PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ENTOCORT® ENEMA

budesonide dispersible tablets

0.02 mg/mL budesonide, when reconstituted, Rectal

Glucocorticosteroid Enema (ATC code: A07EA06)

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Date of Initial Approval:
July 7, 2016

Date of Revision:
January 11, 2021

Submission Control No: 242607

RECENT MAJOR LABEL CHANGES

Not Applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ENTOCORT ENEMA (budesonide) is indicated for:
- the management of distal ulcerative colitis (rectum, sigmoid and descending colon).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

ENTOCORT ENEMA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

ENTOCORT ENEMA (budesonide) is contraindicated for the following:
- Local contraindications to the use of ENTOCORT ENEMA 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 (see WARNINGS AND PRECAUTIONS, Immune, Infections).
- Active tuberculosis.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Not Applicable.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Not Applicable.

4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

4.3 Administration

One ENTOCORT ENEMA (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.

4.4 Reconstitution

ENTOCORT ENEMA is reconstituted by adding one dispersible tablet into the enema bottle, whereafter the bottle is vigorously shaken for at least 15 seconds or until the tablet is completely dissolved. The tablet will disintegrate rapidly and the suspension will turn slightly yellowish.

4.5 Missed Dose

If a dose of ENCOCORT ENEMA is missed, patients should be instructed not to take the missed dose but to resume dosing with the next scheduled dose.

5 OVERDOSAGE

Acute overdosage with ENTOCORT ENEMA (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 ENEMA 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 ENEMA dispersible tablet has been taken orally, treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Rectal	Budesonide enema 0.02 mg/mL consists of 2 components: • Dispersible Tablet (2.3 mg) • Vehicle (115 mL)	Dispersible Tablet Colloidal silicon dioxide Lactose Lactose anhydrous Magnesium stearate Polyvidone, cross-linked Riboflavin-5-phosphate sodium Vehicle Methylparaben Propylparaben Sodium chloride Water purified

ENTOCORT ENEMA (budesonide) 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 in polyethylene bottles. Individually packaged nozzles (applicator enema) are also provided.

Each carton contains 7 dispersible tablets, 7 vehicle solutions, 7 nozzles (applicator enema), and 7 plastic bags to be used when giving the enema.

7 WARNINGS AND PRECAUTIONS

General
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.

Co-administration with CYP3A inhibitors
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, Drug-Drug Interactions).

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

Dependence/Tolerance
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.

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

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

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

Glucocorticosteroid therapy may cause hyperacidity of peptic ulcer.

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

Hepatic/Biliary/Pancreatic
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.

Immune
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.

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

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

Ophthalmologic
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.

Glucocorticosteroids may cause elevation of intraocular pressure in glaucoma patients.

7.1 Special Populations

7.1.1 Pregnant Women

Administration of ENTOCORT ENEMA (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 (see NON-CLINICAL TOXICOLOGY). 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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of ENTOCORT ENEMA in children have not been established, therefore use in this age group is not recommended.

7.1.4 Geriatrics

Not Applicable.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Not Applicable.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

No major side effects attributable to the use of ENTOCORT ENEMA (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.

8.3 Less Common Clinical Trial Adverse Reactions

Not Applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not Applicable.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not Applicable.

8.6 Post-Market Adverse Reactions

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Not Applicable.

9.2 Overview

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

9.3 Drug-Drug Interactions

Oral Contraceptives
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.

CYP3A4 Inhibitors
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 (see WARNINGS AND PRECAUTIONS, General, Co-administration with CYP3A inhibitors).

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.

9.4 Drug-Food Interactions

Not Applicable.

9.5 Drug-Herb Interactions

Not Applicable.

9.6 Drug-Laboratory Test Interactions

Not Applicable.

9.7 Drug-Lifestyle Interactions

Not Applicable.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism 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.

10.2 Pharmacodynamics

The active ingredient of ENTOCORT ENEMA, budesonide, is a potent non-halogenated synthetic glucocorticosteroid with strong topical and weak systemic effects. ENTOCORT ENEMA has a high topical anti-inflammatory potency.

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.

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.

10.3 Pharmacokinetics

Absorption: 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 ± 12%. The plasma half-life after rectal dosing is between 2

and 3 hours in adults.

After rectal dosing, the plasma half-life is almost identical to that seen after intravenous dosing. The half-life of budesonide after intravenous administration is 2-3 h in adults and shorter, 1.5 h, in children.

The pharmacokinetics of budesonide after rectal dosing are summarized in the Table 2 below (mean and S.D. are given).

Table 2. Pharmacokinetics of Budesonide After Rectal Dosing

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]

[1]Ulcerative colitis
[2]After the first dose
[3]After 4 weeks' treatment

Distribution: 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: 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, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, an isozyme of cytochrome P450.

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 anti-inflammatory 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 *vitro* studies with human liver have shown that budesonide is rapidly metabolized to more polar compounds than the parent drug. The glucocorticoid activity of two major metabolites 6β-hydroxybudesonide and 16α-hydroxyprednisolone 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.

Elimination: 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.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: budesonide

Chemical name: Budesonide is a mixture of two isomers:

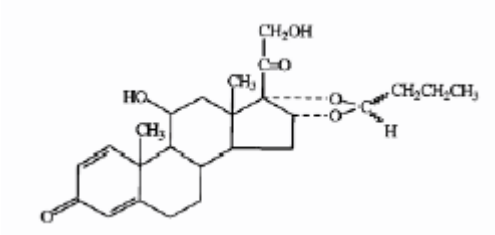
1. Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11β,16α(R)]

   And

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

Molecular formula and molecular mass: $C_{25}H_{34}O_6$
430.5

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Not applicable.

14.2 Study Results

Not applicable.

14.3 Comparative Bioavailability Studies

Not applicable.

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL 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 3 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 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 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 3. 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.

17 SUPPORTING PRODUCT MONOGRAPHS

Not Applicable.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrENTOCORT® ENEMA
budesonide dispersible tablets

Read this carefully before you start taking **ENTOCORT ENEMA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENTOCORT ENEMA**.

What is ENTOCORT ENEMA used for?
ENTOCORT ENEMA is used to treat inflammation and ulcers in the
- large intestine (colon) and
- rectum

ENTOCORT ENEMA is not for use in children under the age of 18.

How does ENTOCORT ENEMA work?
ENTOCORT ENEMA is an anti-inflammatory drug which belongs to the steroid family of drugs. ENTOCORT ENEMA has been shown to help reduce local inflammation.

ENTOCORT ENEMA acts to
- block the production of substances that cause inflammation
- restricts the processes that cause inflammation

What are the ingredients in ENTOCORT ENEMA?
Dispersible Tablets:
Medicinal ingredient: budesonide
Non-medicinal ingredients: colloidal silicon dioxide, lactose, lactose anhydrous, magnesium stearate, polyvidone, riboflavin-5-phosphate sodium

Vehicle (Solution):
Non-medicinal ingredients: methylparaben, propylparaben, sodium chloride, water purified

ENTOCORT ENEMA comes in the following dosage forms:
Dispersible Tablet 2.3 mg and Solution 115 mL.
Enema contains 0.02 mg/mL budesonide, when reconstituted (mixed).

Do not use ENTOCORT ENEMA if:
- you have the following bowel problems
  - holes in bowel
  - blockage of bowel
  - recent surgical procedure to repair bowel separation
  - twisted and /or tubular bowel sections (fistulas)
  - wounds, abscesses or infections in the bowel
- you have any infection(s) in the rest of the body
- you have tuberculosis
- you are allergic to budesonide or any of the ingredients in ENTOCORT ENEMA

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENTOCORT ENEMA. Talk about any health conditions or problems you may have, including if you:

- are taking, have recently taken or might take any of the following medicines:
  - steroid medicines
  - CYP3A inhibitor medicines. This includes antifungal agents (ketoconazole, itraconazole, fluconazole, miconazole). These medicines may increase the effects of ENTOCORT ENEMA.
  - acetylsalicylic acid (Aspirin). Speak to your doctor if you have a blood disorder that prevents your blood from clotting properly.
- are pregnant or plan to become pregnant. It is not known if ENTOCORT ENEMA can harm your unborn baby. Your doctor will decide whether giving you ENTOCORT ENEMA outweighs the potential risk to the unborn baby.
- are breastfeeding or planning to breastfeed. ENTOCORT ENEMA (budesonide) is excreted in human breast milk.
- have a condition that causes inflammation of the filters found in the kidneys
- have liver disease
- have diverticulitis (a condition that causes inflammation of certain parts of the intestines)
- have brittle bones. ENTOCORT ENEMA can cause the thinning of bones that lead to osteoporosis.
- have muscle weakness
- have thrombophlebitis (a condition that causes inflammation of a vein due to a blood clot)
- have glaucoma. ENTOCORT ENEMA may worsen your glaucoma by increasing the pressure in your eyes.
- have diabetes. ENTOCORT ENEMA may worsen your diabetes.
- have high blood pressure
- have an overactive thyroid gland
- have had mental health problems
- have ulcers in your
  - stomach
  - upper section of the small intestines
- have a heart condition such as
  - the heart's ability to pump blood is reduced
  - the blood supply to the heart becomes damaged

Other warnings you should know about:
Treatment with ENTOCORT ENEMA can increase your risk of certain side effects, including:

- **Eye problems:** ENTOCORT ENEMA can cause serious eye problems such as cataracts (cloud vision), glaucoma (increased pressure in eye) or rare diseases that cause a build-up of fluid in your eyes. Tell your doctor right away if you get blurred vision, loss of vision or other vision changes.
- **Infections**: ENTOCORT ENEMA can cause new infections that may be difficult to detect. Contact your doctor if you think you have been exposed to chicken pox or measles.

Transfer from systemic steroid drugs to ENTOCORT ENEMA:

- ENTOCORT ENEMA may cause allergies (red itchy skin, runny and congested nose) that were previously controlled when using other steroid drugs.
- Taking ENTOCORT ENEMA after using other steroid drugs may reduce the function of the hypothalamic-pituitary-adrenal glands. This can lead to a decrease in your own body's

hormone production.
- Taking ENTOCORT ENEMA after using “cortisone” tablets may cause temporary symptoms that you experienced when you first started taking “cortisone” tablets (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.

Ending treatment

You may experience certain side effects when stopping treatment. Speak to your doctor before you stop taking ENTOCORT ENEMA. You may experience the following symptoms when you suddenly stop treatment:

- pain in muscles and joints
- tiredness
- headache
- nausea
- vomiting

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ENTOCORT ENEMA:

- estrogens and oral contraceptives
- medicines used to treat fungal infections such as ketoconazole, fluconazole, itraconazole, miconazole
- medicines used to treat HIV such as ritonavir, cobicistat
- cyclosporine, used to suppress the immune system
- erythromycin, troleandomycin, used to treat bacterial infections

How to take ENTOCORT ENEMA:

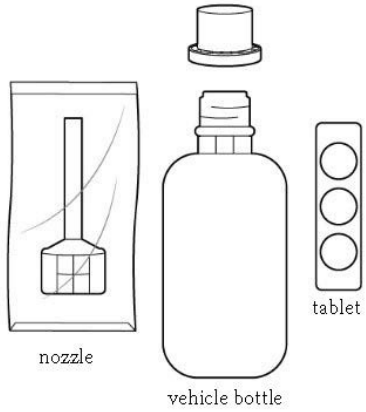
- Do not stop using ENTOCORT ENEMA even if you feel better. Your doctor will tell you when to stop taking ENTOCORT ENEMA.
- ENTOCORT ENEMA has been specifically prescribed for your current condition. Do not use it for other problems unless your doctor tells you to do so.
- Never give your medicine to someone else.
- Before using this, or any other enema with rigid tubing, colostomy and ileostomy patients should consult with their doctor.
- Follow your doctor’s directions carefully. They may differ from the information in this leaflet.
- ENTOCORT ENEMA is a ‘retention enema’. This means that the solution is meant to be held in the rectum for as long as possible. The longer it is kept there the more time it has to work and the better the results should be.

Usual Adult Dose

- Administer once a day in the evening before going to bed.
- Normally, your treatment will last for 4 weeks. Your doctor may extend the treatment to 8 weeks.

The contents of the ENTOCORT ENEMA kit include **(Figure 1)**:

Figure 1



- 7 dispersible tablets wrapped in foil, inside a small box
- 7 plastic bottles containing 115 mL solution
- 7 nozzles (applicator enema)
- 7 plastic bags to be used when giving the enema

How To Prepare ENTOCORT ENEMA for use

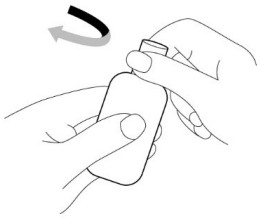
1. Unscrew the cap of one of the plastic bottles.

2. Take **one** of the dispersible tablets from its foil strip. Drop the dispersible tablet into **one** bottle as shown below **(Figure 2)**.

Figure 2

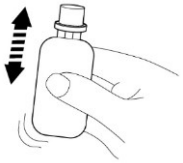
3. Place the cap back onto the bottle. Screw the cap tightly by turning the cap clockwise as shown below (**Figure 3**).

Figure 3



4. Shake the bottle well for at least 15 seconds as shown below (**Figure 4**), or until you cannot see the tablet in the solution any more. Solution should turn slightly yellowish.

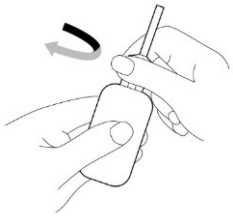
Figure 4



5. Unscrew the cap and remove the cap from the bottle.

6. Unpack **one** nozzle from the pouch labelled 'Applicator Enema'. Screw the nozzle on the bottle tightly by turning the nozzle clockwise as shown below (**Figure 5**).

Figure 5



7. The enema is now ready and should be used immediately.

Inserting the enema into your rectum

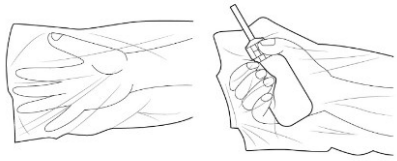
Important Information:
- The nozzle can be lubricated with petroleum jelly if use is uncomfortable.
- You will find it more comfortable to use ENTOCORT ENEMA if you empty your bowels and bladder before using it.
- ENTOCORT ENEMA can stain your bedding. It is best to protect your bedding with a plastic sheet in case any of the solution is spilled.

To insert the enema into your rectum, follow the instructions below:

1. Undress from the waist down, then lie down on your side. Choose whichever side is most comfortable. Try to lie down so that your bottom is slightly higher than the rest of your body. For example, you can raise the bottom of the bed onto blocks or place one or two pillows under your bottom. This will help to keep the solution in your rectum.

2. If you wish, hold the bottle using one of the plastic bags as shown below (**Figure 6**). This use of the plastic bag is optional.

Figure 6



3. Shake the bottle again.

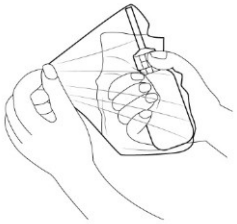
4. Gently ease the nozzle into your rectum as far as is comfortable.

5. Squeeze the bottle, this will push most of the solution into your rectum. However, you will not be able to empty the whole bottle. It has been designed to keep some solution after being used.

6. Then remove the nozzle from your rectum.

7. If you used a plastic bag, remove it from your hand by pulling it forward over the bottle. This will leave the bottle inside the bag, ready to be disposed of as shown below (**Figure 7**).

Figure 7



8. Roll over onto your stomach. Stay like this for 5 minutes to stop any solution coming out of your rectum.

9. Find a comfortable position to sleep in that helps you to keep the solution in your rectum for as long as possible. The longer it is kept there the more time it has to work and the better the results should be.

Overdose:
Do not use ENTOCORT ENEMA more often or over a longer period than your doctor has prescribed. If by accident you take more ENTOCORT ENEMA than prescribed on a single occasion no harmful effects should occur. If too much ENTOCORT ENEMA is used over a longer period (months or more) it is possible that side effects may arise, see “Serious side effects and what to do about them”. If you think that this may have happened to you, contact your doctor immediately.

If you think you have taken too much ENTOCORT ENEMA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose of ENTOCORT ENEMA, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using ENTOCORT ENEMA?
These are not all the possible side effects you may have when taking ENTOCORT ENEMA. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of ENTOCORT ENEMA are:

- upset stomach or gut
    - gas in stomach or bowels
    - nausea
    - diarrhea

Other possible side effects of ENTOCORT ENEMA are:

- agitation
- insomnia or sleepiness
- skin discolouration
    - rash
    - red spots which burn, itch or sting

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Behavioural changes** such as depression, anxiety, mood swings and feelings of unease	**X**		
UNCOMMON **Unintentional movements or extreme restlessness** possibly accompanied by muscle spasms or twitching	**X**		
Clouding of the eye's natural lens including the back of the lens leading to blurred vision		**X**	
VERY RARE **Severe allergic reactions** with symptoms such as rash, swelling of tissues, and/or difficulties in breathing			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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.

Storage:
Store the tablets and the solution 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.

If you want more information about ENTOCORT ENEMA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by calling 1-855-831-5420.

This leaflet was prepared by Tillotts Pharma GmbH, Warmbacher Strasse 80, 79618 Rheinfelden, Germany.

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Last Revised: January 11, 2021