ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) IN THE MEMBER STATES

Member State EU/EEA	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Czech Republic		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	Tafen Aqua 32µg nosní spray Tafen Aqua 64 µg nosní spray	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
Denmark		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	Budesonid Sandoz	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
France		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	BUDESONIDE SANDOZ 64 µg/dose, suspension pour pulvérisation nasale	64 mcg/dose	Nasalspray, suspension	Nasal use	1,28 mg/ml
Germany		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	Budesonid Sandoz 32 Mikrogramm/Sprühstoß Nasenspray, Suspension Budesonid Sandoz 64 Mikrogramm/Sprühstoß Nasenspray, Suspension	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
Netherlands		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	Budesonide Sandoz 32 microgram/dosis, neusspray, suspensie Budesonide Sandoz 64 microgram/dosis, neusspray, suspensie	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
Norway		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11	Budesonid Sandoz	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml

		83607 Holzkirchen Germany					
Poland		Sandoz Pharmaceuticals GmbH Raiffeisenstraße 11 83607 Holzkirchen Germany	Tafen Nasal 32 Tafen Nasal 64	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
Sweden		Sandoz A/S C.F. Tietgens Boulevard 40 DK-5220 Odense SØ Danmark	Desonix	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	0,64 mg/ml 1,28 mg/ml
United Kingdom		Sandoz B.V. Veluwezoom 22 1327 AH Almere Netherlands	Budesonide Aqua 64 micrograms Nasal Spray	32 mcg/dose 64 mcg/dose	Nasalspray, suspension	Nasal use	1,28 mg/ml

ANNEX II

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF BUDESONIDE SANDOZ AND ASSOCIATED NAMES (SEE ANNEX I)

Budesonide Sandoz is an aqueous nasal spray containing budesonide, a glucocorticosteroid with a high local anti-inflammatory effect, indicated for the treatment and prevention of signs and symptoms of seasonal and perennial allergic rhino-conjunctivitis (SAR, PAR) as well as of nasal polyps. The product was submitted under the Decentralised Procedure with Germany as Reference Member State, as a hybrid application (Art.10 (3)) and is claimed to be almost identical to the reference product, Rhinocort, with the addition of ascorbic acid (as antioxidant) being the only difference. To support the application, the Applicant submitted one clinical study in adults. During the procedure it was concluded that therapeutic equivalence to the reference product was demonstrated in adults, the safety in adults was therefore considered proven and no PK data was required. However, disagreement between the member states involved in the procedure regarding the inclusion of children and adolescents remained, and the procedure was referred to the CHMP. The CHMP adopted the following List of Questions focusing on the paediatric and adolescent indication:

How can comparable safety in the paediatric population be concluded based on the facts that:

a.) Comparable systemic exposure of the test and reference product has not unequivocally been shown in the adult population. The impact of the differences of the two preparations is unknown.

b.) Children will receive the same dose as adults, most likely exposing this more vulnerable population to higher systemic budesonide concentrations.

c.) No paediatric data has been presented so far in this application. Paediatric Adverse Events like growth retardation have not been addressed.

Question 1a

Comparable systemic exposure of the test and reference product has not unequivocally been shown in the adult population. The impact of the differences of the two preparations is unknown.

Budesonide Sandoz and the originator product have the same pharmaceutical form, contain the same amount of active substance and have identical delivery devices. The maximal daily dose of Budesonide Sandoz was determined as being 256 µg/d. A clinical study conducted by the Applicant, demonstrated therapeutic equivalence to the originator, indicated similar local availability of budesonide and identified no safety concerns that could be attributed to an increased systemic availability. The Applicant stated that the only difference with the originator product is an additional 0.01% of ascorbic acid, a well-characterised chemical substance and a well-established excipient in locally applied products, with no reported adverse effects. The impact of ascorbic acid on the unidirectional mucosal permeability of budesonide was assessed and the results show that addition of ascorbic acid at a concentration of 600µM did not facilitate mucosal permeability. In addition, ascorbic acid is a physiological constituent of the nasal lining fluid, and in conclusion, the Applicant considered that the mucosal permeability can be regarded as essentially similar for both products. The Applicant discussed the available knowledge regarding the systemic exposure of intranasally applied budesonide including its high topical potency and low systemic bioactivity, primarily due to absorption through the nasal mucosa and the metabolism steps involved. The most sensitive and accurate methods of detection of systemic corticosteroid bioactivity available (measurement of endogenous cortisol secretion from the adrenal cortex) found measurable effects but only at doses above 400 µg/d. The Applicant also stated that nasally applied budesonide did not significantly alter hypothalamic-pituitary-adrenal (HPA) axis function in the originator's clinical studies. In the therapeutic equivalence study, systemic exposure was determined indirectly by measurement of 12-h free cortisol in the urine, correcting for creatinine excretion. The results obtained suggest that budesonide is not systemically available, that the pharmacokinetic profile does not differ significantly between the two formulations, that no systemic effects are to be expected and that the products are comparable with regards to the biopharmaceutic properties. Neither clinical data from the literature nor the clinical studies conducted by the originator indicate any adverse systemic effects for

budesonide doses up to 400 µg daily and therefore, the Applicant considered that no "systemic adverse reactions" are expected and that no additional data are necessary.

The CHMP agreed with the rationale for including ascorbic acid as an anti-oxidant and that the amount of ascorbic acid contained in Budesonide Sandoz will not affect the pharmacokinetics/pharmacodynamics of the product. The CHMP noted the clinical equivalence study and agreed that therapeutic equivalence has been demonstrated in adults, although no formal bioequivalence studies on systemic exposure were performed, neither in adults nor in children. But because therapeutic equivalence has been demonstrated in adults, similarity including safety can be inferred for children, provided that no differences between adults and children are expected. No detectable effects on hypothalamic-pituitary-adrenal (HPA) axis function have been observed at the recommended dose, which is in agreement with the rapid hepatic metabolism of the substance and the elimination half-life, suggesting that neither Budesonide Sandoz nor Rhinocort influence cortisol excretion. Finally, the CHMP agreed that no local safety related issues are expected for Budesonide Sandoz nasal spray and that there is no evidence that the safety of Budesonide Sandoz in children is different from that of the originator.

Question 1b

Children will receive the same dose as adults, most likely exposing this more vulnerable population to higher systemic budesonide concentrations.

The Applicant stated that a number of key studies in the paediatric population have indicated that intranasal corticosteroids are effective and well-tolerated and discussed single studies from the literature. The pharmacokinetics and pharmacodynamics properties of intranasal applied budesonide in children were shown to be comparable to those in adults from all aspects. The results of a study in children and adolescents with perennial rhinitis were in line with the observations for adults, and no consistent differences in 24-hour urinary cortisol measurements were observed, therefore no systemic effects are expected in the paediatric population, irrespective of plasma budesonide concentrations. Because the recommended maximum daily dose of the originator is considerably larger than for Budesonide Sandoz, it must be assumed that the safety of these doses has been assessed in this spopulation. In order to justify the omission of bioavailability studies in the paediatric population, the Applicant stated that the results from a therapeutic equivalence study did not provide any indication of differences in systemic exposure or adverse events resulting from the active substance. In conclusion, the Applicant considered that the pharmacology of budesonide in the paediatric population has been well investigated and characterised and that it is reasonable to assume that Budesonide Sandoz will be therapeutically equivalent to the originator in the paediatric population as equivalence has been convincingly demonstrated in the adult population. The Applicant therefore concludes that there is no justification for additional clinical data in the paediatric population.

The CHMP noted that several published studies indicate that INCs taken at the recommended dosages do not affect the hypothalamic-pituitaryadrenal axis in children and that the long-term treatment for 1 to 2 years with intranasal budesonide daily in children with perennial allergic rhinitis reveals no negative effects on growth or endogenous cortisol production. The CHMP therefore agrees with the argumentation concerning the dosage in children, and furthermore considered that in the context of a hybrid application, if therapeutic equivalence to the originator is proven, the new hybrid product should adopt the dosing recommendations of the originator. The benefit/risk balance and the dosages were assessed during the Marketing Application of the originator and as the originator has been approved for children with the adult dose, the benefit/risk of this dose is positive, including in paediatric populations.

Question 1c

No paediatric data has been presented so far. Paediatric AEs like growth retardation have not been addressed

The Applicant stated that growth is divided into 3 distinct age-related phases and that conclusions from studies in one age group cannot be generalised to other age groups. Clinically, the most

important outcome measure of human growth is the final height in relation to the expected final height. When results from growth studies are evaluated, it is important to realise that an effect on growth found in short- or intermediate-term studies is not necessarily equivalent to an effect on final adult height and that height measurements made over a period of less than one year are liable to error and misinterpretation. The Applicant discussed a number of knemometry studies (which measure the length of the lower-leg), concluding that knemometry and short-term growth studies have limitations and do not correlate to long-term growth. The Applicant stated that available studies show that budesonide has no effect on growth as measured by knemometry in doses below 400 µg/d and that it can be virtually excluded that locally applied corticosteroids cause relevant permanent growth retardation, clinically relevant growth suppression or reduced adult height. Budesonide nasal powder (200 and 400 µg once daily) was shown not to affect the HPA axis in 83 children and adolescents with SAR in a 4-week study. Furthermore, the safety profile of Budesonide Sandoz in the therapeutic equivalence trial was similar to that of both the originator product and the placebo and it is therefore reasonable and justified to assume comparable safety in all target populations, including children ≥ 6 years of age and adolescents. The Applicant is of the opinion that Budesonide Sandoz and the originator show comparable local tolerability and systemic safety in children and are fully interchangeable. Therefore, no new or additional aspects concerning the safety for Budesonide Sandoz in the paediatric population can be expected from additional studies.

The CHMP agrees with the responses. An excessive level of systemic glucocorticoids would reduce the endogenous production of cortisol, which can be detected by evaluating basal HPA activity, therefore measurements of HPA function, such as area-under-the curve cortisol concentrations and urinary free cortisol excretion, are considered the most sensitive indicators of INC systemic bioavailability, while stimulation tests of HPA-axis function are not as sensitive in identifying the systemic bioavailability of the INCs, but predict the likelihood of adverse events more accurately. Studies in children with allergic rhinitis have generally been consistent with adult studies in terms of demonstrating a lack of HPA-axis suppression with INCs. Additionally, any dose-related, short-term effects of inhaled corticosteroids on growth velocity identified suggest that compensatory mechanisms are involved. Finally, therapeutic equivalence is proven for this hybrid application, therefore the efficacy and safety are considered equivalent for adults and can be extrapolated to children. Since for nasal application no differences are expected between adults and children with respect to the systemic exposure, no additional measurements of adverse events such as growth retardation are necessary.

GROUNDS FOR POSITIVE OPINION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the overall benefit/risk ratio of Budesonide Sandoz in children is positive and that the application for Budesonide Sandoz, in the treatment of seasonal and perennial allergic rhino-conjunctivitis (SAR, PAR) as well as nasal polyps, is approvable.

Whereas

- the ascorbic acid contained in the product is not expected to impact the systemic exposure of budesonide,

- the pharmacology of budesonide is well established for the originator, with respect to the administration, dosage and adverse events in children,

- the therapeutic equivalence of Budesonide Sandoz to the originator in adults has been established and

- the safety profile for children of Budesonide Sandoz is not expected to differ from that of the originator,

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Budesonide Sandoz and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered (metered) dose of 0.05 ml nasal spray, suspension contains 32 micrograms of budesonide.

The delivered (metered) dose of 0.05 ml nasal spray, suspension contains 64 micrograms of budesonide.

Excipient(s):

0.06 mg of potassium sorbate / 0.05 ml nasal spray, suspension

For a full list of excipients, see section 6.1.
[To be completed nationally]

3. PHARMACEUTICAL FORM

Nasal spray, suspension.
White homogeneous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of signs and symptoms of seasonal and perennial allergic rhinitis

Treatment of signs and symptoms of nasal polyps

4.2 Posology and method of administration

For nasal use only.
The dosage should be determined individually. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.
The duration of the therapy with Budesonide nasal spray should be restricted to the period of allergen exposure and depends on the nature and the characteristics of the allergen. For a full therapeutic benefit regular use is essential.

Allergic rhinitis

Initial dose
Adults, adolescents and children from 6 years of age:
The recommended initial dose of 256 micrograms may be administered once daily in the morning or divided into two administrations, in the morning and in the evening.
Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
2 actuations into each nostril once daily in the morning or
1 actuation into each nostril in the morning and in the evening

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
4 actuations into each nostril once daily in the morning or
2 actuations into each nostril in the morning and in the evening.

Children should be treated under guidance of an adult.

Treatment of seasonal allergic rhinitis should be initiated, if possible, before the patient is exposed to allergens.

Concomitant therapy may sometimes be necessary to treat the symptoms affecting the eye caused by the allergy.

Maintenance dose
The desired clinical effect appears within about 1-2 weeks.
Afterwards, the lowest dose should be chosen that keeps the patient just without symptoms. No better efficacy is to be expected with a dose greater than 256 micrograms.

Nasal polyps
Adults, adolescents and children from 6 years of age:
The recommended dose for the treatment of nasal polyps is 256 micrograms. The dose may be administered once daily in the morning or divided into two administrations, in the morning and in the evening.

Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
2 actuations into each nostril once daily in the morning or
1 actuation into each nostril in the morning and in the evening

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
4 actuations into each nostril once daily in the morning.
2 actuations into each nostril in the morning and in the evening.

Children should be treated under guidance of an adult.

After the desired clinical effect has appeared, the lowest dose should be chosen that keeps the patient without symptoms.

Method of administration

1. Gently blow your nose to clean the nostrils, if necessary.
2. Shake the bottle (figure 1). Remove the protective cap.

Figure 1.

3. Hold the bottle as shown in figure 2. Before using Budesonide nasal spray suspension for the first time you must prime the nozzle (i.e. fill it with medicine). Pump the nozzle up and down several times (5-10 times), spraying into the air until an even mist is seen. The priming effect remains for approximately 24 hours. If a longer period of time passes before the next

dose is taken, the nozzle must be primed (filled with medicine) again. If Budesonide nasal spray suspension is used at shorter intervals it is sufficient to spray just once into the air.

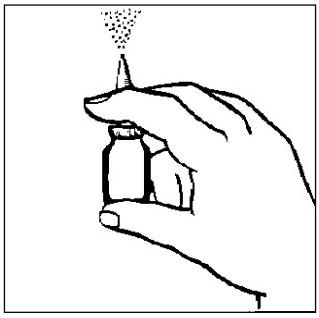

Figure 2.

4. Insert the tip of the nozzle into your nostril as shown in figure 3 and spray once (or more if your doctor has told you to). Use the pray into the other nostril in the same way. Note, it is not necessary to breathe in at the same time as you spray.

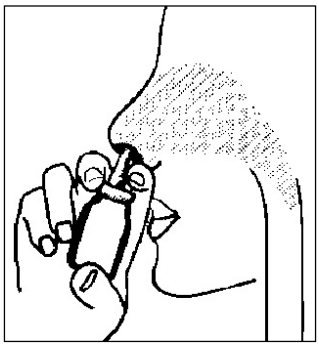

Figure 3.

5. Wipe the nozzle with a clean tissue and replace the protective cap.
6. Store the bottle in an upright position.

Cleaning your Budesonide nasal spray suspension
You should clean the plastic nozzle of Budesonide nasal spray suspension regularly, and at any time the spray of medicine is not coming out as it should. If this happens, first check if the nozzle is primed with medicine (see earlier). If after priming the nozzle again the pump is still not working, clean the nozzle by using the following instructions:

- Remove the plastic nozzle with a clean tissue and wash in warm – not hot – water.
- Rinse the nozzle thoroughly, dry it and then replace onto the top of the bottle.
- Never try to unblock the nozzle by using a pin or other sharp object.

After cleaning the nozzle must be primed (filled with medicine) again before use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses.

It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is

maintained. In addition, consideration should be given to referring the patient to the paediatric specialist.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence of higher than recommended doses being used then additional systemic corticosteroid cover should be considered during period of stress or elective surgery.

In case of infections of the nose caused by bacteria or fungi, Budesonide nasal spray suspension should be used only if concomitant antibacterial or antifungal treatment is carried out.

In continuous long-term treatment, the nasal mucosa should be inspected regularly e.g. every 6 months.

Impaired liver function influences the pharmacokinetics of corticosteroids. Severe impairment of hepatic function influences the pharmacokinetics of orally administered budesonide resulting in increased systemic availability and reduced elimination capacity. However, the intravenous pharmacokinetic of budesonide in healthy volunteers and patients with liver cirrhosis is approximately the same. Consideration of potential systemic effects may be needed in severe impairment of hepatic function.

Budesonide nasal spray is not recommended in patients with epistaxis and in patients, with herpetic infection of oral, nasal or ophthalmic region.

Budesonide nasal spray is not recommended in patients with nasal ulcerations, in cases of recent surgery or nasal trauma until it is fully recovered.

Special care is needed in patients with tuberculosis.

The use of budesonide nasal spray is not recommended in patients with infections of the airways.

The patient should be informed that the full effect is not achieved until after a few days of treatment. Treatment of seasonal rhinitis should, if possible, start before exposure to the allergens.

This medicinal product contains potassium sorbate and may cause skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of oral ketoconazol 200 mg once daily and oral budesonide (3 mg single dose) increased the plasma concentrations of budesonide on average 6-fold. When ketoconazol was administered orally 12 hours after the budesonide dose, the concentrations of budesonide increased on average 3-fold. There is no information about this interaction following nasal administration of budesonide, but increased plasma concentrations are expected. The combination should be avoided as there are no dose recommendations for the combination, but if not possible the time interval between the administrations of the two drugs should be as long as possible. A reduction of the dose may also be considered. Concomitant administration of other potent inhibitors of CYP3A4 (e.g.: ketoconazol, ciclosporin, ethinylestradiol und troleandomycin) is likely to result in a marked increase of budesonide plasma concentrations.

4.6 Pregnancy and lactation

Data on a limited number (over 2000) of exposed pregnancies indicate no adverse effects of budesonide on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies have shown reproductive toxicity (see section 5.3).

The potential risk for humans is unknown. Budenoside nasal spray should be used during pregnancy only if clearly needed.
As it is not known to which extent budesonide is excreted into breast milk, use in lactation requires that the therapeutic benefit to the mother be weighed against any potential risk to the neonate.

4.7 Effects on ability to drive and use machines

Budesonide Sandoz has no influence on the ability to drive or use machines.

4.8 Undesirable effects

When patients are transferred from systemic corticosteroid (oral or parenteral) to Budesonide nasal spray suspension, adverse reactions outside the nasal area which were previously under control by systemic therapy e.g. allergic conjunctivitis or dermatitis, may become unmasked. They should be treated additionally if needed.

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses.

Undesirable effects frequencies were defined as follows:

- very common (≥1/10)
- common (≥1/100 to <1/10)
- uncommon (≥1/1,000 to <1/100)
- rare (≥1/10,000 to <1/1,000)
- very rare (<1/10,000), not known (cannot be estimated from the available data)

Eye disorders	Rare: glaucoma, cataract (with long-term treatment)
Respiratroy, thoracic and mediastinal disorders	Common: local symptoms like nasal mucosa irritation, slight haemorrhagic secretion, epistaxis (immediately after application) Very rare: ulcerations of nasal mucosa, perforation of nasal septum
Skin and subcutaneous tissue disorders	Uncommon: immediate or delayed hypersensitivity reaction (urticaria, rash, itching, dermatitis, angioedema)
Musculoskeletal and connective tissue disorders	Rare: osteoporosis (with long-term treatment)
Endocrine disorders	Rare: growth suppression in children (see section 4.4), Very rare: adrenal supression

4.9 Overdose

An acute overdose with Budesonide nasal spray suspension is unlikely even if all the sprays contained in the bottle are administered all at once. Administration of doses higher than recommended (see section 4.2) for a longer period (over months) may result in suppression of hypothalamic-pituitary-adrenal axis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, Corticosteroids,
ATC Code: R01AD05

Budesonide is a glucocorticosteroid with a strong topical anti-inflammatory effect on the nasal mucosa and weak systemic effects after topical administration.

5.2 Pharmacokinetic properties

Following intranasal application budesonide is absorbed through nasal and to some extent through gastrointestinal mucosa. The systemic availability of budesonide is 33% of the delivered intranasal amount of budesonide.
In adults the maximal plasma concentration after administration of 256 micrograms of budesonide is 0,64 nmol/L and is reached within 0,7 hours.
The area under the curve (AUC) after administration of 256 micrograms of Budesonide nasal spray suspension is 2.7 nmol*h/L in adults and 5.5 nmol*h/L in children, indicating a higher systemic exposure in children.
At clinically relevant doses the kinetics of budesonide are dose proportional.
The volume of distribution of budesonide is approximately 3 L/kg. Protein binding is 85-90%.
Budesonide is eliminated through metabolism, mainly by the enzyme CYP3A4. Budesonide has a high systemic clearance (appr. 1.2 L/min) and the half-life in plasma following an intravenous dose is on average appr. 4 hours. The metabolites are eliminated in the urine in unchanged or conjugated form. The main metabolites 6-beta-hydroxybudesonide and 16-alpha-hydroxyprednisolon are almost ineffective.
Orally ingested budesonide is in the first passage rapidly and extensively biotransformed by the liver (90%) to metabolites with lower glucocorticosteroid activity. Budesonide in not metabolised locally in the nasal mucosa.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans at therapeutic doses based on studies of chronic toxicity, genotoxicity and carcinogenicity.
Glucocorticosteroids including budesonide have produced teratogenic effects in animals, including cleft palate and skeletal abnormalities. Similar effects are considered unlikely to occur in humans at therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dispersible cellulose (Microcrystalline cellulose and carboxymethylcellulose sodium, (89:11, w/w))
Polysorbate 80
Potassium sorbate E 202
Glucose, anhydrous
Disodium edetate
Hydrochloric acid, concentrated
Ascorbic acid E 300
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening: 3 months

6.4 Special precautions for storage

Do not store above 30°C
Do not freeze.

6.5 Nature and contents of container

Not all pack sizes may be marketed.

[To be completed nationally]

6.6 Special precautions for disposal <and other handling>

No special requirements

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Box

1. NAME OF THE MEDICINAL PRODUCT

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
[See Annex I - To be completed nationally]
Budesonide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.05 ml dose (one spray) of this nasal spray, suspension, contains 32 micrograms of budesonide

Each 0.05 ml dose (one spray) of this nasal spray, suspension, contains 64 micrograms of budesonide

3. LIST OF EXCIPIENTS

Dispersible cellulose (Microcrystalline cellulose and carboxymethylcellulose sodium, (89:11, w/w))
Polysorbate 80
Potassium sorbate E 202
Glucose, anhydrous
Disodium edetate
Hydrochloric acid, concentrated
Ascorbic acid E 300
Purified water

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, suspension.
[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Nasal Use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Shake the bottle

Important: Pump may need to be primed before use (see enclosed instructions)

8. EXPIRY DATE

EXP
After first opening: 3 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C
Do not freeze

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 AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
[See Annex I - To be completed nationally]
Budesonide
Nasal Use

2. METHOD OF ADMINISTRATION

Nasal Use
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Budesonide Sandoz and associated names (see Annex I) 32 µg nasal spray suspension
Budesonide Sandoz and associated names (see Annex I) 64 µg nasal spray suspension
[See Annex I - To be completed nationally]

Budesonide

[To be completed nationally]

In this leaflet:

1. WHAT Budesonide Nasal Spray IS AND WHAT IT IS USED FOR

Budesonide Nasal Spray contains budesonide, a synthetic corticosteroid. Corticosteroids are a group of medicines which help fight inflammation.
Budesonide Nasal Spray is used for:

- the treatment and prevention of the symptoms of allergies like hay fever (eg caused by grass pollen)
- the treatment and prevention of the symptoms of year-round nasal allergy caused for example by house dust (chronic rhinitis)
- for the treatment of symptoms of nasal polyps (small growths on the lining of the nose).

2. BEFORE YOU USE Budesonide Nasal Spray

Do not NOT use Budesonide Nasal Spray
You must NOT use Budesonide Nasal Spray:

- if you are hypersensitive (allergic) to budesonide, or any of the other ingredients of Budesonide Nasal Spray suspension (see section 6. Further Information).

Take special care with Budesonide Nasal Spray

- if you are a child and are taking high doses of this medicine for a long time, your doctor will check your height regularly
- if you have been taking this medicine continuously for a long time, your doctor will want to examine the inside of your nose at least every six months
- if you have been taking higher than recommended doses of this medicine: your doctor may prescribe steroid tablets during periods of stress (such if you have an infection) or before an operation
- if you have any ulcers in your nose
- if your have infectious blisters on your lips (a cold sore), in the nose or aroud your eyes
- if you suffer frome nosebleeds
- if you have had an operation on your nose or any other injury to your nose that has not yet fully recovered
- if you have a bacterial or fungal infection of your nose: You should use Budesonide nasal spray if you were prescribed treatment for the infection as well

- if you have problems with your liver because the amount of budesonide could build up in your body. Your doctor might need to check your liver, and as a result, may need to reduce your dose
- if you were told by your doctor you have infection of airways or lung tuberculosis. This is an infection that can affect your lungs.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines without a prescription.
Make sure you tell your doctor if you are taking
ketoconasole tablets, a medicine used to treat fungal infections, such as thrush. It may increase the concentration of budesonide in your body.
You should also tell your doctor if you are takng any other medicines such as:
- troleandomycin, a medicine to treat bacterial infections
- itraconasole, a medicine to treat fungal infections
- ciclosporin, immune suppression drug used e.g. in connection with transplants
- ethinylestradiol, used for contraception.

It is possible that these medicines could also increase the concentration of budesonide in your body.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
You should not use Budesonide nasal spray **if you are pregnant** unless you have discussed this with your doctor.
Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.
Breast-feeding mothers should not use Budesonide nasal spray. Be sure to tell your doctor immediately if you are breast-feeding.

Driving and using machines
This medicine does not affect your ability to drive and use machines at the recommended dose (see section 3. How to use Budesonide nasal spray).

Important information about some of the ingredients of Budesonide Nasal Spray suspension
Potassium sorbate is an ingredient of Budesonide Nasal Spray. It may cause irritation of the skin or mucous membranes (e.g. contact dermatitis).

3. HOW TO USE Budesonide Nasal Spray

Budesonide Nasal Spray is intended for **nasal use.** It should be sprayed into your nostrils as described below.

Dosage
Always use Budesonide Nasal Spray exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The dose should be adjusted to suit you. Use the lowest dose which still relieves your symptoms.

Allergic rhinitis
Starting dose
Adults, adolescents (12 years of age and older) and children older than 6 years of age:
The recommended starting dose of Budesonide nasal spray is a total of **8** [Nationally completed name] 32 micrograms/dose nasal spray, suspension] **sprays** (256 micrograms) **each day**.

You can **either** use this medicine:
- once daily by applying 4 sprays into each nostril in the morning

or

- twice daily by applying 2 sprays into each nostril in the morning and 2 sprays into each nostril in the evening.

The recommended starting dose of Budesonide nasal spray is a total of **4** [Nationally completed name] 64 micrograms/dose nasal spray, suspension] **sprays** (256 micrograms) **each day**.

You can **either** use this medicine:
- once daily by applying 2 sprays into each nostril in the morning

or
- twice daily by applying 1 spray into each nostril in the morning and 1 spray into each nostril in the evening.

Children should be treated under guidance of an adult.

Ideally, you should start to use this medicine up to 14 days before you expect your symptoms to start. For example, if you have hay fever, start using this medicine about 2 weeks before your hay fever symptoms usually begin to be a problem and stop using this medicine after the end of season of allergen exposure.

Maintenance dose
It takes 7 to 14 days for this medicine to work. After this, your doctor may lower your dose.

Nasal polyps
Adults, adolescents (12 years of age and older) and children older than 6 years of age:
The recommended starting dose of Budesonide nasal spray is a total of **8** [Nationally completed name] 32 micrograms/dose nasal spray, suspension] **sprays** (256 micrograms) **each day**.
You can **either** use this medicine:
- once daily by applying 4 sprays into each nostril in the morning

or
- twice daily by applying 2 sprays into each nostril in the morning and 2 sprays into each nostril in the evening.

The recommended starting dose of Budesonide nasal spray is a total of **4** [Nationally completed name] 64 micrograms/dose nasal spray, suspension] **sprays** (256 micrograms) **each day**.
You can **either** use this medicine:
- once daily by applying 2 sprays into each nostril in the morning

or
- twice daily by applying 1 spray into each nostril in the morning and 1 spray into each nostril in the evening.

Children should be treated under guidance of an adult.

Once the effect is achieved, the lowest dose which relieves your symptoms should be used.
Using more than the recommended 8 [Nationally completed name] 32 micrograms/dose nasal spray, suspension] sprays of this medicine each day will **not** make this medicine work any better.

Using more than the recommended 4 [Nationally completed name] 64 micrograms/dose nasal spray, suspension] sprays of this medicine each day will **not** make this medicine work any better.

Duration of treatment:
Your doctor will tell how long your treatment with Budesonide nasal spray suspension will last. You must use this medicine regularly or it will not work properly. Do not stop treatment even if you feel better unless told to by your doctor.

If you don’t experience an immediate relief, you should continue using your medicine regularly as it may take a few days to start working.

Method of administration

1. Gently blow your nose to clean the nostrils, if necessary.
2. Shake the bottle (figure 1). Remove the protective cap.

Figure 1.

3. Hold the bottle as shown in figure 2. Before using Budesonide Nasal Spray for the first time you must prime the nozzle (i.e. fill it with medicine). Pump the nozzle up and down several times (5-10 times), spraying into the air until an even mist is seen. The priming effect remains for approximately 24 hours. If a longer period of time passes before the next dose is taken, the nozzle must be primed (filled with medicine) again. If Budesonide Nasal Spray is used at shorter intervals it is sufficient to spray just once into the air.

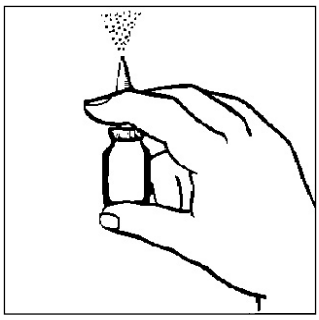

Figure 2.

4. Insert the tip of the nozzle into your nostril as shown in figure 3. Spray once (or more if your doctor has told you to). Spray into the other nostril in the same way. Note, it is not necessary to breathe in at the same time as you spray.

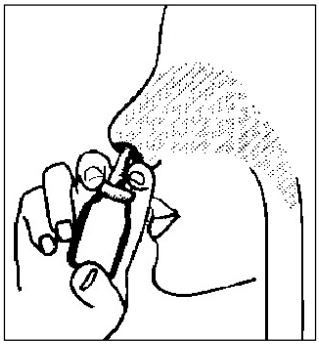

Figure 3.

5. Wipe the nozzle with a clean tissue and replace the protective cap.
6. Store the bottle in an upright position.

Cleaning your Budesonide Nasal Spray
You should clean the plastic nozzle of Budesonide Nasal Spray regularly, and at any time the spray of medicine is not coming out as it should. If this happens, first check if the nozzle is primed with medicine (see earlier). If after priming the nozzle again the pump is still not working, clean the nozzle by using the following instructions:

- Remove the plastic nozzle with a clean tissue and wash in warm – not hot – water.
- Rinse the nozzle thoroughly, dry it and then replace onto the top of the bottle.
- Never try to unblock the nozzle by using a pin or other sharp object.
- After cleaning the nozzle must be primed (filled with medicine) again before use.

If you use more Budesonide Nasal Spray than you should
If you use more Budesonide Nasal Spray than you should, continue with your usual dose. You are unlikely to experience any medical problems.
However, if you have been using more 8 [Nationally completed name] 32 micrograms/dose nasal spray, suspension] sprays a day for more than a month consult your doctor immediately.
However if you have been using more than 4 [Nationally completed name] 64 micrograms/dose nasal spray, suspension] sprays a day for more than a month consult your doctor immediately.

If you forget to take Budesonide Nasal Spray
If you forget to use your medicine on time, use it as soon as possible, then go back to your regular dosing schedule. Never use more sprays in one day than your regular dosing schedule, to make up for a missed dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Budesonide Nasal Spray can cause side effects, although not everybody gets them. This medicine generally only treats symptoms affecting the nose (eg congestion or a "runny nose"). If you were previously treated with steroid tablets or injections but your doctor has now prescribed this medicine instead, you might experience a worsening of some of your other symptoms (eg red and itchy eyes). If this happens, your doctor will need to treat these other symptoms separately.
Side effects of nasal corticosteroids are more likely to occur if you have been using them at high doses for a number of months.

The following side effects can occur during treatment with Budesonide Nasal Spray:

Common side effects (fewer than 1 patient in every 10 and more than 1 patient in every 100 patients treated)
These may occur immediately after using this medicine:

- occasional sneezing, dry nose or stinging in your nose
- slightly bloody discharge from your nose
- nose bleed

Uncommon side effects (fewer than 1 patient in every 100 and more than 1 patient in every 1.000 patients treated):

- swollen face, tongue and/or pharynx and/or difficulty to swallow or hives together with difficulties to breathe (angioedema): if this happens **you should contact your doctor immediately**
- hives (an itchy rash that looks like nettle rash)
- rash
- itching
- irritation of the skin

Rare side effects (fewer than 1 patient in every 1.000 and more than 1 patient in every 10.000 patients treated):
These may occur after using this medicine for a long time:

- fragile bones
- increased pressure in the eyes
- clouding of the eye lenses
- slowing of the growth rate in children and adolescents, particularly after taking high doses for a long time

Very rare side effects (fewer than 1 patient in every 10.000 patients treated), or where the frequency is not known (cannot be estimated from the available data):

- a hole in the cartilage dividing your nostrils
- sore patches in your nose
- adrenal supression. This may cause symptoms such as anorexia, abdominal pain, weight loss, nausea, headache, vomiting, decreased level of consciousness, low blood sugar,levels and seizures. Situations which may potentially trigger acute adrenal crisis include trauma, infection, surgery or any rapid reduction in dosage. If you notice these symptoms **you should contact your doctor immediately.**

Potassium sorbate, an ingredient of this medicine, might cause irritation of the skin or mucous membranes, such as the inside if your nose.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Budesonide Nasal Spray

Keep out of the reach and sight of children.

Do not use **Budesonide Nasal Spray** after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.
Do not freeze.

Discard the opened bottle with any remaining solution after 3 months.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What X contains

- The active substance(s) is (are)…
- The other ingredient(s) is (are)...

[To be completed nationally]

What Budesonide Nasal Spray Suspension looks like and contents of the pack
Budesonide Nasal Spray looks like a white homogeneous suspension

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:>

[See Annex I - To be completed nationally]

This leaflet was last approved in.

[To be completed nationally]