

# AUSTRALIAN PRODUCT INFORMATION - ENTOCORT® (BUDESONIDE) MODIFIED RELEASE CAPSULES

## 1. NAME OF THE MEDICINE

budesonide

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENTOCORT contains 3 mg of budesonide and is a hard gelatin capsule filled with gastric acid-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 ileum and the ascending colon.

Excipients with known effect: sugars.

For the full list of excipients, see section [6.1 LIST OF EXCIPIENTS](#).

## 3. PHARMACEUTICAL FORM

ENTOCORT 3 mg modified release capsules are two-piece hard gelatin capsule, size 1 with an opaque light grey body and an opaque pink cap. The cap has black print CIR 3mg.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

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

### 4.2 DOSE AND METHOD OF ADMINISTRATION

#### **Dosage**

#### *Adults*

The recommended daily dose for induction of remission is 9 mg, administered once daily in the morning. The dose should be taken before meals.

When treatment with ENTOCORT modified release capsules is to be discontinued, the dose should be tapered over the last 2 to 4 weeks of therapy and not stopped abruptly. The total duration of therapy should be no more than 12 weeks in any single course.

#### *Children*

There is presently no experience with ENTOCORT modified release capsules in children.

#### *Elderly*

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

#### **Method of administration**

The modified release capsules should be swallowed whole with water. The modified release

capsules must not be chewed.

### 4.3 CONTRAINDICATIONS

Systemic or local bacterial, fungal or viral infections.

Hypersensitivity to any of the ingredients listed in section [6.1 LIST OF EXCIPIENTS](#).

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### **Identified precautions**

Caution should be taken in patients with tuberculosis, 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.

#### ***Transferring from systemic glucocorticosteroids***

During transfer from conventional systemic steroid therapy to ENTOCORT, symptoms related to the change in systemic steroid dose may occur e.g., allergic symptoms such as rhinitis and eczema may recur.

Particular care is needed in patients who are transferred from systemic glucocorticoid treatment with higher systemic effect to ENTOCORT. These patients 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.

#### ***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 suppression and adrenal insufficiency***

As with all glucocorticosteroids, some degree of adrenal suppression may occur in particularly sensitive patients, therefore, monitoring of haematological and adrenal function is strongly advised and patients should be instructed to carry an appropriate warning card.

In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended.

#### ***Discontinuation***

Some patients may 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 may occur. In these cases, a temporary increase in the dose of systemic glucocorticosteroids is sometimes necessary.

#### ***CYP3A interactions***

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 (see also section [4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS](#)).

### ***Chronic use***

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

### ***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. See section [4.8 ADVERSE EFFECTS \(UNDESIRABLE EFFECTS\)](#).

### ***Gastrointestinal tolerance***

The toxicity of ENTOCORT, with focus on the gastrointestinal tract, has been studied in cynomolgus monkeys in doses up to 5 mg/kg ( $\geq 25$  times the recommended daily dose in man) after repeated oral administration for up to 6 months. No effects were observed in the gastrointestinal tract, either at gross pathology or in the histopathological examination.

### ***Excipients***

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit. It is essentially sodium-free.

### **Use in hepatic impairment**

Compromised hepatic function has an influence on the pharmacokinetics of budesonide with a reduced elimination rate and an increased oral systemic availability.

### **Use in the elderly**

Refer to section [4.2 DOSE AND METHOD OF ADMINISTRATION](#) and section [4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE](#).

### **Paediatric use**

Refer to section [4.2 DOSE AND METHOD OF ADMINISTRATION](#) and section [4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE](#)

### **Effects on laboratory tests**

Refer to section [4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS](#).

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibition of this enzyme can therefore increase systemic exposure of budesonide. During concomitant administration of drugs which are potent CYP3A4 inhibitors (such as ketoconazole), plasma concentrations of budesonide can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of ENTOCORT should be considered.

### **Ketoconazole**

The kinetic properties of budesonide were investigated in healthy subjects with or without ketoconazole 200 mg daily. The mean AUC for budesonide was 31.6 nmol.h/L, after administration of ketoconazole for three consecutive days this increased to 238.2 nmol.h/L. The relative systemic availability increased 7-fold. If concomitant treatment of ketoconazole and oral budesonide is indicated, the dose of budesonide should be reduced if systemic glucocorticoid side effects occur.

### **Grapefruit juice**

The systemic exposure for oral budesonide increases about two times after the intake of grapefruit juice. As with other drugs primarily metabolised through CYP3A4, regular ingestion of grapefruit or grapefruit juice should be avoided with budesonide administration.

### **Cimetidine**

The kinetics of budesonide were investigated in healthy subjects with or without cimetidine, 1000 mg daily. After a 4 mg oral dose of budesonide the values of  $C_{max}$  with and without cimetidine were 5.1 and 3.3 nmol/L. The corresponding values for systemic availability of budesonide were 12 and 10%, respectively. This indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance.

### **Other interactions**

No other data have been reported regarding interactions between budesonide and other drugs in patients with Crohn's disease.

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**

### **Effects on fertility**

No data available.

### **Use in pregnancy – Category B3**

In animal studies, budesonide was found to cross the placental barrier.

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities of fetal development and fetal adrenal suppression. The relevance of this finding to humans has not been established.

However, as with other drugs the administration of ENTOCORT during pregnancy requires that the benefits for the mother are weighed against the risks for the fetus.

### Use in lactation

Budesonide is excreted in breast milk. Due to the low systemic bioavailability of oral budesonide (see [section 5.2 PHARMACOKINETIC PROPERTIES](#)), the amount of drug present in the breast milk is likely to be low, depending on the dose given. However, there are no study data on the use of oral budesonide by nursing mothers or their infants. Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue ENTOCORT, taking into account the clinical importance of ENTOCORT to the mothers and the given dose.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ENTOCORT has no or negligible influence on the ability to drive and use machines.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical studies

ENTOCORT is generally well tolerated. In clinical studies most adverse events were of mild to moderate intensity and of a non-serious character.

Data from three controlled clinical trials including ENTOCORT 9 mg (n=268), prednisolone 40 mg (n=145) and placebo (n=66) showed no statistically significant differences in frequency for any adverse events when comparing the ENTOCORT 9 mg group and placebo.

**Table 1. Adverse events reported for ENTOCORT during clinical trials**

Adverse event	Budesonide 9 mg n=268 (%)	Placebo n=66 (%)	Prednisolone 40 mg n=145 (%)
<b>Gastrointestinal</b>			
Dyspepsia	24 (9)	2 (3)	17 (12)
Nausea	35 (13)	5 (8)	18 (12)
Flatulence	19 (7)	4 (6)	12 (8)
Vomiting	19 (7)	5 (8)	6 (4)
Abdominal pain	18 (7)	7 (11)	6 (4)
<b>Cardiovascular</b>			
Palpitation	7 (3)	- (-)	12 (8)
<b>Central Nervous System</b>			
Headache	75 (28)	14 (21)	31 (21)
Dizziness	27 (10)	4 (6)	18 (12)
<b>Respiratory</b>			
Respiratory infection	35 (13)	6 (9)	20 (14)
<b>Skin</b>			
Rash	11 (4)	4 (6)	3 (2)
<b>Other</b>			
Cushing syndrome	83 (31)	16 (24)	69 (48)
Back pain	26 (10)	6 (9)	17 (12)
Insomnia	17 (6)	3 (5)	16 (11)
Fatigue	22 (8)	5 (8)	11 (8)
Pain	20 (7)	6 (9)	17 (12)
Arthralgia	12 (4)	4 (6)	6 (4)
Sweating increased	14 (5)	2 (3)	26 (18)

Data from the three controlled clinical trials showed statistically that the relative risk of glucocorticosteroid side effects with ENTOCORT 9 mg is reduced compared to prednisolone 40 mg on an overall basis, and in particular with respect to moon face, acne and buffalo hump. The relative risk for glucocorticoid adverse event, particularly occurrence of moon face, was increased relative to placebo.

### Tabulated list of adverse reactions

The following suspected adverse reactions is based on clinical trials and/or spontaneous post-marketing reports.

The following definitions apply to the incidence of undesirable effects: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot estimate from the available data).

**Table 2. Adverse drug reactions by frequency and system organ class (SOC)**

SOC	Frequency	Reaction
Immune system disorders	Very rare	Anaphylactic reaction
	Not known	Hypersensitivity reactions such as angioedema
Endocrine disorders	Common	Cushingoid features
Metabolism and nutrition disorders	Common	Hypokalemia
Psychiatric disorders	Common	Behavioural changes such as nervousness, insomnia, mood swings and depression
	Uncommon	Anxiety
	Rare	Aggression
Nervous system disorders	Uncommon	Tremor, psychomotor hyperactivity
Eye disorders	Rare	Cataract including subcapsular cataract, blurred vision (see also section 4.4)
Cardiac disorders	Common	Palpitations
Gastrointestinal disorders	Common	Dyspepsia
Skin and subcutaneous tissue disorders	Common	Skin reactions (urticaria, exanthema)
	Rare	Ecchymosis
Musculoskeletal and connective tissue disorders	Common	Muscle cramps
	Very rare	Growth retardation
Reproductive system and breast disorders	Common	Menstrual disorders

### Description of selected adverse reactions

Side effects typical of systemic glucocorticosteroids (Cushingoid features), reduced growth velocity and adrenal suppression may occur. These side effects are dependent on dose, treatment time, concomitant and previous glucocorticosteroid intake and individual sensibility.

Long term experience with ENTOCORT is limited. Although not reported during short term trials ENTOCORT, the possible occurrence of adverse effects typical of glucocorticosteroids, such as osteoporosis, diabetes, cataracts must be considered.

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

## 4.9 OVERDOSE

Acute overdosage with ENTOCORT, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses systemic corticosteroid effects such as hypercorticism and adrenal suppression as well as osteoporosis may appear. If such changes occur the dosage of ENTOCORT should be discontinued consistent with accepted procedures for discontinuing prolonged oral therapy with systemic steroids.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Studies in animals and humans have shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dose range. This is explained by the extensive first-pass hepatic degradation of budesonide after systemic absorption, approximately 85-90%, in combination with the low potency of formed metabolites. The exact mechanism of action of budesonide in the treatment of Crohn's disease is not fully understood. Anti-inflammatory actions, such as blocking the inflammatory cell influx and inhibition of inflammatory mediator release by inhibition of the arachidonic acid pathway, are probably important. The intrinsic potency of budesonide, measured as affinity to the glucocorticoid receptor, is about 15 times higher than that of prednisolone.

ENTOCORT modified release capsules 9 mg have been shown in clinical pharmacology studies and controlled clinical trials to have equal efficacy, but less effect on the hypothalamus-pituitary-adrenal (HPA) axis and inflammatory markers than prednisolone 40 mg in the treatment of Crohn's disease.

ENTOCORT in studies of up to 8 weeks produced a dose dependent suppression of morning plasma cortisol, on 24-hour plasma cortisol (AUC 0-24 h) and on 24-hour urine cortisol, however, at the recommended dose of 9 mg once daily this effect was significantly less than that seen with prednisolone 20-40 mg daily. ACTH tests have shown that ENTOCORT, compared with prednisolone, have less impact on adrenal function. In one study, adrenal dysfunction, as measured by short ACTH test, was seen in 58% of patients on 9 mg ENTOCORT versus 84% on 40 mg prednisolone. The long-term effect of ENTOCORT on bone density and growth has not been studied in patients with Crohn's disease. In a 5-day study in healthy volunteers, 9 mg, and 15 mg doses of ENTOCORT were shown to have a similar suppressant effect on osteocalcin levels as 20 mg prednisolone.

#### Clinical trials

A dose-finding study (n=258) conducted over 12 weeks demonstrated that the lowest effective dose for inducing remission in active ileal or ileocaecal Crohn's disease with budesonide was 9 mg. The recommended dosage of 9 mg once daily has been compared with prednisolone 40 mg for the efficacy of inducing remission in two other studies of equal size (n=176 and 177, respectively). In one study, ENTOCORT was significantly slower at inducing remission with a median time of 29 days to remission compared to 16 days for prednisolone 40 mg. Another

study showed ENTOCORT was faster at reaching remission compared to prednisolone, with a median time of 17 days for ENTOCORT 9 mg and 28 days for prednisolone 40 mg. The percentage of patients in remission after 8 weeks' treatment showed no statistically significant differences in either of the two studies. In one study the remission rate in the ENTOCORT group was 52% compared with 65% for prednisolone, while in the other study the remission rate in both groups was 60%. The overall incidence of glucocorticosteroid associated side effects was statistically significantly lower with ENTOCORT. In one study (n=178) the incidence of glucocorticosteroid side effects was 50% for 9 mg ENTOCORT and 59% for 40 mg prednisolone. In another study (n=176) the corresponding figures were 33% for 9 mg ENTOCORT and 55% for 40 mg prednisolone.

No clinical studies have been conducted in children or the elderly.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

After oral dosing of plain micronised budesonide, absorption is rapid and seems to be complete. Following oral dosing of ENTOCORT modified release capsules 9 mg, taken immediately before breakfast, mean maximum plasma concentration is approximately 5-10 nmol/L ( $C_{max}$ ) at 3-5 hours ( $T_{max}$ ). Systemic availability in healthy subjects is approximately 10%, the same as after oral dosing of plain micronised budesonide, which indicates absorption is complete.

While ENTOCORT modified release capsules have equivalent systemic absorption to plain budesonide capsules, it has a longer  $T_{max}$ , due to its gastric-acid resistant, prolonged release properties. In a pharmacokinetic study in healthy volunteers, the absorption of budesonide in the targeted area, the ileum and ascending colon, was 58% and 34%, respectively, for ENTOCORT modified release capsules and capsules containing plain budesonide. Terminal ileal and ascending colon absorption in patients with Crohn's disease was more variable (range 3-84%; mean 42.5%).

Following a single dose of ENTOCORT modified release capsules in patients with active Crohn's disease, systemic availability is about 20%. After repeated dosing for 8 weeks, the systemic availability decreases but remains above that seen in healthy subjects.

### Distribution

The volume of distribution of budesonide in adult man is approximately 3 L/kg indicating a high tissue affinity. Plasma protein binding averages 85-90% in humans.

### Metabolism

Budesonide is extensively biotransformed by first-pass hepatic degradation (~90% in man) to more polar metabolites of low glucocorticosteroid potency. The glucocorticosteroid activity of the major metabolites, 6 $\beta$ -hydroxybudesonide and 16 $\alpha$ -hydroxy-prednisolone, is less than 1% of that of budesonide.

### Excretion

Excretion of budesonide given as ENTOCORT modified release capsules is rate limited by its absorption, and the terminal half-life averages 4 hours.



## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic effects of budesonide were found.

### Carcinogenicity

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. No oncogenic effect was noted in the mouse. One study indicated an increased incidence of brain gliomas in male Sprague-Dawley rats given budesonide, however the results were considered equivocal. Further studies performed in male Sprague-Dawley and Fischer rats showed that the incidence of gliomas in the budesonide treated rats was low and did not differ from that in the reference glucocorticoid groups or the controls. It has been concluded that treatment with budesonide does not increase the incidence of brain tumours in the rat.

In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. This was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in a repeat study in male Sprague-Dawley rats thus indicating a class effect of corticosteroids.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

The excipients are ethylcellulose, tributyl acetylcitrate, methacrylic acid copolymer, triethyl citrate, dimeticone 1000, polysorbate 80, purified talc and Sugar Spheres (ARTG PI No. 2535).

The capsule shell is made from gelatin, titanium dioxide, iron oxide black, iron oxide red, iron oxide yellow, colloidal anhydrous silica, liquid paraffin and sodium lauryl sulfate.

The capsules are printed with TekPrint SW-9008 Black Ink (ARTG PI No. 2328).

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutics Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Replace the cap firmly after use.

### 6.5 NATURE AND CONTENTS OF THE CONTAINER

A pack of 90 modified release capsules are provided in a high-density polyethylene bottle, with a polypropylene screw cap including a desiccant. The modified release capsules should be dispensed and stored in the original container.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with the local requirements.

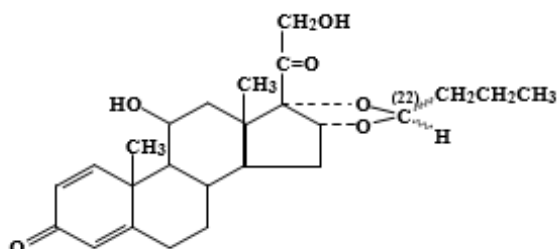
## 6.7 PHYSICOCHEMICAL PROPERTIES

Budesonide is a white to off white powder, freely soluble in chloroform, sparingly soluble in ethanol and practically insoluble in water and heptane. Budesonide is a mixture of two epimeric forms, epimer A and epimer B, in a 50:50 ratio. The epimer mixture melts with decomposition between 224°C and 231.5°C.

The active ingredient, budesonide, is a non-halogenated glucocorticoid structurally related to 16 $\alpha$  hydroxyprednisolone. The chemical name is 16 $\alpha$ , 17 $\alpha$ -22R, S- propylmethylenedioxy-pregna-1,4-diene-11 $\beta$ , 21-diol-3, 20-dione.

### Chemical structure

budesonide



### CAS number

51333-22-3

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

## 8. SPONSOR

Chiesi Australia Pty Ltd  
Suite 3, 22 Gillman Street  
Hawthorn East, VIC 3123  
Email: [medicalaffairs.au@chiesi.com](mailto:medicalaffairs.au@chiesi.com)

## 9. DATE OF FIRST APPROVAL

16 January 1998

## 10. DATE OF REVISION

03 January 2023

### Summary table of changes

Section changed	Summary of new information
4.4	Addition of excipient warnings
4.7	Revision of information
4.8	Addition of hypersensitivity reactions such as angioedema. Inclusion of tabulated summary of adverse drug reactions by frequency and system organ class (SOC).
All	Minor editorial and formatting changes