) observed both during placebo and active treatment groups. There were no deaths and no other serious adverse events reported during the study period.
There were no other notable differences in the analyses of the remaining secondary endpoints (both safety and efficacy) in this study compared with the analyses of the same endpoints in the similar study carried out without the Volumatic spacing device and tables and text in respect of these endpoints are presented in the Clinical Expert Statement, Appendix 5-3 (Pages 8-11).

Conclusion

The Applicant concludes that as mean growth rates in the BDP HFA 100μg bd and BDP CFC 100μg bd treatment groups were almost identical, for both the ITT and PP analysis sets and the lower limit of the one-sided 97.5% confidence interval for the difference in the mean growth rates was above the predefined level of −0.20nm/week, BDP HFA 100μg bd can be considered non-inferior to BDP CFC 100μg bd as assessed by LLGR.

The secondary safety endpoints in respect of lower leg growth rate would suggest that there is no difference between treatment comparisons and that the mean lower leg growth rate was lower for all three active treatments when compared with baseline. However, the differences between active treatments and baseline were not statistically significant.

5.2.2 Pharmaceutical Assessor’s Comment

50 & 100μg/actuation – Studies DM/PR/3303/004/03 and DM/PR/3303/005/03

The mean delivered dose and mean fine particle dose for the HFA and CFC-containing batches used in studies DM/PR/3303/004/03 and DM/PR/3303/005/03 when measured with and without the spacing device (Volumatic) are shown in the table below:

Mean delivered and fine particle doses for batches used in studies DM/PR/3303/004/03 and DM/PR/3303/005/03 determined with and without a Volumatic spacing device

<table>
<thead>
<tr>
<th></th>
<th>without spacer</th>
<th>with spacer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DD</td>
<td>FPD</td>
</tr>
<tr>
<td>HFA 50 (035095)</td>
<td>47.59</td>
<td>12.28</td>
</tr>
<tr>
<td>CFC 50 (E039)</td>
<td>46.50</td>
<td>12.75</td>
</tr>
<tr>
<td>CFC 100 (D034357B*)</td>
<td>90.60</td>
<td>15.92</td>
</tr>
<tr>
<td>CFC 100 (E152)#</td>
<td>86.20</td>
<td>22.37</td>
</tr>
</tbody>
</table>

DD = mean delivered dose
FPD = mean fine particle dose (particles ≤ 4.7μm)
* Study DM/PR/3303/004/03 (without spacer)
# Study DM/PR/3303/005/03 (with spacer)
As expected the use of the spacing device lowers the delivered dose for both the HFA and CFC-containing products. From these data the HFA-containing product has a marginally greater percentage reduction to the delivered dose (~2 times) compared with the CFC-containing products (~1.8 times). Further, consistent with previous in vitro studies (see response to Point 13.2 of the CSM letter dated 18 July 2001 - Appendix 1) this spacing device increases the fine particle dose for both the CFC and HFA-containing products. For this study it would appear that the 50µg strength of the CFC and HFA-containing products were very well matched with comparable delivered and fine particle doses both with and without the spacer. Both of these products would satisfy the proposed specification for mean fine particle dose for the HFA product (around 1/3 of the proposed range of 10-17µg) when used without a spacer. The 100µg CFC-containing products however show diverse results. In particular some of the canisters tested from batch D034337B had characteristics closer to that of a 50µg dose inhaler and as a consequence failed to meet the lower limit proposed for the HFA product of the same strength (19µg). Notably this is the batch that was used in the study without a spacer and therefore could be considered not to adequately represent a doubling dose compared with the 50µg CFC-containing batch used. The batch used in the study evaluating the use of the spacer (E152) had characteristics that are considered more representative of the 100µg strength. It satisfied the specification of the HFA-containing 100µg strength (19-34µg), although at the lower end, and there was an approximate doubling of the fine particle dose compared with the 50µg CFC-containing product both with and without the spacer. To enable direct comparison between these studies it is unfortunate that the Applicant did not use canisters from the same batch for both studies. Although it is recognised that the 100µg CFC-containing batches are representative of the product currently on the market the use of different batches in these studies has produced additional variability to be taken into consideration and some comment from the Applicant would be appropriate. The data however support the use of a spacing device in removing the larger size particle fraction from both preparations that would be likely to deposit in the mouth from where it could be swallowed and potentially increase the systemic uptake.

5.2.3 Statistical Assessor’s Comment

The design and analysis of Studies DM/PR/3303/004/03 and DM/PR/3303/005/03 are thoroughly described in Section 5.2.1. The pharmaceutical and clinical assessors’ comments on this study given in Sections 5.2.2 and 5.2.4 respectively are fully supported. The main methodological concerns with these studies are the choice of non-inferiority margin and the assay sensitivity.
The chosen margin of 0.2 mm/week was justified by looking at the variability of observations from previous studies. All this does is provide information on how wide a confidence interval is likely to be if the two formulations were the same. The clinical significance of a difference of 0.2 mm/week was not discussed in the protocol. At the end of the Clinical Expert Statement (Appendix 5-3) the clinical significance of the results is discussed. The Clinical Expert asserts that reductions in lower leg growth rates of less than 40% compared with lower leg growth rates on placebo are not thought to be associated with a risk of height growth suppression. The Expert continues by stating that the lower leg growth rate was reduced to approximately 0.30 mm/week (23%) for all treatments in the study using the Volumetric spacing device whereas the reduction was approximately to 0.10 mm/week (77%) in the study in which the spacing device was not used. As 23% is much less than 40% the Expert concludes that there is no risk of long-term growth suppression if BDP is given via a spacing device but there is a risk of long-term growth suppression if BDP is given without a spacing device. There are a number of issues with this argument. Firstly, the mean placebo run-in growth rates were 0.45 mm/week: a growth rate of 0.3 mm/week represents a 33% reduction in growth rate not 23%. These figures may differ because one represents the mean percentage reduction in growth rate and the other represents the percentage mean reduction in growth rate. Secondly this application is primarily concerned with the BDP HFA formulation. From the table below (from Study DM/PR/3303/005/03 with spacing device) the percentage mean reduction in growth rate for the HFA formulation compared with placebo was 35.6%. The lower limit of the 95% confidence interval comparing the growth rate of BDP HFA with placebo was -0.32; this corresponds to a 71% reduction in growth rate.

<table>
<thead>
<tr>
<th>Growth rates (mm/week)</th>
<th>Active</th>
<th>Placebo</th>
<th>Active-Placebo Difference</th>
<th>95% two-sided Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean value HFA 100 and placebo</td>
<td>0.29</td>
<td>0.45</td>
<td>-0.16</td>
<td>[-0.32, 0.01]</td>
</tr>
<tr>
<td>Mean value CFC 100 and placebo</td>
<td>0.33</td>
<td>0.45</td>
<td>-0.12</td>
<td>[-0.29, 0.04]</td>
</tr>
<tr>
<td>Mean value CFC 100 and placebo</td>
<td>0.51</td>
<td>0.45</td>
<td>-0.14</td>
<td>[-0.31, 0.02]</td>
</tr>
</tbody>
</table>

Hence although the estimated lower leg growth rates for all active groups are less than 40% of the placebo lower leg growth rates it is not possible to rule out a reduction of 40% from the study in which the spacing device was used. To rule out a difference of 40% a much larger study would be required with a correspondingly smaller non-inferiority margin.
The assay sensitivity of these studies is also a concern. In both studies similar growth rates were seen in all three treatment groups. Clearly these studies did not have the ability to detect differences between BDP 100μg and BDP 200μg. The pharmaceutical assessor highlights reasons why the formulation of BDP CFC 100μg used in Study DM/PR/3303/004/03 (without spacing device) may not have been twice as potent as the formulation of BDP CFC 50μg used in this study. However, the batch of the BDP CFC 100μg used in Study DM/PR/3303/005/03 (with spacing device) did have approximately twice the fine particle dose of the BDP HFA 50μg and BDP CFC 50μg formulations used in this study. Even in this study very similar growth rates were seen in all three treatment groups. Therefore, it is not possible to rule out the possibility that BDP HFA 50μg is as potent as BDP CFC 100μg. When published literature are taken into account, all that can be really concluded is that it would seem unlikely that the BDP HFA formulation was more than four times as potent than the BDP CFC formulation. Of course, increased potency is not necessarily a concern provided it is not associated with a worsening safety profile. Hence on the basis of the data presented it needs to be demonstrated that the BDP HFA formulation is as safe as the BDP CFC formulation. The knemometry studies do not provide any evidence that the BDP HFA formulation is less safe than the BDP CFC formulation, but it should be remembered that these studies were small (n = 24 and 30 respectively) and hence not powered to show differences between active treatment groups. There is fairly clear evidence, albeit not from the same study, that using a spacing device significantly reduces the risk of suppressing growth in children with asthma. The estimated reduction in growth rate for the BDP HFA formulation when used without a spacing device compared with placebo was -0.34mm/week [percentage mean reduction of 79% (95% CI (35%, 123%)].

On the basis of these data it may be appropriate to review the SPCs for the currently marketed formulations of BDP and to insist that the BDP HFA formulation only be used with a spacing device when used in children. The new paediatric data for children using the spacing device when taken in isolation do not provide robust evidence of safety. However, when taken together with the new safety data in adults and the previously available efficacy and safety data in adults and children it might be possible to conclude that sufficient data are available to recommend granting Marketing Authorisations for BDP HFA in all age groups.
5.2.4 Clinical Assessor’s Comment

The two studies presented and discussed above are the studies which were felt to provide the most appropriate way forward following the discussion of the major outstanding issues in respect of the use of these products in children at the Clarification Meeting held in November 2002. At the Clarification Meeting it was proposed that the Applicants should conduct two further studies in children to assess systemic safety and in the light of accepted difficulties in the assessment of the HPA axis in this age group, the inappropriateness of stimulation tests and the unacceptability of repeated venepuncture, it was suggested that systemic effects should be assessed through short-term measures of bone growth rate through knemometry. Knemometry is accurate and reproducible, is well validated in the assessment of systemic activity of inhaled corticosteroids and is without discomfort to the child. It was also felt that the systemic effects of inhaled steroids in children could be assessed through measurement of the urinary cortisol/creatinine ratio and providing two measures of systemic effects might prove to be a valuable means of validating the findings and enabling a comparison of the direct effects of inhaled steroids on bone cells with effects seen on the HPA axis. It was proposed that the two studies required should be identical studies bar the requirement that one study should be carried out with and one carried without administration of the inhaled steroid via the Volumatic spacing device. As in the discussions surrounding the proposed study in adults it was stressed that the Applicants would have to seek advice through the literature and through experts in the field to justify the size of the two studies and to ensure that the studies would be adequately powered to assess safety in this way.

Prior to these two studies being set up further discussions were held with experts in the field and a final meeting was held with the Applicants in April 2003. It was agreed that the primary endpoint in respect of safety would be the effects on short-term growth rate using knemometry and that the urine collections would be 24 hour collections at the beginning and at the end of the study treatment period and possibly also at the mid-point, and that they would include measurement of urinary free cortisol and an assessment of the urinary steroid profile by extracting the seven major steroid metabolites. It was accepted that assessment of the urinary steroid profile is only experimental and not validated but could be viewed alongside the knemometry data. The study would be powered for knemometry outcomes and not on the HPA axis assessments.
The Expert states that these findings would predict a low risk probability for long-term growth suppression following BDP HFA 100μg bd and BDP CFC 100μg bd dose regimens if administered without using a spacing device and that no such risk could be predicted if the same dose regimens of BDP HFA and BDP CFC were administered via the Volumatic spacing device (see Clinical Expert Statement in Appendix 5-3).

However, following further review of the literature and further analyses, the Statistical Assessor raises issues with this interpretation (see Section 5.2.3, second paragraph, above) and concludes that it is not possible to completely rule out a reduction in growth rate of 40% or more from growth rate seen on placebo/baseline (the lower limit of the 95% confidence interval comparing the growth rate of BDP HFA 100μg bd with placebo (-0.32) may correspond to a 71% reduction in growth rate) in the study in which the Volumatic spacing device was used (Study Code: ...005/03). To completely rule out a reduction in growth rate of 40% or more a much larger study would need to be carried out (with a correspondingly smaller non-inferiority margin).

Other secondary safety endpoints included measures of HPA axis function. Twenty-four hour urine collections enabled an assessment of the 24 hour total cortisol metabolite excretion and the 24 hour urinary free cortisol. It was accepted that the study was not powered appropriately to provide any definitive conclusions but the data could be viewed alongside the knemometry findings.

The findings in respect of the effects seen on the HPA axis are discussed in detail in the Expert Opinion in Appendix 5-4 and also in the Clinical Expert Statement in Appendix 5-3. The conclusions drawn from the data, accepting that the use of total cortisol metabolites as a sensitive measure of the effect of inhaled corticosteroids on the HPA axis is as yet not validated, accepting that immunoassays for urinary free cortisol measurement may be confounded by the co-measurement of corticosteroid metabolites when high doses are studied and accepting that the studies were not powered to assess the systemic activity of BDP on the HPA axis, are as follows:

- No significant suppression of cortisol production was seen following either BDP HFA 100μg bd or BDP CFC 100μg bd and no differences were seen between the two treatments. Suppression of TCM and UFC was less than 15-20% lower than the run-in levels when the inhaled steroids were administered in a dose of 100μg bd. Following BDP CFC 200μg bd both TCM and UFC showed a more frequent reduction but the fall was still no greater than 30% of the levels seen during the run-in period.

- There appeared to be less suppression when the study treatments were inhaled via the Volumatic spacing device.
In the light of the study objectives it was important that compliance with study treatments be measured in both studies and this was assessed through study centre records, by recording administration of inhaled BDP in patient diary cards and by weighing the canister at the beginning and end of the treatment periods. The Clinical Expert reviews compliance in detail in the Clinical Expert Statement (Appendix 5-3) and it is noted that there appeared to be higher compliance in the assessment of the diary card data compared with the assessment of canister weights. The Clinical Expert makes comment that compliance in the study in which the Volumatic spacing device was used was numerically higher during the BDP HFA 100μg bd treatment compared with the other two active treatments regardless of the method of measuring compliance (diary cards or canister weights).

In the assessment of the secondary endpoints of efficacy there were no differences apparent between the three active treatments. This finding is not unexpected as the studies were not powered to assess efficacy.

In Section 5.2 above, Pharmaceutical Assessor’s Comment it can be seen that the delivered dose is lower and the fine particle dose increased when BDP is formulated with either HFA-134a or CFC propellants and is administered via a MDI with Volumatic spacing device. These findings support the use of a spacing device with removal of the larger particles which would otherwise deposit in the mouth and be swallowed and hence potentially increase systemic uptake.

The Pharmaceutical Assessor also comments on the diverse findings seen with the BDP CFC 100μg product (delivering the dose of 200μg bd in the clinical studies) and the fact that the product used in the first of the two studies in children, Study Code: …004/03 has characteristics closer to those of the 50μg strength inhaler with a fine particle dose which failed to meet the lower limit proposed for the BDP HFA product of the same strength, 15.92μg compared with 19μg respectively and therefore cannot be considered to adequately represent a doubling dose compared with the BDP CFC 50μg strength. These findings might account for the lack of separation clinically between the two strengths of BDP CFC used in this study and between the two dose regimens, BDP HFA 100μg bd and BDP CFC 200μg bd.

However these findings might account for the lack of separation seen between different strengths in the first study but not in the second study, the study in which the Volumatic spacing device was used, in this study a different batch of the higher strength BDP CFC was used with characteristics which were more representative of the true strength of the inhaler, i.e. the 100μg strength. However it is of note that although the specification for the fine particle dose was satisfied, it was only at the lower end of the range with a fine particle dose of 22.37μg (range for BDP HFA 100μg strength is 19-34μg); however this fine particle dose did represent an approximate doubling of the fine particle dose of the BDP CFC 50μg strength (12.75μg). These findings make direct comparisons between the two studies difficult.
In conclusion, inhaled corticosteroids do have systemic effects as shown through short-term measures of bone growth rate using knemometry. The study comparing BDP formulated with HFA-134a in a dose of 100 μg bd with BDP formulated with CFC propellants in a dose of 100 μg bd, both formulations administered via a MDI with a Volumatic spacing device, may demonstrate non-inferiority of BDP HFA compared with BDP CFC in respect of effects on bone growth rate. However, this finding is not confirmed when the drugs are administered via the MDI without a spacing device. The use of a spacing device allows up to 50% of the nominal dose to be retained within the spacing device, rather than ending up in the mouth and being swallowed and absorbed, and hence absorption from the gastrointestinal tract is markedly reduced. Use of the Volumatic spacing device markedly reduces the systemic availability of the inhaled corticosteroid and hence reduces systemic effects such as effects on lower leg growth rate and the HPA axis.

The findings in the first study described, Study Code: ...004/03 do not provide evidence of non-inferiority of BDP formulated with propellant HFA 134a (and administered without a spacing device) when compared with BDP as originally formulated with CFC propellants and administered at the same dose. In light of the findings in respect of the reduction in growth rate seen following both formulations of BDP compared with growth rate on placebo, and following review of previously published data where short-term reduction in growth rate is compared with intermediate-term measures of growth in terms of height and the probability that these doses of BDP do appear to have a low risk probability of producing long-term growth suppression (and therefore probably other systemic effects), it is proposed that Marketing Authorisations should not be granted for the use of this reformulated inhaled steroid in children when administered without a spacing device.

The findings in the second study, Study Code: ...005/03 (with the Volumatic spacing device) differ from the findings in the first study and BDP formulated with propellant HFA-134a may be deemed to be non-inferior to BDP as originally formulated with CFC propellants (when administered at the same dose) in respect of the systemic effects on lower leg growth rate. It is unfortunate and not fully understood why the study was unable to separate the two dose levels of inhaled steroid in respect of their effects on lower leg growth rate in this study. In the light of probable non-inferiority it can be concluded that BDP HFA is no less safe than BDP CFC when administered via the Volumatic spacing device; the findings following review of published data where short-term growth rate is compared with intermediate-term measures of growth in terms of height, might predict that changes in growth rate on these doses of BDP may not be associated with a risk of long-term growth suppression. Therefore, it is proposed that Marketing Authorisations may be granted for the use of this reformulated inhaled steroid in children providing that the drug is always administered via the Volumatic spacing device.
At the Clarification Meeting it was felt that if the findings of a further safety study provided reassurance in respect of safety when this inhaled glucocorticosteroid formulated with HFA-134a is administered to children, such a study would provide reassurance in respect of efficacy and would enable the grant of Marketing Authorisations despite the findings in the original study carried out in respect of efficacy. In this study an increase in FEV₁ (a secondary endpoint) at the end of the 12-week treatment period, an increase which was statistically significantly different from the FEV₁ measured in the treatment group receiving the CFC-containing formulation, suggested that the reformulated product might be supra-bioavailable.

It is proposed that Marketing Authorisations be granted for these products to be used in children but only when administered via the Volumatic spacing device. It is also proposed that the Applicants be asked to comment on the use of different batches of the 100μg strength of BDP formulated with CFCs in the two clinical studies presented as such use has produced additional variability such that full interpretation of the data generated is difficult.

Therefore Point 1 in respect of efficacy and safety in children less than 16 years of age and Point 3 may be considered resolved providing beclometasone dipropionate when formulated with propellant HFA-134a is always administered via the Volumatic spacing device when used in this population of children.

5.3 POINT 4

**Phase IV Safety Study** – arising from Point 7 of the letter dated 18 July 2001 (Appendix 1)

The following issues with regard to the protocol should be addressed:

- The final protocol should make comment on how the three-month reference period prior to the new treatment period will be handled, as this will be an unknown mixture of different treatments or no treatment and in the current draft protocol there are no proposals to collect data on prior treatment.

- While not stipulated in the study protocol, it is possible that comparison with other CFC or HFA cohorts may be conducted. These should be made explicit if intended.

- The final protocol should clarify details in causality assessment, reporting of serious adverse drug reactions and provision of interim reports to the MCA.

- The final protocol must be presented and agreed before Marketing Authorisations are granted.

5.3.1 Company Response

The Applicant has not addressed the above listed issues with regard to the protocol for the Phase IV Safety Study but states that these issues will be considered in the drafting of the final proposed protocol for this study and that this will be submitted and agreed prior to the grant of Marketing Authorisations for these products.