**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

ENTOCORD® 0,02 mg/ml (Enema)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENTOCORD 0,02 mg/ml enema consists of 2 components: a dispersible tablet and a vehicle.

Each tablet contains 2,3 mg of budesonide.

Each ml of vehicle contains 9 mg sodium chloride and the preservatives methylparaben (0,08 % *m/v*) and propylparaben (0,02 % *m/v*).

The tablet contains sugar (lactose, 264,3 mg per tablet).

The enema is reconstituted before use. The volume of the reconstituted enema is 115 ml. Each enema contains 2 mg budesonide per 100 ml (0,02 mg/ml).

For full list of excipients see section 6.1

## 3. PHARMACEUTICAL FORM

Dispersible tablet and solution for rectal suspension.

*Dispersible tablet:*

A faintly yellow, circular, biconvex tablet, packed in aluminium blister.

*Vehicle:*

A clear, colourless solution in a plastic bottle, and an individually packed rectal nozzle.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Ulcerative colitis involving the rectum and sigmoid colon.

**4.2 Posology and method of administration**

**Posology**

The dosage recommendation for adults including the elderly is one ENTOCORD 0,02 mg/ml enema nightly for 4 weeks. Full effect is usually achieved within 2 - 4 weeks. If the patient is not in remission after 4 weeks, the treatment period may be prolonged to 8 weeks.

ENTOCORD 0,02 mg/ml enema consists of 2 parts, a dispersible tablet and a bottle containing a vehicle. The enema is prepared just before use, to be administered in the evening before going to bed.

**Method of administration**

Administer the ENTOCORD 0,02 mg/ml enema per rectum as per instructions in section 6.6.

**4.3 Contraindications**

Hypersensitivity to the budesonide or any of the excipients of ENTOCORD 0,02 mg/ml enema listed in section 6.1.

Patients with local and systemic bacterial, fungal and viral infections.

Safety and efficacy have not been established in children.

**4.4 Special warnings and special precautions for use**

Special care is required in patients who are transferred from systemic glucocorticosteroid treatment with higher systemic effect to ENTOCORD 0,02 mg/ml enema as they may have adrenocortical suppression. Monitoring of adrenocortical function may therefore be considered and the dose of systemic steroid should be reduced cautiously.

Patients may feel unwell in a non-specific way during the withdrawal phase, e.g., they may experience pain in the muscles and joints. Symptoms such as tiredness, headache, nausea and vomiting may occur. A general

insufficient glucocorticosteroid effect should be suspected and a temporary increase in the dose of systemic glucocorticosteroids is sometimes necessary.

Replacement of systemic glucocorticosteroid treatment with a higher systemic effect by ENTOCORD 0,02 mg/ml enema sometimes unmasks allergies, e.g., rhinitis and eczema, which were previously controlled by the systemic medicine. These allergies should be symptomatically controlled with an anti-histamine and/or topical preparations.

Reduced liver function may affect the elimination of glucocorticosteroids. The intravenous pharmacokinetics of budesonide, however, were 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.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis (See section 4.8). 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).

Co-treatment with CYP3A inhibitors, including ketoconazole and 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. If this is not possible, the period between treatments should be as long as possible, and a reduction of the budesonide dose could also be considered (see section 4.5).

When ENTOCORD Enema is used chronically in excessive doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear. However, the dosage form and the route of administration make any prolonged overdosage unlikely.

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.

ENTOCORD tablet contains lactose therefor ENTOCORD 0,02 mg/ml enema is not recommended for patients with rare hereditary problems of galactose intolerance, total lactase deficiency or of glucose-galactose malabsorption.

**4.5 Interaction with other medicines and other forms of interaction**

*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 several fold increase of the systemic exposure to oral budesonide. Therefore, it cannot be excluded that concomitant use of ENTOCORD 0,02 mg/ml enema and ketoconazole may result in increased systemic availability of budesonide.

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.

Concomitant treatment with CYP3A4 inducers such as carbamazepine probably reduces budesonide exposure, which may require a dose increase.

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**

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities of foetal development. The relevance of these findings to man has not been established.

The safety of ENTOCORD 0,02 mg/ml enema in pregnant women has not been established.

**Breastfeeding**

Budesonide is excreted in breast milk. The safety of ENTOCORD 0,02 mg/ml enema in lactating women has not been established. Corticosteroids are known teratogens.

**4.7 Effects on ability to drive and use machines**

ENTOCORD 0,02 mg/ml enema does not affect the ability to drive and use machines.

**4.8 Undesirable effects**

The following definitions apply to the incidence of undesirable effects: Very Common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very rare (< 1/10 000).

| System Organ Class | Frequency | Description |
|---|---|---|
| **Immune system disorders** | Very rare | Anaphylactic reaction |
| | Unknown | Hypersensitivity reactions such as angioedema |
| **Endocrine disorders** | Rare | Signs or symptoms of systemic glucocorticosteroid effects, including hypofunction of the adrenal gland, may occur with ENTOCORD 0,02 mg/ml enema, probably depending on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual |

| | | |
|---|---|---|
| | | sensitivity. At recommended doses, ENTOCORD 0,02 mg/ml enema usually causes no or minor suppression of plasma cortisol |
| **Psychiatric disorders** | Common | Depression |
| | Uncommon | Agitation, insomnia, nervousness, restlessness, psychomotor hyperactivity |
| | Rare | Aggression |
| **Eye disorders** | Rare | Glaucoma, cataract including subcapsular cataract, blurred vision (see also section 4.4) |
| **Gastrointestinal disorders** | Common | Nausea, diarrhoea, flatulence, abdominal pain and constipation |
| | Uncommon | Duodenal or gastric ulcer |
| | Rare | Pancreatitis |
| **Skin and subcutaneous tissue disorders** | Common | Urticaria, exanthema, rash, dermatitis |
| | Rare | Ecchymosis |
| **Musculoskeletal and connective tissue disorders** | Rare | Osteonecrosis |

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

*Description of selected adverse events*

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.

Very rarely a wide range of psychiatric/ behavioural effects may occur, when systemic steroids 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. Healthcare 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**

Systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur when ENTOCORD 0,02 mg/ml enema is used chronically in excessive doses. Discontinue treatment and take appropriate measures to protect the patient against stress situations.

In the event of acute overdosage, no specific antidote is available. If a high dose of ENTOCORD 2,3 mg dispersible tablets has been taken orally, treatment consists of immediate emesis followed by supportive and symptomatic therapy.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

A.11.8 Suppositories and anal ointments

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. ATC Code A07E AO6.

Budesonide is a non-halogenated glucocorticosteroid with local anti-inflammatory effect.

The exact mechanism of action of glucocorticosteroids in the treatment of ulcerative colitis is not fully understood. At recommended doses, ENTOCORD 0,02 mg/ml enema causes no clinically important changes, neither in basal plasma cortisol levels nor in the response to stimulation with ACTH.

**5.2 Pharmacokinetic properties**

**Absorption:**

The systemic availability after oral administration of budesonide is approximately 10 %. After rectal administration of ENTOCORD 0,02 mg/ml enema to healthy volunteers the systemic availability is approximately 15 % (range 3 to 50 %).

As can be expected for medicines 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, the 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 nmol/litre (range 1 - 9 nmol/litre), reached within 1,5 hours.

**Biotransformation:**

Budesonide undergoes an extensive degree (~90 %) 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 CYP3A, a subfamily of cytochrome P450.

**Elimination:**

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 litres/min), and the plasma half-life after I.V. dosing averages 2 - 3 hours.

**Linearity:**

The kinetics of budesonide are linear with dose (as evidenced by dose-proportional increases of $C_{max}$ and AUC after oral dosing of 3,9 and 15 mg budesonide (given as ENTOCORD capsules).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Dispersable tablet*

Colloidal anhydrous silica

Colour [riboflavin-5-phosphate sodium]

Lactose anhydrous

Lactose

Magnesium stearate

Polyvidone, crosslinked

*Vehicle*

Methyl parahydroxybenzoate (preservative)

Propyl parahydroxybenzoate (preservative)

Sodium chloride

Water purified

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

2 years.

The enema is used immediately after reconstitution.

### 6.4 Special precautions for storage

Store at or below 30 °C.

### 6.5 Nature and contents of container

Entocord 0,02 mg/ml, enema consists of 2 components: a dispersible tablet and a vehicle.

*Blister*

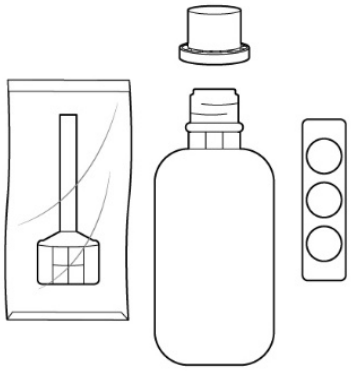
The primary package for the tablets is an aluminium blister package.

*Bottle and nozzle*

The primary package for the vehicle solution is a LDPE bottle. Individually packaged nozzles (enema applicators) are also provided. The final package consists of a blister pack containing 7 dispersible tablets 2,3 mg, 7 bottles of vehicle solution 115 ml, 7 nozzles (enema applicators), and 7 plastic bags to be used when giving the enema.

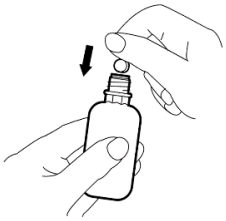
**6.6 Special precautions for disposal and other handling**

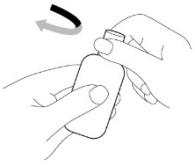
*Directions for use:*



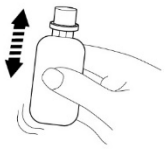
1. Unscrew the cap of one of the plastic bottles.

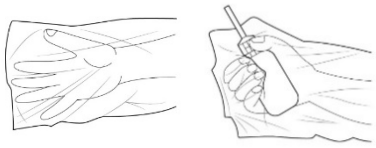
2. Take 1 tablet from the foil pack and place it in the bottle. Replace the cap onto the bottle and screw the cap tightly.





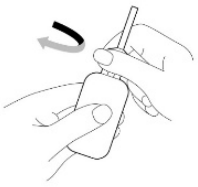
3. Shake the bottle vigorously, for at least 15 seconds or until the tablet has dissolved and a light yellow solution has formed. Put on a plastic glove before using the enema.





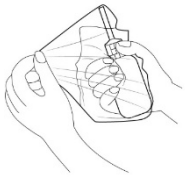
4. Unscrew the cap.

5. Unpack the nozzle and screw the nozzle on the bottle.



6. Lie on your left side. Shake the bottle a couple of times and then remove the protective cover.

7. Insert the rectal pipe into the anus and squeeze out the contents of the bottle as fully as possible. Remove the rectal pipe and draw the plastic glove over the bottle.



8. Roll over onto your stomach and remain like that for 5 minutes. Then choose a comfortable sleeping position. The enema should remain in the intestine for as long as possible, preferably overnight.

*Important*:

9. The prepared solution should be used immediately.

**7. HOLDER OF THE CERTIFICATE OF REGISTRATION**

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive

Route 21 Corporate Park, Nellmapius Drive

Irene, Pretoria

0157

**8. REGISTRATION NUMBER**

29/11.8/0638

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of registration: 20 February 1996

**10. DATE OF REVISION OF THE TEXT**

24 May 2023