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ENTOCORT 2 mg Enema
ASTRAZENECA

budesonide
Tablet and solution for rectal suspension

Composition
Budesonide 2 mg.
The total quantity of budesonide in a dose of prepared rectal suspension (115 ml) is 2.3 mg. On administration of the rectal suspension, a residual volume remains in the pack. This means that the administered dose of budesonide is approximately 2 mg.

Pharmaceutical form
Tablet and solution for rectal suspension.

Entocort rectal suspension consists of two parts: a dispersible tablet, containing micronised budesonide, and an isotonic solution. The rectal suspension is prepared before use.

The tablet is round, faintly yellow, marked BAI on one side and 2.3 on the other. The solution is clear and colourless.

Therapeutic indication
Ulcerative colitis, proctitis.

Posology and method of administration
Adults: 1 dose of prepared rectal suspension containing 2 mg is applied into the rectum every evening for approximately 4 weeks. Full effect is usually achieved within 2-4 weeks. The treatment may be extended to 8 weeks if required.

For administration, the patient should lie on the left side, and then on the stomach for 5 minutes. The rectal suspension should be retained for as long as possible, preferably overnight.

Elderly: Dosage as for adults.

Children: At present, there is no experience of treatment with Entocort rectal suspension in children.

Patients with liver disease: Impaired liver function increases the systemic availability of budesonide.

Contraindications
Bacterial, fungal or viral infections. Hypersensitivity to budesonide or any other ingredient in the product.

Special warning and precautions for use
Special caution is required in the treatment of patients who are changed over from oral steroids, as disturbances of the endogenous cortisol balance (HPA-axis) may be expected. In these patients the dosage of systemic steroid should be cautiously reduced. A value on the hypothalamus-pituitary-adrenocortical function could be of use for the change-over.

Some patients feel generally unwell during the withdrawal phase, with e.g. muscle and joint pain. An inadequate general steroid effect must be suspected if symptoms such as fatigue, headache, nausea and vomiting occur. In these cases a temporary increase in the oral dose of glucocorticosteroids is sometimes necessary.

When Entocort rectal suspension replaces a systemic steroid treatment, this sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic treatment. These allergies should be controlled symptomatically with an antihistamine and/or with local treatment.

In vivo studies have shown that oral administration of ketoconazole (a known inhibitor of CYP3A activity in the liver and in the intestinal mucosa) caused a severalfold increase of the systemic exposure to oral budesonide. Therefore, it cannot be excluded that also concomitant administration of Entocort rectal suspension and ketoconazole may result in increased systemic availability of budesonide. See also Interactions.

If Entocort is used chronically in excessive doses, characteristic systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear. If this occur, the dosing of Entocort should be withdrawn gradually in the same way as after long-term use of oral glucocorticosteroids. The dosage form - rectal suspension - and the route of administration make any prolonged overdosage of Entocort rectal suspension unlikely.

Interaction
The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome 450. Inhibition of this enzyme by e.g. ketoconazole can therefore increase the systemic exposure to budesonide, see Special warning and precautions for use.

Elevated plasma levels and enhanced effects of corticosteroids have been reported in women also receiving oestrogens and contraceptive steroids, but no effects on the plasma concentrations of budesonide were observed at concomitant intake of low-dose combination oral contraceptives.

In recommended doses, cimetidine has a slight but clinically insignificant effect, and omeprazole no effect, on the pharmacokinetics of orally administered budesonide.

Pregnancy and lactation
Pregnancy
Clinical experience from pregnant women is limited. In animal studies corticosteroids have been shown to cause malformations of various types (cleft palate, skeletal malformations). However, these experimental animal results are not thought to have any relevance for humans.

Until further experience is available, Entocort should not be given during pregnancy except after special consideration.

Lactation
It is not known whether budesonide passes into breast milk.

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

Undesirable effects
In clinical trials side effects occurred in approximately 20% of the treated patients.

Common (>1/100):	GI:	Flatulence, diarrhoea, nausea.
	Skin:	Urticaria, rash.
Less common:	Psych.:	Agitation, insomnia.
Rare (<1/1000):	Psych.:	Anxiety.

In rare cases, signs and/or symptoms of systemic glucocorticosteroid effects, including adrenal hypofunction, may occur on rectal administration of glucocorticosteroids. Whether or not these effects occur is probably depending on dose, treatment time, concomitant use of other glucocorticosteroids, previous use of glucocorticosteroids, and individual sensitivity.

Overdose
Acute overdose, even with high doses, is not expected to be a clinical problem.

Pharmacodynamic properties
ATC-code: A07E A06 Glucocorticosteroids for local treatment.

Administered rectally, budesonide has a local anti-inflammatory effect on the intestinal mucous membrane.

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

In the recommended doses, Entocort rectal suspension can in rare cases cause clinically significant changes in basal plasma cortisol levels or in the response to ACTH stimulation.

The effects on morning plasma cortisol and adrenal function are significantly less than with a 25 mg prednisolone enema daily.

Pharmacokinetic properties
Absorption
The systemic availability after oral administration of budesonide is approximately 10%. After rectal administration of Entocort rectal suspension to healthy volunteers the systemic availability is approximately 15% (3-50%). As can be expected for drugs with high first pass metabolism given rectally, the variability is larger than after oral dosing. This is due to individual differences in rectal venous drainage leading to hepatic by-pass. After rectal administration, absorption of budesonide is rapid and essentially terminated within 3 hours.

Distribution
Budesonide has a volume of distribution of approximately 3 litres/kg. Plasma protein binding averages 85-90%. Mean maximal plasma concentration after

rectal administration of 2 mg budesonide is 2-3 nanomol/litre (range 1-9 nanomol/litre), reached within 1.5 hours.

Biotransformation
Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites (6-beta-hydroxy-budesonide and 16-alpha-hydroxyprednisolone) is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome 450.

Elimination
The metabolites are excreted unchanged or in conjugated form, mainly via the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 litres/minute), and the plasma half-life after i.v. dosing averages 2-3 hours.

The kinetics of budesonide are linear with dose (as evidenced by dose-proportional increases of Cmax and AUC after oral dosing of 3.9 and 15 mg budesonide given as Entocort capsules).

List of excipients
1 tablet for rectal suspension contains:

Lactose anhydrous 263 mg, lactose monohydrate 1.3 mg, riboflavine sodium phosphate (E 101), crospovidone, colloidal silica, magnesium stearate

1 ml solution for rectal suspension contains:
Sodium chloride 9 mg, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), water, purified

Special precautions for storage
Do not store above 30°C.

Shelf Life
Please see outer pack.

Pack Size
Please see outer pack

Instructions for use and handling
Entocort 2 mg
Tablet and solution for rectal suspension
Budesonide

How to use Entocort
Entocort should be administered in the evening before going to bed.

Entocort sectal suspension consists of two components - a tablet and a liquid.

The tablet must be dissolved in 1 bottle of liquid before use.

Read the following information before you use Entocort.

Follow the instructions carefully.

How to prepare Entocort
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.
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.

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

4. Lie down on your left side. Shake the bottle again before removing the protective cap.

Empty the contents into the rectum.

5. Roll over on your stomach. Stay in this position for 5 minutes.
6. Choose a suitable position to sleep in. Try to retain the enema as long as possible, preferably the whole night.

Note: The prepared rectal suspension must be used immediately.

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