NEW ZEALAND DATA SHEET

1 PRODUCT NAME (strength pharmaceutical form)

ENTOCORT 3 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 3 mg budesonide

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule 3 mg (19 mm x 7 mm): a two-piece, hard, gelatine capsule, size 1, with opaque, light grey body and opaque, pink cap. The cap has black radial print CIR/3 mg. Each capsule contains approximately 0.35 g of white to off-white budesonide Controlled Ileal Release (CIR) granules representing 3 mg budesonide active ingredient. Average gross mass is approximately 0.42 g.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ENTOCORT capsules are indicated for the induction of remission in patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon.

4.2 Dosage and method of administration

The capsules should be swallowed whole with water. For patients with difficulty swallowing, the capsules may be opened and the contents swallowed after mixing with a tablespoon of apple sauce. It is important that the contents of the capsules are not crushed or chewed.

Adults

The recommended daily dose for induction of remission is 9 mg, administered once daily for up to eight weeks. The dose should be taken in the morning before breakfast. Full effect is usually achieved within 2-4 weeks. When treatment with ENTOCORT capsules is to be discontinued, the dose should be tapered for 2 to 4 weeks and not stopped abruptly.

Children

There are limited data on the use of ENTOCORT capsules in children. The available data are insufficient to support safety and efficacy in the paediatric population, therefore such use cannot be recommended until further data become available.

Influence on Growth

It is recommended that the height of children receiving prolonged treatment with corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated. The benefits of corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. Long-term studies have not been performed in children treated with ENTOCORT capsules.

Elderly

No special dose adjustment is recommended. However, experience with ENTOCORT capsules in the elderly is limited.

4.3 Contraindications

Hypersensitivity to budesonide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

NOTE: Some patients have been treated continuously for up to a year or more with ENTOCORT and although corticosteroid side effects are expected to be less than with prednisolone, caution should be exercised.

Transferring from Systemic glucocorticosteroids

When patients are transferred from systemic glucocorticosteroid treatment with a higher systemic effect compared to ENTOCORT capsules, they may have adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of systemic steroid should be reduced cautiously.

Replacement of high systemic effect glucocorticosteroid treatment with ENTOCORT capsules sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic medication.

Viral Infections

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

HPA Axis

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

Reduced Liver Function

Reduced liver function may affect the elimination of glucocorticosteroids. The intravenous pharmacokinetics of budesonide however was similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide was affected by compromised liver function as evidenced by increased systemic availability.

Visual disturbance

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.

Discontinuation

When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy. 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.

CYP3A4 Interactions

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A4 activity in the liver and in the intestinal mucosa, also see **Interactions with other medicines and other forms of interaction**) may cause a several-fold increase of the systemic exposure to budesonide and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. If treatment with ketoconazole or itraconazole together with budesonide is indicated, reduction of the budesonide dose should be considered if side effects typical of systemic glucocorticosteroids occur.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. As with other drugs primarily being metabolized through CYP3A4, regular ingestion of grapefruit or grapefruit juice, should be avoided in connection with ENTOCORT capsules administration (other juices such as orange juice or apple juice do not inhibit CYP3A4). Also see **Interactions with other medicines and other forms of interaction**.

Chronic Use

When ENTOCORT capsules are used chronically in excessive doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear.

Other conditions

Use with caution in patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

4.5 Interaction with other medicines and other forms of interaction

Elevated plasma levels and enhanced effects of corticosteroids have been reported in women also receiving oestrogens or oral contraceptives. However, a low-dose combination oral contraceptive that more than doubled the plasma concentration of oral prednisolone, had no significant effect on the plasma concentration of oral budesonide.

At recommended doses, cimetidine has slight but clinically insignificant effect and omeprazole no effect on the pharmacokinetics of oral budesonide.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibition by budesonide on other drugs metabolism via CVP3A4 is unlikely, since budesonide has low affinity to the enzyme. Inhibition of CYP3A4 by e.g. ketoconazole, itraconazole and grapefruit juice can however increase the systemic exposure to budesonide (see **Special warnings and precautions for use**).

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

4.6 Fertility, pregnancy and lactation

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities of foetal development. The relevance of this finding to humans has not been established. However, as with other agents, the administration of ENTOCORT capsules during pregnancy requires that the benefits for the mother are weighed against the risks for the foetus.

Budesonide is excreted in breast milk. However, based on data from inhaled budesonide, at therapeutic doses of ENTOCORT exposure to the breast feeding child is anticipated to be low.

4.7 Effects on ability to drive and use machines

ENTOCORT capsules no influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies most adverse events were of mild to moderate intensity and of a non-serious character.

Adverse reactions, which have been associated with ENTOCORT capsules, are given below in Table 1.

Table 1 Adverse drug reactions by frequency and system organ class (SOC)

Frequency	SOC	Reaction
Common 1% to 10%	*Endocrine disorders:*	Cushingoid features
	Metabolism and nutrition disorders:	Hypokalaemia
	Psychiatric disorders:	Behavioural changes such as nervousness, insomnia, mood swings and depression
	Eye disorders:	Blurred vision
	Cardiac disorders:	Palpitations
	Gastrointestinal disorders:	Dyspepsia
	Skin and subcutaneous tissue disorders:	Skin reactions (urticaria, exanthema)
	Musculoskeletal and connective tissue disorders:	Muscle cramps
	Reproductive system and breast disorders:	Menstrual disorders
Uncommon 0·1% to 1%	*Nervous system disorders:*	Tremor, psychomotor hyperactivity
	Psychiatric disorders:	Anxiety
Rare 0·1% to 0·01%	*Psychiatric disorders:*	Aggression

Table 1 Adverse drug reactions by frequency and system organ class (SOC)

Frequency	SOC	Reaction
	Eye Disorders:	Cataract including subcapsular cataract, Vision, blurred (see also section 4.4)
	Skin and subcutaneous tissue disorders:	Ecchymosis
Very rare <0·01%	*Immune system disorders:*	Anaphylactic reaction
	Musculoskeletal and connective tissue disorders:	Growth retardation

Most of the adverse events mentioned in this SmPC can also be expected for other treatments with glucocorticoids.

Side effects typical of systemic glucocorticosteroids (e.g. Cushingoid features and growth retardation) may occur. These side effects are dependent on dose, treatment time, concomitant and previous glucocorticosteroid intake and individual sensitivity.

Clinical studies have shown that the frequency of glucocorticosteroid associated side-effects is substantially reduced (approximately halved) with ENTOCORT capsules compared with prednisolone at therapeutically equivalent doses.

4.9 Overdose

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Thus, acute overdosage with ENTOCORT 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: glucocorticosteroids, ATC Code: A07EA06

5.1 Pharmacodynamic properties

Budesonide is a glucocorticosteroid with high local anti-inflammatory effect. ENTOCORT capsules consist of gelatin capsules filled with gastro-resistant, prolonged release granules for oral use. The granules are practically insoluble in gastric juice, and have prolonged release properties adjusted to release budesonide in the small intestine through the colon.

Topical anti-inflammatory effect

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

Data from clinical pharmacology studies and controlled clinical trials indicate that ENTOCORT capsules act topically. This is supported by a similar efficacy, but significantly less impact on the HPA-axis and systemic inflammatory markers, compared with prednisolone.

HPA axis function

At recommended doses, ENTOCORT capsules cause significantly less effect than prednisolone 20-40 mg daily on morning plasma cortisol, on 24-hour plasma cortisol (AUC 0–24 h) and on 24-hour urine cortisol. Also ACTH tests have shown that ENTOCORT capsules, compared with prednisolone, have significantly less impact on the adrenal function.

Bone mineral density and growth

In a study investigating bone mineral density during treatment with ENTOCORT capsules or prednisolone for up to two years, treatment with ENTOCORT capsules resulted in significantly less bone loss than prednisolone treatment in steroid naïve patients.

5.2 Pharmacokinetic properties

Absorption

After oral dosing of plain micronized budesonide, absorption is rapid and seems to be complete. After dosing of ENTOCORT capsules a major fraction of absorbed medicine is absorbed in the ileum and ascending colon. In patients with active Crohn's disease, the systemic availability after a single dose ranges from 12 to 20%. In healthy subjects the corresponding figures are 9 to 12%.

After repeated dosing for 8 weeks, the systemic availability approaches that in healthy subjects (about 10%).

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%. Following oral dosing of ENTOCORT capsules 9 mg, mean maximal plasma concentration is approximately 5-10 nmol/L, attained between 3-5 hours.

Biotransformation

Budesonide then undergoes extensive biotransformation (≈ 90%) on first passage through the liver to metabolites of 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, a subfamily of cytochrome 450.

Elimination

Elimination of budesonide given as ENTOCORT capsules is rate limited by its absorption, and the plasma half-life averages 4 hours. The metabolites are excreted as such 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 L/min), and the plasma half-life after IV dosing averages 2-3 hours.

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

5.3 Preclinical safety data

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of other glucocorticosteroids.

Budesonide evaluated in six different test systems did not show any mutagenic or clastogenic effects.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups with active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in a repeat study with budesonide as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class-effect.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

The toxicity of ENTOCORT capsules, with focus on the gastrointestinal tract, has been studied in cynomolgus monkeys in doses up to 5 mg/kg (approximately 25 times the recommended daily dose in man) after repeated oral administration for up to 6 months. No effects were observed in the gastrointestinal tract, neither at gross pathology nor in the histopathological examination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:

- Ethylcellulose
- Acetyltributyl citrate
- Methacrylic acid copolymer
- Triethylcitrate (E1505)
- Antifoam M
- Polysorbate 80 (E433)
- Talc (E553b)
- Sugar spheres (consisting of sucrose and maize starch)

Capsule:

- Gelatin
- Titanium dioxide (E 171)
- Iron oxide (E 172)

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

The capsules should be stored below 30°C in the container. Replace the cap firmly after use. Store out of reach of children.

6.5 Nature and contents of container

The capsules are packed in HDPE tablet containers of 100s. The containers are provided with a polypropylene screw cap including a desiccant.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Chiesi New Zealand Ltd
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Airport Oaks, Mangere 2022
New Zealand
Email: medicalaffairs.au@chiesi.com

9 DATE OF FIRST APPROVAL

25 September 1997

10 DATE OF REVISION OF THE TEXT

11 June 2021

SUMMARY OF CHANGES

- Update of Sponsor details following Change of Sponsor from Emerge Health to Chiesi New Zealand.