PRODUCT MONOGRAPH

Pr TEVA-BUDESONIDE

(budesonide suspension for inhalation)

0.125 mg / mL, 0.25 mg / mL and 0.5 mg / mL

Teva Standard

Glucocorticosteroid for the Treatment of Bronchial Asthma

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Inhalation	Suspension / 0.125 mg / mL, 0.25 mg / mL, 0.5 mg / mL	Citric acid, disodium edetate dihydrate, polysorbate 80, sodium chloride, sodium citrate, water for injection

INDICATIONS AND CLINICAL USE

Patients with bronchial asthma, who require maintenance treatment with inhaled glucocorticosteroids, for control of the underlying airways inflammation and who are unable to efficiently use other inhaled formulations.

CONTRAINDICATIONS

- Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis;
- Known hypersensitivity to any components;
- Active or quiescent pulmonary tuberculosis;
- Untreated fungal, bacterial or viral infections of the respiratory system

WARNINGS AND PRECAUTIONS

Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids. Particular care is needed in patients who are transferred from systemically active corticosteroids to TEVA-BUDESONIDE and in patients who required high dose emergency corticosteroid therapy. This is important as deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids. Patients receiving prolonged treatment at the highest recommended dose of inhaled corticosteroids may also be at risk for adrenal insufficiency. After

withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress including worsening of asthma attacks, trauma, surgery or infections, particularly gastroenteritis, or other conditions associated with severe electrolyte loss. Although budesonide may provide control of asthmatic symptoms during these periods, it does NOT provide the systemic steroid which is necessary for coping with these emergencies. Additional systemic corticosteroid should be considered during periods of stress or elective surgery.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Patients previously on high doses of systemic steroids may regain earlier symptoms not related to asthma such as rhinitis and eczema when transferred from oral therapy to TEVA-BUDESONIDE. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. Temporary resumption of systemic steroids may be necessary to treat these conditions.

The development of pharyngeal and laryngeal candidiasis is cause for concern because the extent of its penetration of the respiratory tract is unknown. If oral pharyngeal candidiasis develops, appropriate antifungal therapy should be implemented to eradicate the infection. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each nebulization treatment (see **DOSAGE AND ADMINISTRATION**).

Glucocorticosteroids may mask some signs of infection and new infections may appear during its use.

TEVA-BUDESONIDE is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

The nebulizer chamber should be cleaned after every administration. Wash the nebulizer chamber and mouthpiece or face mask in hot tap water using a mild detergent. Rinse it well and dry by connecting the nebulizer chamber to the compressor or air inlet.

Due to a low output of budesonide, ultrasonic nebulizers should not be used for administration of TEVA-BUDESONIDE.

Two cases of mortality due to cerebral edema and encephalopathy were reported during clinical trials. There was no apparent cause and effect relationship.

There is still insufficient data for the long-term systemic effect of budesonide. The long-term effects of budesonide in developmental or immunologic processes in the mouth, pharynx, trachea, eyes and lungs are unknown. With the recommended therapeutic doses, the risk/benefit ratio seems to be very low. However, as with any other glucocorticosteroid, patients should be carefully followed up for systemic adverse effects, particularly during long-term therapy. 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. To minimize the systemic effects, it is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

In transferring patients from a systemic steroid to TEVA-BUDESONIDE, the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression), may occur in spite of maintenance or improvement of respiratory functions (see **DOSAGE AND ADMINISTRATION**).

It is essential that the patient be instructed that TEVA-BUDESONIDE is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack.

Treatment with TEVA-BUDESONIDE should not be stopped abruptly, but tapered off gradually (see **DOSAGE AND ADMINISTRATION: Clinical Management**).

Pulmonary infiltrates with eosinophilia may occur in patients on TEVA-BUDESONIDE therapy. The causative role of inhalational steroids cannot be ruled out.

Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and height (in children) should be periodically assessed.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

There may be enhanced systemic effects of budesonide in patients with advanced liver cirrhosis, and in those with hypothyroidism. Reduced liver function may affect the elimination of corticosteroids. This may be clinically relevant in patients with severely compromised liver function.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children.

Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops treatment with antiviral agents may be considered.

If, however, a viral upper respiratory infection is present, the patient should adhere to the regular asthma medication. In patients who are known to deteriorate rapidly when they have a viral respiratory infection, a short course of oral corticosteroid therapy should be considered.

Clinical studies have shown that viral upper respiratory infections cause significantly fewer problems in patients who are on regular treatment with topical glucocorticosteroids.

To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of TEVA-BUDESONIDE and the nebulizing equipment.

Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as *Candida albicans* (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women:

In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and in mice. Results from world-wide post marketing experience indicate inhaled budesonide during pregnancy has no adverse effects on the health of the fetus/new born child. Review of published literature of orally inhaled budesonide, including results from a large case control study performed with cases identified from 3 Swedish health registers showed that there was no association between exposure to inhaled budesonide and overall congenital malformations. Results from a similar study performed with intranasal budesonide, using the same 3 Swedish health registers, showed that the use of intranasal budesonide was associated with a subgroup “less severe cardiovascular defects”; however there was no statistically significant association between the use of intranasal budesonide during pregnancy and overall congenital malformations or overall frequency of cardiovascular defects in the offspring. Budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism.

Nursing Women:

Budesonide is excreted in breast milk. The administration of TEVA-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.

ADVERSE REACTIONS

During clinical trials, the most common side effects were cough, throat irritation and hoarseness (2-4%). Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. In rare cases, anaphylactic reactions have been reported following the use of budesonide. Facial skin irritation has occurred in a few cases when a nebulizer with a face mask has been used. To prevent irritation, the facial skin should be washed after use of the face mask. Skin reactions (urticaria, rash, dermatitis, angioedema, etc.) may, in rare cases, occur in association with local corticosteroid therapy. In rare cases, skin bruising has been reported following treatment with inhaled glucocorticosteroids.

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Systemic effects and oropharyngeal complications caused by budesonide were found to be dose-dependent. 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, depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. Candidiasis has been reported by some patients and may occur at therapeutic doses. In rare cases, budesonide may provoke bronchoconstriction in hyperreactive patients.

In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently (see **DOSAGE AND ADMINISTRATION: Clinical Management**).

Post-Market Adverse Drug Reactions

Psychiatric symptoms such as nervousness, restlessness and depression as well as behavioural disturbances in children have been observed.

Cases of growth suppression have been reported for budesonide.

DRUG INTERACTIONS

Budesonide has not been observed to interact with any drug used for the treatment of asthma.

Cimetidine
The kinetics of budesonide were investigated in a study of healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs. 5.1 nmol/L and 10 vs. 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance.

CYP3A4 Inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. CYP3A4 inhibitors like ritonavir and azole antifungals (e.g. ketoconazole and itraconazole) increase the systemic exposure to budesonide. Therefore, concomitant use of budesonide and ritonavir or azole antifungals should be avoided, unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TEVA-BUDESONIDE should be administered from suitable nebulizers. Due to a low output of budesonide, ultrasonic nebulizers should not be used.

The amount of budesonide suspension delivered to the patient in a nebulizer is variable and dependent upon several factors, including the following:

- nebulization time,
- volume fill,
- the characteristics of the nebulizing equipment,
- the inspiratory/expiratory ratio and tidal volume of the patient,
- the use of either a face-mask or a mouth piece.

Data from *ex vivo* studies have estimated that the dose of nebulized budesonide delivered to the patient varies between 9-19% of the nominal dose.

The nebulization time and the dose delivered are dependent on flow rate, volume of nebulizer chamber and volume fill.

Nebulization should take place using a gas flow (oxygen or compressed air) of 6 to 10 L/minute and the suspension nebulized over a 10 to 15 minute period. A suitable volume fill for most nebulizers is 2-4 mL. The manufacturer's instructions concerning cleaning and maintenance of the nebulizer should be strictly followed.

NOTE: Patients should be instructed to rinse their mouths out with water after each nebulization treatment. This will help prevent the occurrence of candidiasis and potential systemic effects. Cleansing dentures has the same effect.

Recommended Dose and Dosage Adjustment

Initial Dose

The dosage of TEVA-BUDESONIDE is individual. The initial dose should be:

Children (3 months to 12 years): 0.25 to 0.5 mg twice daily. In some cases, the dosage may be further increased up to 1 mg twice daily.

Adults: usually 1 to 2 mg twice daily. In some cases, the dosage may be further increased.

Maintenance Dose

The maintenance dose is individual. After the desired clinical effect has been obtained, the maintenance dose should be gradually reduced to the smallest amount necessary for control of symptoms.

Dosage Table

Dose in mg	Volume of TEVA-BUDESONIDE		
	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
0.125 mg	1 mL*	-	-
0.25 mg	2 mL	1 mL*	-
0.5 mg	4 mL	2 mL	-
0.75 mg	-	3 mL	-
1 mg	-	-	2 mL
1.5 mg	-	-	3 mL
2 mg	-	-	4 mL

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

In patients where an increased therapeutic effect is desired, an increased dose of TEVA-BUDESONIDE is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

If only half the contents of an ampoule are used, add Sterile Normal Saline to make up the required volume fill.

Clinical Management

Patients - Non-Steroid Dependent
Treatment with the recommended doses of budesonide usually gives a therapeutic effect within 10 days. However, certain patients might have an excessive collection of mucous secretion in the bronchi which reduces the penetration of budesonide into the bronchial mucosa. In these cases, it is desirable to initially give a short (about 2 weeks) oral corticosteroid regimen in addition to budesonide. The oral treatment is started on a rather large dose which is then gradually reduced. Thereafter, treatment with TEVA-BUDESONIDE only is sufficient. Exacerbations of the asthma caused by bacterial infections are controlled by adequate antibiotic regimens and also by increasing the TEVA-BUDESONIDE dosage.

Patients - Steroid Dependent
Transferral of patients dependent upon oral steroids to treatment with TEVA-BUDESONIDE demands special care mainly because of the slow restitution of the disturbed hypothalamic-

pituitary-adrenal function caused by extended treatment with oral corticosteroids. When TEVA-BUDESONIDE treatment is initiated, the patient should be in a relatively stable phase. TEVA-BUDESONIDE is then given in combination with the previously used oral steroid dose for about 10 days. After this period of time, reduction of the oral corticoid dose may be started gradually. The oral dose is thus reduced to the lowest level which, in combination with TEVA-BUDESONIDE, gives a stable respiratory capacity.

In adults, the usual rate of withdrawal of the systemic corticosteroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close observation. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. A slow rate of withdrawal cannot be overemphasized. If withdrawal symptoms appear, the previous dosage of the systemic drug should be resumed for a week before further decrease is attempted. During withdrawal, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to continue with TEVA-BUDESONIDE, but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should continue more slowly.

In many cases it may be possible to completely replace the oral steroid with TEVA-BUDESONIDE treatment. In other patients, a low oral steroid maintenance dosage may be required. The length of time needed for the body to regain its natural production of corticosteroid in sufficient quantity is often extended. Thus, during severe asthma attacks or physically stressing situations such as severe infections, trauma, and surgical operations, it is necessary to resume systemic steroids (in large dosages) in order to avoid adrenocorticoid insufficiency. Acute exacerbations, especially in connection with increased viscosity and mucous plugging, may require complementary treatment with a short course of oral corticosteroids which are gradually tapered as symptoms subside.

During transfer from oral therapy to TEVA-BUDESONIDE, a lower general steroid action is experienced. The patients might regain earlier symptoms (rhinitis, eczema) or suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. In these cases, further medical support may be required.

OVERDOSAGE

Occasional overdosing will not give any obvious symptoms in most cases but it will decrease the plasma cortisol level. Other pharmacological effects are an increase in the number and percentage of circulating neutrophils, while the number and percentage of eosinophils will decrease concurrently. Stopping the treatment or decreasing the dose will abolish the induced effects.

Habitual overdosing may cause hypercorticism and hypothalamic-pituitary-adrenal suppression. Decreasing the dose or stopping the therapy will abolish these effects, although the restitution of

the HPA-axis may be a slow process and during periods with pronounced physical stress (severe infections, trauma, surgical operations, etc.) it may be advisable to supplement with systemic steroids.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

The active ingredient of TEVA-BUDESONIDE, budesonide, is a potent non-halogenated synthetic glucocorticosteroid with strong topical and weak systemic effects.

Budesonide has a high topical anti-inflammatory potency and it is rapidly biotransformed in the liver. This favourable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life.

The late reaction can be significantly inhibited if budesonide is given at least 2 hours before a bronchial challenge. Pretreatment for 1 - 4 weeks with inhaled budesonide may inhibit the immediate bronchial reaction.

After therapeutic use of orally inhaled budesonide, several weeks may pass before the full effect is obtained.

STORAGE AND STABILITY

Store at 5-30°C in an upright position. Keep protected from light. Once envelope is opened, use ampoules within 3 months. Opened ampoules must be used within 12 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-BUDESONIDE is provided in ampoules made of LD-polyethylene. Each ampoule contains 2 mL suspension of 0.125 mg / mL, 0.25 mg / mL or 0.5 mg / mL. Sheets of 5 ampoules are packed in an envelope of foil laminate. Four envelopes are packed in each carton.

Non-medicinal: citric acid, disodium edetate dihydrate, polysorbate 80, sodium chloride, sodium citrate, water for injection.

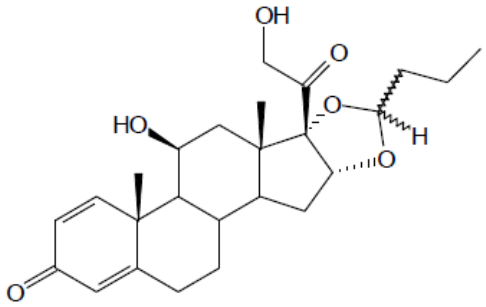
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Budesonide
Chemical Name:	16α, 17α-Butylidenedioxy-11ß, 21-dihydroxypregnal, 4-diene-3, 20-dione
Other Chemical Name:	*C-22S* (epimer A) and the *C-22R* (epimer B) epimers of 16α, 17-[(1RS)-Butylidenebis(oxy)]-11ß, 21-dihydroxypregna-1,4-diene-3,20-dione (R,S)-11ß, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3,20-dionecyclic-16,17-acetal with butyraldehyde

Chemical Structure:



Molecular Formula:	$C_{25}H_{34}O_6$
Molecular Weight:	430.5 g/mol
Description:	Budesonide is a glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white fine powder and is freely soluble in methylene chloride, sparingly soluble in alcohol, practically insoluble in water. Budesonide melts at 221°C to 232°C, with decomposition.

CLINICAL TRIALS

Comparative Bioavailability Studies

A waiver from conducting comparative *in vivo* studies was granted; bioequivalence of TEVA-BUDESONIDE (Budesonide Suspension for Inhalation) 0.125 mg/mL, 0.25 mg/mL and 0.5 mg/mL by Teva Canada Limited to the Canadian Reference Product, Pulmicort Nebuamp by AstraZeneca Canada Inc., was demonstrated by a comparative *in vitro* approach.

PHARMACOLOGY

Studies with animals have shown that budesonide has a 2-10 times better ratio between topical anti-inflammatory and systemic glucocorticoid effects than that obtained with beclomethasone dipropionate or triamcinolone acetonide. In the blanching test for topical anti-inflammatory activity in humans, budesonide was about twice as potent as beclomethasone dipropionate. Beclomethasone dipropionate was, however, more active than budesonide with regard to systemic activity as measured by depression of morning plasma cortisol. The favourable topical anti-inflammatory activity to systemic effect ratio demonstrated by budesonide is most probably due to its high glucocorticoid receptor affinity and high first pass metabolism with a short half-life.

Budesonide has been shown to counteract the mainly "IgE" mediated lung anaphylaxis in guinea pigs.

No significant bronchorelaxing activity, either *in vitro* or *in vivo*, could be demonstrated. Budesonide did not potentiate beta-mediated bronchorelaxation, and did not affect theophylline-induced relaxation of respiratory airway smooth muscle in guinea pigs.

Budesonide exhibits typical glucocorticoid effects in that subcutaneous administration to adrenalectomized rats induced glycogen deposition in the liver, increased urinary volume and only slightly affected sodium excretion.

Whole body autoradiography in mice has shown budesonide and its metabolites to have a similar distribution pattern to other glucocorticosteroids with a high distribution to endocrine organs.

Human Pharmacokinetics

Peak plasma level occurred within 30 minutes after inhalation of 1 mg budesonide (via metered dose aerosol). The plasma half-life is 2.0±0.2 hours, similar to that found after intravenous administration (2.8±1.1 h). The systemic bioavailability of budesonide after inhalation is calculated to be 72.8±42.0% of the dose retained by the patient after mouth rinsing. After oral administration, peak plasma concentrations of unchanged compound were found after about 3 hours. The oral bioavailability is calculated to be 10.7±4.3%. Since budesonide acts locally in the lung, plasma levels are not predictive of therapeutic efficacy or safety.

The distribution volume (V_d) of budesonide is 301.3±41.7 L, indicating the high tissue affinity of the drug. Plasma protein binding is estimated at 88.3±1.5%.

In human volunteers who inhaled tritiated budesonide (via metered dose aerosol) 31.8±7.5% of the discharged dose was recovered in the urine (0-96 hours) while during the same period, 15.1±4.3% of the dose could be recovered in the faeces. In those subjects who took the compound orally, 45.0±5.0% was recovered in the urine, 29.6±2.5% in the faeces.

In vitro studies with human liver have shown that budesonide is rapidly metabolized to more polar compounds than the parent drug. Two major metabolites have been isolated and identified as 6β-hydroxybudesonide and 16α-hydroxyprednisolone. The glucocorticoid activity of these two metabolites was at least 100-fold lower than the parent compound as shown in the rat ear edema test. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns could be detected. Negligible biotransformation was observed in human lung and serum preparations.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD_{50} (mg/kg) After 3 Weeks
Mouse	Male	s.c.	35 ± 18
Mouse	Male	p.o.	> 800
Mouse	Female	p.o.	> 800
Rat	Male	s.c.	15.1 ± 4.4
Rat	Female	s.c.	20.3 ± 7.1
Rat	Male	p.o.	~ 400

Surviving animals exhibited a marked decrease in body weight gain.

Toxicity After Repeated Administration of Budesonide to Rats, Rabbits and Dogs:

Animal			Daily Dose Levels			Route of Administration	Duration	Toxic Effects
Species	Strain	Number and Sex Per Group	No. of Dose Groups	mg/kg	mg/animal			
Rat	Sprague-Dawley	6 males 6 females	4	0.05 0.5 5.0 50.0		p.o.	1 month	Atrophy of adrenal gland and lymphoid system. Gastric ulceration.
Rat	Wistar	10 males 10 females	3	0.02 0.10 0.2-0.5		inhalation	3 months	Hair loss, dose related reduction in lymphocytes, leukocytes, increase in neutrophils. In high dose group, reduced adrenal, thymic, splenic and hepatic weights. No pulmonary impairment observed.
Rat	Wistar	40 males 40 females	3	0.005 0.01 0.05		Inhalation	12 months	As above
Rabbit	New Zealand White	3 males 3 females	2		0.025 0.1	s.c.	1 month	High dose caused slight liver mass increase, slight decrease in adrenal mass, thymal regression.
Dog	Beagle	1 male 1 female	3	0.01 0.1 1.0		p.o.	1 month	High dose - Typical steroid effects - adrenal, lymphoid system atrophy, increased fat in myocardium, glycogen in liver.
Dog	Beagle	2 males 2 females	3	0.02 0.06 0.2		inhalation	6 weeks	High dose - induced thymal atrophy, adrenal atrophy. No changes in respiratory system observed.
Dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	6 months	High dose - decreased plasma cortisol, cortical atrophy of the adrenal gland, thymal regression. Slight visceral obesity.
Dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	12 months	High dose - obesity, alopecia, females showed no evidence of estrous cycle. Systemic steroid effects -lymphoid and adrenal atrophy.

Teratology and Reproduction Studies

Effects on Pregnancy

Rat: Daily doses of 20, 100, and 500 µg/kg body mass were administered subcutaneously to pregnant rats during days 6-15 of gestation. In the high dose group, all of the rats showed a deteriorated general condition including piloerection, drowsiness, decreased food consumption and decreased body mass gain. Fetal loss was increased and pup masses decreased in comparison to the control group. The frequency of fetal abnormalities was also increased. Doses in excess of 100 µg/kg must be considered teratogenic in the rat.

Daily doses of 0.01, 0.05 and 0.1-0.25 mg/kg were administered by inhalation to pregnant rats during days 6-15 of gestation. At the highest dose a slight significant reduction in fetal weight gain was observed, but there was no evidence of any effect on fetal development attributable to budesonide at any dose level.

Rabbit: Daily doses of 5, 25, and 125 µg/kg body mass were administered subcutaneously during days 6-18 of gestation. In the low and medium dose groups, food consumption and body mass gain were decreased during the fourth gestational week. Some doses also showed signs of diarrhea and vaginal bleeding. In the high dose group, all doses aborted at the end of the gestation period. In the medium dose group, a marked increase in the frequency of abnormalities, mainly skeletal defects, was observed. Most commonly, defects were skull and vertebral abnormalities.

Effects on Fertility and General Reproductive Performance

Rat: To evaluate the effect of budesonide on fertility and general reproductive performance, daily doses of 0.01, 0.05, 0.19 µmol/kg were given subcutaneously to males for 9 weeks prior to and throughout mating. Females received the same doses for two weeks before, throughout gestation and up to 21 days postpartum. The offspring of the high group showed a decrease of peri- and post-natal viability. Dams showed a decrease in body mass gain.

Mutagenicity Studies

Budesonide showed no mutagenic activity in the Ames Salmonella/microsome plate test or in the mouse micronucleus test.

Carcinogenicity

The carcinogenic potential of budesonide was evaluated in long term mouse and rat studies.

Chronic Drinking Water Study in Mice
Budesonide was administered in the drinking water for 91 weeks to three groups of CD®-1 mice at dose levels of 10, 50 and 200 µg/kg/day.

A statistically significant dose-related decrease in survival was noted for the males only. All other evaluation criteria were comparable in all groups. Upon microscopic examination, a variety of spontaneous lesions was observed which were not related to treatment. No carcinogenic effect was present.

Chronic Drinking Water Study (104 Weeks) with Budesonide in Rats
Three rat carcinogenicity studies have been performed. In the first study, budesonide was administered for 104 weeks in doses of 10, 25 and 50 µg/kg/day.

A small but statistically significant increase in gliomas was noted in male animals from the high dose group. These results were considered equivocal since the S-D rat is very variable with regard to spontaneous glioma incidence.

To elucidate these results, two further 104 week carcinogenicity studies with budesonide 50 µg/kg/day were performed, one using male S-D rats, and one using male Fischer rats (which have a lower and less variable incidence of gliomas). Prednisolone and triamcinolone acetonide were used as reference glucocorticoids in both studies.

The results from these new carcinogenicity studies in male rats did not demonstrate an increased glioma incidence in budesonide treated animals, as compared to concurrent controls or reference glucocorticosteroid treated groups.

Compared with concurrent control male S-D rats there was also an increased incidence of liver tumors in the mid and high dose groups in the original study.

This finding was confirmed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in the repeat study in male S-D rats thus indicating a class effect of glucocorticosteroids.

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13. PULMICORT® NEBUAMP® 0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL (budesonide suspension for inhalation) Product Monograph, AstraZeneca Canada Inc., Canada. Submission Control Number 164889. Date of Revision: August 20, 2013

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr TEVA-BUDESONIDE
(budesonide suspension for inhalation)
Teva Standard
0.125 mg/mL, 0.25 mg/mL and 0.5 mg/mL

This leaflet is part III of a three-part "Product Monograph" published when TEVA-BUDESONIDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-BUDESONIDE. Contact your doctor or pharmacist if you have any questions about the drug.

Before using TEVA-BUDESONIDE, read this leaflet carefully. It contains general points about TEVA-BUDESONIDE and should add to more specific advice from your doctor or pharmacist.

Please keep this leaflet to refer to until you have used up all TEVA-BUDESONIDE units in this package.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-BUDESONIDE is the brand name for an inhaled drug called budesonide. It belongs to a group of medicines called corticosteroids which are used to reduce inflammation.

What it does:
Asthma is caused by inflammation in the airways. TEVA-BUDESONIDE reduces and prevents this inflammation. In some cases, several weeks of regular use may be needed before the full effect is seen.

When it should not be used:
TEVA-BUDESONIDE will not relieve an asthma attack that has already started. Many inhalers contain bronchodilators to provide rapid relief. If your doctor prescribed one of these, you should follow his or her directions when you have an acute attack of asthma.

What the medicinal ingredient is:
TEVA-BUDESONIDE contains budesonide as the active ingredient and comes in concentrations of 0.125 mg/mL, 0.25 mg/mL or 0.5 mg/mL.

Each unit contains 2 mL. This means that 1 unit of the 0.125 mg/mL strength contains 0.25 mg of active drug. One unit of the 0.25 mg/mL strength contains 0.5 mg of the active drug. One unit of the 0.5 mg/mL strength contains 1.0 mg of active drug.

What the non-medicinal ingredients are:
TEVA-BUDESONIDE contains the following non-medicinal ingredients; Citric acid, disodium edetate dihydrate, polysorbate 80, sodium chloride, sodium citrate, water for injection.
Check with your doctor if you think you may be allergic to any of these non-medicinal ingredients.

What dosage forms it comes in:
TEVA-BUDESONIDE is a suspension for inhalation.

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-BUDESONIDE talk to your doctor or pharmacist:
- about **all** health problems you have now or have had in the past, especially if you have had lung tuberculosis or any other recent infection or liver problems;
- about other medicines you take, including ones you can buy without a prescription;
- if you take, or have taken steroid medicines within the past several months;
- if you are pregnant, plan to become pregnant, or are breast-feeding;
- if you are allergic to 'non-medicinal' substances like food products, preservatives or dyes, which may be present in TEVA-BUDESONIDE. See '**What the non-medicinal ingredients are**'
- if you have ever had a bad, unusual or allergic reaction to any medicine containing budesonide;

While taking TEVA-BUDESONIDE; if you develop an infection or a respiratory infection, contact your doctor to see if you can continue taking TEVA-BUDESONIDE.

Do not take TEVA-BUDESONIDE
- if you are allergic to budesonide or to the other ingredients in TEVA-BUDESONIDE. See '**What the non-medicinal ingredients are**'.
- To treat a sudden attack of breathlessness. You will probably need a different kind of medicine (i.e. a fast acting relief medication) in a different colour puffer than may already have been given to you. If you have more than one medicine, be careful not to confuse them.
- If you have an untreated infection (fungal, bacterial, or viral) or tuberculosis in the respiratory tract.

INTERACTIONS WITH THIS MEDICATION

If you take medications against fungal infections or Ritonavir (medication used to treat HIV infection or

AIDS). These medications may interact with TEVA-BUDESONIDE.

PROPER USE OF THIS MEDICATION

How to take TEVA-BUDESONIDE Properly:
TEVA-BUDESONIDE is for use in a nebulizer or respirator. **Do not use in an ultrasonic nebulizer.** Be sure you know how to use your nebulizer or respirator before you start this drug.

Nebulization should take place using a gas flow (oxygen or compressed air) of 6 to 10 L/minute. A suitable volume fill for most nebulizers is 2 to 4 mL.

It is important that you use TEVA-BUDESONIDE daily as recommended by your doctor, even when you feel well. Do not take more doses than prescribed by your doctor. Using more can increase the chance of unwanted effects. **Contact your doctor right away if your asthma seems worse.**

Before use, check to make sure the strength on the label matches the strength your doctor prescribed.

Follow these directions for each dose of TEVA-BUDESONIDE:

1. Remove one TEVA-BUDESONIDE from a sheet of 5 units. Return the other units to the envelope.
2. Gently shake the unit.
3. Open by holding the unit upright and twisting off the top 'wing'.

4. Slowly squeeze the contents of the unit into the nebulizer cup. If you only need to use half the contents of a unit, add sterile saline to the cup as instructed by your doctor or pharmacist. Before you use the rest of the unit for the next dose, swirl it gently.
5. Connect one end of the cup to the face mask or mouthpiece, and the other end to the air pump.
6. Just before you start treatment, gently shake the contents of the cup again. Then start the treatment.
7. Breathe calmly and evenly until no more mist comes out (about 10-15 minutes).
8. Rinse your mouth and spit out as soon as you are done.
9. If you use a face mask, wash your face after treatment.

Cleaning: When you have finished, you have to clean the nebulizer. Wash the cup and the mouth piece or mask in warm water, using a mild detergent. Rinse well. Dry by connecting the nebulizer cup to the compressor or to the air inlet. See the manufacturer's instructions for complete details.

Usual dose:
The dosage of TEVA-BUDESONIDE is individual.
Follow your doctor's directions carefully. They may differ from the information in this leaflet.

Suggested doses are:
Initially:
Children (3 months to 12 years): 0.25 to 0.5 mg twice daily.
Adults: usually 1 to 2 mg twice daily.

Maintenance:
After the desired effect has been obtained, your doctor can reduce your dose to the smallest amount necessary to control your asthma symptoms.

Dosage Table:

Dose (mg)	Volume of TEVA-BUDESONIDE		
	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
0.125	1 mL*	-	-
0.25	2 mL	1 mL*	-
0.5	4 mL	2 mL	-
0.75	-	3 mL	-
1	-	-	2 mL
1.5	-	-	3 mL
2	-	-	4 mL

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

Missed dose:
If you miss a dose of TEVA-BUDESONIDE, take it as soon as possible. Then go back to your regular schedule. If it is almost time for your next dose, skip the missed dose and take the next dose on time.

Never take a double dose of TEVA-BUDESONIDE to make up for ones you missed. If you are still unsure, check with your doctor or pharmacist to see what you should do.

Do not stop treatment with TEVA-BUDESONIDE abruptly. Treatment should be tapered off gradually.

Overdose:
If you think you have taken too much TEVA-BUDESONIDE contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, TEVA-BUDESONIDE may cause side effects in some people.

The most common side effects are cough, throat irritation, thrush (fungal infection) in the mouth and hoarseness. Other side effects that may occur are bad taste, headache, nausea, dryness of the throat, tiredness, thirst and diarrhea. Skin irritation on the face has been reported in a few cases when a nebulizer with a face mask has been used. This can be prevented by washing the face after use of the face mask, or applying a thin layer of Vaseline® on the face, before using the mask.

In rare cases, skin reactions like rash, nervousness, restlessness, depression, behavioural disturbances, bruising, and a feeling of tightness of the airways may occur. Severe allergic reactions may also occur in rare cases following the use of TEVA-BUDESONIDE.

If you take TEVA-BUDESONIDE for a long period and at higher doses you may develop symptoms of adrenal insufficiency. If you develop symptoms such as tiredness, headache, nausea, vomiting, pain in muscles and joints, please contact your doctor.

A slowing of growth in children may occur.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If any side effects bother you, please contact your doctor.

This is not a complete list of side effects. For any unexpected effects while taking TEVA-BUDESONIDE, contact your doctor or pharmacist.

Do not stop taking TEVA-BUDESONIDE on your own. Your doctor may want to slowly reduce your dose, especially if you have been using TEVA-BUDESONIDE for a long time. Although rare, symptoms of steroid withdrawal (i.e. fatigue, muscle or joint aches) may occur if TEVA-BUDESONIDE is stopped too quickly.

If you have to go into hospital for an operation, take your TEVA-BUDESONIDE with you and tell your doctor what medicine(s) you are taking.

HOW TO STORE IT

Remember to **keep TEVA-BUDESONIDE well out of the reach of children** when you are not using it.

Always keep unopened units in the foil envelope so they are well protected from light.

Do not use TEVA-BUDESONIDE after the expiry date marked on the foil envelope and outer carton.

- Record the date when the foil envelope is first opened. Do not use units from a foil envelope that has been opened for 3 months or more.
- If you are only required to use half the contents of a unit, the remainder must be used within 12 hours after the unit has been opened. If you do not use a full unit for each dose, protect the rest from light.

Store TEVA-BUDESONIDE at 5-30°C in an upright position. Keep protected from light. Once envelope is opened, use ampoules within 3 months. Opened ampoules must be used within 12 hours.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about TEVA-BUDESONIDE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information Leaflet by visiting the Health Canada website (http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

IMPORTANT: PLEASE READ

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