Budesonide

0500170/11

Budecort® Respules®

250 mcg/mL and 500 mcg/mL
(500 mcg/2mL and 1000mcg/2mL)
Nebulizing Suspension

Drugs for Obstructive Airway Diseases

1. NAME OF THE MEDICINAL PRODUCT

Budesonide (BUDECORT RESPULES) Nebulizing Suspension, 250 mcg/mL (500mcg/2mL) and 500 mcg/mL (1000mcg/2mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One single dose unit contains 500 mcg or 1000 mcg budesonide per 2 mL.
For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Sterile nebuliser suspension. White to off-white suspension in plastic single dose units.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Budesonide (BUDECORT RESPULES) Nebulizing Suspension is indicated in patients with:

- bronchial asthma requiring treatment with glucocorticosteroids for control of the underlying airway inflammation for:
    - maintenance treatment
    - acute exacerbations
- exacerbations of chronic obstructive pulmonary disease (COPD)
- croup (acute viral upper respiratory tract infection also known as viral laryngotracheobronchitis or laryngitis subglottica) in infants and children

4.2 Posology and method of administration

Bronchial asthma

Maintenance treatment for bronchial asthma:

The dosage of Budesonide (BUDECORT RESPULES) Nebulizing Suspension is individual, and should be titrated to the lowest effective maintenance dose once control of asthma is achieved.

Administration can be once or twice daily. Once daily administration can be used for daily doses of 250 mcg - 1000 mcg.

Recommended initial dose:

Adults/Elderly: 1000 mcg - 2000 mcg total daily dose

Children 6 months or older: 250 mcg - 500 mcg total daily dose. In patients depending on oral glucocorticosteroids, a higher starting dose, e.g., 1000 mcg total daily dose may be considered.

Maintenance doses:

Adults/Elderly:	500 - 4000 mcg total daily dose. In very severe cases the dose may be further increased.
Children 6 months or older:	250 - 2000 mcg total daily dose.

Once daily dosing may be considered both in adult and in paediatric patients, who require a maintenance dose of 250 mcg to 1000 mcg budesonide per day. Once daily administration can be initiated both in noncorticosteroid treated patients and in patients well-controlled by inhaled glucocorticosteroids. The dose can be administered either in the morning or in the evening. If deterioration of asthma occurs, the dose should be increased and divided over the day as necessary.

Onset of effect in maintenance treatment

Improvement in asthma control following maintenance treatment with inhaled Budesonide (BUDECORT RESPULES) Nebulizing Suspension can occur within 3 days of initiation of treatment, although maximum benefit may not be achieved for 2-4 weeks.

Acute Exacerbations of Asthma

Adults:

Daily recommended dose is 4 to 8 mg and can be divided into 1 to 4 administrations. In very severe cases the dose may be further increased. Maximum dose at one occasion should not exceed 4 mg. Treatment with nebulised Budesonide (BUDECORT RESPULES) Nebulizing Suspension for acute exacerbations can be continued until clinical improvement, but for no longer than 10 days.

Children: (6 months to 17 years)

Daily recommended dose is 1.5 to 4 mg, doses up to 6 mg can be considered in children 5 years or above. Daily dose can be divided into 1 to 4 administrations. Maximum dose at one occasion should not exceed 3 mg. Treatment with nebulised Budesonide (BUDECORT RESPULES) Nebulizing Suspension for acute exacerbations can be continued until clinical improvement, but for no longer than 10 days.

In both adults and children, nebulised budesonide is not a substitute for systemic corticosteroids in life threatening asthma. Treatment for exacerbations may be followed by ICS (Inhaled Corticosteroids) containing therapy in appropriate doses using suitable delivery systems.

Onset of effect for acute Exacerbations of Asthma

Following an initial dose, an effect is expected after a few hours.

Patients maintained on oral glucocorticosteroids

Budesonide (BUDECORT RESPULES) Nebulizing Suspension may permit replacement or significant reduction in dosage of oral glucocorticosteroids with maintained or improved asthma control.

Initially, Budesonide (BUDECORT RESPULES) Nebulizing Suspension should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately one week the oral dose is gradually reduced to the lowest possible level. A slow rate of withdrawal is strongly recommended. In many cases it is possible to completely substitute the oral glucocorticosteroid with Budesonide (BUDECORT RESPULES) Nebulizing Suspension.

During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with Budesonide (BUDECORT RESPULES) Nebulizing Suspension but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should be continued more slowly. During periods of stress or during a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

Exacerbations of COPD

Patients should be treated with daily doses of 4 to 8 mg of Budesonide (BUDECORT RESPULES) Nebulizing Suspension, divided into 2 to 4 administrations, until clinical improvement but for no longer than 10 days.

Onset of effect

Following inhaled administration of Budesonide (BUDECORT RESPULES) Nebulizing Suspension for the treatment of exacerbations of COPD the time to symptom improvement is comparable to administration of systemic corticosteroids.

Croup:

In infants and children with croup, the usual dose is 2 mg of nebulized budesonide. This dose is given as a single administration, or as two 1 mg doses separated by 30 minutes. Dosing can be repeated every 12 hours up to 36 hours or until clinical improvement.

Onset of effect

Results from clinical trials with Budesonide (BUDECORT RESPULES) Nebulizing Suspension for treatment of croup showed that a clinically significant improvement of 2 points or more in symptoms score was observed between 1 to 2 hours after treatment initiation. A statistically significant symptom improvement versus placebo was observed 2 hours post-treatment.

Dose division and miscibility

Budesonide (BUDECORT RESPULES) Nebulizing Suspension can be mixed with 0.9% saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate or ipratropium. The admixture should be used within 30 minutes.

Single dose units can be divided, to allow dose adjustment. The single dose unit is marked with a line (Budesonide (BUDECORT RESPULES) Nebulizing Suspension 250 mcg/mL and 500 mcg/mL only). This line indicates the 1 mL volume when the single dose unit is held up-side down. If only 1 mL is to be used, empty the contents until the surface of the liquid reaches the indicator line. Store the opened single dose unit in the envelope, protected from light. Opened single dose units should be used within 12 hours.
Please note that if only 1 mL is used the remaining volume is not sterile.

Table 1 Dosage table

Dosage in mcg	**Volume of Budesonide (BUDECORT RESPULES) Nebulizing Suspension**	
	250 mcg/mL	500 mcg/mL
250	1 mL*	-
500	2 mL	-
	250 mcg/mL	500 mcg/mL
750	3 mL	-
1000	-	2 mL
1500	-	3 mL

Table 1 Dosage table

Dosage in mcg		Volume of Budesonide (BUDECORT RESPULES) Nebulizing Suspension
2000	-	4 mL
4000	-	8 mL

* This should be mixed with 0.9% saline up to a volume of 2 mL.

Instruction for correct use of Budesonide (BUDECORT RESPULES) Nebulizing Suspension

Budesonide (BUDECORT RESPULES) Nebulizing Suspension should be administered via a jet nebuliser equipped with a mouthpiece or suitable face mask. The nebuliser should be connected to an air compressor with an adequate air flow (5-8 L/min), and the fill volume should be 2-4 mL.

NOTE: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which are packed together with each nebuliser
- that Ultrasonic nebulisers are not suitable for the administration of Budesonide (BUDECORT RESPULES) Nebulizing Suspension and therefore are not recommended
- Budesonide (BUDECORT RESPULES) Nebulizing Suspension can be mixed with 0.9% saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate and ipratropium. The admixture should be used within 30 minutes.
- to rinse the mouth with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush
- to wash the facial skin with water after using the face mask to prevent irritation
- to adequately clean and maintain the nebuliser according to the manufacturer's instructions

4.3 Contraindications

History of hypersensitivity to budesonide or any of the ingredients.

4.4 Special warnings and special precautions for use

Budesonide (BUDECORT RESPULES) Nebulizing Suspension is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for increased anti-inflammatory therapy, e.g., higher doses of inhaled budesonide or a course of oral glucocorticosteroid.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. 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. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Some patients feel unwell in a non-specific way during the withdrawal phase, e.g., pain in muscles and joints. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases, a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies, e.g., rhinitis and eczema, which were previously controlled by the systemic drug. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Reduced liver function may affect the elimination of corticosteroids. This may be clinically relevant in patients with severely compromised liver function.

In vivo studies have shown that oral administration of ketoconazole and itraconazole (known inhibitors of CYP3A4 activity in the liver and in the intestinal mucosa, see also section 4.5 Interactions) may cause an increase of the systemic exposure to budesonide. This is of limited clinical importance for short-term (1 to 2 weeks) treatment but should be taken into consideration during long-term treatment.

The long-term local and systemic effects of Budesonide (BUDECORT RESPULES) Nebulizing Suspension in man are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved. Physicians should closely monitor the growth of children taking corticosteroids by any route and weigh the benefit of corticosteroid therapy and asthma control against the possibility of growth suppression.

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 asthma.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibitors of this enzyme, e.g., ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide; see section 4.4 Special warnings and special precautions for use.

At recommended doses, cimetidine has slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

4.6 Pregnancy and lactation

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the foetus/newborn child.

As with other drugs the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the foetus. Inhaled glucocorticosteroids should be considered for the treatment of asthma because of the lower systemic effects compared with oral glucocorticosteroids required to achieve similar pulmonary responses.

Budesonide is excreted in breast milk. However, at therapeutic doses Budesonide (BUDECORT RESPULES) Nebulizing Suspension has no effects on the suckling child are anticipated. Budesonide (BUDECORT RESPULES) Nebulizing Suspension can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Budesonide (BUDECORT RESPULES) Nebulizing Suspension has no effect on the ability to drive and use machines.

4.8 Undesirable effects

Clinical trials, literature reports and post-marketing experience suggest that the following adverse drug reactions may occur:

Table 2	**Undesirable effects**
Common (>1/100, <1/10)	Mild irritation in the throat
	Candida infection in the oropharynx
	Hoarseness
	Coughing
Rare (>1/10 000, <1/1 000)	Nervousness, restlessness, depression, behavioural disturbances
	Immediate and delayed hypersensitivity reactions including rash, contact-dermatitis, urticaria, angioedema, bronchospasm and anaphylactic reaction
	Skin bruising

In rare cases, through unknown mechanisms, drugs for inhalation may cause bronchospasm.

In rare cases signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Facial skin irritation has occurred in some cases when a nebuliser with a face mask has been used. To prevent irritation the facial skin should be washed with water after use of the face mask.

4.9 Overdose and Treatment

Acute overdosage with Budesonide (BUDECORT RESPULES) Nebulizing Suspension, even in excessive doses, is not expected to be a clinical problem.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. Pharmacotherapeutic group: Other anti-asthmatics, inhalants, glucocorticoids. ATC-code R03B A02

Topical anti-inflammatory effect

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions involving T-cells, eosinophils and mast cells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important. The intrinsic potency of budesonide, measured as the affinity to the glucocorticoid receptor, is about 15 times higher than that of prednisolone.

A clinical study in asthmatics comparing inhaled and oral budesonide at similar plasma concentrations demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and patients, manifested as decreased bronchial obstruction in the immediate as well as the late allergic reaction.

Exacerbations of asthma

Inhaled budesonide has been shown to effectively treat and prevent exacerbations of asthma in both children and adults.

In a double-blinded, placebo-controlled, randomised study of moderate to severe acute asthma, the efficacy of nebulised budesonide (2.4 mg divided into 3 doses, at half hourly intervals) was

compared to oral prednisolone (2 mg/kg, single dose), both added to nebulised salbutamol treatment. Eighty children, 2 years to 12 years of age admitted to emergency department were included. After one hour, oxygen saturation, respiratory rate and symptom scores (pulmonary index and respiratory distress) were significantly improved in the budesonide group compared to the prednisolone group. The proportion of patients ready for discharge at the end of 2 hours after the third dose of nebulisation was significantly higher in the budesonide group than in the prednisolone group (54% versus 18%, $p<0.001$).

The effect of nebulised budesonide 1 mg twice daily, when added to standard bronchodilator treatment and on top of systemic steroids was evaluated in double-blind randomised, placebo-controlled trial in 100 preschool children (7 months to 6 years of age) hospitalised for moderate to severe asthma exacerbation. All patients received 1 mg/kg/day of intravenous methylprednisolone for up to 5 days, and nebulized salbutamol and ipratropium bromide, for 2 days. Length of hospital stay was significantly shorter in the budesonide group than in placebo group (median: 44 versus 80 hours, respectively; $p=0.01$). Cumulative discharge rates were significantly higher in the budesonide group at 48, 60 and 72 hours (60% versus 24%, ($p<0.001$); 68% versus 32%, ($p<0.001$); and 76% versus 48% patients, ($p=0.004$), respectively).

The efficacy of nebulised budesonide (1.5 mg divided into 3 doses of 0.5 mg over 1 hour) added to a systemic corticosteroid (oral prednisolone 2 mg/kg) and bronchodilators was evaluated in a double-blind, randomised, placebo-controlled study comprising 945 children 2 years to 12 years of age with moderate to severe asthma exacerbation. In the subpopulation of patients with most severe exacerbation, hospitalisation rate was significantly lower in the budesonide group vs. placebo (35.5% vs. 53.4%; Odds Ratio=0.42; 95% CI=0.19, 0.94; $p=0.03$, i.e., reduction in odds by 58%).

The clinical efficacy and safety of nebulised budesonide in three doses (1 mg twice daily, 2 mg twice daily and 2 mg four times daily) compared with intravenous prednisolone 40 mg/day was evaluated in an open-label, randomised, controlled trial comprising 85 adult patients with severe acute asthma. All groups received nebulized terbutaline, oxygen and anti-infective treatment. At 24 hours post treatment both the budesonide 8 mg/day and prednisone groups showed significant improvements in clinical symptom score with no statistically significant difference between groups. At 72 hours of treatment, clinical symptom scores, FEV_1 and arterial blood gases improved for all four groups. There was no statistically significant difference between budesonide 4 mg/day, 8 mg/day and prednisolone groups ($p>0.05$). A statistically significant difference was noted compared to dose of 2 mg/day ($p<0.05$) favoring higher doses of budesonide or prednisolone treatment. At 10 days of treatment, clinical symptom scores, lung function and arterial blood gases improved for all four groups with no statistically significant difference. However, elevated blood glucose, and decreased plasma cortisol concentration compared to baseline was noted in the prednisolone group and not in any of the budesonide groups.

Exercise-induced asthma

Therapy with inhaled budesonide, administered either as once or twice daily has been effective when used for prevention of exercise-induced bronchoconstriction.

Budesonide has been shown to decrease airway reactivity to histamine and methacholine in hyperreactive patients.

Exacerbations of COPD

Several studies on nebulised budesonide, 4-8 mg/day has shown to effectively treat exacerbations of COPD.

The efficacy of budesonide was evaluated in an open label, randomised, comparative study in 78 hospitalised patients with acute exacerbations of COPD in two parallel groups receiving nebulised budesonide(n=37) 4 mg/day (2 mg twice daily) or intravenous infusion of prednisolone 120–180 mg/day (n=41) for 7-14 days. Patients treated with nebulized budesonide or prednisolone showed similar improvements in FEV_1, SpO_2 (saturation as measured by pulse oximetry) and symptoms (CAT score).

In a multi-center randomised controlled, single-blind study involving 471 patients with acute exacerbations of COPD, patients were treated with nebulised budesonide 6 mg/day (2 mg three times/day); or intravenously injected methylprednisolone (40 mg/day) for 10 days. Clinical efficacy of nebulised budesonide in comparison to systemic methylprednisolone as measured by FEV_1, $PaCO_2$ and symptoms (CAT score) was comparable, while PaO_2 improved more in the methylprednisolone group.

In a double-blind randomised placebo-controlled study involving 199 patients with acute exacerbations of COPD, patients were treated with nebulised budesonide 8 mg/day (2 mg four times a day (n=71) or 30 mg oral prednisolone every 12 hours (n=62) or placebo (n=66) for 3 days. Improvement in post bronchodilator FEV_1 compared to placebo was 0.10 L for budesonide and 0.16 L for prednisolone; the difference between the active treatments was not statistically significant. The proportion of patients showing clinical improvement in postbronchodilator FEV_1 of at least 0.15 L was greater in the nebulised budesonide group (34%) and the prednisolone group (48%) than in the placebo group (18%). The differences were statistically significant for both active treatments versus placebo ($p < 0.05$) but not between the active treatments.

Clinical – croup

A number of studies in children with croup have compared Budesonide (BUDECORT RESPULES) Nebulizing Suspension with placebo. Examples of representative studies evaluating the use of Budesonide (BUDECORT RESPULES) Nebulizing Suspension for the treatment of children with croup are given below.

Efficacy in children with mild to moderate croup

A randomised, double-blind, placebo-controlled trial in 87 children (aged 7 months to 9 years), admitted to hospital with a clinical diagnosis of croup, was conducted to determine whether Budesonide (BUDECORT RESPULES) Nebulizing Suspension improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of Budesonide (BUDECORT RESPULES) Nebulizing Suspension (2000 mcg) or placebo was given followed by either Budesonide (BUDECORT RESPULES) Nebulizing Suspension 1000 mcg or placebo every 12 hours. Budesonide (BUDECORT RESPULES) Nebulizing Suspension statistically significantly improved

croup score at 12 and 24 hours and at 2 hours in patients with an initial croup symptom score above 3. There was also a 33% reduction in the length of stay.

Efficacy in children with moderate to severe croup

A randomised, double-blind, placebo-controlled study compared the efficacy of Budesonide (BUDECORT RESPULES) Nebulizing Suspension and placebo in the treatment of croup in 83 infants and children (aged 6 months to 8 years) admitted to hospital for croup. Patients received either Budesonide (BUDECORT RESPULES) Nebulizing Suspension 2 mg or placebo every 12 h for a maximum of 36 h or until discharge from hospital. The total croup symptom score was assessed at 0, 2, 6, 12, 24, 36 and 48 hours after the initial dose. At 2 hours, both Budesonide (BUDECORT RESPULES) Nebulizing Suspension and placebo groups showed a similar improvement in croup symptom score, with no statistically significant difference between the groups. By 6 hours, the croup symptom score in the Budesonide (BUDECORT RESPULES) Nebulizing Suspension group was statistically significantly improved compared with the placebo group, and this improvement versus placebo was similarly evident at 12 and 24 hours.

Growth

Asthma as well as inhaled glucocorticosteroids may affect growth.

Effects of Budesonide (BUDECORT RESPULES) Nebulizing Suspension on growth have been studied in 519 children (age 8 months to 9 years) in three prospective randomised, open-label studies.

Overall, there was no significant difference in growth between children treated with Budesonide (BUDECORT RESPULES) Nebulizing Suspension and those treated with conventional asthma therapy. Two studies (n=239 and 72 respectively) showed a 7 mm and 8 mm greater growth after one year's treatment with Budesonide (BUDECORT RESPULES) Nebulizing Suspension compared to the control group, conventional asthma therapy including inhaled glucocorticosteroids (not statistically significant), while in one study (n=208) the growth during one year was 8 mm lower in the Budesonide (BUDECORT RESPULES) Nebulizing Suspension group than in the control group, conventional asthma therapy without inhaled glucocorticosteroids (statistically significant difference).

5.2 Pharmacokinetic properties

Absorption

In adults the systemic availability of budesonide following administration of Budesonide (BUDECORT RESPULES) Nebulizing Suspension via a jet nebuliser is approximately 15% of the nominal dose and 40% to 70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug. The maximal plasma concentration, occurring about 10 to 30 minutes after start of nebulisation is approximately 4 nmol/L after a single dose of 2 mg.

Distribution

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

Biotransformation

Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Elimination

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after intravenous dosing averages 2-3 hours.

Linearity

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

Children

In 4-6 year-old asthmatic children, the systemic availability of budesonide following administration of Budesonide (BUDECORT RESPULES) Nebulizing Suspension via a jet nebuliser (Pari LC Jet Plus with Pari Master compressor) is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half that in healthy adults. The maximal plasma concentration, occurring approximately 20 minutes after start of nebulisation is approximately 2.4 nmol/L in 4-6 years old asthmatic children after a 1 mg dose.

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.

The exposure (C_{max} and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6-year-old children is comparable to that in healthy adults given the same delivered dose by the same nebuliser system.

5.3 Preclinical safety data

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, e.g, decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of other glucocorticosteroids.

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 two repeat studies, 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 one of two repeat studies 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 that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate, Sodium chloride, Polysorbate 80, Citric acid anhydrous, Sodium citrate, Water for injections

6.2 Incompatibilities

No known incompatibilities. For proven compatible products, see Section 4.2 on Posology and method of administration.

6.3 Shelf-life

Please refer to the expiry date on the outer carton.
After opening the envelope, single dose units should be used within 3 months.
Opened single dose units should be used within 12 hours. Please note that if only 1 mL is used the remaining volume is not sterile.

6.4 Storage

Store a temperature not exceeding 30°C. Do not freeze.
Store in an upright position and protected from light. After opening of the aluminium foil envelope, the unused single dose units should be kept in the envelope to protect them from light.

6.5 Nature and contents of container

The container is a single dose unit made of LD-polyethylene. Each single dose unit contains 2 mL suspension. The single dose unit is marked with a line (Budesonide (BUDECORT RESPULES) Nebulizing Suspension 250 mcg/mL and 500 mcg/mL only). This line indicates the 1 mL volume when the single dose unit is held up-side down.

One sheet of 5 single dose units is packed in a sealed laminated aluminium foil envelope. Pack size: 20 single dose units 2 mL.

6.6 Instructions for use, handling and disposal

See section 4.2. Dosage and method of administration

How to use Budesonide (BUDECORT RESPULES) Nebulizing Suspension

1) Before use, re-suspend the contents of the sterile single dose by using a gentle swirling motion.
2) Hold the sterile single dose unit upright and open by twisting off the wing
3) Place the open (i.e. 1 mL) of the single dose units are to be used, withdraw the desired volume and discard any remaining portion

NOTE:

1. Rinse your mouth out with water after each dosing occasion
2. If you see a facemask, make sure that the mask fits tightly while you are inhaling.
3. Wash your face after the treatment.

Cleaning

The nebulizer chamber and the mouthpiece, or the facemask, should be cleaned after each use. Wash the parts in hot tap water using a mild detergent or according to the instructions supplied by the manufacturer of the nebulizer. Rinse well and dry by connecting the nebulizer chamber to the compressor of air inlet.

6.7 Availability

DRP-9930 – Budesonide (BUDECORT RESPULES) 250mcg/mL – Box of 20 x 2mL
DRP-9932 – Budesonide (BUDECORT RESPULES) 500mcg/mL – Box of 20 x 2mL

CAUTION

Foods, Drug, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

Date of First Authorization

DRP-9930 – Budesonide (BUDECORT RESPULES) 250mcg/mL: 28 April 1993
DRP-9932 – Budesonide (BUDECORT RESPULES) 500mcg/mL: 18 February 1993

Date of Revision of Text
December 2022

Based on CDS dated December 2018 and September 2019 with ANGEL Ref.: Doc ID-000390559 v.5.0 and v.7.0
Philippine-specific Text ANGEL Ref.: Doc ID-000207106 v.9.0

Imported by the Marketing Authorization Holder
AstraZeneca Pharmaceuticals (Phils.), Inc.
16th Floor, Inoza Tower, 40th Street
Bonifacio Global City, Taguig, Philippines
Manufactured by AstraZeneca AB
SE-151 85 Södertälje, Sweden