SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ENTOCORD® 3 mg (modified-release hard capsules).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ENTOCORD 3 mg modified-release capsule contains: budesonide 3,0 mg.

Contains sugar (sucrose 320 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release hard capsules

A 2-piece hard gelatine capsule with opaque, light grey body and opaque, pink cap. The cap has black radial print CIR/3 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction of remission in patients with mild to moderate Crohn's disease involving the ileum and/or the ascending colon; in adults and children 11 years and older.

4.2 Posology and method of administration

Posology

Adults:

The recommended daily dose in mild to moderate active disease is 9 mg, administered as 9 mg once daily in

the morning, for up to 8 weeks. Full effect is usually achieved within 2-4 weeks.

Children 11 years and above, with a body weight over 25 kg:

The recommended daily dose in mild to moderate active disease is 9 mg, administered once daily in the morning, for up to 8 weeks. Full effect is usually achieved within 2-4 weeks. Once control of symptoms is achieved, treatment should be titrated to the lowest effective dose.

Special populations

Elderly:

Dosage as for adults. However, experience with ENTOCORD 3 mg in the elderly is limited.

NB: Treatment with ENTOCORD 3 mg should be tapered before cessation.

Method of administration

For oral administration.

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

4.3 Contraindications

Hypersensitivity to budesonide (the active substance) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Side effects typical of ENTOCORD 3 mg may occur. Potential systemic effects include glaucoma.

Visual disturbance

Visual disturbance may be reported with ENTOCORD 3 mg 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.

Caution should be taken in patients with tuberculosis, systemic or local 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.

Particular care is required when considering the use of ENTOCORD 3 mg in patients with existing or previous history of severe affective disorders in themselves or in their first-degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Systemic effects of steroids may occur, particularly when prescribed at high doses and for prolonged periods. Such effects may include Cushing's syndrome, adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma and very rarely a wide range of psychiatric/behavioural effects (see Section 4.8).

During transferral from conventional systemic steroid therapy to ENTOCORD 3 mg, symptoms related to change in systemic steroid dose may occur, such as adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of ENTOCORD 3 mg should be reduced cautiously.

Replacement of high systemic effect glucocorticosteroid treatment with ENTOCORD 3 mg, sometimes unmasks allergies, e.g., rhinitis and eczema, which were previously controlled by the systemic medicine.

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 medicines may be considered.

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.

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 such as ENTOCORD 3 mg is sometimes necessary.

Reduced liver function may affect the elimination of ENTOCORD 3 mg. The pharmacokinetics after oral ingestion of budesonide was affected by compromised liver function as evidenced by increased systemic availability in patients with moderately severe hepatic cirrhosis. The intravenous pharmacokinetics of budesonide however was similar in cirrhotic patients and in healthy subjects.

Co-treatment with CYP3A inhibitors, including ketoconazole and cobicistat-containing products, is expected to increase the risk of systemic side effects.
If treatment with ketoconazole together with ENTOCORD 3 mg is indicated, the period between treatments should be as long as possible and a reduction of the ENTOCORD 3 mg dose should be considered if side effects typical of systemic glucocorticosteroids occur (see also section 4.5).

After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral ENTOCORD 3 mg increased about 2 times. As with other medicines primarily being metabolised through CYP3A4, ingestion of grapefruit or juice of it, should be avoided in connection with ENTOCORD 3 mg administration as the bioavailability of ENTOCORD 3 mg is doubled with

the combination (other juices such as orange juice or apple juice do not inhibit CYP3A4). (See section 4.5).

When ENTOCORD 3 mg capsules are used chronically, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ENTOCORD 3 mg.

4.5 Interaction with other medicines and other forms of interaction

Although not studied, concomitant administration of colestyramine may reduce ENTOCORD 3 mg uptake, in common with other medicines.

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, omeprazole was without effect on the pharmacokinetics of oral budesonide, whereas cimetidine has a slight but clinically insignificant effect.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome 450. Inhibition by budesonide on other medicines metabolism via CYP3A4 is unlikely, since budesonide has a low affinity to the enzyme. Inhibition of CYP3A4 by e.g. ketoconazole and grapefruit juice can however increase the systemic exposure to budesonide. (See section 4.4).

Concomitant treatment with CYP3A4 inducers such as carbamazepine may reduce budesonide exposure, which may require a dose increase of ENTOCORD 3 mg.

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

Pregnancy

Safety in pregnancy has not been established.

In pregnant animals, administration of budesonide is associated with abnormalities of foetal development.

Breastfeeding

ENTOCORD 3 mg is excreted in breast milk.

Based on data from inhaled budesonide, at therapeutic doses of ENTOCORD 3 mg exposure to the suckling child is anticipated to be low.

4.7 Effects on ability to drive and use machines

There is no information available regarding the effects of ENTOCORD 3 mg on the ability to drive and use of machines. An influence is however unlikely.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Reaction**
Cardiac disorders:	Common: (1 % to 10 %)	Palpitations
Endocrine disorders:	Common: (1 % to 10 %)	Cushingoid features
	Very Rare:	Growth retardation

	(< 0,01 %)	
Gastrointestinal disorders:	Common: (1 % to 10 %)	Dyspepsia
Eye disorders:	Common: (1 % to 10 %)	Blurred vision
	Rare: (< 0,1 %)	Glaucoma, cataract including subcapsular cataract (see also section 4.4)
Musculoskeletal and connective tissue disorders:	Common: (1 % to 10 %)	Muscle cramps
Skin and subcutaneous tissue disorders:	Common: (1 % to 10 %)	Exanthema; urticaria
	Rare: (< 0,1 %)	Ecchymosis
Psychiatric disorders:	Common: (1 % to 10 %)	Behavioural changes such as nervousness; insomnia; mood swings and depression
	Uncommon: (0,1 % to 1 %)	Anxiety
	Rare: (< 0,1 %)	Aggression
Reproductive system and breast disorders:	Common: (1 % to 10 %)	Menstrual disorders
Metabolism and nutrition disorders:	Common: (1 % to 10 %)	Hypokalaemia
Nervous system disorders:	Uncommon: (0,1 % to 1 %)	Tremor, psychomotor hyperactivity
Immune system disorders:	Very Rare: (< 0,01 %)	Anaphylactic reaction
	Unknown:	Hypersensitivity reactions such as angioedema

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.

Very rarely a wide range of psychiatric/ behavioural effects may occur, when systemic steroids such as ENTOCORD 3 mg are prescribed at high doses and for prolonged periods. (See section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Thus, acute overdosage with ENTOCORD 3 mg, 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 supportive and symptomatic therapy.

Chronic overdosage may lead to systemic corticosteroid effects, such as Cushingoid features. If such changes occur, the dose of ENTOCORD 3 mg should be gradually reduced until treatment is discontinued, in accordance with normal procedures for the discontinuation of prolonged oral glucocorticosteroid therapy.

5. PHARMACOLOGICAL PROPERTIES

A. 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic group: Corticosteroids acting locally. ATC-code: A07E A06.

Budesonide is a glucocorticosteroid with local anti-inflammatory effect. ENTOCORD 3 mg consists 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 from the small intestine through the colon.

5.1 Pharmacodynamic properties

The exact mechanism of action of budesonide 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.

5.2 Pharmacokinetic properties

Absorption:

After oral dosing of plain micronised budesonide, absorption is rapid and seems to be complete. After dosing of ENTOCORD 3 mg capsules a major fraction of absorbed compound is absorbed in the ileum and ascending colon. Mean systemic availability after single dose ranges from about 10 % in healthy volunteers to 20 % in patients with active Crohn’s disease.

Distribution:

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

Biotransformation:

Budesonide undergoes an extensive degree of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxybudesonide and 16-alpha-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 ENTOCORD 3 mg 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 litre/min), and the plasma half-life after IV dosing averages 2-3 hours.

Linearity:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule:

Acetyl tri-n-butyl citrate

Antifoam M

Ethylcellulose

Methacrylic acid copolymer

Polysorbate 80

Sugar spheres (consisting of sucrose and maize starch)

Talc

Triethyl citrate

Hard capsule body:

Black iron oxide, CI 77.499

Foodgrade oil,

Gelatin

Silicon dioxide colloidal

Sodium lauryl sulphate

Titanium dioxide, CI 77.891

Cap:

Foodgrade oil

Gelatin

Red iron oxide, CI 77.491

Silicon dioxide colloidal

Sodium lauryl sulphate

Titanium dioxide, CI 77.891

Yellow iron oxide, CI 77.492

Printing ink consisting of black iron oxide, CI 77.499: shellac, silicon antifoam, soya lecithin ***or*** ammonium hydroxide, black iron oxide, CI 77.499, potassium hydroxide and shellac.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC. The capsules should be stored in the container. Replace the cap firmly after use.

6.5 Nature and contents of container

50 and 100 capsules in a white round HDPE container with a white polypropylene screw cap provided with a desiccator capsule.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria,0157

8. REGISTRATION NUMBER

31/21.5.1/0215

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 16 February 1998

10. DATE OF REVISION OF THE TEXT

11 January 2023