Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rhinocort Turbohaler, 100 micrograms per metered dose, Nasal Powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 100 micrograms Budesonide.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nasal powder
Rhinocort Turbohaler is a metered dose, powder, nasal inhaler. White to off-white rounded granules which break into a fine nasal powder on inhalation.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Seasonal and perennial allergic rhinitis and vasomotor rhinitis.
Treatment of nasal polyps.

4.2 Posology and method of administration

Posology
Treatment of seasonal and perennial allergic rhinitis and vasomotor rhinitis
Adults: The recommended dose is 400 mcg. Rhinocort Turbohaler may be given once daily (two applications into each nostril in the morning). When good effect has been achieved the dosage may be reduced to one application into each nostril.

Rhinocort Turbohaler may also be given twice daily (one application into each nostril morning and evening).

If symptoms are not controlled, or persist for longer than 2 weeks of treatment, medical advice should be sought. Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods.

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

Elderly: Dosage as for adults.

Paediatric population: There are insufficient data to recommend the use of Rhinocort Turbohaler in children.

Treatment of nasal polyps
Adults: The recommended dose is 200 mcg twice daily (one application into each nostril morning and evening).

If symptoms are not controlled, or persist for longer than 2 weeks of treatment, medical advice should be sought. Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods.

Elderly: Dosage as for adults.

Paediatric population: There are insufficient data to recommend the use of Rhinocort Turbohaler in children.

Method of administration
Note: It is important to instruct the patient:

- To carefully read the instructions for use in the patient information leaflet, which is packed with each Turbohaler
- To breathe in quickly and hard through nose
- Never to breathe out through inhaler

The patient may not taste or feel any medication when using Turbohaler due to the small amount of drug dispensed.

The outside of the nasal adapter should be cleaned regularly (weekly) with a dry tissue. The nasal adapter should never be washed.

4.3 Contraindications

Hypersensitivity to the active substance.

4.4 Special warnings and precautions for use

Use of excessive doses of, or long-term treatment with, glucocorticosteriods may lead to signs or symptoms of hypercorticism, suppression of HPA function and/or suppression of growth in children.

Special care is needed in patients with fungal and viral nasal infections in the airways, and in patients with active or quiescent pulmonary tuberculosis.

Special care is demanded in treatment of patients transferred from oral steroids to Rhinocort where disturbances in the hypothalamic pituitary-adrenal axis could be expected.

Concomitant treatment of seasonal rhinitis may sometimes be necessary to counteract eye symptoms caused by the allergy.

Reduced liver function affects the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing’s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of budesonide should also be considered (see section 4.5).

<u>Visual disturbance</u>
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric population
The long-term effects of nasal glucocorticosteroids in children are not fully known. Physicians should closely follow the growth of children taking glucocorticosteroids for longer term by any route, and weigh the benefits of the glucocorticosteroid therapy against the possibility of growth suppression. Until greater experience has been achieved, continuous long-term treatment of children is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Budesonide has not been observed to interact with any drug used for the treatment of rhinitis.

The metabolism of budesonide is primarily mediated by CYP3A enzymes. Inhibitors of these enzymes, e.g. itraconazole, ketoconazole, HIV protease inhibitors or cobicistat can therefore increase systemic exposure to budesonide (see section 4.4 and section 5.2). The combination of Rhinocort with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. A reduction of the budesonide dose could be considered. If Rhinocort is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible.

The influence of cimetidine on budesonide kinetics and dynamics after concomitant oral and intravenous administration is of minor clinical importance.

When used in conjunction with other agents such as systemic corticosteroids readjustment of dosage should be carried out with caution.

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.6 Fertility, pregnancy and lactation

Pregnancy
Results from prospective epidemiological studies and from worldwide post marketing experience indicate no increased risk for overall congenital malformations from the use of inhaled or intranasal budesonide during early pregnancy. As with other drugs the administration of Rhinocort during pregnancy requires that the benefits for the mother are weighed against the risk for the foetus.

Breast-feeding
Budesonide is excreted in breast milk. However, at therapeutic doses of Rhinocort no effects on the breast fed child are anticipated. Rhinocort can be used in breast−feeding.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study, the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentration observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

4.7 Effects on ability to drive and use machines

Rhinocort Turbohaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse events
Adverse reactions, which have been associated with budesonide, are given below, listed by system organ class and frequency. Frequency is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000) and not known (cannot be estimated from the available data).

Immune system disorders	Uncommon	Immediate and delayed hypersensitivity reactions including urticaria, rash, dermatitis angioedema and pruritus
	Rare	Anaphylactic reaction
Endocrine disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation
Eye disorders	Unknown	Raised intraocular pressure or Glaucoma Cataract
	Rare	Vision, blurred (see also section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Haemorrhagic secretion and epistaxis Nasal Irritation (sneezing, stinging and dryness)
	Rare	Nasal ulcer Nasal septum perforation Dysphonia
	Very Rare	Ulceration of mucous membrane
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm
Injury, poisoning and procedural complications	Rare	Contusion*

* based on mechanistic plausibility and extrapolation from other budesonide/corticosteroid formulations.

In rare cases, signs or symptoms of systemic glucocorticosteroid-side effects may occur with nasal glucocorticosteroids probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity (see section 4.4).

Paediatric population
Growth retardation has been reported in children receiving intranasal steroids. Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Acute overdose with Rhinocort even in excessive doses, is not expected to be a clinical problem.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, corticosteroids.
ATC Code: R01A D05.

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.

A clinical study in seasonal rhinitis comparing intranasal (pressurised aerosol) and oral budesonide with placebo showed that the therapeutic effect of budesonide may be fully explained by a local action of budesonide.

Controlled clinical investigations have documented Rhinocort to give good therapeutic results with few adverse effects in allergic and vasomotor rhinitis.

Budesonide given prophylactically has also shown protective effects against the immediate allergic reaction. During long-term treatment in adults and children with perennial rhinitis, Rhinocort (pressurised aerosol) has proved to be well tolerated.

At recommended dosage Rhinocort Turbohaler does not cause any clinically important changes neither in basal plasma cortisol levels nor in the response to stimulation with ACTH in patients with rhinitis. However, dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers after short-term administration of Rhinocort Turbohaler.

5.2 Pharmacokinetic properties

Absorption
The systemic availability of oral budesonide in man is low (about 10%). With reference to the metered dose, the systemic availability of budesonide from Rhinocort Turbohaler is 22%. After application of budesonide in solution directly on the nasal mucosa, all the dose is systemically available, indicating that budesonide does not undergo local metabolism in the nose.

Distribution
Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%. The maximal plasma concentration after administration of 800micrograms budesonide from Rhinocort Turbohaler is 1.1nanomol/L and is reached within 0.4 hours.

Biotransformation
Budesonide undergoes an extensive degree (~ 90%) of biotransformation in the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxybudesonide and 16-alpha - hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. Budesonide does not undergo local metabolic inactivation in the nose.

Elimination
The metabolites are excreted as such or in conjugated form mainly via the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma half-life after i.v. dosing averages 2-3 hours.

Linearity
The kinetics of budesonide are dose-proportional at clinically relevant doses.

5.3 Preclinical safety data

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (Beclometasone dipropionate, flucinolone acetonide). Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe or similar to those observed after administration of the other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

Budesonide evaluated in six different test systems did not show any mutagenic or clastogenic effects.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups with active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups. Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class-effect.

Available clinical experience shows no indication that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man. Budesonide has been used successfully for the treatment of asthma for many years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Replace the cover properly after use.

6.5 Nature and contents of container

The nasal container consists of a number of assembled plastic details, the main parts being the dosing mechanism, the drug substance store, the desiccant store and the nasal adapter. The inhaler is protected by an outer tubular cover screwed onto a bottom plate.

Each inhaler contains 200 metered doses.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

See section 4.2

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0970/051/001

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