

**Public Clinical Assessment Report
Paediatric data**

**Pulmicort Nebuliser Suspension 0.125/ 0.25/ 0.5 mg/ml
Budesonide**

Marketing Authorisation Holder: AstraZeneca

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| Date of this report: | 01.06.2006 |
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ADMINISTRATIVE INFORMATION

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| Currently approved indication(s): | Patients with bronchial asthma who require maintenance treatment with glucocorticosteroids for control of the underlying airway inflammation. |
| Pharmaceutical form(s) affected by this variation: | Nebuliser suspension for inhalation |
| Strength(s) affected by this procedure: | 0.125/ 0.25/ 0.5 mg/ml |

I. RECOMMENDATION

Based on the review of the paediatric data on safety and efficacy, the Rapporteur and Co-Rapporteur consider that the paediatric indication for Pulmicort (budesonide), in the treatment of asthma that requires treatment with glucocorticosteroids is confirmed. It is the Rapporteur's / Co-Rapporteur's opinion that the amendments proposed in chapter IV of this report should be implemented in the SPCs, (if not already included).

I.1 Scope of the variation

None proposed by the MAH.

II. SCIENTIFIC DISCUSSION

II.3 <clinical aspects>

Pulmicort Nebuliser suspension has been approved in Finland in 1990 as first European country. It is approved for the treatment of asthma in adult and paediatric patients in more than 70 countries world-wide. It has been approved in most member states of the EU. In European countries Pulmicort has been approved for children from up to ≥ 0.5 years with a maximum dose of 2 mg /d. In contrast to the European countries, in the US Pulmicort Nebuliser solution has been approved for the treatment of asthma in children of 12 months to 8 years with a dose range of 0.25 mg/ d to 1.0 mg/d. The FDA concluded that the studies did not contain a sufficient number of patients below 12 months. For this variation the MAH submitted altogether 15 studies in paediatric patients. Pulmicort nebuliser suspension has been nationally approved. Because of the lack of a homogeneous European SPC, the Core data sheet has been assessed.

<III.3.1 Clinical pharmacology>

<N/A>

<III.3.2 Clinical efficacy>

Main study(ies)

Study code: 04-3069

Study phase: III

Country: USA (26 sites)

Study design: Randomised, placebo-controlled, double-blind, 4 parallel groups

Objective: to compare the relative efficacy and safety of budesonide nebuliser suspension, 0.25 mg, 0.5 mg and 1.0 mg administered QD, vs placebo, in paediatric non-steroid dependent asthmatic patients aged six month to eight years.

Study and control drugs: BUD NEB 0.25 QD, 0.5 QD, 1.0 QD mg/ml, Placebo QD

Duration: 12 weeks (08/94-12/95)

Main inclusion criteria: Paediatric non-steroid dependent asthmatics (six months to eight years), diagnosis of asthma as defined by the NIH, including: frequent exacerbations of cough and or wheezing, including nocturnal asthma, with infrequent severe exacerbations, during the last six month, daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least three months prior Visit 1, if capable of lung function test: basal FEV1 $\geq 50\%$ of predicted and reversibility $\geq 15\%$ after inhaled bronchodilator.

Primary endpoints: Mean changes from baseline in night-time (NTSC) and daytime asthma (DTSC) symptom scores over the 12 week-treatment phase

No. of randomised patients: N= 359

Mean age: 4.2 years (0-8 years)

Results:

Efficacy: All active treatment groups showed significant improvement compared to placebo in daytime and night-time asthma symptom scores and number of days of use of breakthrough medication. In the subset of patients capable of performing lung function tests, the 0.5 mg and the 1.0

mg groups, in contrast to the 0.25 mg group, showed clinically and statistically significant improvement compared to placebo.

Main efficacy results:

| | Placebo N= 92 | BUD NEB 0.25 mg QD N= 91 | BUD NEB 0.5 mg QD N= 82 | BUD NEB 1.0 mg QD N= 93 |
|---|------------------|--------------------------------|-------------------------------|-------------------------------|
| NTSC | -0.16 | -0.49*** | -0.42** | -0.42** |
| DTSC | -0.26 | -0.57** | -0.46* | -0.50* |
| Number of days use of Breakthrough Medication | -4.19 | -6.26* | -6.31* | -5.98* |

* p≤ 0.050, **p≤ 0.010, *** p ≤0.0010 vs placebo

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between active treatment groups and placebo. There were no clinical signs of HPA-axis suppression. There were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to placebo. The most frequently reported AEs are displayed in the table below. SAEs: 10 (2 at baseline, 1 placebo (bronchospasm), 7 BUD NEB (bronchospasm, pneumonia, meningitis, atelectasis, hypoxia, cellulitis), DAEs: 4.

Most frequently reported AEs that were more frequent in at least one of the BUD NEB groups:

| AE | Placebo N= 92 | BUD NEB 0.25mg N= 91 | BUD NEB 0.5 mg N= 83 | BUD NEB 1.0 mg N= 93 |
|-----------------|------------------|----------------------------|----------------------------|----------------------------|
| Sinusitis | 14% | 8% | 13% | 15% |
| Rhinitis | 10% | 5% | 10% | 14% |
| Coughing | 4% | 5% | 8% | 9% |
| Pharyngitis | 8% | 4% | 5% | 11% |
| Bronchitis | 3% | 3% | 7% | 5% |
| Bronchospasm | 4% | 5% | 5% | 4% |
| Infection viral | 3% | 5% | 5% | 2% |
| Gastroenteritis | 4% | 4% | 4% | 6% |
| Diarrhoea | 3% | 4% | 6% | 1% |
| Headache | 10% | 9% | 7% | 11% |
| Epitaxis | 0% | 3% | 5% | 2% |

Rapporteur's comment: This is one of the larger studies. Although it is not fully in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (e.g. duration, inclusion criteria not in accordance with/ no stratification according to the GINA criteria) this randomized, double-blind and placebo controlled study demonstrates the efficacy of budesonide nebuliser solution administered QD compared to placebo. Stratification according to age groups would have been helpful in assessing efficacy and safety in the different age groups. No BID group was included; therefore conclusion on the inferiority/superiority of this dosing scheme can not be drawn.

The reported AEs are consistent with what is expected in this patient population. The higher frequency of SAEs could be attributed to the larger sample size in the BUD NEB group. For a stratification for age (< 12months, ≥ 12months <4 years, ≥ 4 years) with assessment of efficacy and safety in the different age groups please refer to the applicant's response to Q1. Data on HPA suppression was only collected in a small subset of patients (N= 26, 26, 25, 30 for placebo, 0.25 mg, 0.5 mg, 1.0 mg, respectively).

Co-Rapporteur's comment: This study was one of the pivotal studies for the US approval. The significant improvements of primary and secondary efficacy variables compared to placebo did not show a clear dose-dependant pattern.

Study code: 04 3100

Study Phase: III

Country: USA (38 sites)

Study design: Multi-centre, randomised, placebo-controlled, double-blind, 5 parallel groups

Objective: to compare the relative efficacy and safety of BUD NEB, 0.25 mg QD, 0.25 mg BID, and 1.0 mg QD, versus placebo, in paediatric asthmatic patients aged six months to eight years

Study and control drugs: BUD NEB 0.25 QD, 0.25 BID, 0.5 BID, 1.0 QD mg/ml, Placebo

Duration: 12 weeks (05/95-06/96)

Main inclusion criteria: Paediatric mild to moderate asthmatics (six months to eight years), Diagnosis of asthma as defined by the NIH, including: frequent exacerbations of cough and/or wheezing, including nocturnal asthma, with infrequent severe exacerbations, during the last six month, daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least three months prior Visit 1, if capable of lung function test: basal FEV1 ≥ 50% of predicted and reversibility ≥ 15% after inhaled bronchodilator.

Primary endpoints: Mean changes from baseline in night-time and daytime asthma symptom scores over the 12 week-treatment phase

No. of randomised patients: N= 481

Mean age: 4.1 years (0-8 years)

Results:

Efficacy: All active treatment groups showed greater reduction in daytime (DTSC) and night-time (NTSC) asthma symptom scores compared to placebo, which were statistically significant in all but the 0.25 mg QD group. In the subset of patients capable of performing PEF manoeuvres, there were significantly greater improvements in both the morning and the evening PEF in all active treatment groups, however the improvements in the 0.25 mg QD group for the morning PEF and in the 1.0 mg group for the evening PEF did not reach statistical significance.

Summary of efficacy results:

| | Placebo N= 92 | BUD NEB | | | |
|---|------------------|-------------------|---------------------|--------------------|-------------------|
| | | 0.25mg QD N=93 | 0.25 mg BID N=97 | 0.5 mg BID N=96 | 1.0 mg QD N=93 |
| NTSC | -0.13 | -0.28 | -0.49*** | -0.42** | -0.40** |
| DTSC | -0.19 | N=92 -0.28 | -0.40* | -0.46** | -0.37* |
| Number of days use of breakthrough medication | -2.36 | -4.39* | -5.22*** | -4.92** | -4.38* |
| Morning PEF | N=32 -0.2 | N=32 10.9 | N=34 23.0** | N=29 24.8** | N=34 17.1* |
| Evening PEF | N=32 | N=32 | N=34 | N=29 | N=34 |

| | | | | | |
|------|--------------|--------------|--------------|---------------|--------------|
| | 1.9 | 16.8* | 19.2* | 21.0** | 14.1 |
| FEV1 | N=28 0.04 | N=31 0.07 | N=33 0.08 | N=29 0.17* | N=34 0.11 |

*p≤ 0.050, ** p≤ 0.010, ***p≤0.001, vs placebo

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between active treatment groups and placebo. There were no clinical signs of HPA-axis suppression. There were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to placebo. The SAEs and DAEs were rare during the study. SAEs: 15 (4 Placebo; 11 BUD NEB, the nature of SAEs is comparable between groups), DAEs: 6 (2 Placebo, 4 BUD NEB, the nature of these AEs is comparable between groups).

Summary of most frequently reported AEs that occurred in a higher frequency in at least one of the BUD NEB groups:

| AE | Placebo N=95 | BUD NEB | | | |
|-----------------------|-----------------|--------------------|---------------------|--------------------|-------------------|
| | | 0.25 mg QD N=94 | 0.25 mg BID N=99 | 0.5 mg BID N=97 | 1.0 mg QD N=95 |
| Respiratory infection | 29% | 32% | 30% | 41% | 38% |
| Rhinitis | 9% | 10% | 9% | 13% | 8% |
| Pharyngitis | 5% | 3% | 6% | 3% | 3% |
| Pain | 0% | 1% | 1% | 3% | 5% |
| Infection viral | 3% | 5% | 6% | 3% | 4% |
| Moniliasis | 2% | 6% | 4% | 2% | 6% |
| Gastroenteritis | 6% | 6% | 7% | 7% | 3% |
| Vomiting | 2% | 2% | 6% | 5% | 2% |
| Ear infection NOS | 3% | 2% | 4% | 6% | 6% |

Rapporteur's comment: This is also one of the larger studies. Although it is not fully in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (e.g. duration, inclusion criteria not in accordance with/ no stratification according to the GINA criteria) this study supports the efficacy claim. Stratification according to age groups (< 12months, ≥ 12months <4 years, ≥ 4 years) is shown in the answer to Q 1.. There is a higher frequency of respiratory infections in the BUD NEB group which has been addressed in the answer to Q5. The remaining AEs are in the line with what has to be expected in this patient population.

Co-Rapporteur's comment: This was another pivotal study for the US approval. The 0.5 mg BID regimen achieved the most consistent efficacy, followed by 0.25 mg BID and 1.0 mg QD.

Study code: 04 3072

Study Phase: III

Country: USA (17 sites)

Study design: Randomised, placebo-controlled, double-blind, 4 parallel groups

Objective: to compare the relative efficacy and safety of budesonide nebuliser suspension, 0.25 mg, 0.5 mg, and 1.0 mg BID, vs placebo, in inhaled steroid-dependent paediatric asthmatic patients aged four to eight years.

Study and control drugs: BUD NEB 0.25 BID, 0.5 BID, 1.0 BID mg/ml, Placebo

Duration: 12 weeks (05/94-11/96)

Primary endpoints: Mean changes from baseline in night-time and daytime asthma symptom scores over the 12 week-treatment phase

No. of randomised patients: N= 178

Mean age: 6.2 years (4-9 years)

Main inclusion criteria: Paediatric inhaled steroid dependent asthmatics (four to eight years), Diagnosis of asthma as defined by the NIH, including: frequent exacerbations of cough and/ or wheezing, including nocturnal asthma, with infrequent severe exacerbations, during the last six month, daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least three months prior Visit 1, if capable of lung function test: basal FEV1 \geq 50% of predicted and reversibility \geq 15% after inhaled bronchodilator.

Results:

Efficacy: There were significantly greater improvements in daytime (DTSC) and night-time (NTSC) asthma symptom scores in all budesonide groups compared to the placebo group. The morning PEF showed significantly greater improvement in all active treatment groups compared to placebo. More (43%) patients discontinued from the placebo group compared to the BUD NEB group (13%, 12%, 20% for 0.25 mg BID, 0.5 mg BID, 1.0 mg BID, respectively; $p \leq 0.023$ BUD NEB vs placebo). 36% of the patients in the placebo group discontinued due to worsening of asthma compared to 11%, 2%, 13% for the 0.25 mg BID, 0.5 mg BID, 1.0 mg BID groups, respectively ($p \leq 0.015$ BUD NEB vs placebo)

Main efficacy results:

| | Placebo N= 44 | BUD NEB | | |
|--|------------------|----------------------|--------------------|---------------------|
| | | 0.25 mg BID N= 47 | 0.5 mg BID N=42 | 1.0 mg BID N= 44 |
| NTSC | -0.08 | -0.36* | -0.37* | 0.36* |
| DTSC | -0.11 | -0.45* | -0.53** | N=45 -0.55** |
| Number of days of use of breakthrough Medication | -3.14 | -5.56* | -6.66** | -6.00* |
| Morning PEF (L/min) | -1.3 | 15.3** | 11.8* | 10.4* |
| Evening PEF (L/min) | 3.0 | 14.9 | 11.6 | 13.2 |
| FEV1 (L) | N=41 -0.01 | N=46 0.05 | N=42 0.08* | N=45 0.07 |

* $p \leq 0.050$, ** $p \leq 0.010$, vs Placebo

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between active treatment groups and placebo. There were no clinical signs of HPA-axis suppression. There were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to placebo (including nasal and oral fungal cultures). The SAEs and DAEs were rare during the study. SAEs: 2 (1 Placebo; 1 BUD NEB), DAEs: 5 (2 Placebo; 3 BUD NEB).

Summary of most frequently reported AEs that occurred in higher frequency in at least one of the BUD NEB groups:

| AE | Placebo N= 44 | BUD NEB BID | | |
|----|------------------|-------------|--------|--------|
| | | 0.25 mg | 0.5 mg | 1.0 mg |

| | | N= 47 | N=42 | N= 45 |
|-----------------------|-----|-------|------|-------|
| Respiratory infection | 34% | 36% | 38% | 38% |
| Rhinitis | 9% | 15% | 12% | 11% |
| Coughing | 2% | 13% | 10% | 7% |
| Pharyngitis | 9% | 6% | 12% | 7% |
| Flu-like disorder | 0% | 0% | 5% | 4% |
| Otitis media | 5% | 11% | 2% | 7% |
| Moniliasis | 0% | 0% | 10% | 2% |
| Gastroenteritis | 2% | 6% | 2% | 7% |
| Headache | 5% | 15% | 5% | 9% |
| Earache | 2% | 0% | 5% | 0% |
| Conjunctivitis | 0% | 6% | 0% | 0% |
| Rash | 2% | 6% | 0% | 0% |

Rapporteur's comment: This is also one of the larger placebo-controlled studies. It is also not fully in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (e.g. duration, inclusion criteria/patient stratification not in accordance with the GINA criteria). A higher dose group of 1.0 mg BID was investigated. Significant improvements in several main parameters in the active treatment groups that support the efficacy claim were established.

The HPA-function was only assessed in a small subset of patients (placebo :8; 0.25 mg BID: 14; 0.5 mg BID: 11, 1.0 mg BID: 13). No patient in the placebo group shifted from normal at baseline to abnormal under treatment in the ACTH stimulation test compared to 2, 1, 1 patient in the 0.25 mg BID, 0.5 mg BID, 1.0 mg BID BUD NEB group. Most of the reported AEs have already been labelled and are consistent with what is expected in this patient population. The frequency of AEs in the highest dose group is comparable to the lower dose groups.

Co-Rapporteur's comment: This was the third pivotal study for the US approval. The significant improvements of the efficacy variables were, to large extent, not dose-dependent. The numerical decrease in the adjusted mean change in ACTH-stimulated cortisol level from baseline was greater in the 1.0 BID group than in placebo suggesting a systemic effect.

Study code: DX-RES 2000

Study Phase: IIIB

Country: USA (36 sites)

Study design: Multi-centre, randomised, active-controlled, open-label, 2 parallel groups

Objective: to assess the effects of BUD NEB 0.5 mg/d compared with nebulised sodium cromoglycate on asthma-related health outcomes in paediatric patients 2 to 6 years of age requiring anti-inflammatory therapy for mild persistent to moderate persistent asthma

Study and control drugs: BUD NEB: 0.5 mg/d for the first 8 weeks, then 0.25 to 2.0 mg/d (depending on individual need). Nebulised sodium cromoglycate: 20 mg four times a day for 8 weeks then titrated.

Duration: 52 weeks (09/97-03/99)

Primary endpoints: Rate of asthma exacerbations over 52 week treatment period.

No. of randomised patients: N= 335

Mean age: 3.8 years (2-6 years)

Main inclusion criteria: Paediatric patients (2-6 years) with mild persistent or moderate persistent asthma as defined by the NIH with asthma symptoms more frequent than two times a week, with

nocturnal symptoms more than two times a month, one or more exacerbations requiring systemic steroids during the last 6 months or at least two exacerbations during the prior 9 months, daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least 3 months.

Results:

Efficacy: There were significant differences in favour of Pulmicort Nebuliser suspension compared to Sodium cromoglycate nebuliser solution: mean asthma exacerbation rates (1.23/yr vs. 2.41/yr, $p \leq 0.001$), mean time to first asthma exacerbation (216 days vs. 147 days, $p \leq 0.001$), mean time to first use of additional chronic asthma medication (320 days vs 235 days, $p \leq 0.001$), mean change in breakthrough medication (-6.17 vs -4.07, $p \leq 0.001$), mean change in night-time asthma symptom score (-0.54 vs -0.30, $p \leq 0.001$), and mean daytime symptom score (-0.63 vs -0.35, $p \leq 0.001$).

Safety: There were a total of 45 serious AEs in 22 patients during open-label treatment: 9 (6%) patients with 17 SAEs in the sodium cromoglycate group and 13 (8%) patients with 28 SAEs in the budesonide group. All of the SAEs were judged by the investigator as unlikely related to study treatment. There were no clinically relevant differences in the type, incidence, or severity of AEs between the two treatment groups, nor any clinically relevant in laboratory tests, vital signs, or physical examination outcomes. There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between the two treatment groups. There was no evidence of HPA-axis suppression in patients treated with Pulmicort nebuliser suspension. The height measurements (stadiometry) showed a difference in growth velocity of 0.87 cm, which was statistically significant.

Summary of most frequently reported AEs:

| AE | Sodium cromoglycate N= 162 | BUD NEB N= 168 |
|-----------------------|-------------------------------|-------------------|
| Respiratory infection | 57% | 57% |
| Sinusitis | 26% | 30% |
| Pharyngitis | 21% | 20% |
| Rhinitis | 13% | 13% |
| Bronchitis | 14% | 11% |
| Pneumonia | 6% | 6% |
| Coughing | 5% | 5% |
| Otitis media | 28% | 30% |
| Viral infection | 15% | 11% |
| Fever | 20% | 21% |
| Gastroenteritis | 9% | 8% |
| Vomiting | 5% | 8% |
| Diarrhoea | 3% | 9% |
| Rash | 4% | 6% |
| Headache | 4% | 5% |
| Conjunctivitis | 4% | 6% |

Rapporteur's comment: This study is also not totally in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma (e.g. stratification of patients according to asthma severity.) It compares BUD NEB to nebulised sodium cromoglycate, a weak controller medication, but lacks a placebo arm recommended in patients with mild persistent asthma. 21 patients had protocol violations in the inclusion/exclusion criteria. Nevertheless the study demonstrated superior efficacy over the reference product. The patients treated with BUD NEB had a slower growth velocity compared to the reference product. These AEs are reflected in the SPC of BUD

NEB. The remaining frequencies and nature of AEs are comparable between groups with no unexpected AEs in both groups.

Supporting studies:

Study code: SD-004-0765

Study Phase: III

Country: Japan (11 sites)

Study design: Randomized, open-label, 2 parallel groups

Primary objective: to investigate the efficacy and safety of BUD NEB at a daily dose of 0.5-1.0 mg administered for 24 weeks as once daily or twice daily inhalation to Japanese children with bronchial asthma, by evaluation of the frequency of asthma attacks, frequency and severity of AEs, and effects on clinical laboratory values

Study and control drugs: BUD NEB: 0.5 mg/d (QD or BID) could be increased to 1.0 mg/d at week 6, if clinical response was insufficient.

Duration: 24 weeks (07/03-08/04)

Primary endpoints: Change in frequency of asthma attacks per week at week 12 from baseline.

No. of randomised patients: N= 61

Mean age: 2.0 years (0-4 years)

Main inclusion criteria: Japanese paediatric asthma patients, aged 0.5-4 years, which required treatment with inhaled steroids, before inclusion in treatment period: 6 or more days with symptoms during the last 14 days.

Results:

Efficacy: The frequency of asthma attacks decreased from 9.92/ week at baseline to 2.93/ week at week 12 (change of -6.99/ week, $p < 0.001$). The mean change from baseline to week 12 was comparable between the final doses.

Safety: 15 (24.6%) patients reported SAEs up to week 12 and 24 (39.3%) patients reported SAEs during the whole 24-week treatment period. No patient was discontinued due to SAEs. None of the SAEs was judged by the investigator to be related to the investigational product. There were no deaths and one DAE. There were 273 AEs in 61 patients, which was a relatively higher rate than in corresponding 12 week US studies. The pattern of AEs was similar during the run-in period and during active treatment, indicating that the higher frequency of AEs in the study was not a consequence of the treatment. There were no new or unexpected AEs observed.

Rapporteur's comment: This is a small uncontrolled study conducted in the Japanese population. Therefore it is not of much relevance to this assessment but on the other side, its results do not contradict a positive benefit-risk-relation for BUD NEB.

Co-Rapporteur's comment: This was an open Japanese study comparing two doses of 0.25 and 0.5 mg. The mean plasma level cortisol decreased from baseline to week 12, without further decrease between Week 12 and Week 24. No symptoms or signs suggesting adrenal hypofunction or dysfunction were observed during the study period.

Study code: 04-9239

Study Phase: IIB

Country: France

Study design: Randomised, double blind, 2 parallel groups

Objective: to compare two doses of BUD NEB 0.25 mg BID and 1.0 mg BID, over 12 weeks in protecting from acute exacerbation in moderate to severe asthmatic infants.

Study and control drugs: BUD NEB: 0.25 mg BID, 1.0 mg BID

Duration: 12 weeks (09/92-07/93)

Primary endpoints: Number of patients with at least one exacerbation and time to first exacerbation.

No. of randomised patients: N= 67

Mean age: 20.7 months (6-40 months)

Main inclusion criteria: Children 6 months to 3 years with asthma defined as recurrent exacerbations of dyspnoea associated with wheezing, at least 3 exacerbations during the last 12 months, instable

asthma with either persistent daily symptoms during the previous month or at least one exacerbation during the previous month, treatment with ketotifen for at least two month.

Results:

Efficacy: There were no significant differences between the treatment groups in the number of patients who had an exacerbation (48% in the lower dose group vs 37% in the higher dose group, $p=0.33$), nor in the time to first exacerbation ($p=0.30$). However, the high dose group had significantly less day- and night-time wheeze and used less oral salbutamol.

Safety: Both doses were well tolerated. The reported AEs mainly refer to the respiratory system and are in line with what was reported in the other studies. DAE: 2; SAE: 8.

Rapporteur's comment: This is a small uncontrolled study comparing two different doses of BUD NEB. It also evaluates the maximum recommended dose of 2 mg/d in children of at least 0.5 years. The number of patients of this young age is not given. Considering the low number of patients enrolled this number has to be quite small. Ketotifen is used as co-medication. This is not the drug of choice for the therapy of asthma/ recurrent wheezing nowadays. No significant differences for the primary endpoints between the treatment groups were established during the 12 weeks treatment period. The scope of AEs is in line with the other studies and the labelling.

Co-Rapporteur's comment: Only the Study Report, without figures and tables is submitted. The higher dose did not have any advantage over the lower dose on the primary efficacy variable. Significant better effect of the higher dose was seen for some, but not all secondary variables.

Study code: 04-9258

Study Phase: IIIB

Country: Portugal

Objective: to investigate whether BUD NEB in doses of 1.0 mg BID or 0.5 mg BID would be more effective than nebulised placebo to protect against acute exacerbations in moderate to severe asthmatic infants

Study design: Randomised, double blind, placebo-controlled, 3 parallel groups

Study and control drugs: BUD NEB: 0.5 mg BID, 1.0 mg BID, Placebo

Duration: 12 weeks (03/93-08/94)

Primary endpoints: Patients with asthma exacerbations requiring oral/systemic steroids, asthma symptoms, and physician global assessment of asthma

No. of randomised patients: N= 92

Mean age: 22.5 months (7-46 months)

Main inclusion criteria: Children 6 months to 3 years with asthma defined as recurrent exacerbations of dyspnoea associated with wheezing, at least 3 exacerbations during the previous 12 months, persistent daily symptoms during the previous 15 days or at least one exacerbation per month during the previous 3 month, treatment with ketotifen for at least 15 days previous to randomisation.

Results:

Efficacy: Seven patients in the placebo group (23%), 10 in the 0.5 mg BID group (32%) and 8 in the 1 mg BID group (28%) had at least one exacerbation of asthma during the 12 weeks treatment period. The difference between groups was not statistically significant ($p=0.74$).

Safety: All treatments were well tolerated. 18 patients in the placebo group, 20 patients in the 0.5mg BID group and 19 patients in the 1.0 mg BID group had at least one AE. The nature of AEs (mainly respiratory system) was in accordance with what is expected in this patient population and what is reflected in the label. DAE: 0; SAE: 4 (all BUD NEB group: 2 pneumonia, 2 asthma attack).

Rapporteur's comment: This is a small placebo-controlled study. The incidence of asthma exacerbations was the lowest in the placebo group with no significant differences between groups. The short duration of 12 weeks might have contributed to this fact. The co-medication ketotifen is no longer the therapy of choice for the therapy of asthma/ recurrent wheezing in children. The safety profile is in accordance with the label and with what is expected in the enrolled population.

Co-Rapporteur's comment: Only the Study Report, without all the appendices, is submitted. This was a small study with the same objectives as 04-9239 and 04-9270, the results were not conclusive.

Study code: 04-9270

Study Phase: IIB

Country: Israel

Study design: Randomised, double blind, 2 parallel groups

Objective: to compare the relative efficacy and safety of two starting dose schedules: a high dose followed by stepwise decrease or a continuous low dose.

Study and control drugs: Group A: BUD NEB: start with 1.0 mg BID thereafter 25% decrease every second day reaching 0.25 mg BID maintenance dose. Group B: BUD NEB 0.25 mg BID.

Duration: 8 days + 9 weeks (09/93-06/95)

Primary endpoints: Asthma symptom score, mean time to clinical response.

No. of randomised patients: N= 48

Mean age: Group A: 21.5 months, Group B: 17.1 months (0.5-3 years)

Main inclusion criteria: paediatric patients (0.5-3 years) with recurrent wheezing inadequately controlled with bronchodilator therapy

Results:

Efficacy: There was a statistically significant decrease of asthma symptoms in Group A after the first treatment week (59% improvement in wheezing ($p=0.0001$), 39% in diurnal cough ($p=0.036$), and 38% in nocturnal cough ($p=0.04$), compared to a 2%, 14%, 11% improvement in group B respectively. Mean time to clinical response was 3.0 days in group A and 5.7 days in group B ($p=0.02$). After the first week of treatment, a further gradual reduction of symptoms was noted in both groups. However mean symptom scores continued to be lower in group A for the remainder of the maintenance period.

Safety: The high dose starting schedule was not associated with any significant change in serum cortisol. Side effects were mostly mild (fever, vomiting, diarrhoea). SAE:2; DAE:1.

Rapporteur's comment: This is a small study comparing two different dosing schedules. The results suggest that higher starting doses with subsequent stepwise reductions might be of advantage to control asthma patients with unstable disease. No further information on the nature or frequency of AEs is given.

Co-Rapporteur's comment: At study end, ACTH stimulated cortisol levels were similar to baseline levels in both groups.

Analysis performed across trials (pooled analyses and meta-analysis):

N/A

<III.3.3 Clinical safety>

The MAH did not give a summary on the submitted trials concerning patient exposure, adverse events and so on. Therefore the studies conducted mainly to establish safety are summarised below.

Study code: 04-3069b (Extension of 04-3069)

Study Phase: III

Country: USA (26 sites)

Study design: Multi-centre randomized open-label, active-controlled, parallel-group.

Objective: to assess the long-term safety of the lowest individual maintenance dose of BUD NEB when administered for a period of up to one year as compared to conventional asthma therapy in paediatric asthmatic patients aged six months to eight years

Study and control drugs: BUD NEB: 0-1.0 mg QD, Control group: Conventional asthma therapy

Duration: 52 weeks (10/94-12/96)

Primary endpoints: Mainly safety (e.g. AEs, HPA-axis function)

No. of randomised patients: N= 272

Mean age: 4.2 years (0.5-8 years)

Inclusion criteria: Successful completion of 04-3069, or discontinued from 04-3069 because of need for oral corticosteroids for worsening asthma

Results:

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between active treatment groups and conventional therapy after the treatment for up to one year. There were no clinical signs of HPA-axis suppression. After adjusting for the length of the study, there were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to conventional asthma therapy, and differences in vital signs, or physical examination, or in nasal or oral fungal cultures between treatment groups. The mean measured growth velocity over one year for all patients in the BUD NEB group was 6.55 ± 2.08 cm compared to 7.39 ± 2.52 cm in the conventional asthma therapy group. There were statistically significant differences in the estimated growth velocities between treatment groups for all patients ($p=0.002$) and male patients ($p=0.002$), but not for female patients ($p=0.416$) (growth velocity in female patients was 6.91 ± 2.43 BUD NEB; 7.56 ± 2.33 Placebo). SAEs: 21 (placebo: 4; BUD NEB: 17), DAEs: 2 (1 placebo, 1 BUD NEB).

Summary of incidences of most frequently reported adverse events that began during open-label treatment:

| AE | Conventional asthma therapy N= 90 | BUD NEB N= 182 |
|-----------------------|--------------------------------------|-------------------|
| Respiratory infection | 54% | 65% |
| Sinusitis | 21% | 26% |
| Rhinitis | 10% | 16% |
| Pharyngitis | 11% | 12% |
| Bronchitis | 8% | 8% |
| Coughing | 7% | 7% |
| Bronchospasm | 7% | 6% |
| Pneumonia | 10% | 5% |
| Fever | 19% | 25% |
| Flu-like disorder | <3% | 4% |
| Pain | 3% | 3% |
| Epistaxis | <3% | 3% |
| Otitis media | 17% | 19% |
| Moniliasis | <3% | 4% |
| Gastroenteritis | 6% | 12% |
| Pharynx disorder | 0% | 3% |
| Rash | 7% | 8% |
| Dermatitis fungal | 0% | 3% |
| Headache | 13% | 13% |
| Conjunctivitis | 4% | 8% |
| Eye infection NOS | <3% | 3% |

Efficacy: There were similar reductions in the daytime and night-time asthma symptom scores. The subset of patients able to perform consistent PEF showed similar improvements in morning and evening PEF. There was numerically lower systemic steroids use in Pulmicort Nebuliser Suspension treatment group, and numerical improvement in health status scores. More patients discontinued from

the conventional asthma therapy group (32% vs 14%, $p=0.001$). More patients in the conventional asthma therapy group than in the BUD NEB group discontinued due to worsening asthma (16% vs <1%, $p<0.001$).

Rapporteur's comment: This study was mainly designed to establish longer term safety. The reported AEs are in line with what is expected in this patient population and with the labelling. This is an active controlled study. Conventional asthma therapy was not standardized. Though the use of inhaled steroids was forbidden in this group seemingly 3% of the patients used beclomethasone. The HPA-axis function was only assessed in a subset of patients (N= 14 Placebo, N= 40 BUD NEB). 14% of the patients in the BUD NEB group compared to 0% in the conventional asthma group had normal ACTH stimulation tests at baseline and abnormal ones after therapy. The growth velocity was significantly lower in the BUD NEB group. These facts are already reflected in the SPC.

Co-Rapporteur's comment: This study was an open-label extension of the 04-3069 study. In the conventional asthma therapy group, the asthma therapy used were cromolyn sodium 79%, albuterol; 52%, nedocromil 8%; theophylline 6%, beclomethasone 3% and ipratropium 1%.

There was a numerically but not statistically significant decrease in the adjusted mean change in ACTH-stimulated cortisol levels from baseline in the budesonide group (-22.3 nmol/L) compared to conventional asthma therapy (39.1 nmol/L), see table J below from Study Report. In the budesonide group, 14 % of patients who had normal responsiveness in ACTH-stimulated cortisol levels at baseline showed abnormal responsiveness at Week 52 as compared to 0% in the conventional asthma therapy group.

The growth velocity (cm/year) was a significantly reduced in the budesonide group compared to the conventional asthma therapy group, 0.84 cm, see table L and figure E below from Study Report.

Table J. Summary Results of ACTH-Stimulated Cortisol Tests for Patients Who Completed One Year of Open-Label Treatment, Excluding Data From Clinical Center #17.¹

| Variable | | Open-Label Treatment | |
|--|----------|-----------------------------|----------------------------------|
| | | Conventional Asthma Therapy | Budesonide Nebulizing Suspension |
| <u>Cortisol Levels (nmol/L)</u> | | | |
| All patients: | | | |
| Basal: | Baseline | 249 | 320 |
| | Week 52 | 304 (n=16) | 301 (n=41) |
| ACTH Stimulated: | Baseline | 690 | 691 |
| | Week 52 | 725 (n=14) | 651 (n=40) |
| Male Patients: | | | |
| Basal: | Baseline | 228 | 333 |
| | Week 52 | 274 (n=8) | 318 (n=32) |
| ACTH Stimulated: | Baseline | 659 | 693 |
| | Week 52 | 681 (n=7) | 664 (n=30) |
| Female Patients: | | | |
| Basal: | Baseline | 271 | 272 |
| | Week 52 | 334 (n=8) | 238 (n=9) |
| ACTH Stimulated: | Baseline | 721 | 684 |
| | Week 52 | 768 (n=7) | 613 (n=10) |
| <u>Adjusted Mean Changes in ACTH-Stimulated Cortisol Levels from Baseline²</u> (p-value vs. conventional asthma therapy) | | | |
| All Patients | | 39.1 | -22.3 (p=0.293) |
| Male Patients | | 87.1 | -9.1 (p=0.284) |
| Female Patients | | 3.1 | -70.6 (p=0.356) |

¹ Data source: Section 14.3.5, Table 4b.

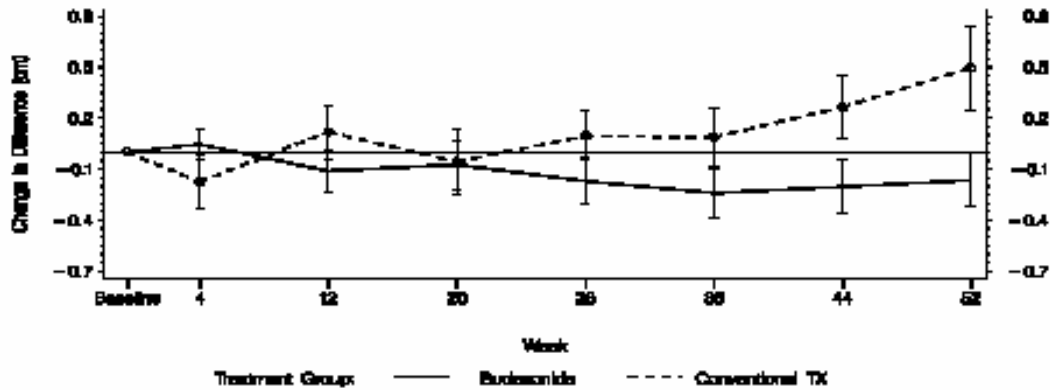
² Means adjusted for Center Effect.

Table L. Summary of Mean Measured Growth Velocity (cm/year) Over One Year (Week 0 to Week 52) for Patients Who Completed One Year of Open-Label Treatment.

| Stratification Group | Treatment Group | n | Mean Measured Growth Velocity ¹ |
|----------------------|-----------------|-----|--|
| All Patients | Budesonide | 150 | 6.55±2.08 |
| | Conventional | 58 | 7.39±2.51 |
| Male Patients | Budesonide | 103 | 6.38±1.89 |
| | Conventional | 36 | 7.28±2.64 |
| Female Patients | Budesonide | 47 | 6.91±2.43 |
| | Conventional | 22 | 7.56±2.33 |

¹ Data source: Table 22, of Section 14.3.5.

Figure E. The Mean (\pm Standard Error) Changes From Baseline in the Difference Between Observed Heights and Standard Median Height for all the Patients Who Completed One Year of Open-Label Treatment.



Study code: 04-3100b (Extension of 04-3100)

Study Phase: III

Country: USA (29 sites)

Study design: Multi-centre, randomized, active-controlled, parallel-group

Objective: to assess the long-term safety of the lowest individual maintenance dose of BUD NEB when administered for a period of up to one year as compared to conventional asthma therapy in paediatric asthmatic patients aged six months to eight years

Study and control drugs: BUD NEB: 0-1.0 mg QD, Control group: Conventional asthma therapy (including ICSs)

Duration: 52 weeks (11/95-06/97)

Primary endpoints: Mainly safety (e.g. AEs, HPA-axis function, skeletal age)

No. of randomised patients: N= 307

Mean age: 4.0 years (0.5-8 years)

Inclusion criteria: Successful completion of 04-3100, or discontinued from 04-3069 because of need for oral corticosteroids for worsening asthma

Results:

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between active treatment groups and conventional therapy. There were no clinical signs of HPA-axis suppression. There were no deaths during the study; there were 33 SAEs in 28 patients (11 SAEs in 11 patients (11%) in the conventional treatment group, and 22 SAEs in 17 patients (8%) in the budesonide treatment group). One patient discontinued from the BUD NEB group due to an AE (unusual behaviour in a patient with attention deficit disorder). After adjusting for the length of the study, there were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to conventional asthma therapy, and differences in vital signs, or physical examination. There were no differences in growth velocities between groups assessed by stadiometry (mean growth velocities were 6.96 cm /yr and 6.21 cm /yr in the budesonide and in the conventional treatment groups, respectively). The assessments to determine the possible effects of study treatment on skeletal growth (determined by external and internal (medullary cavity) diameters, and the cortical thickness of the midshaft of the second metacarpal from left hand x-rays) showed no significant differences between Pulmicort nebuliser and conventional asthma therapy in the mean differences between observed skeletal age and chronological age over one year of treatment.

Summary of most frequently reported AEs that were reported in equal or higher frequency in the BUD NEB group:

| AE | Conventional asthma therapy | BUD NEB |
|-----------------------|-----------------------------|---------|
| Respiratory Infection | 47% | 54% |
| Sinusitis | 31% | 40% |
| Pharyngitis | 21% | 23% |
| Rhinitis | 10% | 19% |
| Bronchitis | 8% | 13% |
| Coughing | 6% | 9% |
| Pneumonia | 6% | 7% |
| Stridor | 4% | 4% |
| Fever | 21% | 31% |
| Flu-like disorder | 4% | 6% |
| Pain | 4% | 5% |
| Otitis media | 22% | 25% |
| Moniliasis | 3% | 6% |
| Gastroenteritis | 9% | 9% |
| Vomiting | 2% | 8% |
| Abdominal pain | 4% | 5% |
| Rash/ Rash pustular | 7% | 10% |
| Eczema | 3% | 5% |
| Urticaria | 2% | 5% |
| Headache | 4% | 8% |

Efficacy: There were similar reductions in the daytime and night-time asthma symptom scores. The subset of patients able to perform consistent PEF showed similar improvements in morning and evening PEF. There was numerically lower systemic steroids use in the Pulmicort Nebuliser Suspension treatment group, and numerical improvement in health status scores. The proportion of patients who were discontinued from the conventional asthma therapy treatment group was significantly greater (29% vs 13%; p=0.001).

Rapporteur's comment: The relevance of this study is reduced by the fact that in the control group ICS were allowed (25% of the patients in the conventional asthma therapy group used beclometasone). This could explain the comparable growth rates and efficacy parameters.

Co-Rapporteur's comment: This study was an open-label extension of the 04-3100 study. The results on systemic effects as ACTH stimulation tests and growth velocity are difficult to interpret. The patients in the conventional treated group used inhaled steroids (46%) and a slightly higher average dose of oral prednisone. There was also higher dropout rate in children aged two years or less in the conventional treated group which also could affect the growth velocity results. In both treatment groups the mean increase in cortisol levels after ACTH stimulation were decreased at Week 52 compared to baseline. The adjusted mean changes in ACTH stimulated cortisol levels from baseline to Week 52 were numerically, but not significantly, reduced in patients on budesonide compared to those on conventional therapy. Psychiatric disorders were reported more frequently in the budesonide group (unusual behaviour, 1%, nervousness, 1%, aggressive reaction, 0.5%, euphoria, 0.5%, paroniria, 0.5%), than in conventional therapy group (unusual behaviour, 1%).

Study code: SD-004-0732

Study Phase: IV

Country: USA and its territories

Study design: Multi-centre, randomised, double-blind, placebo-controlled

Primary objective: to evaluate the safety of once-daily administration of BUD NEB compared with placebo for the treatment of mild to moderate asthma or recurrent or persistent wheezing in infants between the ages of 6 and 12 months.

Study and control drugs: BUD NEB: 0.5 mg QD, 1.0 mg QD, Placebo

Duration: 12 weeks (09/00-06/02)

Primary endpoints: mainly safety (e.g. HPA-axis function, AEs)

No. of randomised patients: N=141

Mean age: 8.4 months (5-12 months)

Main inclusion criteria: Paediatric patients (6-12 months) diagnosed with asthma or who had at least 2 episodes of persistent or recurrent wheezing and who might benefit from inhaled anti-inflammatory therapy.

Results:

Safety: The results did not indicate suppressive effects on adrenal function compared to placebo. The mean changes from baseline in the ACTH-stimulated minus basal plasma cortisol levels were similar among the 3 treatment groups, with no apparent decreases in cortisol levels resulting from active treatment. A shift to values < 500 nmol/L were observed in 7 patients (4, 2, and 1 in the 0.5 mg, 1.0 mg and placebo groups respectively). The overall incidence of AEs was 90%, 98%, and 88% in the 0.5 mg, 1.0 mg and placebo groups, respectively. The safety profile of Pulmicort nebuliser suspension, characterised by rates and types of AEs, SAEs and DAEs, was generally comparable to placebo and consistent with the labelling of the product.

Summary of AEs most frequent AEs that were reported more frequently in at least one BUD NEB group compared to placebo:

| AE | Placebo N= 48 | BUD NEB 0.5 mg N= 44 | BUD NEB 1.0 mg N= 49 |
|-----------------------|------------------|-------------------------|-------------------------|
| Respiratory infection | 46.9% | 50.0% | 45.8% |
| Otitis media | 40.8% | 27.3% | 47.9% |
| Rhinitis | 20.4% | 27.3% | 20.8% |
| Vomiting | 10.2% | 15.9% | 10.4% |
| Tooth disorder | 4.1% | 15.9% | 12.5% |
| Sinusitis | 8.2% | 13.6% | 8.3% |
| Rash | 6.1% | 9.1% | 10.4% |
| Conjunctivitis | 8.2% | 0.0% | 14.6% |
| Pharyngitis | 4.1% | 0.0% | 14.6% |
| Gastroenteritis | 6.1% | 2.3% | 8.3% |
| Dermatitis contact | 4.1% | 4.5% | 8.3% |
| Bronchospasm | 4.1% | 6.8% | 4.2% |
| Anorexia | 2.0% | 2.3% | 6.3% |
| Respiratory disorder | 4.1% | 0.0% | 6.3% |
| Nervousness | 0.0% | 2.3% | 6.3% |
| Bronchitis | 2.0% | 4.5% | 2.1% |
| Pneumonia | 0.0% | 2.3% | 4.2% |

| | | | |
|--------|------|------|------|
| Eczema | 2.0% | 4.5% | 0.0% |
|--------|------|------|------|

Efficacy: BUD NEB resulted in greater reduction in daytime (DTSC) and night-time (NTSC) symptoms compared with placebo.

Summary of efficacy results:

| Mean change from baseline | Placebo N=46 | BUD NEB 0.5mg QD N= 45 | BUD NEB 1.0 mg QD N= 43 |
|---------------------------|-----------------|------------------------------|-------------------------------|
| DTSC | -0.4 | -0.6 | -0.4 |
| NTSC | -0.4 | -0.6* | -0.4 |

* Ancova p-value <0.05 vs placebo

Rapporteur's comment: This placebo-controlled study did not give an unequivocal proof of efficacy in the enrolled population, but it showed some effect of inhaled Budesonide at last in the 0.5 mg QD group. The inconsistent effect might be due to the rather unspecific inclusion criteria or the once daily use. The safety profile is in line with the labelling and the patient collective.

Co-Rapporteur's comment: This study is the only one which has been reviewed at the FDA website: <http://www.fda.gov/cder/pediatric/summaryreview.htm> .

The study was requested by the FDA due to limited safety and efficacy data in children below 1 year of age. Pulmicort Respules is approved for the maintenance treatment of asthma and as prophylactic therapy in children from the age 12 months in the US. The FDA judged that efficacy has not been sufficiently evaluated in children six to 12 months.

The review comments the shift in serum cortisol levels, the length measurements and cases of pneumonia.

Within the total study population, there were seventy-six children who had their serum cortisol levels measured, 28, 17 and 31 subjects in the BIS 0.5 mg, 1.0 mg, and placebo arms respectively. As mentioned above 7 patients (4 of whom received 0.5 mg, 2 of whom received 1 mg and 1 whom received placebo) showed a shift from normal baseline cortisol level (≥ 500 nmol/L) to a subnormal level (< 500 nmol/L) at week 12. There were also 8 patients who showed a shift from subnormal stimulated cortisol levels at baseline to normal values at week 12 (2 received BIS 0.5 mg, 3 received BIS 1mg, and 3 received placebo). One patient with BIS 0.5 and 3 in the placebo group had subnormal stimulated cortisol level both at baseline and at week 12.

Body length (crown-heel) was also measured, however not with one of the golden standard methods as stadiometry. A dose dependent decrease in growth velocity was seen by a mean growth velocity of 3.7 cm, 3.5 cm, and 3.1 cm in the placebo, BIS 0.5 and BIS 1.0 mg treatment group respectively.

Pneumonia was observed more frequently in patients treated with BIS than in the placebo group, 2 in the 0.5mg group, 1 in the 1mg group and 0 in the placebo group. Otherwise the safety profile of BIS, characterised by rates and types of AEs, SAEs, and DAEs, was generally comparable to placebo and consistent with the safety profile in children older than 12 months.

The review of study SD-004-0732 resulted in some amendments to the FDA Drug Information (DI) regarding Pulmicort Respules. The results of the study with the shift to subnormal serum cortisol levels, the dose dependent decrease in growth velocity and the three cases of pneumonia are described in the Pharmacodynamic and in the Paediatric Use section. The FDA DIs are more comprehensive than the European SPCs.

Study code: 04-3072b (Extension of 04-3072)

Study Phase: III

Country: USA (14 sites)

Study design: Multi-centre, randomized, open-label, active-controlled, parallel-group
Objective: to assess the long term safety of the lowest maintenance dose of BUD NEB when administered for a period of up to one year as compared to conventional asthma therapy in paediatric patients aged between four to eight years

Study and control drugs: BUD NEB: 0-1.0 mg QD, Control group: Conventional asthma therapy (including ICS)

Duration: 52 weeks (08/95-11/97)

Primary endpoints: Mainly safety (AEs, HPA-axis function, skeletal age ect.)

No. of randomised patients: N= 91 (planned=120)

Mean age: 6.2 years (4-9 years)

Main inclusion criteria: Successful completion of 04-3069, or discontinued from 04-3072 because of need for oral corticosteroids for worsening asthma

Results:

Safety: There were no significant effects on basal and post-ACTH-stimulated plasma cortisol levels between the active treatment group and conventional therapy (14 patients in BUD NEB group, 8 patients in conventional asthma therapy group were assessed). There were no clinical signs of HPA-axis suppression. There were no deaths during the study; there were 9 SAEs in 8 patients (10% of patients in the conventional treatment group, and 8% of patients in the budesonide treatment group). One patient discontinued the study due to an AE. After adjusting for the length of the study, there were no clinically relevant differences in the type, incidence, severity or clinical significance of AEs compared to conventional asthma therapy, and differences in vital signs, or physical examination. There were no significant differences in growth velocities between groups assessed by stadiometry (mean growth velocities were 5.68 cm /yr and 4.97 cm /yr in the budesonide and the conventional treatment groups, respectively). The assessments to determine the possible effects of study treatment on skeletal growth (determined by external and internal (medullary cavity) diameters, and the cortical thickness of the midshaft of the second metacarpal from left hand x-rays) showed no significant differences between Pulmicort nebuliser and conventional asthma therapy in the mean differences between observed skeletal age and chronological age over one year of treatment. (SAEs: 5 conventional asthma therapy, 4 BUD NEB, DAEs: 1 BUD NEB)

Summary of most frequent adverse events occurring more often in the BUD NEB group than in the conventional asthma group:

| AE | Conventional asthma therapy | BUD NEB |
|-----------------------|-----------------------------|---------|
| Respiratory infection | 40% | 49% |
| Sinusitis | 30% | 31% |
| Pharyngitis | 20% | 31% |
| Bronchitis | 7% | 15% |
| Pneumonia | 3% | 13% |
| Coughing | 3% | 10% |
| Fever | 20% | 23% |
| Flu-like disorder | 3% | 7% |
| Otitis media | 13% | 20% |
| Moniliasis | 7% | 10% |
| Vomiting | 7% | 15% |
| Abdominal pain | 7% | 10% |
| Nausea | 0% | 5% |
| Hyperkinesia | 0% | 5% |
| Dysphonia | 0% | 3% |

| | | |
|----------------|----|----|
| Conjunctivitis | 0% | 8% |
|----------------|----|----|

Efficacy: There were similar reductions in the daytime and night-time asthma symptom scores. The subset of patients able to perform consistent PEF showed similar improvements. Fewer patients used oral steroids (56% vs 63%) and at lower average total daily dose (0.65 vs 1.40 mg Prednisone) in the budesonide group than in the conventional treatment group.

Rapporteur's comment: The relevance of this study is reduced by the fact that in the conventional asthma therapy group the use of ICS was allowed (50% beclometasone and fluticasone combined). All effects concerning efficacy and safety are deemed to be class effects of ICS. There are imbalances in baseline to the disadvantage of the conventional asthma therapy group for daytime and night-time asthma scores and number of days of need for breakthrough medication. 25 % of the patients in the conventional asthma treatment group compared to 45 % in the BUD NEB group had a shift from normal to abnormal in their ACTH Stimulation test. Only a very small number for patients took these tests. The reported AEs are in line with the labelling and the patient population.

Co-Rapporteur's comment: This study was an open-label extension of the 04-3072 study. The results regarding systemic effects are difficult to interpret in this study. There was a high proportion of patients on inhaled steroids in the conventional therapy group. There were also more patients in the conventional treatment group who used oral corticosteroid courses. In both groups, the basal cortisol levels and the mean increase in cortisol levels after ACTH stimulation were decreased at Week 52 compared to baseline, suggesting a measurable systemic effect. Psychiatric disorders were reported slightly more frequently in the budesonide group.

Study code: SD-004-0758

Study Phase: IV

Country: USA (48 centres)

Study design: Open-label, non-randomised, parallel-group

Study objective: to study the effect of daily therapy with BUD NEB on the immunogenicity of a live varicella virus vaccine

Study and control drugs: dose and dosage as judged by the investigator; test group: BUD NEB, control group: non-steroidal conventional asthma therapy (NSCAT).

Duration: 6 weeks (10/01-10/03)

Primary endpoints: percentage of patients whose Visit 2 gpELISA value was ≥ 5.0

No. of randomised patients: N=274

Mean age: 1.6 years (0.75-8 years)

Main inclusion criteria: Varicella-naïve paediatric asthma patients (age 10 months to 8 years whose symptoms required maintenance asthma therapy and who were to undergo varicella immunization

Results:

Safety: A seroprotective gpELISA value of 5.0 was achieved in 85% and 90% of the patients in the BUD and NSCAT groups, respectively. Both BUD and NSCAT were generally well tolerated in paediatric patients undergoing varicella immunization. The reported AEs were typical for the patient population. Of the AEs that were classified by the investigators as being study-related, most were attributed by the investigators to the Varicella vaccine. The incidence of AEs was similar between BUD and NSCAT groups. The incidence of SAEs was very low in both treatment groups. SAE: 1, DAE: 0.

Rapporteur's comment: This study has been conducted to assess the immunogenicity of a varicella vaccine in asthmatic patients treated with BUD NEB. Therefore it is of limited value for the assessment of safety and efficacy of BUD NEB. Nevertheless these results might be worth noting in the SPC of the vaccine.

Co-Rapporteur's comment: This study was performed to fulfil and FDA Phase IV commitment. The aim of the study was to investigate if the use of inhaled corticosteroids reduces the immunogenicity of a live virus vaccine, such as that for varicella. As high doses of systemic steroids may have an

immunosuppressant effect. It has not been known if treatment with inhaled steroids could affect the vaccination results. The study did not show any difference in seroconversion between BIS treatment and non-steroidal asthma treatment.

Study code: 04-3121

Study Phase: IV

Country: USA (67 sites)

Study design: Non-randomised, uncontrolled, open-label, named patients (compassionate use)

Objective: to assess the safety of BUD NEB in severe asthmatic patients aged 6 months to 8 years who were dependent on oral glucocorticosteroids and were not adequately controlled by other forms of therapy

Study and control drugs: Dose and dosage as judged by the investigator (mean daily dose: 0.9 mg)

Mean Duration: 495 days (07/95-04/01)

Primary endpoints: Frequency of reported AEs

No. of randomised patients: N=397

Mean age: 2.1 years (0.3-51.5 years)

Main inclusion criteria: Severe, oral steroid-dependent asthma, age 0.5-8 years

Results:

Safety: The incidences at which AEs occurred were consistent among age groups. Increased duration of treatment did not appear to result in the onset of new AEs. Most common AEs: respiratory infection (43.3%), aggravated asthma (31.0%), otitis media (25.7%), and sinusitis (20.4%). 5% of the patients had a laboratory abnormality reported as AE or as clinically significant. None were serious, none were considered severe, and none resulted in the premature discontinuation. 49 patients (12%) reported AEs that were considered by the investigator to be possibly or probably related to study medication. The incidence and types of AEs reported were similar to those noted in the product label, and no unexpected AEs were noted. SAEs were reported by 95 patients: asthma aggravated (n=58), pneumonia (n=26), bronchospasm (n=14), and infection viral (n=12). Two patients died during the study. Neither death was considered related to treatment with Budesonide inhalation suspension by the investigators. SAE: 221, DAE: 6, Death: 2.

Rapporteur's comments: This is an uncontrolled open label compassionate use study. The reported AEs are in line with what has to be expected in this patient population. We'd like to note that 46.8% of the patient did not fulfil the inclusion criteria "daily need for oral glucocorticosteroids".

Co-Rapporteur's comment: The included patients had been treated daily with oral glucocorticosteroids for at least 3 months before study. The two patients who died had finished the study. One patient died 104 days after receiving the last dose of BIS and the other died 14 days after the last received dose.

Study code: SD-004-0144

Study Phase: IV

Country: USA (30 sites)

Study design: Non-randomised, uncontrolled, multi-centre, open-label

Objective: to assess the long term safety of BUD NEB in patients who successfully completed studies 04-3069b/ 3072b/ 3100b or DX-RES-2000, and who still had a medical need for BUD NEB

Study and control drugs: Dose and dosage as judged by the investigator (0.5 to 2.0 mg BUD NEB/d; mean daily dose 0.62 mg)

Duration: As per investigator judgement, maximum 3 years (12/96-11/00)

Primary endpoints: Mainly safety (e.g. AEs, laboratory evaluations, physical examinations)

No. of randomised patients: N=198

Mean age: 5.3 years (2-10 years)

Main inclusion criteria: Paediatric patients (≤ 8 years) with mild, moderate or severe asthma, who successfully completed studies 04-3069b/ 3072b/ 3100b or DX-RES-2000, and who still had a medical need for BUD NEB

Results:

Safety: BUD was well tolerated by the study population over the study period. One of the DAEs (aggressive reaction) was judged by the investigator to be possibly related to the study treatment. There were no clinically important laboratory or physical examination findings that would suggest the presence of a new or unexpected AE associated with the study drug. The frequency of reported AEs was 77.8%, 62%, and 69.1% for the first the second and the third year, respectively. There was no evidence that AEs became more frequent with increasing duration of treatment. There were no reports of deaths and no new safety issues regarding long-term use of BUD were identified. SAE: 34 in 18 patients; DAE: 2.

Efficacy: There was a trend towards increasing FEV1 in the spirometry patient population (84 patients) progressing throughout the 156-week study period. FEV1 was measured in 84 patients at intervals of 13 weeks throughout the study period. The change from baseline in FEV1 increased from 0.016±0.26 L after 13 weeks of treatment to 0.229±0.026 L at the last observed value. It was unclear if this increase was attributable to treatment, the growth of the patients or to “Survivor bias” (only 19.7% completed the study, many patients became capable of using other devices during the study)) where the patients who benefited the most from BUD NEB remained in the trial for the longest period of time.

Rapporteur’s comment: The AEs reported in this longer term safety study are in accordance with the labelling and with what is expected in this patient population. There is no evidence that AEs become more frequent with increasing treatment duration.

Co-Rapporteur’s comment: Study 004-0144 was an extension to previously conducted BIS studies; 04-3069, 04-3072, 04-3100 and DX-RES-2000. One of the DAEs was due to violent behaviour in a 3-year old boy. Such rare side effects are known and are included in the Core SPC with the word “behavioural disturbances”.

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition

The longest study lasted three years. No data on cognitive or somatic development has been provided except for the data summarised above.

III. PSUR DATA

A PSUR summary and overview **concerning all formulations**, covering the period from 1 May 2000 to 30 April 2005, PSUR No.7-11, were enclosed. The completed clinical trials in children during this period is submitted in this procedure and already presented above. Several changes have been made to the safety information of the Core Data Sheet (CDS) during the period, sections 4.4, 4.5, 4.6, 4.8 have all been updated. May 2003, section 5.1 was updated with a new text about the effect of budesonide on the HPA axis function.

Exposure data, see tables below (from MAH’s PSUR overview):

Table 2 Patient exposure in clinical studies (children and adults)

| Report | Time period covered | Patient exposure |
|----------------------|----------------------------|------------------|
| Pulmicort PSUR No.7 | 1 May 2000 – 30 April 2001 | 8100 a |
| Pulmicort PSUR No. 8 | 1 May 2001 – 30 April 2002 | 6700 |
| Pulmicort PSUR No. 9 | 1 May 2002 – 30 April 2003 | 4900 |
| Pulmicort PSUR No.10 | 1 May 2003 – 30 April 2004 | 1750 |

a Patient exposure from PSUR No 7 has been recalculated since number of patients originally included cumulative data from the first clinical study and did not correspond to the specific PSUR period

Table 4 Data on post-marketing experience presented as total number of case reports and estimated patient exposure broken down by PSUR reporting periods (including pMDI, all ages)

| Report | Time period covered | Total No. of case reports | Exposure, treatment days (million) |
|----------------------|----------------------------|---------------------------|------------------------------------|
| Pulmicort PSUR No.7 | 1 May 2000 – 30 April 2001 | 259 | 1 173 |
| Pulmicort PSUR No. 8 | 1 May 2001 – 30 April 2002 | 200 | 1 097 |
| Pulmicort PSUR No. 9 | 1 May 2002 – 30 April 2003 | 243 | 970 |
| Pulmicort PSUR No.10 | 1 May 2003 – 30 April 2004 | 238 | 915 |
| Pulmicort PSUR No.11 | 1 May 2004 – 30 April 2005 | 181 | 903 |

Co-Rapporteur's comment: *The clinical experience of budesonide is huge. The individual case reports regarding children did not reveal any new safety concerns.*

Rapporteur's comment: The Rapporteur agrees with the Co-Rapporteur.

IV. ASSESSMENT OF REQUESTED SUPPLEMENTARY INFORMATION

During the procedure a need for additional information has been identified and a List of Questions was generated. The applicant responded to these questions as detailed below:

Q1.) The data on the use of the maximum dose recommended in the SPC in age group of patients of a.) < 12 months b.) ≥ 12 months < 4 years seems to be limited. The MAH is asked to:

- a) provide data on the number of these patients
- b) comment, if the safety parameters did differ from children of the same group, treated with lower doses
- c) comment, if the safety parameters did differ from children of the higher age groups, treated with the same dose

Summary of the applicant's response:

The applicant acknowledges that there are limited data on the use of the maximum recommended dose (2 mg) in children below 4 years of age. He states that consequently no comment can be provided on whether safety differs in these children as compared with children of the same age treated with lower doses (question b), or compared with children in higher age groups treated with the same dose (question c). The maximum dose is necessary for children with the most severe asthma, and is preferable to using systemic steroids, which would be an alternative treatment. However, even for these children, it is important to reduce the dose to the lowest effective dose, and this is clearly advised in the SmPC.

The Rapporteur suggests adding the following sentence in Section 4.2: "There is only limited experience with the maximum dose of 2 mg/d in children below 4 years of age". The Co-Rapporteur

recommends adding the statement: “The highest (2 mg per day) dose should only be considered in children with severe asthma and during limited period”. The applicant agrees to include the second statement and does not consider the first statement necessary because it will be of no value to the prescriber.

Rapporteur’s comment: *The applicant acknowledges that there is limited data on the use of the maximum dose in children below 4 years of age, but fails to give the exact number of patients. In our opinion the statement “there is only limited experience with the maximum dose of 2 mg/d in children below 4 years of age” would be of value to the prescriber as safety information. Nevertheless the inclusion of the wording proposed by the Co-Rapporteur is also acceptable to us. Therefore “The highest (2 mg per day) dose should only be considered in children with severe asthma and during limited period” should be added to the wording of the SPC.*

Q2.) The MAH is asked to comment on the fact, that no patients > 8 years were planned to be enrolled in the main studies. How has the efficacy and safety been established in these patients. Is there any information on the effects on growth, puberty and so on?

Summary of the applicant’s response:

The data submitted to the FDA that was specifically requested by the European authorities did only refer to patients over 8 years. Efficacy and safety data for children 9 years and older were submitted previously to European health authorities via national procedures leading to approval in Europe.

Since patients are normally transferred from Pulmicort Respules to Pulmicort Turbuhaler when they can use the DPI correctly, there are no data on the effect of isolated use of Pulmicort Respules on growth beyond 12 months. However, evaluation of effect on growth should be based on systemic exposure to budesonide. Since the maximum dose for Pulmicort Respules in children (2 mg) approximately corresponds to the maximum dose of Pulmicort Turbuhaler in children (800 µg) regarding systemic exposure (Agertoft and Pedersen 2002, Agertoft et al 1999), data for Pulmicort Turbuhaler are also of interest in relation to treatment with Pulmicort Respules. The applicant summarizes the short-term and long-term growth data for Pulmicort Turbuhaler and Pulmicort pMDI. In short, there is a number of short-term studies that show reductions in growth in asthmatic children treated with inhaled steroids. The effect is most marked in the beginning of treatment. There is evidence from recent studies with Pulmicort that catch-up growth occurs following the initial decrease in growth rate. As a result most children eventually reach their predicted adult height. No data on puberty are available.

Rapporteur’s/ Co-Rapporteur’s comment: *Although there is no data on puberty available, the issue is considered resolved.*

Q3.) The MAH is asked to provide an analysis of the clinical efficacy and safety of the main studies (including the extensions of these studies) stratified for age (< 12 months, ≥ 12months < 4 years, ≥ 4 years) where applicable.

Summary of the applicant’s response:

In the response to this question, the applicant has chosen to submit already available analyses prepared recently for other health authorities. The age groups used in this analysis do not exactly coincide with the categories requested above, in that there are more intervals in the presented data and the upper cut-off is 5 years rather than 4 years. This presentation of data is relevant and justified, however, since the panorama of normally occurring diseases differs more widely in the younger age groups, and a more detailed presentation of these age groups is therefore more relevant than for the older children. The distribution of patients by age in studies 04-3069, 04-3100, 04-3072 and SD-004-0732 is shown in **Error! Reference source not found.**

Distribution of patient age in US 12-week placebo-controlled studies

| Study | | 04-3069 | 04-3100 | 04-3072 | SD-004-0732 | Total |
|---|-----------------|----------------------|----------------------|--------------------|--------------------------------|-----------------------|
| Target severity ^a | | Mild | Mild to moderate | Moderate to severe | Mild to moderate | - |
| No. of patients for efficacy analysis (all treatment groups, including placebo) | | 358 | 471 | 178 | 141 | 1148 |
| Age (year) | <12 months | 15 (4.2%) | 12 (2.5%) | 0 (0.0%) | 140 (99.3%) | 167 (14.5%) |
| | 1 - <2 yrs | 39 (10.9%) | 58 (12.3%) | 0 (0.0%) | 1 (0.7%) | 98 (8.5%) |
| | 2 - <5 yrs | 149 (41.6%) | 197 (41.8%) | 23 (12.9%) | 0 (0.0%) | 369 (32.1%) |
| | ≥5 yrs | 155 (43.3%) | 204 (43.3%) | 155 (87.1%) | 0 (0.0%) | 514 (44.8%) |
| | <5 yrs total | 203 (56.7%) | 267 (56.7%) | 23 (12.9%) | 141 (100%) | 634 (55.2%) |
| | Mean±SD (range) | 4.2±2.3 (5mo - 8 yr) | 4.1±2.2 (7mo - 8 yr) | 6.2±1.3 (4-9 yr) | 8.4±1.7 ^b (5-12 mo) | 4.0±2.6 (5 mo - 9 yr) |

^a Severity estimated from prior treatment (asthma severity was not used for patient selection).

^b Age in months.

Efficacy

The efficacy results are categorised into <12 months, 1 - <2 years, 2 - <5 years and ≥5 years. In Studies 04-3069 and 04-3100, the results are also stratified by <5 years.

According to the applicant in Studies 04-3069 and 04-3100, no clear conclusion regarding clinical efficacy in patients aged less than 12 months could be made since the number of enrolled patients in this age range was low. In all the other age stratifications, asthma symptom scores decreased. In Studies 04-3069 and 04-3100, clinical efficacy was generally comparable between less than 5 years and 5 years or older. In Study SD-004-0732, where patients were less than 12 months old, budesonide treatment improved asthma symptom scores.

The applicant concluded that across all studies the efficacy of budesonide inhalation suspension was similar in all age groups.

Safety

From the extensive clinical experience including all the formulations of budesonide, no data have suggested that general demographic characteristics, including age and sex, may affect the safety of budesonide.

The applicant summarised adverse events reported in the main US clinical studies by age (<12 months, 1 to <2 years, 2 to ≤5 years, 5 years or older and less than 5 years total). There were differences in the frequency of individual adverse events between the age groups, but within any age group, the frequency of adverse events was generally comparable between the budesonide groups and the placebo group. The applicant concluded that there was thus no evidence that the safety profile of budesonide differs in different age groups.

Rapporteur's comment: *The applicant's conclusion on safety is accepted. For the efficacy part the data submitted shows that the number of patients < 12 months of age in the main efficacy studies (04-3100, 04-3069, 04-3072) is extremely low (SD-004-0732 being mainly a safety study as detailed above). The results of these studies are somehow conflicting. Study SD-004-0732 gives some proof of efficacy in this subpopulation but the applicant should be encouraged to further address this issue in future studies.*

Q4.) Study 04-3069 showed a higher frequency of epistaxis in the BUD NEB group.

a.) The MAH is asked to comment on this fact.

b.) Could it be attributable to the use of a face mask? Please provide a stratified analysis.

Summary of the applicant's comment:

Analysis of the frequency of epistaxis in relation to mode of administration in Study 04-3069 did not indicate a relationship; the incidence of epistaxis was higher after mouthpiece administration than face mask administration (5.3% vs 2.2%). Similar results were found when pooling the data from the placebo-controlled studies 04-3069, 04-3072 and 04-3100. Again, there was no indication that face mask administration led to a higher frequency of epistaxis than mouthpiece administration (facemask: 2.3%, mouthpiece: 4.5%).

In the pooled data, the frequency of epistaxis was higher for budesonide than placebo both after treatment with face mask (2.3% vs 1.5%) and mouthpiece (4.5% vs 0.5%). On the other hand, for the group where mode of administration was not recorded, the frequency was higher for placebo (6.4% vs 2.1%). Neither in Study 04-3069 nor in the pooled data was there a clear dose dependency for the frequency of epistaxis.

The applicant does not consider that there is any clear evidence of a causal relationship between nebulised budesonide and epistaxis for the following reasons:

- The frequency of epistaxis was not higher with face mask administration, where it is likely that more budesonide reaches the nose
- There was no consistent over-representation of epistaxis in the budesonide group
- There was no clear dose-dependency

Rapporteur's/ Co-Rapporteur's comment: *Issue resolved.*

Q5.) Study 04-3100 showed a higher frequency of respiratory infections in the BUD NEB group. The MAH is asked to comment on this fact.**Summary of the applicant's response:**

It is correct that there is a slightly higher incidence of respiratory infection in the budesonide group in Study 04-3100 (35% vs 29%). On the other hand, in Study 04-3069, the frequency was lower in the budesonide group than in the placebo group (37% vs 45%). Furthermore, when all 4 main US studies are pooled, the frequency of respiratory infections is the same in the placebo group and the combined budesonide group (39%). The difference in Study 04-3100 is therefore considered a chance finding.

Rapporteur's/ Co-Rapporteur's comment: *Issue resolved.*

Q6.) Are long-term safety data, namely on developmental parameters, available?

Summary of the applicant's response: As previously explained, the pattern of use of Pulmicort Respules versus Pulmicort Turbuhaler in the growing child precludes the collection of longitudinal data on isolated Pulmicort Respules use into adulthood. However, since the relevant safety parameters depend primarily on systemic exposure, longitudinal data for Pulmicort Turbuhaler are relevant for Pulmicort Respules. Please see the response to Q2 for more detailed information regarding Pulmicort Turbuhaler.

Rapporteur's comment: *Developmental data is not confined to growth data and the applicant should be encouraged to address these issues in future studies.*

Applicant's responses to the proposed changes to the SPC:

Because Pulmicort nebuliser solution is nationally approved across Europe, there is no harmonized SPC. Therefore the Rapporteur assessed the company's Core data sheet (CDS) as a basis for the wording of the SPC, because no other document in English would be easily

available to all Member States. Nevertheless the Rapporteur would like to stress, that he is fully aware of the fact that this is an internal document of the company. The Rapporteur's idea was that the member states could compare their national SPC with the Core data plus the agreed additional passages (that, beyond this procedure, might not necessarily be added to the company's internal document). The variation procedures to come could then be handled accordingly.

The Rapporteurs acknowledge that the aim of the paediatric work sharing is not to harmonise the SPC and PIL as a whole but a harmonisation of the paediatric data throughout Europe taking into account the national Marketing authorisations should be possible and be achieved. A harmonised SPC-proposal would be helpful.

Unfortunately the company did not respond with regard to the CDS but with regard to the Swedish SPC (Co-Rapp's comments) and the German SPC (Rapp's comments). This might prove not very helpful for the remaining member states that do not have those documents. Below we summarise the applicant's answers to the comments on the SPC:

Section 4.1:

Rapporteur's proposal: "... and who are not capable of using a metered dose inhaler or dry powder inhaler" should be added, because this reflects more precisely the current recommendations.

Applicant's response: the applicant states that this wording has already been included in the German SPC.

Rapporteur's /Co-Rapporteur's comment: It is acknowledged that this phrase has already been included in the German SPC, but it is not present in the CDS and might not be present in the SPCs of other Member States. It is the Rapporteur's opinion, that this wording should be included in all SPCs.

Section 4.2:

Rapporteur's proposal: Depending on the MAH's answer to Q1. an addition like "there is only limited experience with the maximum dose of 2 mg/d in children of below x years" might be advisable.

Co-Rapporteur's proposal: "The highest (2 mg per day) dose should only be considered in children with severe asthma and during limited period." should be added.

Applicant's response: AstraZeneca agrees to add the proposed statement (Co-Rapp) "The highest dose (2 mg per day) for children should only be considered in children with severe asthma and during limited periods" but do not consider the proposal of the Rapporteur useful for the prescriber.

Rapporteur's/ Co-Rapporteur's comment: Issue resolved as explained above.

Section 4.4:

Rapporteur's proposal: Some systemic AEs (e.g. glaucoma and cataract) are not listed here. Please bring this chapter in accordance to the current wording agreed by the PhVWP.

Applicant's comment: In the German SmPC, a warning on possible systemic effects such as glaucoma and cataract is already included in section 4.4, this is in line with the current wording agreed by the PhVWP in Germany. Therefore no change is needed for the German SmPC, section 4.4.

Rapporteur's/ Co-Rapporteur's comment: It is acknowledged that this information has already been included in the German SPC, but it is not present in the CDS and might not be present in the SPCs of other Member States. The wording should be included where ever necessary.

Co-Rapporteur’s proposal: The Co-Rapporteur suggested using the SPC-text of Symbicort for the systemic effects in children with a slightly modified wording (proposed amendments are bold and underlined):

*“Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. **The systemic effect is probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved.**”*

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

Pulmicort Nebuliser Suspension

*Potential effects on bone density should be considered particularly in patients on high doses for prolonged periods that have coexisting risk factors for osteoporosis. Long-term studies with inhaled budesonide (**Turbuhaler**) in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of budesonide at higher **doses or of Pulmicort Nebuliser Suspension** is available.”*

Applicant’s response: AstraZeneca suggests adding “***The long-term local and systemic effects of Pulmicort in man are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved***” in section 4.4 which is in line with the company’s Core Data Sheet for Pulmicort. Regarding the other changes suggested by the Co-Rapporteur, AstraZeneca considers that they are not necessary. There is considerable experience showing that use of Pulmicort within the current label is safe. In addition, harmonization with the Symbicort text would remarkably increase the length and complexity of the SmPC and will lead to confusion and questions from patients and prescribers currently already using the product.

The resulting text for Pulmicort would also be considerably longer and more complex than the text of other inhaled steroids on the Swedish market, even the latest one containing budesonide and assessed via Mutual Recognition Procedure.

Pulmicort is a very well known product with well documented and established safety, and a more complex text is not justified when compared to other products containing inhaled budesonide.

Rapporteur’s/ Co-Rapporteur’s comment: *The wording agreed by the PhVWP should be included.*

Section 4.8:

Rapporteur’s proposal: the Rapporteur proposed to amend this section depending on the MAH’s answers.

Applicant’s answer: No revisions to the German SmPC section 4.8 as discussed for Q 4-6 are deemed necessary.

Rapporteur’s/ Co-Rapporteur’s comment: *Issue resolved.*

Co-Rapporteur's proposal: The Co-Rapporteur suggests the following wording derived from Symbicort:

"Adverse reactions whose have been associated with budesonide, are given below, listed by system organ class and frequency. Frequency is defined as: very common ($\geq 1/10$), common ($\geq 1/100$) and $< 1/10$), uncommon ($\geq 1/1\ 000$ and $< 1/100$), and very rare $< 1/10000$).

| | | |
|---|-----------|---|
| Immune system disorders | Rare | Exanthema, urticaria, pruritus, dermatitis, angioedema |
| Endocrine disorders | Very rare | Signs or symptoms of systemic glucocorticosteroid effects (including hypofunction of the adrenal gland) |
| Infections and infestations | Common | Candida infections in the oropharynx |
| Psychiatric disorders | Uncommon | Agitation, restlessness, nervousness, sleep disturbances |
| | Very rare | Depression, behavioural disturbances (mainly in children) |
| Respiratory, thoracic and mediastinal disorders | Common | Mild irritation in the throat, coughing, hoarseness |
| | Rare | Bronchospasm |
| Skin and subcutaneous tissue disorders | Uncommon | Bruises |

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4).

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, see also 4.4.

Applicant's response:

AstraZeneca suggests to add a sentence under the table already within section 4.8 of Pulmicort Swedish SmPC, "*...and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.*" This is in line with the company's Core Data Sheet.

The adverse reactions and frequencies used in the current section 4.8 for Pulmicort are based on the data available for Pulmicort in the AstraZeneca safety databases, and in our opinion these frequencies should be used.

Harmonization with Symbicort section 4.8 will lead to confusion and questions from patients and prescribers currently already using the product.

Thus, AstraZeneca does not consider it is appropriate to harmonize section 4.8 with Symbicort.

Co-Rapporteur's comment: *No comment. Issue resolved*

Section 5.1:

Co-Rapporteur's proposal: There are short paragraphs regarding systemic effects and growth in children in the Swedish national SPC and in the MAH's Core SPC for Pulmicort Nebuliser Suspension and Pulmicort Turbuhaler. As similar texts now are proposed to 4.4 (in line with the Symbicort SPC), comments on these issues are not proposed for 5.1.

Applicant's response: As AstraZeneca agrees to add specific statements regarding systemic effects in the Swedish SmPC sections 4.4 and 4.8 no amendment of section 5.1 is considered necessary.

Co-Rapporteur's comment: No comment. Issue resolved

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rapporteur's and Co-Rapporteur's conclusion: *The MAH conducted altogether 15 studies to establish efficacy and safety of BUD NEB in the therapy of persistent asthma in children. The studies enrolled altogether 3365 patients aged 0.5 to more than 8 years. The longest study lasted 3 years. Though most of these studies are not completely in accordance with the Note for guidance on the clinical investigation of medicinal products in the treatment of asthma, overall a positive benefit-risk-relation can be concluded for BUD NEB. The reported AEs have mostly already been included in the SPC. Nevertheless the efficacy data on patients below < 12 months is rather sparse as is the data on children < 4 years of age using the highest dose as well as data on development with long-term treatment. The applicant should be encouraged to address these issues in future studies. For the time being it is the Rapporteur's/ Co-Rapporteur's opinion that the SPCs should be amended (wherever necessary) as follows:*

Section 4.1:

"... and who are not capable of using a metered dose inhaler or dry powder inhaler" should be added.

Section 4.2:

"The highest dose (2 mg per day) for children should only be considered in children with severe asthma and during limited periods."

Section 4.4:

The chapter should be brought in accordance to the current wording agreed by the PhVWP.

Additional changes to the Swedish SPC agreed by the Applicant and the Co-Rapporteur are listed above.

No further comments requesting changes were received from the CMS. Therefore this report is considered to be final.

It is suggested that these amendments should be implemented in the countries where the respective wordings have not already been included in the SPCs using variation procedures.

