

PRODUCT MONOGRAPH

 **ENTOCORT[®]**

(budesonide)

Controlled Ileal Release Capsules 3 mg

Glucocorticosteroid for the Treatment of
Crohn's Disease Affecting the Ileum and/or Ascending Colon

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr ENTOCORT®

(budesonide)

Controlled Ileal Release Capsules 3 mg

THERAPEUTIC CLASSIFICATION

Glucocorticosteroid for the Treatment of
Crohn's Disease Affecting the Ileum and/or Ascending Colon

ACTIONS AND CLINICAL PHARMACOLOGY

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

The exact mechanism of action of glucocorticosteroids in the treatment of Crohn's disease is not fully understood. Anti-inflammatory actions, such as the inhibition of inflammatory mediator release and inhibition of immunological cellular responses, are probably important.

Data from clinical pharmacology studies and controlled clinical trials indicate that ENTOCORT capsules, at least partly, act topically. Budesonide 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 CYP 3A4, 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 by the liver with a short half-life. A glucocorticosteroid with such a profile is of particular importance for the local treatment of inflammatory bowel diseases such as Crohn's disease. With regard to treatment of this disease 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.

INDICATIONS AND CLINICAL USE

ENTOCORT (budesonide) capsules are indicated for:

- the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and
- the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

CONTRAINDICATIONS

ENTOCORT (budesonide) capsules are contraindicated for the following:

- Systemic or local bacterial, fungal or viral infections.
- Known hypersensitivity to any of the ingredients.
- Active tuberculosis.

WARNINGS

Glucocorticosteroids can reduce the response of the HPA-axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a conventional glucocorticosteroid is recommended.

Special care is demanded in treatment of patients transferred from conventional systemic steroids to ENTOCORT (budesonide) capsules as disturbances in the HPA-axis could be expected in these patients.

PRECAUTIONS

Glucocorticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during glucocorticosteroid therapy. Viral infections such as chicken pox and measles can have a more serious or fatal course in patients on immunosuppressant glucocorticosteroids. 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.

Although treatment with ENTOCORT (budesonide) capsules causes significantly less lowering of plasma cortisol compared to conventional glucocorticosteroids, the knowledge with regard to treatment during the following conditions is limited and therefore cautioned: active peptic ulcer, osteoporosis, acute glomerulonephritis, myasthenia gravis, exanthematous diseases, diverticulitis, thrombophlebitis, psychic disturbances, diabetes (or family history of diabetes), cataracts and glaucoma (or family history of glaucoma) which may cause elevation of intraocular pressure, hypertension, hyperthyroidism, acute coronary disease, limited cardiac

reserve and pregnancy. In such cases the benefits of an oral glucocorticosteroid must be weighed against the risks.

With the recommended therapeutic doses of budesonide, the risk/benefit ratio seems to be low for the long-term systemic effects. However, as with any other glucocorticosteroid, patients should be carefully followed up for systemic adverse effects. During long-term therapy, adrenal function and haematological status should be periodically assessed.

Particular care is needed in patients who are transferred from systemic glucocorticosteroid treatment with higher systemic effect to ENTOCORT capsules. When ENTOCORT is used to replace prednisolone in steroid dependent patients, the daily dose should not exceed 6 mg. When treatment with ENTOCORT capsules is initiated, the prednisolone dose should be tapered, as these patients may experience adrenal cortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients. Some patients feel unwell in a non-specific way during the withdrawal phase, e.g., pain in muscles and joints. Sometimes, this can also unmask allergies e.g. rhinitis and eczema, which were previously controlled by the systemic drug. 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.

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

Glucocorticosteroids should be used with caution in patients if there is a probability of bowel perforation as well as the probability of obstruction, abscess or other pyogenic infection and fresh intestinal anastomoses. Aggravation of diabetes mellitus or stimulation of manifestations of latent diabetes mellitus may be caused by glucocorticosteroid therapy.

There may be an enhanced systemic effect of budesonide in patients with liver cirrhosis since the metabolism of budesonide may be impaired 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 in the intestinal mucosa, see Interactions - Ketoconazole) caused a four to seven fold increase of the systemic exposure to oral budesonide. If treatment with ketoconazole (and possibly other azoles such as fluconazole, itraconazole or miconazole) together with budesonide is indicated, reduction of the budesonide dose should be considered if side effects typical of systemic glucocorticosteroids occur.

After extensive intake of grapefruit juice (observed in male subjects taking in 600 mL of concentrated grapefruit juice per day for 4 days), the systemic exposure for oral budesonide increased approximately 2-fold. Grapefruit juice inhibits CYP3A activity predominantly in the intestinal mucosa. As with other drugs primarily being metabolized through CYP3A, regular ingestion of grapefruit or its juice, should be avoided in connection with budesonide administration (other juices such as orange juice or apple juice do not inhibit CYP3A). See Interactions - Grapefruit Juice.

Glucocorticosteroid therapy may cause hyperacidity of peptic ulcer.

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

Usage During Pregnancy

Administration of ENTOCORT capsules 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 glucocorticosteroids 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 capsules 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 capsules 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 possibly other azoles such as fluconazole, itraconazole or miconazole), cyclosporin, troleandomycin, erythromycin or grapefruit juice 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.

Ketoconazole

Ketoconazole, a potent inhibitor of cytochrome P 450 3A, the main metabolic enzyme for corticosteroids, increases plasma levels of orally ingested budesonide.

Omeprazole

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

ADVERSE REACTIONS

In clinical trials, most adverse events experienced by patients or healthy volunteers receiving ENTOCORT (budesonide) capsules were of mild to moderate intensity and were classified as non-serious. A total of 577 patients with Crohn's disease were treated with ENTOCORT capsules for induction and maintenance of remission, in controlled clinical trials.

Adverse events reported in patients during induction of remission (n=399) with ENTOCORT capsules included dyspepsia (9%), muscle cramps (4%), palpitations (2%), blurred vision (3%), skin reactions including rash and urticaria (6%), and menstrual disorders (2%).

A similar adverse event profile was reported in patients during 3 long term (up to 12 months) maintenance treatment studies (n=178) with ENTOCORT capsules. The nature and incidence of adverse events was generally the same or less than observed during treatment for induction of remission.

Other side effects that have been reported include hypokalemia, tremor and behavioural changes such as nervousness, insomnia, and mood swings.

Side effects typical of systemic glucocorticosteroids (such as Cushingoid features and reduced growth velocity) may occur. The systemic effects of budesonide on the HPA-axis were found to be dose-dependent.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Reports of acute toxicity and/or death following overdosage with glucocorticosteroids are rare. Thus, acute overdosage with ENTOCORT (budesonide) capsules, even in excessive doses, is not expected to be a clinical problem. In the event of acute overdosage, no specific antidote is available. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

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 HPA-suppression. Decreasing the dose or stopping the therapy, with the accepted procedures for discontinuing prolonged oral therapy with systemic steroids, 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 conventional systemic steroids.

DOSAGE AND ADMINISTRATION

Active Disease

The recommended daily dose for induction of remission is 9 mg, administered once daily in the morning, for up to 8 weeks. The dose should be taken before meals. Full effect is usually achieved within 2 - 4 weeks.

Maintenance of Remission

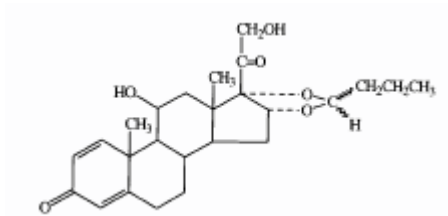
Following an 8 week course of treatment for the active disease and once the patient's symptoms are controlled (CDAI <150), ENTOCORT 6 mg is recommended, administered daily in the morning before breakfast, for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months, an attempt to taper to complete cessation is recommended. The rate of tapering should be patient-specific and the patient should be monitored by the treating physician during this period. Continued treatment with ENTOCORT 6 mg for more than 3 months has not been shown to provide substantial clinical benefit.

The capsules should be swallowed whole with water, and not chewed, broken or crushed before being swallowed.

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-butyldienebis(oxy)-11,21-dihydroxy-, [11 β ,16 α (R)]

and

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

Molecular Formula: C₂₅H₃₄O₆

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

Active: budesonide, micronized 3 mg/capsule

Non-medicinal: Ethylcellulose
Acetyltributyl citrate
Methacrylic acid copolymer
Triethylcitrate
Dimethicone
Polysorbate 80
Talc
Sugar Spheres (sucrose and maize starch)
Gelatin
Sodium lauryl sulphate
Titanium dioxide
Iron oxide

Stability and Storage Recommendations

The capsules are provided in a high density polyethylene bottle, with a polypropylene screw cap. A desiccant canister is included in the bottle. The capsules should be dispensed and stored in the original container.

The patient should be advised to keep the bottle tightly capped.

Store at controlled room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

ENTOCORT 3 mg capsules are two-piece hard gelatin capsules with an opaque light grey body and an opaque pink cap. The cap has ^{CIR}3 mg in black radial print.

The capsules are provided in a high density polyethylene bottle of 100's.

INFORMATION TO THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

 ENTOCORT[®] Capsules

(budesonide)

Read this leaflet carefully. It has been prepared by the makers of ENTOCORT Capsules to help you get the most benefit from this medicine. It contains general points about ENTOCORT Capsules and should add to more specific advice from your doctor or pharmacist.

This Leaflet Should Not Replace Your Doctor's or Pharmacist's Advice. Because of your health condition, they may have given you different instructions. If so, be sure to follow their advice. Also, if you have any questions or concerns after reading this leaflet, talk to your doctor or pharmacist.

WHAT IS ENTOCORT?

ENTOCORT is a brand name for a drug called budesonide. It is an anti-inflammatory drug which belongs to the steroid family of drugs.

WHAT IS IN ENTOCORT CAPSULES?

ENTOCORT Capsules are filled with a large number of small grains and contain 3 mg of the medicine budesonide. When swallowed, the medicine passes through the stomach intact, and is gradually released in the small bowel.

Most medicines contain more than just the active drug. These are needed to keep medicines in a form you can use. Check with your doctor if you think you might be allergic to any of these items: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer, triethylcitrate, dimethicone, polysorbate 80, talc, sugar spheres (sucrose and maize starch), gelatin, sodium lauryl sulphate, titanium dioxide and iron oxide.

HOW DO ENTOCORT CAPSULES WORK?

ENTOCORT Capsules are used in the treatment of Crohn's disease in the small bowel and/or in the first part of the large bowel.

Crohn's disease is an inflammatory bowel disease, which causes symptoms such as stomach pain, diarrhoea and fever. ENTOCORT capsules reduce the inflammation and improve the symptoms.

WHAT SHOULD I DO BEFORE STARTING ENTOCORT CAPSULES?

Be sure you've told your doctor:

- about **all** health problems you have now or have had in the past, especially tuberculosis and any other recent infection, liver disease, brittle bones (osteoporosis), stomach ulcer, high blood pressure, cataracts or any other eye diseases, diabetes or a family history of diabetes or glaucoma;
- about **all** other medicines you take, particularly if you take medicines against fungal infections, including ones you can buy without a prescription;
- about **any** operation you are about to have or plan to have;
- regular ingestion of grapefruit or its juice should be avoided during treatment with ENTOCORT capsules, since intake of grapefruit can increase the amount of budesonide that is absorbed from the gut (other fruits such as orange or apple do not influence the uptake of budesonide);
- if you take, or have taken steroid medicines within the past several months;
- if you are pregnant, plan to become pregnant or are breastfeeding;
- if you have ever had an allergic, bad or unusual reaction to ENTOCORT Capsules or the medicine budesonide;
- if you are allergic to “non-medicinal” substances like food products, preservatives, or dyes, which may be present in ENTOCORT Capsules (See ‘What is in ENTOCORT Capsules’).

HOW DO I TAKE ENTOCORT CAPSULES PROPERLY?

Take all doses of ENTOCORT Capsules, as recommended by your doctor, even if you feel better. The full effect of ENTOCORT Capsules is usually achieved within 2-4 weeks. Do not miss doses, or take extra doses, unless your doctor tells you. If you miss a dose, just take the next dose on time. Never take a double dose of ENTOCORT capsules to make up for missed doses.

Tell your doctor if you get an infection. Avoid exposure to chicken pox and measles.

ENTOCORT Capsules should be swallowed whole with water. The capsules must not be broken or chewed. ENTOCORT Capsules should be taken before meals.

Acute Treatment

The usual dose for treatment of acute symptoms is 9 mg per day, for up to 8 weeks. The dose can be given once daily as three 3 mg capsules in the morning.

Long Term Treatment

The usual starting dose for long-term treatment is 6 mg per day. Take two 3 mg capsules in the morning, before breakfast. Your doctor may want to change the dose, depending on the activity of your disease.

Continue taking ENTOCORT Capsules until your doctor tells you to stop. Your doctor may want to slowly reduce the dose.

Note: If your medication has been changed from “cortisone” tablets (such as prednisone, prednisolone or methylprednisolone) to ENTOCORT capsules 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.

Overdose

Telephone your doctor, regional poison control centre or go to your nearest hospital immediately if you think that you or anyone else may have taken too many ENTOCORT Capsules even if there are no signs of discomfort or poisoning.

ARE THERE ANY SIDE EFFECTS?

ENTOCORT Capsules, like any medication, may cause side effects in some people. These may not be caused by ENTOCORT Capsules in your case, but only a doctor can assess this.

Side effects that do occur are usually mild to moderate. However, be sure to tell your doctor if any of the following side effects bother you: swelling of the face; indigestion; menstrual problems; behavioural changes such as insomnia, mood swings and nervousness; muscle cramps; trembling; rapid or irregular heart beats; blurred vision, itching and skin rash. Allergic reactions with symptoms such as rash, swelling of tissues, and difficulty in breathing may also occur, as well as low potassium levels in the blood.

Other unwanted effects which cannot be predicted may occur in rare cases. If you have any bothersome or unusual effects while using ENTOCORT Capsules, check with your doctor or pharmacist right away.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them.

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

WHERE SHOULD I KEEP ENTOCORT CAPSULES?

Remember to **keep ENTOCORT Capsules well out of the reach of children.**

ENTOCORT Capsules come in a container with a drying agent. Always keep ENTOCORT Capsules in the container. If you don't, moisture from the air may damage the capsules.

Store ENTOCORT Capsules at room temperature (15-30°C) and in a dry place. Do not keep them in the bathroom medicine cabinet or other warm, moist places.

Do not use ENTOCORT Capsules after the expiry date marked on the package.

Note:

This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using ENTOCORT Capsules.

This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing. Please refer to the Consumer Information Leaflet located at www.astrazeneca.ca, to see if more up-to-date information has been posted.

Customer Inquiries: 1 800 668-6000

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Mississauga, Ontario
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CLINICAL TRIALS

Treatment of Active Disease

The safety and efficacy of ENTOCORT (budesonide) capsules were evaluated in 611 patients (n=399 treated with ENTOCORT, n=66 given placebo and n=146 treated with prednisolone) with mild to moderate active Crohn's disease of the ileum and/or ascending colon in 3 randomized, double-blind multicentre studies with a parallel group design. The study patients ranged in age from 17 to 85 (mean 36) years, 39% were male and 99.5% were Caucasian. The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining efficacy in these studies. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal mass, body weight and hematocrit). Clinical improvement, defined as a CDAI score of ≤ 150 assessed after 8 weeks of treatment, was the primary efficacy variable in these comparative efficacy studies of ENTOCORT capsules (P values below 5% were considered significant). Safety assessments in these studies included monitoring of adverse experiences. A checklist of potential symptoms of hypercorticism was used.

Study One (Table 1) involved 258 patients and tested the safety and efficacy of graded doses of ENTOCORT capsules (1.5 mg b.i.d., 4.5 mg b.i.d. or 7.5 b.i.d.) versus placebo. The 3 mg per day dose level (data not shown in Table 1) could not be differentiated from placebo (P = 0.13). The remission rates (CDAI ≤ 150) in the 9 mg arm were found to be significantly higher than those in the placebo group subsequent to the completion of an 8 week treatment period (51% versus 20%, P = 0.0004). There was no additional benefit seen when the daily ENTOCORT dose was increased from 9 mg to 15 mg per day (P = 0.34, data not shown in Table 1). The median CDAI score after Week 8 of treatment decreased in the 9 mg arm by 121 points relative to baseline (median CDAI score at baseline was 290) in comparison to a decrease of 21 points in the placebo group.

Studies 2 and 3 (Table 1) compared ENTOCORT capsules (4.5 mg b.i.d. and/or 9 mg o.m.) with oral prednisolone (initial dose of 40 mg, given once daily). At baseline, the median CDAI score was 277 in both studies. Results presented for Study 2 and Study 3 correspond to data collected subsequent to an 8 week treatment period. In Study 2, 13% fewer patients in the ENTOCORT 9 mg o.m. group experienced clinical improvement than in the prednisolone group (no statistical difference, P = 0.12). Equal clinical improvement rates (60%) were seen in the ENTOCORT 9 mg o.m. and the prednisolone groups in Study 3 (no statistical difference, P = 0.062). The decrease in median CDAI score seen in Study 3 between the ENTOCORT 9 mg o.m. and prednisolone groups was 141 and 149 points, respectively.

The proportion of patients with normal plasma cortisol values (≥ 150 nmol/L) was significantly higher in the ENTOCORT groups in both Studies 2 and 3 (59% - 66%) than in the prednisolone groups (24%).

Table 1 Clinical Improvement Rates (CDAI ≤150) After 8 weeks of Treatment

Clinical Study	ENTOCORT 9 mg (o.m.)	ENTOCORT 4.5 mg (b.i.d.)	Placebo	Prednisolone (o.m.)
1		31/61 (51%)	13/64 (20%)	
2	45/86 (52%)			56/85 (65%)
3	35/58 (60%)	25/60 (42%)		35/58 (60%)

Note: o.m. - dose administered once daily in morning, b.i.d. - dose administered twice daily.

Maintenance of Clinical Remission

The efficacy and safety of ENTOCORT capsules for maintenance of clinical remission were evaluated in 3 double-blind, placebo-controlled, multicentre 12-month trials in which 270 patients were randomized and treated once daily with 3 mg or 6 mg ENTOCORT or placebo (n=178 treated with ENTOCORT). Patients ranged in age from 18 to 71 (mean 36) years. Forty one percent of the patients were male and 99.6% were Caucasian. The mean CDAI at entry was 98. In 2 of the 3 clinical studies conducted, 80% (156/195) of the patients enrolled had exclusively ileal disease (disease location was not recorded in the third study). Colonoscopy was not performed following treatment. ENTOCORT 6 mg/day prolonged the time to relapse, defined as an increase in CDAI of at least 60 units to a total score >150 or withdrawal due to disease deterioration. The median time to relapse in the pooled population of the 3 studies was 154 days for patients taking placebo and 263 days for patients taking ENTOCORT 6 mg/day (P = 0.011). ENTOCORT 6 mg/day reduced the proportion of patients with loss of symptom control relative to placebo in the pooled population for the 3 studies at 3 months (26% vs. 45% for placebo).

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 3A) which is responsible for the metabolism of budesonide in these organs.

Human Pharmacology

Pharmacodynamics

Mode of Action

The pathogenesis of Inflammatory Bowel Disease in general, and of Crohn's Disease (CD) in particular is not known. However, inflammatory immune responses are probably prominent features. Glucocorticosteroid drugs have the potential to interact with many aspects of this response, as they have a wide range of inhibitory activities against multiple cell types and mediators. Of importance in CD is probably the blocking of inflammatory cell influx, the inhibition of inflammatory mediator release by blockage of the arachidonic acid pathway, and the blocking of cytokine-mediated immune events. The intrinsic potency of budesonide, measured as the affinity to the glucocorticoid receptor, is about 15 times higher than that of prednisolone. Clinical pharmacology and clinical data strongly indicate that budesonide capsules, at least partly, act topically. Patients with inflammatory bowel disease have been found to have a reduced bone mineral density (BMD). A two year multi-centre, open, randomized trial in 272 patients was conducted to compare the influence of treatment with budesonide capsules or prednisolone on BMD in subject's with Crohn's disease affecting the ileum and/or the ascending colon. Statistically significantly less BMD of the lumbar spine was discovered with budesonide (0.011g/cm²) than prednisolone (0.04g/cm²) in steroid-naïve patients. Treatment with budesonide (as needed up to 9 mg/day) or prednisolone (as needed up to 40 mg/day) in this study were both found to be safe and generally well tolerated. However, subjects treated with budesonide experienced significantly less glucocorticosteroid side effects than subjects treated with prednisolone.

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. Treatment with budesonide capsules in daily doses of 3 to 15 mg for 8 weeks, and 3 to 6 mg for up to 1 year, affect circulating cells and systemic inflammatory markers (C-reactive protein and orosomucoid) to a very small extent.

Pharmacokinetics

Absorption and Distribution

The site of uptake of controlled ileal release budesonide has been studied in healthy subjects and in patients with Crohn's disease using inert ¹¹¹In-labelled pellets as markers of intestinal transit. These studies indicate that budesonide is continuously released during passage through the small intestines and ascending colon. In one study in 8 healthy subjects, 68% and 69% of totally absorbed budesonide was absorbed in the ileum and ascending colon in a fasting and fed state, respectively. In another study in 6 healthy subjects, the absorption values immediately before and after breakfast were 58% and 52%, respectively. In a study in 6 patients with Crohn's disease, 42% of budesonide, following administration after breakfast, was absorbed in the ileum and ascending colon. The lower mean value in patients as compared to healthy subjects may be explained by two patients, where the residence time in

the ileum and the ascending colon was extremely short (1.6 h) as compared to an average of 13.8 h and 17.3 h in the rest of the patients and healthy volunteers, respectively.

The volume of distribution of budesonide in healthy subjects (range 2.2 to 3.9 L/kg), and in patients with CD (range 1.6 to 3.2 L/kg), is large and the plasma protein binding (85-90%) is extensive compared with other synthetic glucocorticosteroids. 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. Following oral dosing of budesonide capsules 9 mg, mean maximal plasma concentration is approximately 5-10 nmol/L, attained at 3-5 hours.

Metabolism and Excretion

The half-life of budesonide after intravenous administration is 1.9-3.6 h in adults and shorter, 1.5 h, in children. In patients with CD, the plasma half-life after intravenous dosing is 2.4 h (range 2.1 to 2.8 h). After oral dosing with budesonide capsules, the mean terminal half-life for budesonide ranges between 3.0 and 5.1 h, with no discernible difference between patients and healthy subjects. Elimination of budesonide given as budesonide capsules is rate limited by its absorption, and the terminal half-life averages 4 hours.

The systemic clearance of budesonide (0.9-1.4 L/min) is high compared with other glucocorticosteroids. After oral dosing of budesonide capsules, the systemic availability in healthy subjects is approximately 10%, which is similar to oral dosing of plain micronized budesonide (6-13%) indicating complete absorption. After a single dose of budesonide capsules in patients with active CD, the systemic availability ranges from 12-20%. In healthy subjects the corresponding figures are 9-12%.

In human volunteers who inhaled tritiated budesonide, $31.8 \pm 7.5\%$ of the discharged radioactivity was recovered in the urine (within 96 hours of administration) while during the same period, $15.1 \pm 4.3\%$ of the radioactivity could be recovered in the faeces. In those subjects who took the compound orally, $45.0 \pm 5.0\%$ was recovered in the urine, $29.6 \pm 2.5\%$ 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. The toxicity of budesonide capsules, with a focus on the

gastrointestinal tract, has been studied in Cynomolgus monkeys after repeated oral administration.

Acute Toxicity

The acute toxicity studies with budesonide after oral and subcutaneous administration are summarized in Table 2.

Table 2 Acute Toxicity Of Budesonide In Mice And Rats.

Species	Sex	Route	LD50 (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 plain budesonide, as well as the toxicity of budesonide capsules after once daily oral administration of doses up to 5000 µg/kg/day, for 4 to 26 weeks to monkeys.

Table 3 Toxicity After Repeated Administration Of Budesonide To Rats, Rabbits, Dogs And Monkeys.

Animal		No. And Sex per Group	No. of Dose Groups	Budesonide Formulation	Daily Dose Levels		Route of Administration	Duration	Toxic Effects
Species	Strain				mg/kg	mg/animal			
Rat	Sprague-Dawley	6 males 6 females	4	plain	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	plain	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	plain	0.005 0.01 0.05		inhalation	12 months	As above.
Rabbit	New Zealand White	3 males 3 females	2	plain		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	plain	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	plain	0.02 0.06 0.2		inhalation	6 weeks	High dose - induced thymal atrophy, adrenal atrophy. No changes in respiratory system observed.

Species	Animal Strain	No. And Sex per Group	No. of Dose Groups	Budesonide Formulation	Daily Dose Levels		Route of Administration	Duration	Toxic Effects
					mg/kg	mg/animal			
Dog	Beagle	5 males 5 females	3	plain	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	plain	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.
Monkey	Cynomolgus	2 males 2 females	4	CIR capsules	0 0.1 0.33 1.0		p.o.	4 weeks	No toxic effects attributable to treatment were observed.
Monkey	Cynomolgus	4 males 4 females	4	CIR capsules	0 0.5 2.0 5.0		p.o.	26 weeks	Medium/high dose - body weight change, slightly reduced cortisol levels. High dose - slightly higher liver and lower adrenal weight, elevated glucose levels in females, elevated plasma protein and reduced cellularity in males.
All effects observed were consistent with those expected during prolonged glucocorticosteroid exposure.								CIR - Controlled Ileal Release	

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.

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 administration of the drug.

Oral administration of budesonide to rats for 1 month disclosed no adverse effects on the gastrointestinal tract at doses up to 500 µg/kg although at 500 µg/kg atrophy of spleen and adrenals were noted as well as fat deposition in the liver, effects typical of a glucocorticoid. 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 a 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.

In a 12-month inhalation study (mainly oral/gastrointestinal deposition and absorption) in rats, histological examination disclosed the absence of bile duct hyperplasia of the liver at 50 µg/kg (high dose). This is a glucocorticoid effect since bile duct hyperplasia is 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 a slight liver enlargement with increased glycogen deposition at 100 µg/kg. No adverse effects were noted on the gastrointestinal tract. A 12-month oral inhalation study in dogs (doses between 20-200 µg/kg) disclosed increased liver weight and glycogen deposition at 200 µg/kg. There were no adverse effects on the gastrointestinal tract at any dose level.

Oral administration of 100-1000 µg/kg/day budesonide capsules to Cynomolgus monkeys for 4 weeks disclosed no treatment-related clinical signs. Budesonide capsules given orally to Cynomolgus monkeys for 26 weeks disclosed no effects on the gastrointestinal tract at doses up to 5000 µg/kg/day.

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