SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

Bunase 200 (Budesonide Pressurised Inhalation BP 200 mcg)

Strength

200mcg

Pharmaceutical form

Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation contains:

Budesonide..... 200mcg

3. PHARMACEUTICAL FORM

Pressurised metered dose inhaler containing suspension aerosol filled in aluminum canister fitted with suitable metered valve and 19ml actuator 0.48mm orifice, dark blue coloured cap and light blue body. Each Canister is been labeled and further packed in a carton along with Patient Information Leaflet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild, moderate, and severe persistent asthma.

(Note: Budesonide is not suitable for the treatment of acute asthma attacks.)

4.2 Posology and method of administration

Posology

The therapeutic effect begins after a few days′ treatments and reaches its maximum after some weeks of treatment.

When transferring a patient to Budesonide from other inhalation devices, the treatment should be individualised. The previous active substance, dose regimen, and method of delivery should be considered.

The patients should be prescribed a starting dose of inhaled budesonide which is appropriate for the severity or level of control of their disease. The dose should be adjusted until control is achieved and then titrated to the lowest dose at which effective control of asthma is maintained.

Lower strengths of Budesonide are available for appropriate dose adjustment, if necessary.

The starting dose for adults (including the elderly and adolescents 12 to 17 years) with mild asthma (Step 2) and for children 6 to 11 years of age is 200-400 micrograms/day. If needed, the dose can be increased up to 800 micrograms/day. For adult patients with moderate (Step 3) and severe (Step 4) asthma the starting dose can be up to 1600 micrograms/day. The maintenance dose should be adjusted to meet the requirements of an individual patient taking into account the severity of the disease and the clinical response of the patient.

Twice daily dosing

Adults with mild, moderate or severe asthma (including the elderly and adolescents 12 to 17 years): The usual maintenance dose is 100-400 micrograms twice daily. During periods of severe asthma, the daily dose may be increased up to 1600 micrograms administered in divided (two) doses and subsequently reduced when asthma has stabilised.

Children 6 to 11 years: The usual maintenance dose is 100-200 micrograms twice daily. If needed, the daily dose may be increased up to 800 micrograms administered in divided (two) doses and subsequently reduced when asthma has stabilised.

Once daily dosing

Adults with mild to moderate asthma (including the elderly and adolescents 12 to 17 years): In patients who have not previously received inhaled corticosteroids the usual maintenance dose is 200-400 micrograms once daily. In patients already controlled on inhaled corticosteroids (eg budesonide or beclometasone dipropionate) administered twice daily, once daily dosing up to 800 micrograms may be used.

Children 6 to 11 years with mild to moderate asthma: In steroid naive patients or patients controlled on inhaled corticosteroids (eg budesonide or beclometasone dipropionate) administered twice daily the usual maintenance dose is 200-400 micrograms once daily.

The patient should be transferred to once daily dosing at the same equivalent total daily dose (with consideration of the drug and the method of delivery). The dose should be subsequently reduced to the minimum needed to maintain good asthma control. Patients should be instructed to take the once daily dose in the evening. It is important that the dose is taken consistently and at the same time each evening.

There are insufficient data to make recommendations for the transfer of patients from newer inhaled corticosteroids to once daily Budesonide.

Patients, in particular those receiving once daily treatment, should be advised that if their asthma deteriorates (e.g. increased frequency of bronchodilator use or persistent respiratory symptoms) they should double their corticosteroid dose by administering twice daily. They should be advised to contact their doctor as soon as possible.

A rapid-acting inhaled bronchodilator should be available for the relief of acute symptoms of asthma at all times.

Patients maintained on oral glucocorticosteroids

The transfer of patients treated with oral corticosteroids to the inhaled corticosteroid and their subsequent management requires special care. The patients should be in a reasonably stable state before initiating a high dose of inhaled corticosteroid through twice daily dosing in addition to their usual maintenance dose of systemic corticosteroid. After about 10 days, withdrawal of the systemic corticosteroid is started by reducing the daily dose gradually (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. It may be possible to completely replace the oral corticosteroid with inhaled corticosteroid

Method of administration

For inhalation use. For optimum response, Budesonide inhalation powder should be used regularly.

Instructions for use and handling

It should be ensured that the patient is instructed in the use of the inhaler by a doctor or pharmacist.

Easyhaler is an inspiratory flow-driven device. This means that when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note: It is important to instruct the patient

- To carefully read the instructions for use in the patient information leaflet which is packed together with each inhaler.
- That it is recommended to keep the device in the protective cover after opening the foil bag to enhance the stability of the product during use and makes the inhaler more tamper proof.
- To shake and actuate the device prior to each inhalation.
- In the sitting or standing position, to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs.
- Never to breathe out through the mouthpiece as this will result in a reduction in the delivered dose. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- Never to actuate the device more than once without inhalation of the powder. Should this happen the patient is instructed to tap the mouthpiece onto a table top or the palm of a hand to empty the powder, and then to repeat the dosing procedure.
- To always replace the dust cap and close the protective cover after use to prevent accidental actuation of the device (which could result in either overdosing or under dosing the patient when subsequently used).
- To rinse the mouth out with water or brush the teeth after inhaling the prescribed dose to minimise the risk of oropharyngeal candidiasis and hoarseness.
- To clean the mouthpiece with a dry cloth at regular intervals. Water should never be used for cleaning because the powder is sensitive to moisture.
- To replace Budesonide when the counter reaches zero even though powder can still be observed within the device.

4.3 Contraindications

Hypersensitivity to budesonide or to the excipient listed in section 6.1 (lactose, which contains small amounts of milk protein).

4.4 Special warnings and precautions for use

Budesonide is not indicated for the treatment of acute dyspnoea or status asthmaticus. These conditions require an inhaled short-acting bronchodilator.

Patients should be aware that Budesonide inhalation powder is prophylactic therapy and therefore has to be used regularly even when asymptomatic for optimum benefit and should not be stopped abruptly.

Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

Patients who have previously been dependent on oral corticosteroids may, as a result of prolonged systemic corticosteroid therapy, experience effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral corticosteroid therapy and hence oral steroid-dependent patients transferred to budesonide may remain at risk from impaired adrenocortical function for some considerable time. In such circumstances hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.

During transfer from oral therapy to inhaled budesonide symptoms may appear that had previously been suppressed by systemic treatment with glucocorticosteroids, for example symptoms of allergic rhinitis, eczema, muscle and joint pain. Specific treatment should be co-administered to treat these conditions.

Some patients may feel unwell in a non-specific way during the withdrawal of systemic corticosteroids despite maintenance or even improvement in respiratory function. Such patients should be encouraged to continue treatment with inhaled budesonide and withdrawal of oral corticosteroid unless there are clinical signs to indicate the contrary, for example signs which might indicate adrenal insufficiency.

As with other inhalation therapies paradoxical bronchospasm may occur, manifest by an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Budesonide should be discontinued immediately, the patient should be assessed and, if necessary, alternative treatment instituted.

When despite a well monitored treatment, an acute episode of dyspnoea occurs, a rapid-acting inhaled bronchodilator should be used and medical reassessment should be considered. If despite maximum doses of inhaled corticosteroids asthma symptoms are not adequately controlled, patients may require short-term treatment with systemic corticosteroids. In such a case, it is necessary to maintain the inhaled corticosteroid therapy in association with treatment by the systemic route.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

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.

Oral candidiasis may occur during the therapy with inhaled corticosteroids. To reduce the risk of oral candidiasis and hoarseness patients should be advised to rinse out the mouth properly or brush the teeth after each administration of inhaled corticosteroid. Oral candidiasis may

require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary (see section 4.2)

Exacerbation of clinical symptoms of asthma may be due to acute respiratory tract bacterial infections and treatment with appropriate antibiotics may be required. Such patients may need to increase the dose of inhaled budesonide and a short course of oral corticosteroids may be required. A rapid-acting inhaled bronchodilator should be used as "rescue" medication to relieve acute asthma symptoms.

Special care and adequate specific therapeutic control of patients with active and quiescent pulmonary tuberculosis is necessary before commencing treatment with Budesonide. Similarly patients with fungal, viral or other infections of the airways require close observation and special care and should use Budesonide only if they are also receiving adequate treatment for such infections.

In patients with excessive mucous secretion in the respiratory tract, short-term therapy with oral corticosteroids may be necessary.

Reduced liver function affects the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Possible systemic effects may then result and therefore HPA axis function in these patients should be monitored at regular intervals.

Concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A inhibitors should be avoided. If this is not possible the time interval between administration of the interacting drugs should be as long as possible (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Lactose, the excipient in the product, contains small amounts of milk proteins and can therefore cause allergic reactions.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. itraconazole, ketoconazole, ritonavir, nelfinavir, ciclosporin, ethinylestradiol, cobicistat and troleandomycin can therefore increase systemic exposure to budesonide several times (see section 4.4).

This is of little clinical significance for a short term treatment (1-2 weeks), but should be taken into account for long term treatment.

Co-treatment with 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.

Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered.

Limited data about this interaction for high-dose inhaled budesonide indicate that marked increases in plasma levels (on average four- fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 μg).

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

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. 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. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

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.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks 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.

Breast-feeding

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

Maintenance treatment with inhaled budesonide (200 or 400 microg 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 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.

Administration of inhaled budesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The possible adverse reactions are presented in system organ class order sorted by frequency.

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)

	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	oropharyngeal candidiasis				
Immune system disorders			hypersensitivity reactions (including rash contact dermatitis, urticaria, angioedema and anaphylactic reaction)		
Endocrine disorders			hypocorticism, hypercorticism, signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth		

			retardation*		
Psychiatric disorders		anxiety**, depression**	behavioural changes (predominantly in children), restlessness, nervousness		psychomotor hyperactivity, sleep disorders, aggression, irritability, psychosis
Eye disorders		cataract***, vision, blurred (see also section 4.4)		glaucoma	
Respiratory, thoracic and mediastinal disorders	cough, throat irritation		hoarseness, dysphonia, bronchospasm (see section 4.4)		
Gastrointestinal disorders	difficulty in swallowing				
Skin and subcutaneous tissue disorders			pruritus, erythema, bruising		
Musculoskeletal and connective tissue disorders		muscle spasm		decreased bone density	
Nervous system disorders		tremor			

Treatment with inhaled budesonide may result in candida infection in the oropharynx. Experience has shown that candida infection occurs less often when inhalation is performed before meals and/or when the mouth is rinsed after inhalation. In most cases this condition

responds to topical anti-fungal therapy without discontinuing treatment with inhaled budesonide.

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. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled budesonide than with oral corticosteroids.

Paediatric population

Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

**Clinical trials with 13119 patients on inhaled budesonide and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on inhaled budesonide and 0.63% on placebo; that of depression was 0.67% on inhaled budesonide and 1.15% on placebo.

***In placebo-controlled studies, cataract was also uncommonly reported in the placebo group.

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 anysuspected adverse reactions.

4.9 Overdose

Symptoms of overdose

The acute toxicity of budesonide is low. Chronic use in excessive doses can result in systemic glucocorticosteroid effects, such as increased susceptibility to infection, hypercorticism and adrenal suppression. Atrophy of the adrenal cortex can occur and the ability to adapt to stress can be impaired.

Therapeutic management of overdose

For acute overdosage, even in excessive doses, is not expected to be a clinical problem. The treatment with inhaled budesonide should be continued at the recommended dose to control asthma. HPA axis function recovers in a few days.

In stress situations, it may be necessary to administer corticosteroids as a precaution (eg high doses of hydrocortisone). Patients with adrenocortical atrophy are regarded as being steroid-dependent and must be adjusted to the adequate maintenance therapy of a systemic corticosteroid until the condition has stabilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

- ***Pharmacotherapeutic group and ATC code***

  Glucocorticoids. ATC code: R03BA02.

- ***Mechanism of action***

  Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action.

- ***Pharmacodynamic effects***

  Topical anti-inflammatory effect

  The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

  Onset of effect

  After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment, although maximum benefit may not be achieved for up to 4 weeks.

Airway reactivity

Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

Exercise-induced asthma

Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma.

HPA axis function

A study in healthy volunteers with Budesonide has shown dose-related effects on plasma and urinary cortisol. At recommended doses, budesonide causes less effect on the adrenal function than prednisolone 10mg, as shown by ACTH tests.

Paediatric population

Limited data from long term studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment (see section 4.4).

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.

5.2 Pharmacokinetic properties

The activity of Budesonide is due to the parent active substance, budesonide, which is provided as a mixture of two epimers (22R and 22S). In glucocorticoid receptor affinity studies, the 22R form is twice as active as the 22S epimer. These two forms of budesonide do not interconvert. The terminal half-life is the same for both epimers (2-3 hours). In asthmatic patients, approximately 15-25% of the inhaled budesonide dose from Easyhaler reaches the lungs. The largest fraction of the inhaled dose is retained in the oropharynx and swallowed if the mouth is not rinsed out.

Absorption

After oral administration of budesonide, peak plasma concentration is achieved in about 1-2 hours and the absolute systemic availability is 6-13%. In plasma, 85-95% of budesonide is bound to proteins. In contrast, peak plasma concentration is reached approximately 30 minutes after inhalation. Most of budesonide delivered to the lungs is systemically absorbed.

Distribution

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

Biotransformation

Budesonide is mainly eliminated by metabolism. Budesonide is rapidly and extensively metabolised in liver via cytochrome P4503A4 to two major metabolites. The *in vitro* glucocorticoid activity of these metabolites is less than 1% of that of the parent compound. Negligible metabolic inactivation has been observed in human lung and serum preparations.

Elimination

Budesonide is excreted in urine and faeces in the form of conjugated and non-conjugated metabolites.

Linearity/Non-Linearity

The kinetics of budesonide is 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.

Special patient populations

The exposure to budesonide may be increased in patients with liver disease.

5.3 Preclinical safety data

Non-clinical data with budesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.

In animal studies on reproductive toxicity, glucocorticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal results do not seem to be relevant for humans given recommended doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tetrafluoroethane (Propellant HFA 134A).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months.

6.4 Special precautions for storage

Store below 30°C, Do not freeze. Protect from frost and direct sunlight.

Store the inhaler with the mouth piece down.

6.5 Nature and contents of container

Canister 19ml, Plain

6.6 Special Precaution for Disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

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8. MARKETING AUTHORIZATION NUMBER

H2020/CTD/5199/1262ER

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

10. DATE OF REVISION OF TEXT

18th Nov 2023

References:

https://www.medicines.org.uk/emc/product/242/smpc