SUMMARY OF PRODUCT CHARACTERISITCS

1. NAME OF THE MEDICINAL PRODUCT

Budesonide Aqueous Nasal Spray BP 0.2%w/v

1.1 International Non-Proprietary Name (INN)

Budesonide Aqueous Nasal Spray BP 0.2%w/v

1.2 Strength

0.2%w/v

1.3 Pharmaceutical form

Nasal Spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each spray delivers:
Budesonide BP..... 200 mcg
Active
Budesonide BP..... % w/v
Excipients…..... q.s.

Batch Size: 100 Ltr

Sr. No.	Item Name
1.	Budesonide
2.	Microcrystalline Cellulose and Carboxymethylcellulose Sodium
3.	Glycerin
4.	Polysorbate 80
5.	Disodium EDTA
6.	Potassium Sorbate *
7.	Hydrochloric Acid
8.	Distilled Water

3. PHARMACEUTICAL FORM

Nasal Spray

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prevention of signs and symptoms of persistent asthma.

Treatment of signs and symptoms of nasal polyps.

4.2 Posology

Route 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.

Rhinitis (Adults including the elderly)

Recommended start dose	Once daily dosing	Twice daily dosing
256 micrograms per day	Two applications of 64 micrograms into each nostril each morning	One application of 200 micrograms into each nostril morning and evening
If good effect is achieved, one application of 64 micrograms into each nostril each morning.		

The patient should be informed that the full effect of Benacort is not achieved until after a few days treatment. Treatment of seasonal rhinitis should, if possible, start before exposure to the allergens. If symptoms are not controlled, or persist for longer than 2 weeks of treatment, medical advice must be sought. This medicine should not be used continuously for longer than 3 months.

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

The dose should be titrated to the lowest dose at which effective control of symptoms is

achieved

Maintenance dose:

When a satisfactory effect has been achieved, budesonide dose should be reduced to the minimum effective dose. The maximal daily dosage should not exceed 400 µg. The patient should be informed that the full effect of budesonide is not achieved until after a few days treatment. Treatment of seasonal rhinitis should, if possible, start before exposure to allergens. Concomitant treatment to control eye symptoms and nasal obstruction may be required during the initial days of treatment.

Treatment of nasal polyps.

The recommended dose is twice daily 200 micrograms, to be administered as 2 puffs into each nostril.

Paediatric population

Influence on growth It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reevaluated with the aim of reducing the dose of nasal corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist. Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses.

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 upright, with one finger held on either side of the nozzle 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.

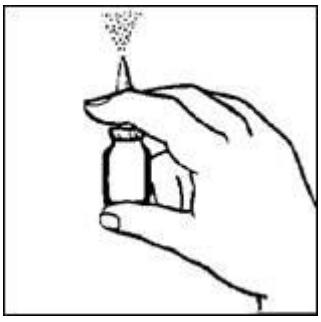

Figure 2.

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

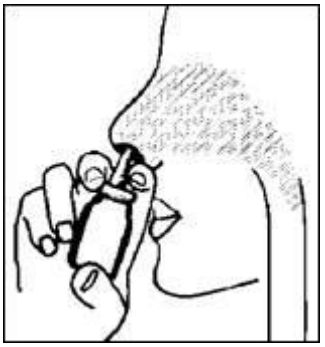

Figure 3.

5. Wipe the nozzle with a clean tissue and replace the protective cap.

6. Store the bottle in an upright position.

7. 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 claning the nozzle must be primed (filled with medicine) again before use.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients

4.4 Special warnings and precautions for use

Treatment should be stopped or the advice of a doctor or pharmacist should be sought if an improvement is not seen within 2 weeks or if symptoms have improved but are not adequately controlled.

This medicine should not be used for more than 3 months continuously.

Special care is required in the treatment of patients transferred from oral corticosteroids to this medicine where disturbances of the hypothalamic-pituitary-adrenal (HPA) axis could be expected.

Special care is needed in patients with fungal and viral infections of the airways.

Patients should consult a physician before use if:

• They are using a corticosteroid 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 severe or frequent nose bleeds, or have had 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 physician if they develop signs or symptoms of an infection, such as persistent fever, while taking this medicine.

Special care is needed where there is an infection in the nasal passages or sinuses.

Concomitant treatment 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).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Budesonide nasal spray 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, is expected to increase the risk of systemic side effects (see section 4.4). 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. 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. If this medicine is co-administered with anti-fungals (such as itraconazole and 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 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.

Breast-feeding

Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide 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 breast feeding.

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

4.7 Effects on ability to drive and use machines

Budesonide nasal spray may have a moderate influence on the ability to drive or use machines. Budesonide 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). 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.

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)

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

SOC	frequency	ADR
Immune system disorders	Uncommon	Hypersensitivity (Immediate and delayed hypersensitivity reactions including erythema, urticaria, rash, dermatitis, angioedema and pruritus)
	Very rare	Anaphylactic reaction
Endocrine disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation
Eye disorders	Rare	Vision, blurred
	Not known	Cataract (with long-term treatment) Raised intraocular pressure or Glaucoma
Respiratroy, thoracic and mediastinal disorders	Common Very rare	Epistaxis Haemorrhagic secretion Nasal discomfort (sneezing, stinging and dryness)
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*

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 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 suckling child is anticipated to be low.

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 nasal glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity

Paediatric population

Growth retardation has been reported in children receiving intranasal steroids.

4.9 Overdose

Acute overdose with Budesonide Nasal Spray 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: R03BA02

Budesonide is a synthetic glucocorticoid. After oral inhalation, it has a local anti-inflammatory effect on the bronchial mucosa.

Budesonide penetrates cellular membranes and binds to a cytoplasmic receptor protein. This complex enters the nucleus and induces there the biosynthesis of specific proteins, like macrocortin (lipocortin). The hormone-like effects occur after a certain latency period (30-60 min) and result in an inhibition of phospholipase A2. It is also possible that therapeutically effective doses of Budesonide (like other anti-inflammatory glucocorticosteroids) suppress cytokine-induced COX-2 expression.

Clinically, the anti-inflammatory effect results e.g. in improvement of the symptoms, such as dyspnoea. The hyperresponsiveness of the bronchial tract to exogenic challenges is

reduced.

Clinical Safety

Paediatric population

Slit lamp examinations were performed in 157 children (5-16 years old), treated with an average daily dose of 504 µg for 3-6 years. Findings were compared with 111 age-matched asthmatic children. Inhaled budesonide was not associated with an increased occurrence of posterior subcapsular cataract.

Influence on plasma cortisol concentration

Studies in healthy volunteers with inhaled budesonide have shown dose-related effect on plasma and urinary cortisol. At recommended doses, inhaled budesonide causes significantly less effect on adrenal function than prednisone 10 mg, as shown by ACTH test.

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels appear approximately 30 minutes after inhalation.

Systemic bioavailability after inhalation is up to 37% and the concentration in human plasma after inhalation of a single dose of 1600 micrograms is 0.63 nmol/L.

The trigger threshold of the powder inhaler (=Novolizer)which must be overcome for successful inhalation is to be found at inspiratory flows through the inhaler of 35 - 50 l/min. Dose linearity for switching from Budesonide Novolizer 200 µg to Budesonide Novolizer 400 µg was shown at flow rates of 60 l/min upwards.

The fine particle dose (particles < 5 µm) measured in vitro in the clinically relevant range is approximately 30 – 50 % related to the nominal dose. In healthy subjects, approximately 20 – 30 % of the metered dose of budesonide passes into the lungs. The remainder deposits in mouth, nose and throat and a large part of it is swallowed.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85 - 90%.

Linearity

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

Paediatric population

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic

children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults.

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 behavioural exposures below the teratogenic dose range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose and Carboxymethylcellulose Sodium USP

Glycerin BP

Polysorbate 80 BP

Disodium EDTA BP

Potassium Sorbate BP *

Hydrochloric Acid BP

Distilled Water q.s. to Make

6.2 Incompatibilities

None reported

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool and dry place below 25°C. Do not freeze. Keep out of reach of children.

6.5 Nature and contents of container

Spray form with actuator in HDPE Bottle..

7. REGISTRANT

8. MANUFACTURER

Biodeal Pharmaceuticals Pvt. Ltd.

Vill. Saini Majra, Nalagarh-Ropar Road, Nalagarh,

Dist Solan 1741101 (HP) INDIA

9. DATE OF REVISION OF THE TEXT

To be given after registration approval from PPB.

10. DOSIMETRY (IF APPLICABLE)

Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable