SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Rhinocort Aqua 32 micrograms/dose nasal spray, suspension
Rhinocort Aqua 64 micrograms/dose nasal spray, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.05 ml) contains 32 micrograms or 64 micrograms of budesonide.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seasonal and perennial allergic rhinitis and vasomotor rhinitis. Prophylactically in patients with nasal polyps following polypectomy. Symptomatic treatment in nasal polyposis.

4.2 Posology and route of administration

The dosage should be adjusted individually.

**Rhinitis**

Adults and children from 6 years: The recommended initial dose is 256 micrograms per day. The dose may be administered once daily in the morning or divided into two administrations, morning and evening. This means 128 micrograms (2 x 64 micrograms) into each nostril in the morning or 64 micrograms into each nostril morning and evening.

No further effect has been seen with doses higher than 256 micrograms per day.

For elderly patients the dosage is the same as for adults.

When the desired clinical effect has been achieved, the dose should be reduced to the lowest amount that is needed to control the symptoms. Clinical trials show that a dose of 32 micrograms in each nostril in the morning may be sufficient for some patients.

In some patients relief of symptoms is already obtained within 5-7 hours after the start of treatment. The patient should be informed that the full effect is only obtained after several days of treatment (in rare cases only after 2 weeks). Treatment of seasonal allergic rhinitis should therefore, if possible, start before exposure to the allergens.

In cases of severe nasal congestion an initial addition of a vasoconstrictor may be required.
Supplementary treatment may sometimes be necessary in order to counteract possible ocular symptoms caused by the allergy.

For the indication allergic rhinitis, the 32 micrograms/dose strength is available without prescription, for use for a maximum of 3 months.

**Symptomatic treatment and prevention of nasal polyps**
The recommended dose is 256 micrograms per day. The dose may be administered once daily in the morning or divided into two administrations, morning and evening. When the desired clinical effect has been achieved, the dose should be reduced to the lowest amount that is needed to control the symptoms.

### 4.3 Contraindications

Previous hypersensitivity to budesonide or to any of the excipients.

### 4.4 Special warnings and precautions for use

In long-term treatment with high doses, systemic effects of glucocorticosteroids such as hypercortisolism, adrenal suppression and/or retarded growth in children may occur (see Paediatric population below).

Care must be exercised in the treatment of patients who are being transferred from systemically acting glucocorticosteroids to Rhinocort Aqua and if there is suspected disturbed pituitary-adrenocortical function. In these patients there should be a careful reduction of the systemic steroid dose and testing of hypothalamic-pituitary-adrenocortical function should be considered. They may also need the addition of systemic steroids in connection with periods of stress, e.g. surgery, trauma, etc.

Impaired hepatic function affects the elimination of corticosteroids, which leads to a reduced rate of elimination and increased systemic exposure. Pay attention to possible systemic effects. Special caution is needed in patients with active or latent lung tuberculosis, and in patients with fungal or viral infections (e.g. herpes) of the airways.

**Visual disturbance**

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.

Rhinocort Aqua should not come into contact with the eyes. If Rhinocort Aqua comes into contact with the eyes, rinse immediately with water.

Concomitant treatment with ketoconazole or other potent CYP3A4-inhibiting drugs should be avoided. If this is not possible, the time interval between administrations of the agents should be as long as possible (see section 4.5).

Systemic effects may occur with nasal corticosteroids, especially at high doses during long periods of treatment. It is less likely that these effects will occur in intranasal treatment than when corticosteroids are administered orally, and these effects may vary between patients and with different corticosteroid preparations. Possible systemic undesirable effects may include Cushing’s syndrome, Cushing-like symptoms, adrenal suppression, inhibited growth in height...
of children and adolescents, cataracts, glaucoma, and more rarely a range of psychological disorders or behavioural disorders including psychomotor hyperactivity, sleep disorders, agitation, depression or aggression (especially in children).

Paediatric population
Long-term effects of nasal steroids in children have not been elucidated. Treatment with medicines containing cortisone can lead to slower growth. Regular monitoring of height is recommended in children and adolescents receiving long-term treatment with corticosteroids, irrespective of the administration form. If retarded growth is suspected, this should be investigated. The benefits of glucocorticosteroid treatment should be placed in relation to the possible risk of inhibited growth.

4.5 Interaction with other medicinal products and other forms of interaction

Budesonide has not been observed to interact with medicinal products that are used to treat rhinitis.

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, may therefore increase systemic exposure to budesonide several times. Oral ketoconazole 200 mg once daily increased the plasma concentrations of oral budesonide (3 mg in a single dose) on average six-fold when administered simultaneously. When oral ketoconazole was administered 12 hours after budesonide, the concentration increased on average three-fold. There is no information about this interaction for nasal budesonide, but also in such cases greatly increased plasma levels are expected. Since there are no data to support a dosage recommendation to be given in cases of nasal administration, the combination must be avoided. If this is not possible, the time interval between administration of ketoconazole and that of budesonide must be as long as possible and a reduction of the budesonide dose may also be considered. Other potent inhibitors of CYP3A4 also probably cause a marked increase in the plasma levels of budesonide.

Elevated plasma concentrations and increased effects of corticosteroids have been observed in women who were also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of combined low dose contraceptive pills.

As adrenal function may be inhibited, an ACTH stimulation test for diagnosis of pituitary failure may show an incorrect result (low value).

4.6 Fertility, pregnancy and lactation

Pregnancy

Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the foetus and newborn child from the use of inhaled budesonide during pregnancy. It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. In animal studies, glucocorticosteroids have been shown to induce malformations (see Section 5.3). This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to the foetus.

Lactation
Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide no effects on the suckling child are expected. Budesonide can be used during breast-feeding.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic, lactating women results in negligible systemic exposure to budesonide in the suckling child.

In a pharmacokinetic study the estimated daily dose in the child was 0.3% of the mother’s daily dose at both dose levels and the mean plasma concentration in the infant was estimated at a 600th part of the concentrations that were observed in the mother’s plasma, assuming complete oral bioavailability in the child. The concentrations of budesonide in the infant’s plasma samples were all below the quantification limit.

Based on data from the inhaled budesonide and the fact that budesonide shows linear pharmacokinetic properties within the therapeutic dose interval after nasal, inhaled, oral and rectal administration, exposure of the suckling child is expected to be low.

4.7 Effects on ability to drive and use machines

Rhinocort Aqua does not affect ability to drive or operate machinery.

4.8 Undesirable effects

Approx. 5% of treated patients may be expected to experience side effects in the form of local irritation.

In below table the undesirable effects are listed according to classification and frequency. Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000) Very rare (<1/10,000), No known frequency (cannot be calculated from available data).

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Uncommon</th>
<th>Immediate and delayed hypersensitivity reactions, including urticaria, rash, dermatitis angioedema and pruritus.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rare</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Endocrine system disorders</td>
<td>Rare</td>
<td>Signs and symptoms of systemic corticosteroids effects, including inhibited adrenal function and inhibited growth in height</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Rare</td>
<td>Dysphonia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>No known frequency</td>
<td>Cataract</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vision, blurred (see also section 4.4)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Local irritation, epistaxis, haemorrhagic nasal secretion.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Nasal septum perforation, ulceration of mucous membranes.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>Bruising</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>Muscle spasm</td>
</tr>
</tbody>
</table>
Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity.

Paediatric population
Inhibition of growth in height has been reported in children who are given intranasal steroids. Because of the risk of inhibition of growth in the paediatric population growth must be monitored as described in section 4.4.

**Reporting of suspected adverse reactions:**
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649

### 4.9 Overdose

Acute overdosage with Rhinocort Aqua, even high doses, is not expected to cause any clinical problems. If Rhinocort Aqua is used in high doses for a long period, the systemic effects characteristic of glucocorticosteroids such as hypercortisolism and adrenal suppression may occur.

### 5. Pharmacological Properties

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids  
ATC code: R01AD05  
Mechanism of effect: Budesonide is a glucocorticosteroid with a powerful local anti-inflammatory effect.

The precise mechanism of action of glucocorticosteroids in the treatment of rhinitis is not fully understood. Anti-inflammatory effects such as inhibited release of inflammatory mediators and inhibition of cytokine-mediated immune response are probably significant. The activity of budesonide, measured as its affinity for glucocorticosteroid receptors, is approx. 15 times higher than that of prednisolone.

Clinical effect and safety  
Budesonide given prophylactically prior to nasal provocation has proved to protect against immigration of eosinophils and hyperreactivity.

At recommended doses, Rhinocort Aqua does not cause any clinically significant changes either in basal plasma cortisol levels or in the response to stimulation with ACTH. However, dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers following short-term administration of Rhinocort Aqua.

A dose-response relationship has not been demonstrated in clinical trials in children with seasonal or perennial allergic rhinitis or in adults with perennial allergic rhinitis.
Vasomotor rhinitis (non-allergic perennial rhinitis) has not been documented with Rhinocort Aqua in the strengths 32 and 64 micrograms/dose.

**Paediatric population**

**Clinical efficacy**
The therapeutic efficacy of Rhinocort Aqua nasal spray has been evaluated in several thousand adults and children. Most studies were carried out with intranasally administered doses of 32 to 256 μg of Rhinocort Aqua once daily. Examples of representative studies that evaluated the use of Rhinocort Aqua for the treatment of children with seasonal and perennial allergic rhinitis are given below. The primary effect variable was the combined nasal symptom score (CNSS), which is the sum of the individual nasal symptom scores for three nasal symptoms (blocked nose, runny nose and sneezing, each of which was estimated on a scale of 0-3).

**Seasonal allergic rhinitis**

**Paediatric population**
A 2 week, randomised, double blind, placebo controlled study with parallel groups evaluated the efficacy and safety of Rhinocort Aqua 16, 32 and 64 μg once daily in 400 children (aged from 2 to 5 years) with allergic rhinitis (seasonal or perennial). A marked reduction from the baseline value of CNSS was shown in all treatment groups, including placebo. The difference between Rhinocort Aqua 64 μg and placebo treatment was not statistically significant.

**Perennial allergic rhinitis**

**Paediatric population**
A 6 week, randomised, double blind, placebo controlled study with parallel groups evaluated the efficacy and safety of Rhinocort Aqua 128 μg once daily in 202 children (aged from 6 to 16 years) with perennial allergic rhinitis. The primary effect variables were CNSS and the value of peak nasal inhalation flow (PNIF). Rhinocort Aqua gave statistically significant greater improvement in CNSS and PNIF than placebo. The principal effect of Rhinocort Aqua occurred 12 hours after the first dose for CNSS and 48 hours for PNIF.

**Clinical safety**

**Paediatric population**
In a randomised, double blind, placebo controlled study of growth 229 pre-pubertal children aged from 4 to 8 years were given Rhinocort Aqua 64 micrograms once daily or placebo for 12 months after a 6 month baseline period. In this study the rate of growth was similar in the treatment groups with Rhinocort Aqua and placebo after 12 months of treatment; the mean difference in the rate of growth (placebo – Rhinocort Aqua) was 0.27 cm/year (95% confidence interval: −0.07 to 0.62).

**Effect on plasma hydrocortisone concentration:**
At recommended doses Rhinocort Aqua causes no clinically relevant changes in basal plasma hydrocortisone concentrations or in ACTH stimulation. In healthy volunteer subjects dose-dependent suppression of hydrocortisone concentrations was seen in plasma and urine after short term administration of Rhinocort Aqua.

### 5.2 Pharmacokinetic properties

**Absorption**
The systemic availability of budesonide from Rhinocort Aqua is 33 % of the measured dose.

The peak plasma concentration in adults from 256 micrograms of budesonide from Rhinocort Aqua is 0.64 nmol/l, and is reached within 0.7 hours. The AUC (area under the curve) after
administration of 256 micrograms of budesonide from Rhinocort Aqua is 2.7 nmol x hours/litre in adults.

**Distribution**
Budesonide has a volume of distribution of approx. 3 l/kg. Binding to plasma proteins is approx. 85-90 %.

**Metabolism**
Budesonide undergoes extensive (~90%) first pass metabolism in the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity of the principal metabolites, 6-beta-hydroxybudesonide and 16-alpha-hydroxyprednisolone, is less than 1 % of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Budesonide does not undergo local metabolism in the nose.

**Elimination**
The metabolites are excreted unchanged or in conjugated form, primarily via the kidneys. No intact budesonide was detected in urine.
Budesonide has high systemic clearance (~1.2 l/min) and the half-life in plasma after intravenous administration is on average approx. 4 hours.

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

**Paediatric population**
Budesonide has a systemic clearance of about 0.5 l/min in children with asthma at the age of 4-6 years. Clearance per kilo body weight in children is about 50% higher than in adults. The terminal half life of budesonide after inhalation is about 2.3 hours in children with asthma. This is about the same as in adults. The area under the curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 5.5 nmol x hours/litre in children, which indicates higher systemic glucocorticosteroid exposure in children than in adults. At clinically recommended doses the pharmacokinetics of budesonide are dose-proportional and plasma exposure is correlated to the patient’s weight. This should therefore be taken into account when paediatric doses are set.

5.3 **Preclinical safety data**

Conventional studies with regard to general toxicity, genotoxicity and carcinogenicity did not show any particular risks for humans. In reproduction studies in animals corticosteroids, such as budesonide, were shown to be able to cause malformations of various kinds (cleft palate, skeletal malformation). However, the experimental animal results do not appear to have any relevance for humans with recommended doses of Rhinocort Aqua.

6. **Pharmaceutical Particulars**

6.1 **List of excipients**

Microcrystalline cellulose
Carmellose sodium
Anhydrous glucose
Polysorbate 80
Disodium edetate
Potassium sorbate (E 202)
Hydrochloric acid
Purified water

The amount of preservative, potassium sorbate (E 202), is 1.2 mg/ml in both strengths.

6.2 Incompatibilities
-

6.3 Shelf-life
2 years

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

6.5 Nature and contents of container
Brown glass bottles fitted with a spray pump and nasal applicator.

Pack sizes:

<table>
<thead>
<tr>
<th>Drug Strength</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinocort Aqua 32 μg/dose</td>
<td>120 doses</td>
</tr>
<tr>
<td>Rhinocort Aqua 64 μg/dose</td>
<td>120 doses</td>
</tr>
</tbody>
</table>

6.6 Special precautions for disposal and other handling
Before Rhinocort Aqua is used for the first time, the nasal applicator must be primed with the drug. Therefore, shake the bottle, and spray into the air until there is an even mist. The effect of this lasts for approx. 24 hours. If a longer period elapses before the next dose is taken, the nasal applicator must be primed with the drug again. This time it is sufficient to spray just once into the air.

How the patient should take Rhinocort Aqua is described in detail in the package leaflet.

7. MARKETING AUTHORITY
AstraZeneca AB, S-151 85 Södertälje, Sweden.

8. MARKETING AUTHORITY NUMBER(S)

<table>
<thead>
<tr>
<th>Drug Strength</th>
<th>Authority Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinocort Aqua 32 μg/dose</td>
<td>18341</td>
</tr>
<tr>
<td>Rhinocort Aqua 64 μg/dose</td>
<td>18340</td>
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</table>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
31 August 1999/15 November 2005

10. DATE OF REVISION OF THE TEXT
17 May 2017