1. NAME OF THE MEDICINAL PRODUCT

Benacort® Hayfever Relief for Adults 64 micrograms, nasal spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation contains: Budesonide 64 micrograms (1.28 mg/ml).

Excipient with known effect:

Potassium sorbate (E202) 1.2 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of seasonal allergic rhinitis (hayfever) in adults aged 18 years and over. This medicine provides symptomatic relief from nasal congestion, runny nose, sneezing, itchy nose and associated sinus discomfort.

4.2 Posology and method of administration

Posology

Adults aged 18 years and over, including the elderly

Patients should commence treatment with two sprays into each nostril each morning. Once symptoms are under control, a maintenance dose of one spray into each nostril each morning may be used. Total daily administration should not exceed four sprays (256 micrograms).

If symptoms recur patients should revert to the starting dose. The lowest dose at which effective control of symptoms is achieved should be used.

If symptoms persist or are not adequately controlled after 7 days of treatment patients should consult their doctor or pharmacist. This medicine should not be used continuously for longer than 1 month without seeking medical advice.

Patients should be reminded of the importance of taking this medicine regularly.

The patient should be informed that the full effect of this medicine is not achieved until after a few day's treatment.

Paediatric population: This medicine should not be used in children and adolescents under 18 years of age.

Method of administration

For nasal inhalation.

For further details on how to administer the medicine, see Section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients taking HIV medicines including atazanavir, indinavir, nelfinavir, ritonavir, saquinavir or cobicistat-containing products (see section 4.4).

4.4 Special warnings and precautions for use

Patients should consult a pharmacist or doctor before using this medicine if:

- They are using a corticosteroid product for conditions such as asthma, allergies or skin rash
- They currently have or have been exposed to someone who has tuberculosis, chicken pox or measles.
- They have fungal or viral infections of the airways.
- They have severe or frequent nose bleeds, recent nose ulcers or nose surgery or a nose injury that has not healed.
- They have ever been diagnosed with glaucoma or cataracts.
- They have an eye infection or diabetes.

Patients should consult a pharmacist or doctor if they develop signs or symptoms of an infection, such as persistent fever, while taking this medicine.

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

Reduced liver function affects the elimination of corticosteroids, causing a lower elimination rate and higher systemic exposure. This may lead to possible systemic side effects.

Systemic effects of intranasal corticosteroids may occur, particularly at high doses when used 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).

In cases of clinically significant adrenal suppression, additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Co-treatment with CYP3A inhibitors including cobicistat-containing products is expected to increase the risk of systemic side effects. The combination 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.

This product contains potassium sorbate (E202) which may cause local skin reactions, (e.g. contact dermatitis).

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.

The long-term effects of intranasal glucocorticosteroids in children are not fully known. This medicine should not be used for children or adolescents under 18 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

This medicine 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. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, clarithromycin, HIV protease inhibitors e.g. atazanavir, indinavir, nelfinavir, ritonavir and saquinavir, and cobicistat-containing products, are expected to increase the risk of systemic side effects (see section 4.4). Concomitant use of this product with HIV medicines is contraindicated (see section 4.3). The combination of this medicine 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. The interaction 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. If this medicine is co-administered with anti-fungals (such as itraconazole or ketoconazole), the period between treatments should be as long as possible. A reduction of the budesonide dose should be considered

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 this medicine 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.

Breastfeeding

Budesonide is excreted in breast milk. At therapeutic doses of this medicine no effects on the breast-fed infant are anticipated since maternal systemic exposure after intranasal administration is low, so minimal exposure to intranasal budesonide in breast-fed infants is expected. This medicine may therefore be considered for use during breastfeeding.

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 concentrations 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 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.

As with other drugs the administration of this medicine during pregnancy or breastfeeding requires that the benefits for the mother are weighed against the risk for the foetus or nursing infant. This medicine should not be used during pregnancy or breast-feeding without first consulting a doctor or pharmacist.

4.7 Effects on ability to drive and use machines

This medicine may have a moderate influence on the ability to drive and use machines. This medicine may cause blurred vision, patients should therefore be cautioned about engaging in activities such as driving a car or operating machinery, until they have established their own response to the drug.

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with budesonide are listed below by System Organ Class (SOC). The frequencies are defined in accordance with current guidance, as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10 000 and <1/1000), very rare (<1/10 000) and not known (cannot be estimated from the available data).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Immune system disorders	Uncommon	Hypersensitivity (Immediate and delayed hypersensitivity reactions including erythema, 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	Rare	Vision, blurred (see also section 4.4)
	Not known	Cataract Raised intraocular pressure or Glaucoma
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis Haemorrhagic secretion Nasal discomfort (sneezing, stinging and dryness)
	Rare	Dysphonia Nasal septum perforation Nasal ulcer
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
General disorders and and administration site conditions	Very rare	Mucosal ulceration
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 such as Cushing's syndrome, Cushingoid features, psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children), may occur with intranasal 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose with this medicine even in excessive doses, is not expected to be a clinical problem.
Inhalation of high doses of corticosteroids may lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis function.

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 non-halogenated glucocorticosteroid with a high local anti-inflammatory action within the respiratory tract.

It is used intranasally for the treatment of seasonal allergic rhinitis. Intranasal corticosteroids are quickly metabolised to less active metabolites, are minimally absorbed, and have been associated with few systemic adverse effects. Studies have shown that control of seasonal allergic rhinitis symptoms by intra-nasal corticosteroids is dependent on local activity.

Glucocorticoid potency is closely related to their glucocorticoid receptor (GR) binding affinity within the target cell. This receptor binding triggers a cascade of biochemical reactions within the target cell, thereby affecting the rate of protein synthesis. This is responsible for the anti-inflammatory effect of glucocorticoids. Upon GR activation, there is a decrease in the production of cytokines and other inflammatory mediators such as kinins, histamine and platelet activating factor. Corticosteroids also reduce the number of circulating T lymphocytes and inhibit activation of other T lymphocytes. The inhibition of T lymphocytes and cytokine production reduce the recruitment and influx of circulating eosinophils, macrophages and basophils into the nasal epithelium.

5.2 Pharmacokinetic properties

Absorption

Budesonide is moderately lipophilic and systemic exposure is primarily due to its rapid absorption through the nasal mucosa. The systemic bioavailability of budesonide following intranasal administration is 6 to 16%.

The systemic availability of budesonide from this medicine, with reference to the metered dose is 33%. In adults, the maximal plasma concentration after administration of 256 micrograms budesonide from this medicine is 0.64 nM and is reached within 0.7 hours. The AUC after administration of 256 micrograms budesonide from this medicine is 2.7 nmol.h/L in adults.

Distribution

Budesonide is distributed widely into tissues with plasma protein binding averaging between 85 and 90%. The epimers of budesonide have large volumes of distribution – 424 L for 22R-budesonide and 245 L for 22S budesonide. 22R- budesonide has a larger volume of distribution than the 22S epimer due to its greater lipophilicity. At steady state, the active, unbound form of budesonide has a volume of distribution of approximately 3 L/kg in both adults and children.

Metabolism

Budesonide is metabolized in the liver primarily via oxidative and reductive pathways. Budesonide undergoes an extensive degree (~90%) of biotransformation on first passage by CYP3A4 enzymes to metabolites of low glucocorticosteroid activity. Major metabolites, 6β-hydroxy-budesonide and 16α-hydroxyprednisolone, have similar half-lives but are relatively inactive compared to budesonide having less than 1% of its glucocorticoid and anti-inflammatory activity.

Elimination

Budesonide is excreted primarily as metabolites in the urine and faeces. No intact budesonide has been detected in the urine. Budesonide systemic clearance is 0.92 to 1.4 L/min. The half-life of unchanged budesonide following both inhalation and intravenous administration averages between 2 to 4 hours.

Elderly

There are no budesonide pharmacokinetic data available in elderly patients.

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 glucocorticoids studied (beclomethasone dipropionate, flucinolone acetonide). Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than 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. 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 on 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 heptocellular neoplasms in man. Budesonide has been used successfully in the treatment of seasonal allergic rhinitis for several years.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not appear to be relevant in humans at the recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids in increased risk for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Potassium sorbate (E202)
Glucose anhydrous
Microcrystalline cellulose (E460)
Carboxymethylcellulose sodium (E466)
Polysorbate 80 (E433)
Hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.
Use within 2 months of first opening the nasal spray.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

This medicine is an aqueous solution of budesonide in a 10 ml amber/brown glass (type II) bottle. The bottle is fitted with a spray pump and contains 60 actuations.

6.6 Special precautions for disposal and other handling

Before using this medicine for the first time the nozzle must be primed (filled with the medicine). To do this the bottle should be shaken and the protective cap removed. The bottle should then be held upright and the nozzle pumped 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 loaded with medicine again. This time it is sufficient to spray just once into the air.

a. The patient should be instructed to blow their nose before using this medicine. Then the bottle needs to be shaken and the protective cap removed.

b. Holding the bottle upright, with one finger held on either side of the nozzle, the patient should insert the tip of the nozzle into one nostril. The nozzle should be directed to the side of the nose, and away from the middle of the nose (the nasal septum). The nozzle should be pressed down once or twice depending on the dose required. The spray should then be administered into the other nostril in the same way. Note: it is not necessary to inhale at the same time as spraying.

c. The nozzle needs to be wiped with a clean tissue after use and the protective cap replaced. The bottle should be stored in an upright position.

d. **Keeping the nozzle clean**
The plastic nozzle should be cleaned regularly and at any time the spray of medicine is not coming out as it should. If this happens, first the nozzle should be checked to ensure that it is primed with medicine (see earlier). If, after the nozzle is primed again, the pump is still not working, the nozzle should be cleaned by using the following instructions:

The plastic nozzle should be removed with a clean tissue and washed in warm, not hot, water. The nozzle should then be rinsed thoroughly, dried and then replaced onto the top of the bottle. The nozzle should not be unblocked with a pin or other sharp object. After cleaning, the nozzle must be primed (filled with medicine) again before use.

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Buckinghamshire

HP12 4EG

UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 15513/0409

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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