

PRODUCT MONOGRAPH

FrENTOCORT[®] ENEMA

budesonide enema

0.02 mg/mL, when reconstituted

Glucocorticosteroid for the Treatment of Distal Ulcerative Colitis

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THERAPEUTIC CLASSIFICATION

Glucocorticosteroid for the Treatment of Distal Ulcerative Colitis

ACTIONS AND CLINICAL PHARMACOLOGY

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

ENTOCORT has a high topical anti-inflammatory potency. It undergoes an extensive degree (approximately 90%) of biotransformation in the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β -hydroxybudesonide and 16 α -hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, an isozyme of cytochrome P450.

The favourable separation between topical anti-inflammatory and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life.

A glucocorticosteroid with such a profile is of particular importance for the local treatment of inflammatory bowel diseases (IBD) such as ulcerative colitis (UC). With regard to treatment of these diseases with glucocorticosteroids, it is essential to achieve a high local anti-inflammatory activity in the bowel wall with systemic side-effects, e.g. on the hypothalamic pituitary adrenal (HPA) axis function, as low as possible. At the recommended doses, budesonide enema causes no or small suppression of plasma cortisol.

Pharmacokinetics

Absorption in healthy subjects after rectal dosing of 2 mg budesonide low viscosity enema is rapid and essentially complete within 3 hours. The mean maximal plasma concentration after rectal administration is 3.0 ± 2.0 nmol/L, reached within 1.5 hours. Similar results are obtained in patients suffering from distal ulcerative colitis. The mean systemic availability after rectal dosing is $15 \pm 12\%$. The plasma half-life is between 2 and 3 hours in adults.

INDICATIONS AND CLINICAL USE

ENTOCORT (budesonide) is indicated in the management of distal ulcerative colitis (rectum, sigmoid and descending colon).

CONTRAINDICATIONS

ENTOCORT (budesonide) is contraindicated for the following:

- Local contraindications to the use of ENTOCORT include imminent bowel perforation as well as the probability of obstruction, abscess or other pyogenic infection, fresh intestinal anastomoses, extensive fistulas and sinus tracts.
- Systemic or local bacterial, fungal or viral infections.
- Known hypersensitivity to any of the ingredients.
- Active tuberculosis.

WARNINGS

Special care is demanded in treatment of patients transferred from systemic steroids to ENTOCORT (budesonide) as disturbances in the hypothalamic-pituitary-adrenal axis could be expected in these patients. The dose of systemic steroid should be reduced cautiously.

PRECAUTIONS

Glucocorticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. Viral infections such as chicken pox and measles can have a more serious or fatal course in patients on immunosuppressant corticosteroids. In adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed to chicken pox or measles, 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.

At recommended doses, budesonide enema causes no clinically important changes in basal plasma cortisol levels or in the response to stimulation with ACTH. The effects on morning plasma cortisol and adrenal function are significantly less compared with prednisolone enema 25 mg daily. However, knowledge with regard to treatment of the following conditions is limited and therefore cautioned: active or lateral peptic ulcer, osteoporosis, acute glomerulonephritis, myasthenia gravis, exanthematous diseases, diverticulitis, thrombophlebitis, psychic disturbances, diabetes, hypertension, hyperthyroidism, acute coronary disease, limited cardiac reserve and pregnancy. In such cases the benefits of a corticosteroid enema must be weighed against the risks.

There are still insufficient data on the long-term systemic effect of budesonide. 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. During long-term therapy, pituitary-adrenal function and haematological status should be periodically assessed.

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.

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 systemic glucocorticosteroids is sometimes necessary.

Replacement of systemic glucocorticosteroid treatment with higher systemic effect with ENTOCORT (budesonide) Enema sometimes unmask allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic drug.

Glucocorticosteroid enemas should be administered with caution in patients with severe ulcerative colitis because these patients are predisposed to perforations of the bowel wall.

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

Aggravation of diabetes mellitus or stimulation of manifestations of latent diabetes mellitus may be caused by corticosteroid therapy.

There may be an enhanced effect of budesonide in patients with liver cirrhosis and, as with other glucocorticosteroids, there may be enhanced effects in those with hypothyroidism. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide are, however, similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability.

In vivo studies in male subjects have shown that oral administration of ketoconazole (a known inhibitor of CYP3A activity in the liver and the intestinal mucosa, caused a four to seven fold increase of the systemic exposure to oral budesonide. Therefore, it cannot be excluded that concomitant administration of budesonide enema and CYP3A inhibitors, including ketoconazole and cobicistat-containing products (and possibly other azoles such as fluconazole, itraconazole or miconazole) may result in increased systemic availability of budesonide. If this is not possible, the period between treatments should be as long as possible. See Drug Interactions.

Glucocorticosteroid therapy may cause hyperacidity of peptic ulcer.

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

Glucocorticosteroids may cause elevation of intraocular pressure in glaucoma patients.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Usage During Pregnancy

Administration of ENTOCORT (budesonide) during pregnancy should be avoided unless there are compelling reasons. 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. The relevance of these findings to humans has not yet been established. In the absence of further studies in humans, 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 during pregnancy should be carefully observed for hypoadrenalism.

Lactation

Budesonide is excreted in breast milk. However, based on data from inhaled budesonide, at therapeutic doses of ENTOCORT, exposure to the infant is anticipated to be low. The use of ENTOCORT in nursing mothers requires that the possible benefits of the drug be weighed against the potential hazards to the mother, or infant.

Children

The safety and effectiveness of ENTOCORT in children have not been established, therefore use in this age group is not recommended.

Drug Interactions

To date, budesonide has not been observed to interact with other drugs used for the treatment of inflammatory bowel diseases.

Elevated plasma levels and enhanced effects of corticosteroids have been reported in women also receiving estrogens or oral contraceptives. However, a low-dose combination (ethinylestradiol/desogestrel: 30 µg/150 µg) oral contraceptive that more than doubled the plasma concentration of oral prednisolone had no significant effect on the plasma concentration of oral budesonide.

The metabolism of budesonide is primarily mediated by CYP3A4, an isozyme of cytochrome P450. Inhibition of this enzyme by e.g. ketoconazole and cobicistat-containing products (and possibly other azoles such as fluconazole, itraconazole or miconazole), cyclosporin, troleandomycin or erythromycin can therefore increase the systemic exposure to budesonide.

Cimetidine

The kinetics of budesonide were investigated in healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values of 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.

Omeprazole

At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE REACTIONS

No major side effects attributable to the use of ENTOCORT (budesonide) have been reported. During clinical trials, the frequency of subjectively reported side effects in a total of 247 patients and healthy volunteers given 2 mg budesonide, once daily in the morning, was low.

The most common adverse reactions are gastrointestinal disturbances, e.g., flatulence, nausea, diarrhoea. These symptoms were reported in 23 of the 247 patients (9%) receiving 2 mg of budesonide. Psychiatric symptoms (insomnia, agitation, anxiety, depression, dysphoria, emotional lability, somnolence) were reported in 7 patients (3%) receiving 2 mg budesonide. Skin reactions (rash, urticaria) occurred in 5 patients (2%).

Systemic effects of budesonide on the HPA-axis function were found to be dose-dependent. In rare cases, signs or symptoms of systemic glucocorticosteroid effects, including hypofunction of the adrenal gland, may occur with rectally administered glucocorticosteroids, probably depending on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual sensitivity. Rectal administration of high concentrations of budesonide (10 mg/dose) resulted in significant suppression of endogenous cortisol concentrations as measured by plasma and urinary cortisol levels.

In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity may occur.

In very rare cases, anaphylactic reactions have been reported during post marketing use.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Acute overdosage with ENTOCORT (budesonide), even in excessive doses, is not expected to be a clinical problem. When used chronically at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of ENTOCORT should be discontinued consistent with accepted procedures for discontinuing prolonged oral steroid therapy. However, the dosage form, enema, and the route of administration make any prolonged overdosage unlikely.

Occasional overdosing will not give any obvious symptoms in most cases but it will decrease the plasma cortisol level and increase the number and percentage of circulating neutrophils. 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.

If, by mistake, high dose of ENTOCORT dispersible tablet has been taken orally, treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

DOSAGE AND ADMINISTRATION

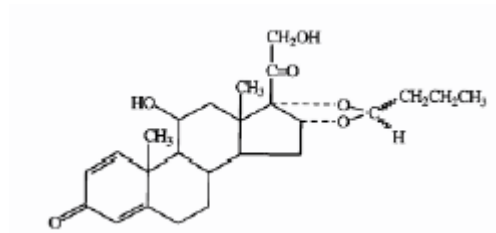
One ENTOCORT (budesonide) retention enema is given nightly to the patient for 4 weeks. If the patient is not in remission after 4 weeks, the treatment period may be prolonged to 8 weeks.

ENTOCORT Enema is reconstituted by adding one dispersible tablet into the enema bottle, whereafter the bottle is vigorously shaken for at least 10 seconds or until the tablet is completely dissolved. The tablet will disintegrate rapidly and the suspension will turn slightly yellowish.

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Structure:



Generic Name: budesonide

Chemical Name: Budesonide is a mixture of two isomers:

1. Pregna-1,4-diene-3,20-dione, 16,17-butyridenebis(oxy)-11,21-dihydroxy-, [11 β ,16 α (R)]

and

2. Pregna-1,4-diene-3,20-dione, 16,17-butyridenebis(oxy)-11,21-dihydroxy-, [11 β ,16 α (S)].

Drug Substance

Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.5

Description: Budesonide is a non-halogenated glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. Budesonide melts at 224°C to 231.5°C, with decomposition.

Composition

Budesonide enema 0.02 mg/mL (I + II) consists of 2 components:

I Dispersible Tablet

Budesonide micronized	2.3 mg
Colloidal silicon dioxide	
Lactose	
Lactose anhydrous	
Magnesium stearate	
Polyvidone, cross-linked	
Riboflavin-5-phosphate sodium	

II Vehicle

Methylparaben
Propylparaben
Sodium chloride
Water purified

Stability and Storage Recommendations

Store at 15-30°C. After preparation of the enema, the solution is intended for immediate use.

AVAILABILITY OF DOSAGE FORMS

ENTOCORT (budesonide) retention enema 0.02 mg/mL consists of 2 components: a dispersible tablet and a vehicle. The enema is reconstituted before use.

The volume of the reconstituted enema is 115 mL. Since the residual volume is about 15 mL, the dose administered to the patient is about 2 mg budesonide.

The tablets are provided in an aluminum blister package and the vehicle is in a polyethylene bottle equipped with a rectular nozzle.

Each carton contains 7 dispersible tablets and vehicle solutions.

PHARMACOLOGY

Animal Pharmacology

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.

Data from preclinical investigations show a rapid elimination of the drug in all investigated species (rat, mouse, rabbit and dog). This rapid systemic elimination is attributed to extensive liver metabolism, mainly via oxidative and reductive pathways. No or insignificant metabolism of budesonide was found in target organs such as lung and skin. This is as a result of low amounts of the enzyme system (Cytochrome P450) which is responsible for the metabolism of budesonide in these organs.

Human Pharmacology

Pharmacodynamics

Mode of Action

The exact mechanism of action of GCS in the treatment of UC is not yet fully understood. Anti-inflammatory actions, such as blocking of inflammatory cell influx and inhibition of inflammatory mediator release by blockage of the arachidonic acid pathway, are probably important. There is evidence that for GCS enemas, the anti-inflammatory action is predominantly local.

Effect on Haematological Parameters

Glucocorticosteroids increase blood neutrophils and decrease blood basophils, eosinophils and lymphocytes within 4 to 6 hours after administration to healthy volunteers. These effects are due to a transient redistribution of cells, with the values returning to normal within 24 hours.

Pharmacokinetics

Absorption

The pharmacokinetics of budesonide after rectal dosing are summarized in the table below (mean and S.D. are given).

No. of Subjects/Patients	Diagnosis	Dose (mg)	Polysorbate	Syst. Avail. (%)	C _{max} (nmol/L)	T _{max} (h)
5	U.C. ¹	2	+	-	2.5 ± 1.4	1.5 ± 0.9
15	Healthy	2	-	15 ± 12	3.0 ± 2.0	1.3 ± 0.4
15	Healthy	2	+	16 ± 11	3.3 ± 1.9	1.3 ± 0.3
24	U.C.	2	-	-	2.1 ± 1.2 ²	1.3 ± 0.6 ²
24	U.C.	2	-	-	2.5 ± 1.7 ³	1.2 ± 0.4 ³

¹Ulcerative colitis

²After the first dose

³After 4 weeks' treatment

The volume of distribution of budesonide (3 L/kg) is large and the plasma protein binding (88%) is extensive compared with other synthetic GCS. The free volume of distribution (i.e., the ratio between volume of distribution and free plasma) is high for budesonide. This reflects a high tissue affinity of the compound.

Metabolism and Excretion

The half-life of budesonide after intravenous administration is 2-3 h in adults and shorter, 1.5 h, in children. After rectal dosing, the plasma half-life is almost identical to that seen after intravenous dosing. Absorption in healthy subjects following a rectal dose of 2 mg budesonide enema is rapid and essentially complete within 3 hours. The mean maximal plasma concentration after rectal administration is 3.0 ± 2.0 nmol/L reached within 1.5 hours. Similar results are obtained in patients suffering from distal ulcerative colitis.

The systemic clearance of budesonide (0.9 - 1.4 L/min) is high compared with other GCS. After oral dosing, the drug is rapidly and extensively absorbed, but the systemic availability is only 10-13%. This is similar to budesonide systemic availability after rectal dosing (15 ± 12%). The between-subject variability in systemic availability is greater after rectal than after oral dosing. Possible reasons for this may be, e.g., different hepatic by-pass due to inter-individual differences in rectal venous drainage and/or microbial degradation of budesonide. These differences are, however, probably of minor clinical importance regarding the efficacy since the effect of budesonide is mainly topical. The favourable topical antiinflammatory activity to systemic effect ratio is most probably due to its high glucocorticoid receptor affinity and high first pass metabolism with a short half-life.

In human volunteers who inhaled tritiated budesonide, 31.8 ± 7.5% of the discharged radioactivity was recovered in the urine (within 96 hours of administration) while during the same period, 15.1 ± 4.3% of the radioactivity 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. Virtually no unchanged budesonide is excreted in the urine.

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 6 β -hydroxybudesonide and 16 α -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

A complete toxicological program (acute, chronic, reproduction, mutagenicity and carcinogenicity studies) has been performed with budesonide after various routes of administration, such as oral, subcutaneous, epicutaneous and inhalation. Most of the studies were performed in rats and dogs. No toxicological studies have been performed with budesonide, using rectal administration.

Acute Toxicity

The acute toxicity studies with budesonide after oral and subcutaneous administration are summarized in the table below.

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

Table 2 summarizes the toxicity information from studies in which rats, rabbits and dogs received repeated oral, inhalation and subcutaneous administration of budesonide.

Teratology and Reproduction Studies

Effects on Pregnancy

Rat

Daily doses of 20, 100, and 500 μ g/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 does also showed signs of diarrhea and vaginal bleeding. In the high dose group, all does 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 dose 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.

Table 2. Toxicity After Repeated Administration Of Budesonide To Rats, Rabbits And Dogs

Animal		No. of Dose Groups	Daily Dose Levels		Route of Administration	Duration	Toxic Effects	
Species	Strain		Number and Sex 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.

Animal		No. of Dose Groups	Daily Dose Levels		Route of Administration	Duration	Toxic Effects	
Species	Strain		Number and Sex Groups	mg/kg				mg/animal
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.
All effects observed were consistent with those expected during prolonged corticosteroid exposure.								

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 tumours 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.

Toxicological Effects on the Gastrointestinal Tract

There are few apparent toxicological effects of low doses of budesonide noted on the gastrointestinal tract which, together with the liver, is a body organ system that will be exposed to high concentrations of budesonide after oral and/or rectal administration of the drug.

Oral administration of budesonide to rats for 1 month disclosed thymus atrophy at 50 µg/kg. At 500 µg/kg atrophy of spleen and adrenals was also noted as well as fat deposition in the liver, effects typical of a glucocorticoid. No adverse effects on the gastrointestinal tract were

noted. However, at 5000 µg/kg ulcerations and bleeding of the gastrointestinal tract were noted as well as pronounced systemic toxicity.

Administration of budesonide, in the drinking water, to rats for 3 months, revealed at necropsy stomach changes including raised white areas or nodules, dark ulcer-like areas, dark or dark-red foci and dark depressed areas among the female treated rats (50-700 µg/kg) and in one high-dosed male out of ten (700 µg/kg). No changes were noted in the control animals (both sexes). Similar stomach changes were also found in three-month drinking water study in mice. No changes were noted at 10 µg/kg but these stomach changes were observed at 50 µg/kg in both sexes. However, no stomach lesions were reported among the high dosed male mice (700 µg/kg). A few control animals were also affected.

Histological examination was not performed in either of these two studies. In a 12-month inhalation study (mainly oral/gastrointestinal deposition and absorption) in rats, effects such as atrophy of lymphoid organs and reduced lymphocyte counts were noted at 50 µg/kg (high dose). Histological examination disclosed the absence of bile duct hyperplasia of the liver. This is generally a glucocorticoid effect. Bile duct hyperplasia is also a normal finding in the senescent rat. There were no adverse effects on the gastrointestinal tract at 50 µg/kg.

Budesonide given orally to dogs for 1 month disclosed atrophy of adrenals and lymphoid organs at 100 µg/kg but not at 10 µg/kg. At 100 µg/kg there was a slight liver enlargement with increased glycogen deposition. No adverse effects were noted on the gastrointestinal tract. A 12-month oral inhalation study in dogs (doses between 20-200 µg/kg) disclosed a dose-related reduction in plasma cortisol. Atrophy of lymphoid organs and adrenals was found at 60 and 200 µg/kg. Increased liver weight and glycogen deposition were obtained at 200 µg/kg. There were no adverse effects on the gastrointestinal tract at any dose level.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrENTOCORT® ENEMA budesonide enema

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

ABOUT THIS MEDICATION

What the medication is used for:

ENTOCORT Enema is used to treat ulcerative colitis (inflammation of the bowel wall) localised in the rectum and the lower large bowel.

What it does:

ENTOCORT is an anti-inflammatory drug which belongs to the steroid family of drugs. ENTOCORT Enema has been shown to help reduce the production of substances and interfere with the processes responsible for the inflammatory response, thereby reducing the inflammation.

When it should not be used:

Do not use ENTOCORT Enema (budesonide) if you:

- have holes in your bowel (perforations), bowel obstructions, twisted and /or tubular bowel sections (fistulas), wounds, abscesses or infections in the bowel
- have any infection(s) in the rest of the body
- have tuberculosis
- are allergic to any of the ingredients in ENTOCORT Enema (see What the medicinal ingredient is and What the nonmedicinal ingredients are).

What the medicinal ingredient is:

budesonide

What the nonmedicinal ingredients are:

The nonmedicinal ingredients of the final solution are: colloidal silicon dioxide, lactose, magnesium stearate, methyl paraben, polyvidone, propyl paraben, riboflavin-5 phosphate sodium, water.

What dosage forms it comes in:

Dispersible Tablet 2.3 mg and Solution 115 mL.
Enema 0.02 mg/mL budesonide, when reconstituted.

WARNINGS AND PRECAUTIONS

BEFORE you use ENTOCORT Enema, talk to your doctor or pharmacist if:

- you have any health problems such as liver disease, diabetes, stomach ulcers, brittle bones (osteoporosis) or glaucoma
- you are taking or have taken steroid medicines within the past several months
- you are pregnant or plan to become pregnant
- you are breastfeeding or planning to breastfeed. ENTOCORT Enema (budesonide) is excreted in human breast milk. Talk to your doctor.

Do not stop using ENTOCORT Enema until your doctor tells you to.

If your symptoms become worse during treatment contact your doctor.

ENTOCORT Enema has been specifically prescribed for your current condition. Do not use it for other problems unless your doctor tells you to do so.

Never give your medicine to someone else.

There is limited information available about the use of ENTOCORT Enema in children.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medications you are taking, including ones you have bought without a prescription.

Drugs that may interact with ENTOCORT Enema include:

- estrogens and oral contraceptives
- ketoconazole, fluconazole, itraconazole, miconazole
- medicines used to treat HIV such as ritonavir, cobicistat
- cyclosporin
- erythromycin, troleandomycin

PROPER USE OF THIS MEDICATION

Usual adult dose:

The dosage is individual. Follow your doctor's directions carefully. They may differ from the information in this leaflet.

Before using this, or any other enema with rigid tubing, colostomy and ileostomy patients should consult with their doctor.

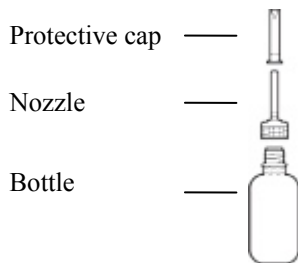
The budesonide enema should be administered in the evening before going to bed.

Note: If your medication has been changed from “cortisone” tablets (such as prednisone, prednisolone or methylprednisolone) to ENTOCORT Enema, you may temporarily experience symptoms, that may have bothered you when you first started taking “cortisone”, e.g. rash, pain in muscles and joints. If any of these symptoms bothers you, or symptoms such as headache, tiredness, nausea or vomiting occur, please contact your doctor.

Do not forget to take ENTOCORT Enema even if you start feeling better.

The budesonide enema (0.02 mg/mL) consists of a dispersible tablet (I) and solution (II).

- I. 1 dispersible tablet contains: Budesonide 2.3 mg, lactose, colour (riboflavin-5-phosphate sodium), and constituents.
- II. 1 bottle (115 mL) of solution contains: Sodium chloride, preservatives (methylparaben and propylparaben) and purified water.



How To Prepare The Enema

1. Remove the nozzle, with the protective cap on, from the bottle.



2. Take a tablet from the aluminum foil pack and put it into the bottle. **DO NOT SWALLOW THE TABLET.**



3. Put the nozzle back on the bottle and make sure that the protective cap is firmly on. Shake the bottle vigorously for at least 10 seconds or until the tablet has dissolved and a slightly yellowish liquid has been formed. The final volume is about 115 mL.



4. A plastic bag has been enclosed which you may use to protect your hand when you administer the enema.



Put your hand inside the plastic bag and grip the bottle.



5. Lie down on your left side. Shake the bottle again before removing the protective cap. Gently insert the nozzle into your rectum and empty the contents of the bottle.

6. Take the nozzle out of your rectum. After use, remove the plastic bag from your hand by pulling it over the bottle.



7. Roll over on your stomach. Stay in this position for

5 minutes.

8. Choose a suitable position to sleep in. Try to retain the enema as long as possible, preferably for the whole night.

NB: After preparation, the budesonide enema is intended for immediate use.

Missed Dose:

If you forget to take an occasional dose of ENTOCORT Enema it is not necessary to make up the missed dose. Just continue with the next dose as prescribed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Do not use ENTOCORT Enema more often or over a longer period than your doctor has prescribed. If by accident you take more ENTOCORT than prescribed on a single occasion no harmful effects should occur. If too much ENTOCORT is used over a longer period (months or more) it is possible that side effects may arise, see “Side Effects and What To Do About Them”. If you think that this may have happened to you, please discuss it with your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects that you may get while you are using ENTOCORT Enema are usually mild. However, be sure to tell your doctor if any of the following side effects bother you:

Common side effects that may occur are indigestion (e.g. gas in stomach or bowels), nausea, diarrhea, skin rash and/or itching.

Uncommon side effects that may occur are agitation and sleeplessness.

A rare side effect that may occur is skin discolouration resulting from bleeding beneath the skin.

Medicines like ENTOCORT Enema called corticosteroids can have various effects on your body. They can

- change the normal production of steroid hormones in your body.
- change the bone mineral density (thinning of the bones that can lead to osteoporosis and fractures), when used for long term.
- cause glaucoma (increased pressure in the eye that can lead to vision problems).
- reduce the function of the adrenal gland (that can lead

to decrease of hormone production).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Behavioural changes such as depression, insomnia and mood swings	√		
Uncommon	Unintentional movements or extreme restlessness possibly accompanied by muscle spasms or twitching	√		
Rare	Behavioural changes such as anxiety and aggression	√		
	Clouding of the eye’s natural lens including the back of the lens leading to blurred vision		√	
Very rare	Severe allergic reactions with symptoms such as rash, swelling of tissues, and/or difficulties in breathing.			√

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

HOW TO STORE IT

Store the tablets and the liquid at room temperature (15-30°C). Do not prepare and use ENTOCORT Enema after the expiry date marked on the outer carton.

Always keep ENTOCORT Enema, including the plastic bags, in a safe place out of sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The most current information, the Consumer Information Leaflet, plus the full Product Monograph, prepared for health professionals can be found at:

www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

or by contacting the sponsor, Tillotts Pharma GmbH, at: Customer Inquiries – 1-855-831-5420.

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