Public Assessment Report

Decentralised Procedure

Lifsar 50 microgram/500 microgram per metered dose
Inhalation powder

Tritenva 50 microgram/500 microgram per metered dose
Inhalation powder

(Salmeterol xinafoate and fluticasone propionate)

Procedure Numbers: UK/H/5582/01/DC
UK/H/5583/01/DC

UK Licence Numbers: PL 17780/0673-0674

Winthrop Pharmaceuticals UK Limited
LIFSAR AND TRITENVA 50 MICROGRAM/500 MICROGRAM PER METERED DOSE INHALATION POWDER

LAY SUMMARY

Lifsar 50 microgram/500 microgram per metered dose Inhalation powder

Tritenva 50 microgram/500 microgram per metered dose Inhalation powder

This is a summary of the public assessment report (PAR) for Lifsar 50 microgram/500 microgram per metered dose Inhalation powder and Tritenva 50 microgram/500 microgram per metered dose Inhalation powder. These medicines are identical to each other apart from the difference in product name and will be referred to as Lifsar and Tritenva in the remainder of this summary.

This summary explains how Lifsar and Tritenva were assessed and their authorisation subsequently recommended. It is not intended to provide practical advice on how to use Lifsar and Tritenva.

For practical information about using Lifsar and Tritenva patients should read the package leaflets or contact their doctor or pharmacist.

What are Lifsar and Tritenva and what are they used for?
The applications for Lifsar and Tritenva were submitted as ‘hybrid applications’. This means that they are similar to a ‘reference medicinal product’ containing the same active substance but that the applicant has provided additional data to demonstrate equivalent safety and efficacy.

The reference medicine for Lifsar and Tritenva already authorised in the European Union (EU) is Seretide Accuhaler 50 microgram /500 microgram /dose inhalation powder, pre-dispensed (PL 10949/0316).

Lifsar and Tritenva are for use in adults 18 years of age and older with chronic obstructive pulmonary disease (COPD). COPD is the name for a collection of lung diseases, including chronic bronchitis, emphysema and chronic obstructive airways disease. Lifsar and Tritenva help to prevent breathing problems associated with COPD. Lifsar and Tritenva reduce the number of flare ups of symptoms related to COPD.

These medicines should not be given to children and adolescents less than 18 years of age because they may not be safe or effective. A lower strength product would be required if this fixed-dose combination orally inhaled product was to be used in the treatment of children.

The reference product is available in the lower strengths of 50 microgram salmeterol/100 microgram fluticasone propionate and 50 microgram salmeterol/250 microgram fluticasone propionate and is, therefore, authorised for use in children of 4 years and older. Lifsar and Tritenva are not available in these lower strengths.

Lifsar and Tritenva help to stop breathlessness and wheeziness coming on. However, they should not be used to relieve a sudden attack of breathlessness or wheezing. If this happens patients need to use a fast-acting “reliever” (“rescue”) inhaler, such as salbutamol. Patients should always have a fast-acting “rescue” inhaler with them.
LIFSAR and Tritenva are not used to treat asthma. The lack of the lower strength products would not only affect downward dose titration but also precludes use of the products in patients with mild and moderate asthma.

**How do Lifsar and Tritenva work?**
Lifsar and Tritenva are fixed-dose combination orally inhaled product containing two active ingredients: salmeterol xinafoate and fluticasone propionate. Salmeterol xinafoate is known as a long-acting bronchodilator. Bronchodilators help the airways in the lungs to stay open. This makes it easier for air to get in and out. The effects last for at least 12 hours. Fluticasone propionate is a corticosteroid which reduces swelling and irritation in the lungs.

**How are Lifsar and Tritenva used?**
The usual dose is one inhalation, twice a day. It is very important that patients follow their doctor’s instructions on how many inhalations to take and how often to take their medicine.

A doctor, nurse or pharmacist should show the patient how to use the inhaler. To use the inhaler its white cover should be removed and the patient should place their lips around the mouthpiece and inhale deeply, the cover should then be replaced on the inhaler. The inhaler has a green colour on its outside which helps the patient know when the inhaler is ready for use and when the inhaler has been used successfully. There is an additional green colour in the dose indicator window which helps patients know approximately how many inhalations of the medicine are left in the device.

These medicines can only be obtained with a prescription.

**What benefits of Lifsar and Tritenva have been shown in studies?**
Studies to establish therapeutic equivalence of Lifsar and Tritenva to Seretide Accuhaler 50 microgram /500 microgram /dose inhalation powder, pre-dispensed were submitted with these applications. The results of these studies indicate that Lifsar and Tritenva have similar levels of safety and efficacy as Seretide Accuhaler 50 microgram /500 microgram /dose inhalation powder, pre-dispensed. Therapeutic equivalence is defined as equivalent efficacy and safety when the new orally inhaled product for which a Marketing Authorisation is sought is compared with an appropriate reference orally inhaled product.

**What are the possible side effects of Lifsar and Tritenva?**
The most common side effects reported with Lifsar and Tritenva, which affect more than one person in 10) are headache (this usually gets better as treatment continues) and increased number of colds.

For the full list of all side effects reported with Lifsar and Tritenva, see section 4 of the package leaflets.

For the full list of restrictions, see the package leaflets.

**Why are Lifsar and Tritenva approved?**
It was concluded that, in accordance with EU requirements, Lifsar and Tritenva have been shown to be therapeutically equivalent to Seretide Accuhaler 50 microgram /500 microgram /dose inhalation powder, pre-dispensed. Therefore, the MHRA decided that, as for Seretide Accuhaler 50 microgram/500 microgram/dose inhalation powder, pre-dispensed, the benefits of Lifsar and Tritenva are greater than their risks.
What measures are being taken to ensure the safe and effective use of Lifsar and Tritenva?
A risk management plan has been developed to ensure that Lifsar and Tritenva are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Lifsar and Tritenva, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously as well.

Other information about Lifsar and Tritenva
Marketing Authorisations for Lifsar and Tritenva were granted on 5 August 2015.

The full PAR for Lifsar and Tritenva follows this summary.

This summary was last updated in September 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction ........................................ Page 6
II Quality aspects ..................................... Page 7
III Non-clinical aspects ............................... Page 11
IV Clinical aspects .................................... Page 12
V User consultation ................................... Page 32
VI Overall conclusion, benefit/risk assessment and recommendation Page 32

Annex 1 - Table of content of the PAR update for MRP and DCP Page 33
I Introduction

Based on the review of the data on quality, safety and efficacy, the Competent Authorities of AT, BG, CY, CZ, DE, DK, EE, IE, IS, IT, LI, LT, LV, MT, NO, PL, PT, RO, SI, SK and the UK considered that the application for Lifsar 50 microgram/500 microgram per metered dose Inhalation powder could be approved and the Competent Authorities of DE, IT and the UK considered that the application for Tritenva 50 microgram/500 microgram per metered dose Inhalation powder could be approved.

These prescription-only medicines (POM) are identical to each other apart from the difference in product names and are indicated for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a FEV₁ < 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations and who have significant symptoms despite regular bronchodilator therapy. Lifsar and Tritenva are intended for use by adults 18 years of age and older only.

These applications were submitted using the Decentralised Procedure (DCP) and were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference medicinal product for the applications for Lifsar and Tritenva is Seretide Accuhaler 50 microgram/500 microgram /dose inhalation powder, pre-dispensed, authorised in the UK to Glaxo Wellcome UK Ltd on 1 February 1999 (PL 10949/0316). This reference product was first authorised in Sweden in December 1998 under the name Seretide Diskus forte.

Salmeterol xinafoate is a selective long-acting (12 hour) β₂ adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor. Salmeterol xinafoate produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β₂ agonists.

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less of the adverse effects than when corticosteroids are administered systemically.

No new non-clinical data have been submitted, which is acceptable given that these are hybrid applications based on an originator product that has been in clinical use for over 10 years.

Three pharmacokinetic studies and one pharmacodynamic study support the granting of these applications. The studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The MHRA considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

A satisfactory Phase I Environmental Risk Assessment has been provided for these products. A commitment has been made to conduct further studies to provide further reassurance that these products do not pose a risk to the environment.

The UK, AT, BG, CY, CZ, DE, DK, EE, IE, IS, IT, LI, LT, LV, MT, NO, PL, PT, RO, SI, and SK (for Lifsar) and the UK, DE, IT (for Tritenva) considered that the applications could be approved on Day 210 of the procedure (1 July 2015). After a subsequent national phase, Marketing Authorisations were granted to Winthrop Pharmaceuticals UK Limited (trading as Zentiva) on 5 August 2015.

II Quality aspects

II.1 Introduction

Lifsar and Tritenva are white powders for inhalation containing salmeterol xinafoate and fluticasone propionate and the excipient lactose monohydrate. Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 45 micrograms of salmeterol xinafoate and 465 micrograms of fluticasone propionate. This corresponds to a metered dose of 50 micrograms of salmeterol xinafoate and 500 micrograms of fluticasone propionate.

The powder is supplied in an inhaler. The inhaler body is grey and white with a grey base and mouthpiece, a white cover and a purple or grey bottom lid. The inhaler and is made of six different plastic materials: polypropylene, polyethylene, acrylonitrile butadiene styrene, thermoplastic elastomer, polybutylene terephthalate and silicon. The inhaler is available in packs of one.

II.2 Drug Substances

INN: Salmeterol xinafoate
Chemical name: (R,S) 4-Hydroxy-α’-[[6-(-4-phenyl butoxyl)hexyl]amino]-methyl]-1,3, benzenedimethanol, 1-hydroxy-2-naphthoate
CAS registry no.: 94749-08-3
Structure:

Molecular formula: \( C_{36}H_{45}O_7N \)
Molecular mass: 603.7
Description: A white to off white, odourless, crystalline powder soluble in methanol, slightly soluble in ethanol and practically insoluble in water

Salmeterol xinafoate is the subject of a European Pharmacopoeia monograph. All aspects of the manufacture and control of the active substance salmeterol xinafoate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.
Satisfactory stability data are presented and support the proposed retest period for the drug substance.

**INN:** Fluticasone propionate  
**Chemical name:** S-fluoromethyl 6α, 9α-difluoro-11β 17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

**Molecular formula:** C_{26}H_{31}F_{3}O_{5}S  
**Molecular weight:** 500.6

Fluticasone propionate is the subject of a European Pharmacopoeia monograph. All aspects of the manufacture and control of the active substance fluticasone propionate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Satisfactory stability data are presented and support the proposed retest period for the drug substance.

### II.3 Medicinal Product

**Pharmaceutical development**

The objective of the development programme was to formulate a stable powder for inhalation comparable in performance to the reference product.

Suitable pharmaceutical development data have been provided for these applications. Comparative *in vitro* data for these products and the reference product have been provided and are satisfactory.

Lactose monohydrate is the only excipient in these products and is controlled in line with the European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided for the lactose monohydrate. The manufacture of lactose monohydrate complies with Public Statement CPMP/571/02.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the products, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial-scale batches and has shown satisfactory results.

**Control of Finished Product**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a
shelf-life of 2 years for unopened product has been set. The shelf-life after first opening is 30 days. The storage precaution for the inhaler is “Keep the cover tightly closed in order to protect from moisture”.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended. A commitment has been made to introduce a new dose counter in the inhaler to improve ease of use.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labelling are satisfactory and in line with current guidance.

A commitment has been made to provide a patient information video for these medicinal products. These medicines will not be marketed in the UK until approval of the patient information video has been obtained.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website.

No label mock-ups have been provided for Lifsar and Tritenva. The following text is the approved label text for Lifsar. The label text for Tritenva is essentially identical to that for Lifsar, apart from the difference in product names and Marketing Authorisation numbers. In accordance with medicines legislation, these medicines will not be marketed in the UK until approval of the label mock-ups has been obtained:

| LABELLING |
| Particulars to appear on the outer packaging carton box |

1. NAME OF THE MEDICINAL PRODUCT
Lifsar 50 microgram 500 microgram per metered dose Inhalation powder
Salbutamol/fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCES
Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 45 micrograms of salbutamol (as salbutamol xinafoate) and 465 micrograms of fluticasone propionate. This corresponds to a metered dose of 50 micrograms of salbutamol (as salbutamol xinafoate) and 500 micrograms of fluticasone propionate.

3. LIST OF EXCIPIENTS
Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
Inhalation powder
60 inhalations
PulmoJet® inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Inhalation use.
Inhale through your mouth into your lungs as directed by your doctor.
Use regularly.
Read the package leaflet carefully before use.
2. INHALE

3. CLOSE

Patient information video
www.gzmojer.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Front panel:
Not for use in children and adolescents.

Side panel:
For use in adults with COPD 18 years of age and older only.
Not for use in asthma.
Not for use in children or adolescents under 18 years of age.

8. EXPIRY DATE

EXP
Once opened, use within 30 days.

9. SPECIAL STORAGE CONDITIONS

Keep the cover tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Zeneca, One Union Street, Guildford, Surrey, GU1 4WS, UK

12. MARKETING AUTHORIZATION NUMBER(s)

FL 177809673

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lifesar 50 500 mcg per dose
III Non-clinical aspects

III.1 Introduction
No new non-clinical data have been submitted and none are required for applications of this type.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)
A Phase I ERA indicated that the product will not pose a risk to the environment. A commitment has also been made to provide a tailored ERA for fluticasone propionate, since it is a corticosteroid and should be considered a potential endocrine disruptor. The applicant has also committed to provide the LogKow data for the environmental risk assessments of both salmeterol xinafoate and fluticasone propionate, to enable assessment of the persistence, bioaccumulation potential and toxicity of these drug substances.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV. CLINICAL ASPECTS

IV.1 Introduction
A small programme of studies was submitted in support of these applications to compare this new orally inhaled fixed-dose combination of salmeterol xinafoate and fluticasone propionate in a single high strength and formulated as an inhalation powder with the reference product.

IV.2 Clinical pharmacology
The clinical programme submitted includes the following studies –

- Study 01 – a pilot comparative bioavailability study using a low strength combination (salmeterol xinafoate 50 micrograms and fluticasone propionate 100 micrograms, not a strength for which a Marketing Authorisation is sought)
- Study 09 – a pivotal high strength combination (salmeterol xinafoate 50 micrograms and fluticasone propionate 500 micrograms) bioequivalence study
- Study 06 – a study evaluating inspiratory profiles generated in special populations
- Study 15 – a study comparing Lifsar/Tritenva high strength (salmeterol xinafoate 50 micrograms and fluticasone propionate 500 micrograms) with Seretide Diskus forte (salmeterol xinafoate 50 micrograms and fluticasone propionate 500 micrograms) which included a Lifsar/Tritenva low strength (salmeterol xinafoate 50 micrograms and fluticasone propionate 100 micrograms) study arm as a “non-zero” control for assay sensitivity.

IV.2.1 Pharmacokinetic studies

Study 01 – pilot study
A pharmacokinetic (PK) study was conducted to compare the single dose pharmacokinetics, inter- and intra-subject PK variability, safety and tolerability of a salmeterol xinafoate/fluticasone propionate (50/100) combinational product, delivered via a novel...
multiple-dose dry powder inhaler (Lifsar/Tritenva 50/100) with Seretide Diskus mite
(reference device) [n=28].

**Study objectives:**

**Primary**
To evaluate the maximum plasma concentration ($C_{\text{max}}$) and the area under the plasma concentration time curve from time zero to the last time point (AUC$_{0-\text{t}_{\text{last}}}$ or AUC$_{0-\text{t}}$) for salmeterol xinafoate and fluticasone propionate and to assess and compare their relative bioavailability following inhalation of a single dose treatment via Lifsar/Tritenva low strength (50/100) [test] and via Seretide Diskus mite (50/100) [reference]

and

To assess and compare the inter- and intra-subject variabilities of Lifsar/Tritenva low strength (50/100) and Seretide Diskus mite (50/100).

**Safety**
To assess and compare the systemic and local safety and tolerability of Lifsar/Tritenva low strength (50/100) and Seretide Diskus mite (50/100).

**Conclusion:**
The results of this pilot pharmacokinetic study suggest that the test product, Lifsar/Tritenva low strength (50/100), and reference product, Seretide Diskus mite (50/100) are not bioequivalent in respect of either salmeterol xinafoate or fluticasone propionate. The test product appears to have higher pulmonary availability and greater systemic exposure for both active drugs in this combination compared with the reference product, which reflects possible enhanced efficacy but a worse systemic safety profile. The benefit/risk balance compared with the reference product is negative.

In the light of these findings the Applicant chose not to develop this low strength product (50/100) further at this stage in the development of this new orally inhaled fixed-dose combination.

**Study 09 — pivotal study**
A pharmacokinetic study was conducted to investigate the pharmacokinetics, safety and tolerability of a salmeterol/fluticasone propionate combinational product delivered via a novel multiple-dose dry powder inhaler (Lifsar/Tritenva 50/500) compared with a marketed reference product (Seretide Diskus forte) administered with or without charcoal (n=40)

**Study objectives:**

**Primary**
To investigate and compare the relative systemic bioavailability of a salmeterol xinafoate/fluticasone propionate fixed-dose combination product following inhalation of a (supratherapeutic) single dose delivered as four sequential actuations via the Lifsar/Tritenva device high strength (50/500) [test] with that of Seretide Diskus forte (50/500) [reference] administered both with and without charcoal blockade

and
**Secondary**

To investigate the bioavailability of salmeterol xinafoate/fluticasone propionate following inhalation of a (supratherapeutic) single dose delivered as four sequential actuations via the Lifsar/Tritenva device high strength (50/500) [test] and the bioavailability of Seretide Diskus forte (50/500) [reference], both administered with and without charcoal blockade, comparing the test product with charcoal blockade with the test product without charcoal blockade and comparing the reference product with charcoal blockade with the reference product without charcoal blockade, in order to quantify the charcoal effect

and

To assess and compare the local and systemic safety and tolerability of Lifsar/Tritenva high strength (50/500) and Seretide Diskus (50/500).

**Study treatments/Study dose regimen:**

- **Test** – Lifsar/Tritenva low strength (50/500) x 4 inhalations as a single dose
- **Reference** – Seretide Diskus low strength (50/500) x 4 inhalations as a single dose
- **Test + activated charcoal**
- **Reference + activated charcoal**

Treatments were separated by a washout-period of at least three days

**Pharmacokinetic findings:**

For both fluticasone propionate and salmeterol xinafoate the ratios and 90% CI for AUC$_{0-t}$, C$_{\text{max}}$ and AUC$_{0-\infty}$ were within the standard bioequivalence acceptance range of 80% to 125%, for both treatment conditions either with or without charcoal.

For fluticasone propionate charcoal blockade did not influence either the rate or the extent of exposure to either the test or the reference product. The 90% CI for the respective ratios (T/TC and R/RC) for AUC$_{0-t}$, C$_{\text{max}}$, and AUC$_{0-\infty}$ were within the standard bioequivalence acceptance range of 80% to 125% for both the test and the reference products. This indicates very low oral bioavailability of fluticasone propionate.

In contrast, for salmeterol xinafoate the rate and extent of exposure were substantially reduced by concomitant administration of activated charcoal for both the test and the reference product. The 90% CI for the respective ratios (T/TC and R/RC) for AUC$_{0-t}$, C$_{\text{max}}$, and AUC$_{0-\infty}$ were above the equivalence acceptance range of 80% to 125% (except for C$_{\text{max}}$ for the test product) and thereby indicating appreciable oral bioavailability of the swallowed fraction of salmeterol xinafoate.

For both the test and the reference products mean concentration-time profiles for fluticasone propionate were similar either with or without activated charcoal, although the profile for the test product was slightly lower that that of the reference product.

For both the test and the reference products mean concentration-time profiles for salmeterol xinafoate were similar either with or without activated charcoal. However lower profiles were observed for both the test and the reference product after administration of either treatment with charcoal.
Concentration-time profiles of salmeterol xinafoate and fluticasone propionate

Fluticasone propionate

Salmeterol

R = reference (Seretide Diskus forte – 50/500), RC = reference with charcoal (Seretide Diskus forte with charcoal), T = test (Lifsar/Tritenva high strength – 50/500), TC = test with charcoal (Lifsar/Tritenva high strength with charcoal).

Safety findings:
Forty subjects were included in the safety evaluation, no subjects were withdrawn and there were no serious adverse events or deaths.

Three events of cough occurred within 5 minutes of inhalation of either the test or reference product and were considered to be inhalation-related local adverse events.

Inhalation of supratherapeutic single doses of fluticasone propionate (Lifsar/Tritenva Inhaler 1600μg and Seretide Diskus forte 2000μg) and salmeterol xinafoate(Lifsar/Tritenva Inhaler 160μg and Seretide Diskus forte 200μg) via the Lifsar/Tritenva 50/500 dry powder inhaler and the marketed Seretide Diskus forte dry powder inhaler were well tolerated by healthy male and female subjects in this study.

The use of the Lifsar/Tritenva Inhaler was not associated with differences in the frequency or severity of adverse events when compared with the marketed reference product, Seretide Diskus forte. No adverse events occurred resulting from the use of either the Lifsar/Tritenva Inhaler or the marketed Diskus Inhaler.

No clinically significant findings and no medically relevant changes were observed with regard to laboratory parameters, vital signs and electrocardiogram evaluation.

The overall tolerability was assessed as good in all subjects.
The safety findings for both the test and the reference product were as expected for such actives. There were no safety issues.

**Conclusion:**
Lifsar/Tritenva high strength (50/500) and Seretide Diskus forte (50/500) can be considered to be bioequivalent with respect to AUC$_{0-t}$, C$_{max}$, and AUC$_{0-\infty}$ for both fluticasone propionate and salmeterol xinafoate when administered either with or without activated charcoal blockade.

For salmeterol xinafoate the extent of exposure was substantially reduced by the co-administration of activated charcoal; this was not seen for fluticasone propionate (low oral bioavailability).

These outcomes were expected and in line with published evidence on the known oral bioavailability of salmeterol xinafoate and the negligible oral bioavailability of fluticasone propionate. These outcomes confirm the validity of the study and the use of the charcoal blockade.

The statistical methods are considered appropriate. All 40 subjects completed all four periods of the study and were included in the analysis of the pharmacokinetic parameters. For one of the 40 subjects the pre-dose value for the concentration of fluticasone propionate was above the limit of quantification; for all other subjects the concentration was below this limit. Therefore the washout period is considered to be sufficient.

The 90% CIs for the ratio of the least square means of the test (Lifsar/Tritenva high strength 50/500) and reference (Seretide Diskus forte 50/500) products for AUO$_{0-4}$ (primary variable) and C$_{max}$ and AUC$_{0-\infty}$ (secondary variables) all fall within the accepted limits of 80-125%, both with and without the ingestion of activated charcoal, and therefore the test and reference products may be deemed to be equivalent. However it should be noted that the point estimates for the ratio of test/reference all fall below unity with the exception of C$_{max}$ for fluticasone propionate.

The findings suggest that the test and reference products are likely to have a similar rate and extent of pulmonary absorption and therefore therapeutic equivalence in respect of efficacy between the test and reference products when administered at high strength (50/500) may be considered to have been established in this pharmacokinetic study in healthy adult subjects. The findings in respect of C$_{max}$ suggest that the test and reference products have similar pulmonary/regional lung deposition patterns and the findings in respect of AUO$_{0-4}$ suggest that the drug available to the lung, the pulmonary available dose, is equivalent between the test and reference products and that the total systemic exposure, including pulmonary and gastrointestinal absorption, is equivalent between the test and reference products.

The use of the charcoal blockade confirmed that the systemic availability of fluticasone propionate is almost entirely subsequent on pulmonary absorption.

The pharmacokinetic findings suggest that the test product, the high strength of this new fixed-dose combination product containing salmeterol xinafoate 50 microgram and fluticasone propionate 500 microgram per actuation, and the reference product, Seretide Diskus forte (50 microgram/500 microgram per actuation), are equivalent in respect of both pulmonary and systemic availability and therefore may be considered to be therapeutically equivalent in respect of both efficacy and safety in adults.
LIFSAR AND TRITENVА 50 MICROGRAM/500 MICROGRAM PER METERED DOSE INHALATION POWDER

UK/H/5582-5583/01/DC

**Study 06 - inspiratory profile study**

A multicenter, randomised, open-label, intra-subject/patient crossover study for acquiring inspiratory profiles with Lifsar/Tritenva, Diskus and Turbuhaler dry powder inhaler devices in healthy adult subjects, children with asthma and adult patients with moderate to severe asthma and adult patients with moderate to very severe COPD (n=124)

**Study objectives:**

**Primary**

To determine inspiratory flow profiles following inhalation from the Lifsar/Tritenva, the Diskus and the Turbuhaler dry powder inhalers (DPIs) in healthy adult subjects, children with asthma or adult patients with moderate to severe persistent asthma, as well as adult patients with moderate to very severe COPD. In addition the inhalation manoeuvres were assessed and stratified by subject/patient population. The inspiratory and expiratory lung function parameters for each subject/patient were determined prior to flow rate measurements and

To show that patients representative of the anticipated target populations are able to attain a sufficient flow rate to release the trigger mechanism of the Lifsar/Tritenva DPI.

**Study device - DPI/Number of inhalations/Mode of administration:**

**Test** – Lifsar/Tritenva DPI – no active drug/empty inhaler x 3 sequential oral inhalations

**Reference** – Diskus DPI – no active drug/empty inhaler x 3 sequential oral inhalations

**Reference** – Turbuhaler DPI – no active drug/empty inhaler x 3 sequential oral inhalations

No active drug was inhaled in this study.

Inhalation flow rate as a function of time was assessed by measuring the subject/patient-generated pressure drop. With each DPI each subject/patient performed three inhalation manoeuvres. Subjects/patients were instructed by study personnel according to an instruction leaflet. The sequence of device use was randomised for each individual subject/patient

**Findings:**

**Demographic data (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>Healthy adult subjects (N = 20)</th>
<th>Children with asthma (N = 20)</th>
<th>Adults with moderate to severe persistent asthma (N = 41)</th>
<th>Adults with moderate to very severe COPD (N = 43)a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td>Male 7 (35)</td>
<td>16 (80)</td>
<td>15 (37)</td>
<td>26 (61)</td>
</tr>
<tr>
<td></td>
<td>Female 13 (65)</td>
<td>4 (20)</td>
<td>26 (63)</td>
<td>17 (40)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median 32</td>
<td>9</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Min, max 19, 70</td>
<td>6, 12</td>
<td>26, 79</td>
<td>49, 77</td>
</tr>
<tr>
<td><strong>FEV₁ [L/s]</strong></td>
<td>Mean (STD) 3.5 (0.79)</td>
<td>2.2 (0.57)</td>
<td>2.2 (1.00)</td>
<td>1.5 (0.46)</td>
</tr>
<tr>
<td><strong>FEV₁/ FVC [%]</strong></td>
<td>Mean (STD) 106 (10.6)</td>
<td>111 (27.9)</td>
<td>71 (23.7)</td>
<td>52 (16.2)</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC [L] Mean (STD) 0.8 (0.09)</td>
<td>1.0 (0.05)</td>
<td>0.6 (0.10)</td>
<td>0.5 (0.01)</td>
</tr>
</tbody>
</table>

a N= 40 for lung function measurements.

COPD = chronic obstructive pulmonary disease, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, ITT = intention-to-treat, max = maximum, min = minimum, N = number of subjects.
Peak inspiratory flow

Peak inspiratory flow rates are summarised in the table below.

For a given device flow rates were similar across all adult populations and were independent of airway obstruction. Slightly smaller flow rates were achieved by children with asthma. Mean (best of three) PIF values with Lifsar/Tritenva DPI were between 67L/min and 77L/min, flow rates which are substantially higher than the minimal flow rate (approximately 20L/min) required to achieve the trigger threshold of the breath-operated Lifsar/Tritenva DPI. In addition all subjects achieved a PIF of >40L/min indicating that all subjects were able to achieve the minimal flow rate required to trigger the inhaler. No subject was excluded during screening through inability to handle the Lifsar/Tritenva device correctly.

Differences between the Lifsar/Tritenva and Turbuhaler in flow rates were not observed in any population (p <0.001) whereas flow rates achieved with the Diskus were consistently larger (by 20 to 30L/min) compared with either the Lifsar/Tritenva or Turbuhaler across all four subject populations (p >0.5). These results are entirely consistent with the reported differences in device resistance between the Lifsar/Tritenva, Turbuhaler and Diskus, with comparable device resistances for Turbuhaler and Lifsar/Tritenva and a much lower device resistance for the Diskus.

<table>
<thead>
<tr>
<th>Peak inspiratory flow rate [L/min] (ITT)</th>
<th>Healthy adult subjects (N = 20)</th>
<th>Children with asthma (N = 20)</th>
<th>Adults with moderate to severe asthma (N = 41)a</th>
<th>Adults with moderate to very severe COPD (N = 43)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best of 3, mean (STD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifsar/Tritenva a</td>
<td>77 (13)</td>
<td>67 (9)</td>
<td>76a (10)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>Diskus</td>
<td>104 (17)</td>
<td>91 (16)</td>
<td>106a (15)</td>
<td>98 (18)</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>77 (11)</td>
<td>67 (13)</td>
<td>77a (11)</td>
<td>71 (12)</td>
</tr>
</tbody>
</table>

a N = 40 analysed.
b N = 41 analysed.
STD = standard deviation.

The results seen for the PIF rate, the primary outcome variable, indicate that for all three devices a sufficient PIF rate is achieved to enable the delivery of a sufficient fine particle fraction to the subject/patients populations studied, regardless of age and gender and regardless of disease (asthma or COPD) and disease severity.

Safety findings:

No serious adverse events, no deaths and no other significant adverse events occurred in the study. No device related events occurred.

No consistent or clinically relevant changes in vital signs were reported and no clinically relevant changes from baseline were measured. No changes in vital signs were documented as adverse events.

No rescue medication was required by patients/subjects during the course of this study.
Overall, the investigational device and the comparators proved to have excellent safety profiles.

**Conclusion:**
The study demonstrated that a wide variety of subjects of different age and with different nature and severity of airway obstruction can operate the Lifsar/Tritenva DPI and generally attain sufficient PIF rates through the device to ensure reliable device function (i.e. trigger release) and drug delivery to the lungs. All subjects attained a PIF through the Lifsar/Tritenva of at least 40L/min on all occasions and hence reached the minimal flow rate to trigger the breath-actuated Lifsar/Tritenva inhaler. Peak inspiratory flow rates achieved through the Lifsar/Tritenva and the Turbuhaler were comparable, consistent with their comparable device resistance characteristics, while PIF rates achieved through the Diskus were consistently larger in all populations, a finding which was to be expected with this lower resistance device. Evaluation of secondary parameters suggested that the devices were comparable.

This study confirms that healthy adults, adults with moderate to severe asthma, adults with moderate to very severe COPD and children with asthma can all generate a peak inspiratory flow rate through the Lifsar/Tritenva dry powder inhaler device of sufficient magnitude to ensure functioning of the device and pulmonary delivery of the actives in this fixed-dose combination. The minimal flow rate required to achieve the trigger threshold of the breath-operated Lifsar/Tritenva DPI is approximately 20L/min; all subjects attained a peak inspiratory flow rate through the Lifsar/Tritenva of at least 40L/min on all occasions. The mean peak inspiratory flow rates across the four populations (healthy adults, adults with moderate to severe asthma, adults with moderate to very severe COPD and children with asthma) are as follows:

- **Lifsar/Tritenva DPI (test product)** – 67, 71, 76 and 77L/min, respectively
- **Diskus DPI (reference product)** – 91, 98, 104 and 106L/min, respectively
- **Turbuhaler DPI (a second reference product)** – 67, 71, 77 and 77L/min, respectively

Flow rates generated in the adult populations seemed to be independent generally of the underlying disease, the severity of airflow obstruction and the age of the subject/patient; flow rates generated in children were generally lower that those achieved in the adult populations studied.

Peak inspiratory flow rates generated through the Diskus, the reference inhaler/device were higher in all four populations compared with the Lifsar/Tritenva and the Turbuhaler devices; these findings are consistent with the lower internal resistance of the reference device compared with the test device and the Turbuhaler for which the internal resistance is similar. It is assumed that the Applicant chose to include the Turbuhaler as a third arm in this study to demonstrate similarity between the test product, the Lifsar/Tritenva device and a dry powder device already available on the market worldwide.

The fine particle dose and delivered dose data for three batches of Lifsar/Tritenva high strength at three different flow rates were collated and compared with those of three batches of the reference product. A comparison of the fine particle size distribution flow rate dependency for Lifsar/Tritenva and Diskus was also included and the results are acceptable.
IV.2.2 Pharmacodynamic study

Study 15 – pharmacodynamic study
A study on the effect of salmeterol/fluticasone propionate fixed-combinational dry powder inhaler (DPI) Lifsar/Tritenva high strength in comparison to the Seretide Diskus forte combinational product on the suppressive hypothalamic-pituitary-adrenal (HPA) axis activity was conducted. This study was a single-centre, randomised, double blind, double dummy, 3-period, 7-day repeated dose crossover study on two different doses (50/500μg bid and 50/100μg bid) in adult subjects (n=90).

This study compared Lifsar/Tritenva high strength with Seretide Diskus forte and included a Lifsar/Tritenva low study arm as a “non-zero” control for assay sensitivity.

Study objectives:

Primary
To compare the effects of Lifsar/Tritenva high strength (50/500μg) [Test 1] administered twice daily over a 7-day treatment period with Seretide Diskus forte (50/500μg) [Reference] on baseline-adjusted (BAL) area under the curve (AUC) for 24-hour plasma cortisol

Secondary
- to compare the effects of Lifsar/Tritenva high strength (50/500μg) [Test 1] administered twice daily over a 7-day treatment period with a Lifsar/Tritenva low (50/100μg) [Test 2] on the baseline-adjusted AUC for 24-hour plasma cortisol
- to compare the effects of Test 1 (50/500μg twice daily) and Reference (50/500μg twice daily) on maximum plasma concentration (C_max) for 24-hour plasma cortisol
- to assess steady-state based on the trough values for fluticasone propionate
- to assess and compare the general and local tolerability and safety of the Test and Reference products

Study treatments/Study dose regimen:
Test 1 – Lifsar/Tritenva high strength (50/500) twice daily for 7 days
Test 2 – Lifsar/Tritenva low (50/100) twice daily for 7 days
Reference – Seretide Diskus forte (50/500) twice daily for 7 days

Test – Lifsar/Tritenva – Placebo one inhalation twice daily
Reference – Seretide Diskus – Placebo one inhalation twice daily

All treatments were administered twice daily, once in the morning and once in the evening and comprised two inhalations, one from the active inhaler, Test 1, Test 2 or the Reference and the other from the alternate placebo inhaler.

Steroid sensitivity testing was carried out with Pulmicort (budesonide) suspension for nebulisation – budesonide 1.0mg/2mL suspension – in a dose of 3mg, followed by a washout period of at least 7 days prior to Day -1 and the commencement of the first treatment period.
Pharmacodynamic findings:
Mean plasma cortisol concentration – linear scale (PDS) – Baseline (07:00 hours on Day -1 to 07:00 hours on Day 1) – First dose of study treatment administered Day 1, 08:00 hours

Mean plasma cortisol concentration – linear scale (PDS) – Treatment from Day 7 (07:00 hours) to Day 8 (07:00 hours) – Morning dose of study treatment administered Day 7, 08:00 hours; evening dose of study treatment administered Day 7, 20:00 hours
Primary Endpoint: Change from Baseline in 24-hour Plasma Cortisol AUC (Lifsar/Tritenva high strength versus Reference – Seretide Diskus forte)

<table>
<thead>
<tr>
<th>Device</th>
<th>N</th>
<th>Delta AUC 0-24h LS Mean [%]</th>
<th>Diff. in delta AUC 0-24h PJ high - Refa [%]</th>
<th>LS Mean 95% CI</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seretide Diskus forte</td>
<td>84</td>
<td>33.93</td>
<td>17.78</td>
<td>7.09 - 14.48</td>
<td>14.3488</td>
</tr>
<tr>
<td>PulmoNet SAL/FP high</td>
<td>84</td>
<td>44.71</td>
<td>10.78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Delta AUC = (AUC0-24h BL - AUC0-24h BID/ AUC0-24h BL) x 100.
Non-inferiority limit was 25.00%
a ANOVA. Lower and upper limit of quantification correspond to non-inferiority tests with 95% CI.

ANOVA = analysis of variance, AUC 0-24h (BL) (BID) = area under the plasma concentration time curve between 0 and 24 hours (at Baseline) (after treatment)
CV = coefficient of variation
Diff. = difference
LS = least square
N = number of subjects included in the analysis
PDS = pharmacodynamic analysis set
PJ = Lifsar/Tritenva
Ref = reference

Treatment with both Lifsar/Tritenva and Seretide Diskus forte produced a fall in plasma cortisol concentration until approximately 20 hours post-dose (morning) following which time plasma cortisol returned to pre-dose concentrations at 24 hours post-dose. The shape of the mean cortisol concentration versus time profile was consistent across the three study treatments; only the magnitude of cortisol suppression changed with the dose of Lifsar/Tritenva administered.

The cortisol plasma concentration versus time curve over 24 hours was similar in terms of course and shape for Lifsar/Tritenva high strength and Seretide Diskus forte; however slightly lower plasma levels with Lifsar/Tritenva high strength were seen compared with Seretide Diskus forte.

For the low dose strength of Lifsar/Tritenva, the mean plasma cortisol concentration versus time curve was higher, as expected, but was similar in terms of course and shape as seen for the high dose products.

Mean baseline cortisol AUC(0-24)BL was similar across all treatment groups and ranged from 1475 h*ng/mL to 1515 h*ng/mL. Mean baseline cortisol CmaxBL values were also consistent across treatment groups and were approximately 156 ng/mL.

Following 7 days of twice daily dosing the mean cortisol AUC(0-24)bid was 816 h*ng/mL for Lifsar/Tritenva high strength and 974 h*ng/mL for Seretide Diskus forte. The Lifsar/Tritenva low strength treatment group displayed a higher mean AUC(0-24)bid of 1372 h*ng/mL.

The mean Cmaxbid across the treatments groups were 117.46 ng/mL, 132.41 ng/mL and 157.66 ng/mL for Lifsar/Tritenva high strength, Seretide Diskus forte and Lifsar/Tritenva low strength, respectively.

Pharmacokinetic findings:

Mean fluticasone propionate serum concentration – linear scale plot (PKS)
The fluticasone propionate trough concentrations indicate that for all three treatments the concentrations have reached steady state by Day 5 of twice daily dosing.

The trough concentrations between the high dose Lifsar/Tritenva and the reference product, Seretide Diskus forte, were similar.

Lifsar/Tritenva low strength had trough concentrations of fluticasone propionate that were lower proportionately when compared with Lifsar/Tritenva high strength.

**Safety findings:**

One serious adverse event (SAE) was reported – one subject experienced a serious treatment-emergent adverse event (TEAE) of acute pyelonephritis (Treatment – Test 1, moderate in severity, not deemed to be related to the study treatment); the subject was withdrawn from the study.

All reported TEAEs were mild to moderate in severity and the overall incidence of TEAEs was similar after administration of the Test 1 and the Reference treatments, but lower after administration of Test 2 study treatment.

Three adverse events (AE) occurred which were considered to be inhalation related, within 5 minutes post-administration of study treatment. All three of these inhalation-related local AEs occurred after administration of Test 1 study treatment, Lifsar/Tritenva high strength and were all considered mild (throat irritation – 2 events; hoarseness – 1 event). These events resolved within 1 to 2 days after administration of the Test 1 study treatment.

There were no deaths during the study.

Laboratory test results, vital signs and ECGs showed no clinically meaningful changes over time and no AEs related to laboratory tests, vital signs and ECG abnormalities were reported.

Overall, there were no safety concerns raised during the study. The observed AE profiles are in line with the current knowledge on the safety profile of fluticasone propionate.
Conclusions:
This study was carried out to compare the test product Lifsar/Tritenva high strength with the reference product Seretide Diskus forte, following multiple dose administration, with regard to effects on cortisol suppression and systemic and local safety and tolerability.

Of the various methods available to assess systemic effects on the HPA axis the 24-hour plasma cortisol area under the concentration time curve (AUC) is recognised as the most reliable method for measuring adrenal suppression subsequent on the use of corticosteroids.

As cortisol is known to be a vulnerable parameter, efforts were made to minimise the background noise and improve standardisation during study conduct based on literature, experience and root cause investigation of a previous similar study. Compared with this previous study, Study 15 used a modified design with increased standardisation of procedures.

A different statistical analysis approach was used.

A "non-zero" dose of the test treatment (Test 2 – Lifsar/Tritenva low strength) was employed to confirm assay sensitivity. For the primary endpoint, 24-hour cortisol AUC values were baseline-adjusted. Furthermore the Applicant made efforts to control aging/instability of the reference over the clinical field phase of 7 months, as much as was feasible.

The proposed non-inferiority (NI) margin of 25.00% is clinically justified as a smaller effect size than the difference of expected treatment effect on cortisol suppression considering the administered dose of 100μg/day of reference i.e., approximately 45% based on literature and clinically significant treatment effect of fluticasone propionate equal to 70%.

Trough fluticasone propionate concentrations were collected on Days 5, 6 and 7 for the assessment of fluticasone propionate pharmacokinetics. Steady state for fluticasone propionate had been reached by Day 5 of twice daily dosing for all three study treatments. Steady state trough fluticasone propionate concentrations were similar between the Test 1 product, Lifsar/Tritenva high strength and the reference product, Seretide Diskus forte.

The assessment of the two dose levels of Lifsar/Tritenva – high strength and low strength – demonstrated a significantly greater suppression of cortisol over the dosing interval with Lifsar/Tritenva high strength compared with Lifsar/Tritenva low strength, with a smaller cortisol AUC(0-24), indicating a sensitive design and assay sensitivity.

The AUC(0-24) BL (arithmetic mean 1474.85, 1515.43, 1479.90 h*ng/mL) and CmaxBL (arithmetic mean 155.99, 156.18, 156.58 ng/mL) for the three cortisol baselines prior to each of the three treatment periods were superimposable demonstrating the robustness of the study design.

The results of this study confirmed corticosteroid-mediated adrenal suppression following inhalation of all three treatments – Lifsar/Tritenva high and low strength test products (Test 1 and Test 2) and the reference product, Seretide Diskus forte and demonstrated the sensitivity of the selected biomarker assay. The observed extent of cortisol suppression with all three treatments was considerably less than the clinically significant effect level, which is thought to be at 70% cortisol suppression.
Non-inferiority was seen in baseline-adjusted cortisol AUC(0-24) for Lifsar/Tritenva high strength (Test 1) compared with the reference product, Seretide Diskus forte, and the mean difference in delta AUC(0-24) (10.78%) and its 90% CI (7.09, 14.48) was well within the non-inferiority margin of 25.00% determined as clinically significant. Non-inferiority was also shown in the 24-hour baseline adjusted AUC of Lifsar/Tritenva high strength compared with the reference product when including violators, thereby further demonstrating the robustness of the data.

Overall this study demonstrated that the effect on cortisol suppression observed with Lifsar/Tritenva high strength (Test 1 product) following 7 days of twice daily dosing, was as expected for this study dose regimen for the reference product, Seretide Diskus forte based on available literature. It was also shown that Lifsar/Tritenva high strength is non-inferior to the reference product, Seretide Diskus forte in respect of HPA axis suppression. The observed difference in change of baseline-adjusted (post-baseline) AUC for 24-hour cortisol levels after twice daily dosing with Lifsar/Tritenva high strength (50/500μg) and Seretide Diskus forte of 11% is negligible when compared with the circadian pattern of physiological cortisol fluctuations confirmed by baseline cortisol measurements in this study indicating natural circadian fluctuations from approximately 156 ng/mL to approximately 20 ng/mL.

Corticosteroid-mediated adrenal suppression was observed with Lifsar/Tritenva and Seretide Diskus forte and with larger suppression observed with Lifsar/Tritenva high strength than with Lifsar/Tritenva low (50/100μg), thereby demonstrating assay sensitivity. The observed extent of cortisol suppression with all three treatments was considerably less than the clinically significant effect level of 70% cortisol suppression. The clinically significant threshold of 70% cortisol suppression is considered as a realistic and conservative estimation based on evidence that high strengths of approved inhaled corticosteroids produce even higher cortisol suppression, of up to 88% for example, following fluticasone propionate in a dose of 2000μg via a pMDI.

Overall, there were no safety concerns raised during the study. The observed adverse event profile is in line with the current knowledge on the safety profile of fluticasone propionate. Data have also been presented in respect of the 95% confidence intervals are also satisfactory.

This study demonstrates that the effect of the test product, Lifsar/Tritenva high strength (50/500μg) on the HPA axis and subsequent cortisol suppression, following seven days of twice daily dosing, was non-inferior to the effect seen with the reference product, Seretide Diskus forte (50/500μg) following seven days of twice daily dosing with the same dose regimen.

The observed difference in change of baseline-adjusted (post-baseline) AUC for 24-hour cortisol levels after twice daily dosing with Lifsar/Tritenva high dose and Seretide Diskus forte of 11% is considered negligible when compared with the known circadian pattern of physiological cortisol fluctuations.

Corticosteroid-mediated HPA axis suppression was observed with Lifsar/Tritenva and Seretide Diskus forte, with larger suppression observed with Lifsar/Tritenva high strength than with Lifsar/Tritenva low strength, demonstrating assay sensitivity. The observed extent of cortisol suppression with all three treatments was considerably less than the clinically significant effect level of 70% cortisol suppression described in the literature.
IV.2.3 Comment on the pharmacokinetic and pharmacodynamic data
Pharmacokinetic equivalence with the reference product in the high strength, Seretide Diskus forte (50/500µg) has been demonstrated for a high strength of this new fixed-dose orally inhaled combination product, Lifsar/Tritenva high strength (50/500µg). Pharmacodynamic equivalence (non-inferiority) in respect of the systemic effects of the corticosteroid component of this orally inhaled fixed-dose combination has also been demonstrated in respect of this high dose strength.

Pharmacokinetic, pharmacodynamic and clinical equivalence have not been demonstrated with the low strength (50/100µg) or the mid strength (50/250µg) of this combination product, Lifsar/Tritenva low and Lifsar/Tritenva mid, respectively. However the Applicant is not seeking Marketing Authorisations for these lower strengths at this time.

Asthma
In the light of the findings in respect of pharmacokinetic equivalence with the reference product at high strength and pharmacodynamic equivalence (non-inferiority) in respect of the systemic effects of the corticosteroid component of this orally inhaled fixed-dose combination, it is possible to conclude that the benefit/risk balance for the high strength of this orally inhaled fixed-dose combination product, Lifsar/Tritenva high strength (50/500µg) might be positive when used in the management of severe asthma.

However, pharmacokinetic equivalence to the reference product has only been shown for Lifsar/Tritenva high strength (50/500µg) and as a strength on its own the use of the product, compared with the use of the reference product (authorised in three strengths – low, mid and high), will be severely restricted. There will be no rôle for this fixed-dose combination product in mild and mild to moderate asthma and there is no provision for downward titration of the dose to attain the minimally effective dose of the inhaled corticosteroid component to control disease. The following statement:

*The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.*

is a standard statement to be included in the SmPCs for inhaled corticosteroids and is a requisite of asthma management. The dose cannot be titrated downwards with the high strength of this new product and therefore advice would be required in the SmPC to the effect that the downward titration to a dose of inhaled corticosteroid below 500 micrograms will require a change to an alternative combination product containing a lower dose of inhaled corticosteroid. This is not appropriate patient management and the potential serious risk to public health is the use of a dose of an inhaled corticosteroid which may be too high for too long a period of time.

Therefore, this new orally inhaled fixed-dose combination inhalation powder containing salmeterol xinafoate and fluticasone propionate in only one high strength is not approvable for use in the management of asthma.

Chronic obstructive pulmonary disease
The inspiratory profile study (Study 06) confirms that healthy adults, adults with moderate to severe asthma, adults with moderate to very severe COPD and children with asthma can all generate a peak inspiratory flow rate through the Lifsar/Tritenva dry powder inhaler device of sufficient magnitude to ensure functioning of the device and pulmonary delivery of the actives in this fixed-dose combination. The minimal flow rate required to achieve the trigger
threshold of the breath-operated Lifsar/Tritenva DPI is approximately 20L/min; all subjects attained a peak inspiratory flow rate through the Lifsar/Tritenva of at least 40L/min on all occasions. The mean peak inspiratory flow rates across the three adult populations seemed to be similar and seemed to be independent generally of the underlying disease, the severity of airflow obstruction and the age of the subject/patient; flow rates generated in children were generally lower that those achieved in the adult populations studied.

Peak inspiratory flow rates generated through the Diskus, the reference inhaler/device were higher in all four populations compared with the Lifsar/Tritenva and the Turbuhaler devices, findings consistent with the lower internal resistance of the reference device compared with the test device and the Turbuhaler for which the internal resistance is similar.

IV.3 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.4 Clinical safety
With the exception of the data generated during the pharmacokinetic and pharmacodynamic studies, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the pharmacokinetic and pharmacodynamic studies.

IV.5 Use in children and adolescents/use in mild and mild to moderate asthma
As Lifsar and Tritenva are only available in a strength of 50 microgram salmeterol xinafoate/500 microgram fluticasone propionate these products do not have

- a dose range for use in children
- dose ranges for use and adults and adolescents with mild and mild to moderate asthma
- the ability to use as initial maintenance therapy in adults and adolescents with moderate persistent asthma
- any provision for downward titration of the dose to attain the minimally effective dose of the inhaled corticosteroid component to control disease

The product literature reflects the fact that, unlike the reference product, these products are not available in the lower strengths of 50 microgram salmeterol/100 microgram fluticasone propionate and 50 microgram salmeterol/250 microgram fluticasone propionate.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lifsar and Tritenva.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| **Systemic effects of inhaled corticosteroids (including adrenal suppression, cataract, glaucoma and decreased bone mineral density)** | Proposed text in SmPC: *Warning in section 4.4 that use of any inhaled corticosteroid, particularly at high doses prescribed for long periods may cause systemic effects (like Cushing’s syndrome, Cushingoid features and related symptoms, adrenal suppression and acute adrenal crisis). Relevant interactions that may increase fluticasone plasma concentration are described in section 4.5. Listed in section 4.8*  
*Information in section 4.9 that acute inhalation of fluticasone propionate doses in excess of those recommended may lead to temporary suppression of adrenal function.*  
*Pharmacokinetic properties in section 5.2*  
*Prescription only medicine* | None proposed                                                                                       |
| **Lower respiratory tract infections (pneumonia) in patients with COPD**     | Proposed text in SmPC: *Warning in section 4.4 that there was an increased reporting of lower respiratory tract infections (particularly pneumonia and bronchitis) in patients with COPD receiving Salmeterol + Fluticasone.*  
*Listed in section 4.8*  
*Pharmacodynamic properties in section 5.1*  
*Prescription only medicine* | None proposed                                                                                       |
<p>| <strong>Hyperglycaemia</strong>                                                           | Proposed text in SmPC: <em>Warning in section 4.4 that very rare cases of increases in blood glucose levels have</em> | None proposed                                                                                       |</p>
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>been reported and that caution should be taken when prescribing to patients with a history of diabetes mellitus. Relevant interactions that may increase blood glucose are described in section 4.5 Listed in section 4.8 Prescription only medicine</td>
<td></td>
</tr>
<tr>
<td>Paradoxical bronchospasm</td>
<td>Proposed text in SmPC: Warning in section 4.4 that as with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Listed in section 4.8 Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypersensitivity reactions including anaphylactic reactions</td>
<td>Proposed text in SmPC: Contraindications in patients with hypersensitivity to any of the active substances or to the excipient in section 4.3 Warning in section 4.4 that the product contains lactose in amount which does not usually cause problems in lactose intolerant people. Listed in section 4.8 Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Medication error with Pulmojet device in patients switching from another marketed device and back</td>
<td>Proposed text in SmPC: Detailed instructions for use of Pulmojet SALFP are provided in section 4.2 Pouchology and method of administration with graphic pictorial guide. Instructions for use are briefed on outer carton including the link and QR code to instructional video. Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Off-label use</td>
<td>Proposed text in SmpC: Therapeutic indications in section 4.1 [Product name] is indicated in adults for the symptomatic treatment of patients with Chronic Obstructive Pulmonary Disease (COPD), with a FEV1 &lt; 60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. [Product name] is intended only for adults and should not be used in children and adolescents below 18 years of age. Posology and detailed description of population of patients for whose is the product aimed are captured in section 4.2 Prescription only medicine Information regarding the age range of patients the product is aimed for is reflected outer packaging carton box.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Interaction with potent CYP3A4 inhibitors</td>
<td>Proposed text in SmpC: Warning in section 4.5 that concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment should therefore be avoided. Relevant interactions increasing systemic exposure and consequently systemic effects of salmeterol and fluticasone are described in section 4.5 Relevant adverse effects resulting from these interactions are listed in section 4.8 Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Serious cardiovascular events</td>
<td>Proposed text in SmPC. <strong>Warning in section 4.4</strong> that rarely, salmeterol/fluticasone may cause cardiac arrhythmias e.g. supraventricular tachycardia, extra-systoles and atrial fibrillation. Relevant interactions that may increase salmeterol plasma concentration (which is responsible of cardiovascular events) are described in section 4.5. Listed in section 4.8. Information in section 4.9 about signs and symptoms of salmeterol overdose which are dizziness, increase in systolic blood pressure, tremor, headache and tachycardia. Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>Proposed text in SmPC. <strong>Warning in section 4.4</strong> that a mild transient reduction in serum potassium at high therapeutic doses may develop. Relevant interactions that may increase salmeterol plasma concentration responsible for potentially serious hypokalaemia are described in section 4.5. Listed in section 4.8. Information in section 4.9 that hypokalaemia can occur in cases of overdose and therefore serum potassium levels should be monitored. Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>Proposed text in SmPC. <strong>Instructions for use in section 4.2</strong> that</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
IV.6 Discussion of the clinical aspects
The grant of Marketing Authorisations is recommended.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Lifsar and Tritenva have been demonstrated to be therapeutically equivalent to the authorised product Seretide Accuhaler 50 microgram/500 microgram/dose inhalation powder, pre-dispensed, although as lower strength products are not included in this product range the product indications are limited to COPD in adults.

Extensive clinical experience with salmeterol xinafoate and fluticasone propionate is considered to have demonstrated the therapeutic value of these compounds. The benefit/risk balance is, therefore, considered to be positive and a Marketing Authorisation may be granted.
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>