

## Product Information

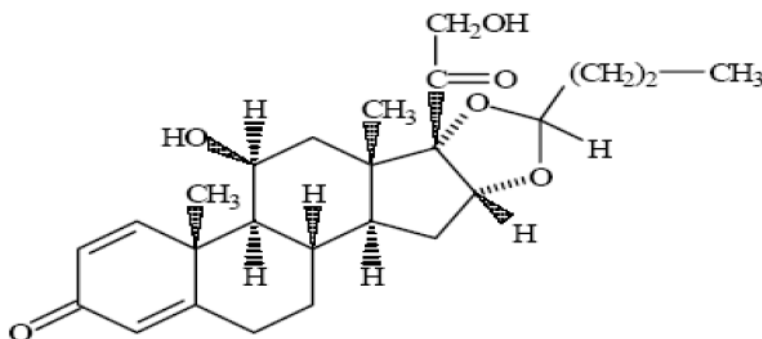
### NAME OF THE MEDICINE

**CORTIMENT<sup>®</sup>** 9 mg prolonged-release tablets

The active ingredient in CORTIMENT is budesonide. Budesonide is a white or almost white, crystalline powder. Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol.

Budesonide is 16 $\alpha$ , 17-[(1RS)-butylidenebis(oxy)]-11 $\beta$ , 21-dihydroxypregna-1,4 -diene-3,20-dione mixture of epimers in C-22: C-22S = epimer A; C-22R = epimer B;

Structure of budesonide



It has molecular formula of C<sub>25</sub>H<sub>34</sub>O<sub>6</sub> and molecular weight is 430.5.  
CAS No. 51333-22-3.

### DESCRIPTION

CORTIMENT prolonged-release tablet contains 9 mg of budesonide. Each tablet is a white to off-white, round, biconvex, film-coated, tablet, approximately 9.5 mm in diameter, approximately 4.7 mm in thickness, debossed on one side with "MX9".

When the protective layer is lost, intestinal fluid then comes into contact with the hydrophilic matrix polymers, which start to swell until a viscous gel matrix is formed. The solvent that penetrates into the gel matrix dissolves the active ingredient from the lipophilic matrices.

CORTIMENT prolonged-release tablets also contain the following excipients:

Tablet core: stearic acid (E570), lecithin powder (E322), microcrystalline cellulose (E460), hydroxypropylcellulose (E463), lactose, silicon dioxide (E551), magnesium stearate (E470b).

Tablet film-coating: methacrylic acid copolymer, talc-purified (E553b), titanium dioxide (E171), triethylcitrate.

CORTIMENT prolonged-release tablets contain lactose and lecithin (of Soya origin).

### PHARMACOLOGY

#### Pharmacodynamics

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, Corticosteroids acting locally,  
ATC code: A07EA06.

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### **Mechanism of action**

The exact mechanism of action of budesonide in the treatment of ulcerative colitis (UC) is not fully understood. In general, budesonide inhibits many inflammatory processes including cytokine production, inflammatory cell activation and expression of adhesion molecules on endothelial and epithelial cells. At doses clinically equivalent to prednisolone, budesonide gives less hypothalamic-pituitary-adrenal (HPA) axis suppression and has a lower impact on inflammatory markers.

Systemic bioavailability of budesonide is about 10% (see Pharmacokinetics/Absorption). Data from clinical pharmacology and pharmacokinetic studies for CORTIMENT prolonged-release tablets indicate that about 96% of drug absorption occurs in the colon, supporting the availability of budesonide at the intended site of action.

CORTIMENT contains budesonide in an extended release tablet core covered by a coating that dissolves in intestinal fluids having a pH greater than 7. Budesonide is then released into the intestinal tract throughout the colon.

### **Pharmacodynamic effects**

Budesonide is a glucocorticoid used in the treatment of inflammatory bowel disease. It does not reduce cortisol levels to the same extent as prednisolone. Its affinity for glucocorticoid receptors is approximately 200 times greater than that of hydrocortisone, and about 15 times that of prednisolone.

### **Pharmacokinetics**

#### **Absorption**

Following single oral administration of CORTIMENT 9 mg in healthy subjects, maximum plasma concentration ( $C_{max}$ ) of budesonide was  $1.35 \pm 0.96$  ng/mL at  $13.3 \pm 5.9$  hours post-dose ( $T_{max}$ ), and the area under the plasma concentration time curve (AUC) was approximately  $13.56 \pm 7.82$  ng.hr/mL. The systemic bioavailability of budesonide is about 10%, due to extensive first pass metabolism in the liver. Concomitant administration of CORTIMENT with food had minimal clinically relevant effect on systemic exposure to budesonide. There was no evidence for accumulation of systemic exposure to budesonide following 7 daily doses of CORTIMENT 9 mg.

#### **Distribution**

Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85–90%.

#### **Metabolism**

Budesonide undergoes extensive biotransformation in the liver to metabolites of low glucocorticoid activity. The glucocorticoid activity of the major metabolites, 6 $\beta$ -hydroxybudesonide and 16 $\alpha$ -hydroxy-prednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

#### **Excretion**

Elimination of budesonide is rate limited by absorption. Budesonide has a high systemic clearance (about 1.2 L/min).

### **CLINICAL TRIALS**

Two similarly-designed, randomised, double-blind, placebo-controlled studies were conducted in adult patients with mild to moderate active UC (defined as an UCDAI of  $\geq 4$  and  $\leq 10$ ). Together, 899 patients with histology consistent with active UC formed the ITT population, of which 232 patients were treated with CORTIMENT 9 mg and 210 patients were treated with placebo once daily for 8 weeks. The primary endpoint was induction of remission after 8 weeks of treatment.

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Remission was defined as an UCDAI score of  $\leq 1$ , with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a  $\geq 1$  point reduction in endoscopy score. In both studies, CORTIMENT 9 mg showed superiority to placebo in inducing remission (Table 1).

Table 1: Effect of CORTIMENT 9 mg prolonged-release tablets on Primary Endpoint:

Study	Remission n/N (%)		P value
	CORTIMENT 9 mg tablet	Placebo	
Study CB-01-02/01	22/123 (17.9)	9/121 (7.4)	0.0143
Study CB-01-02/02	19/109 (17.4)	4/89 (4.5)	0.0047

Statistical difference versus placebo was reached for CORTIMENT 9 mg for both studies and the difference versus placebo was 10.4% and 12.9% respectively.

5-ASA is the Standard of Care for treatment of mild to moderate disease. Results of a head to head comparison with CORTIMENT and 5-ASA are not available. Therefore, the place in the therapeutic work-up remains to be established. Some patients may benefit from treatment initially with CORTIMENT prolonged-release tablets.

### *Paediatric Population*

CORTIMENT prolonged-release tablets were not studied in the paediatric population.

## INDICATIONS

CORTIMENT prolonged-release tablets are indicated in adults for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient or not tolerated.

## CONTRAINDICATIONS

Hypersensitivity to the active substance, to peanut oil or to any of the excipients listed in the DESCRIPTION section.

CORTIMENT prolonged-release tablets contain lactose and lecithin (of Soya origin).

## PRECAUTIONS

Use CORTIMENT prolonged-release tablets 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 the use of glucocorticoids may have unwanted effects.

### ***Hypercorticism and HPA axis suppression***

Glucocorticoids may cause suppression of the HPA axis and reduce the stress response. Where patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is recommended. Since CORTIMENT prolonged-release tablet is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. 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 ADVERSE EFFECTS).

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### ***Transfer from other steroid therapy***

CORTIMENT prolonged-release tablets results in lower systemic steroid levels than conventional oral glucocorticoid therapy. Transfer from other steroid therapy may result in symptoms relating to the change in systemic steroid levels. Signs of adrenocortical suppression has been observed when patients are transferred from systemic corticosteroid treatment with higher systemic effect. Some patients may feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. Replacement of systemic glucocorticoids with low bio-availability formulations such as CORTIMENT prolonged-release tablets may unmask allergies such as rhinitis and eczema that were previously controlled by the systemic drug. Other symptoms associated with steroid withdrawal, such as benign intracranial hypertension may develop. Therefore monitoring of adrenocortical function may be considered in these patients and their dose of systemic steroid should be reduced with caution.

A general insufficient corticosteroid 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 corticosteroids is sometimes necessary.

### ***Immunosuppression and infections***

Suppression of the inflammatory response and immune system increases the susceptibility to infections and their severity. The clinical presentation can be atypical and serious infections such as sepsis and tuberculosis may be masked and may reach an advanced stage before being recognised.

Chicken pox and measles may follow a more serious course in patients on oral glucocorticoids. Particular care should be taken to avoid exposure in patients who have not previously had these diseases. If patients are exposed consider reduction or discontinuation of glucocorticoid treatment at the discretion of the treating physician. Therapy with varicella zoster immunoglobulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be needed. If a diagnosis of chicken pox is confirmed, the illness warrants specialist care and urgent treatment. Patients with compromised immunity who have come into contact with measles should, wherever possible, receive IVIG as soon as possible after exposure.

Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections.

Co-administration of CORTIMENT prolonged-release tablets is likely to reduce the immune response to vaccines.

### ***Increased systemic glucocorticoid susceptibility***

Impaired liver function may affect the elimination of glucocorticoids, and increased systemic availability of oral budesonide has been evidenced in patients with moderately severe hepatic cirrhosis. The risk of systemic adverse effects is increased in patients with severe liver impairment (e.g. liver cirrhosis).

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. If treatment with ketoconazole together with budesonide is indicated, discontinuation of the budesonide treatment should be considered if side effects typical of systemic

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glucocorticoids occur. Following significant intake of grapefruit juice (which inhibits CYP3A activity predominantly in the intestinal mucosa), the systemic exposure to oral budesonide increased by approximately twofold. As with other drugs primarily being metabolised by CYP3A, regular ingestion of grapefruit or grapefruit juice simultaneously with budesonide administration should be avoided (other juices such as orange juice or apple juice do not inhibit CYP3A activity) (see INTERACTIONS WITH OTHER MEDICINES).

### ***Gastrointestinal tolerance***

CORTIMENT prolonged-release tablets contain lactose monohydrate and should not be taken by patients with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

A 28-day oral repeat-dose study in cynomolgous monkeys at doses up to 18 mg/day (at least 25 times the maximal recommended daily dose in humans) reported no significant adverse effects on the gastrointestinal tract.

### ***Other glucocorticosteroid effects***

Particular care is required when considering the use of systemic corticosteroids in patients with current or previous history of severe affective disorders in the patient or any first degree relatives.

### **Effects on fertility**

There are no data on the effect of budesonide on human fertility. Subcutaneous administration of budesonide to rats at doses up to 20 µg/kg/day did not affect fertility.

### **Use in Pregnancy (Category B3)**

In animal studies, budesonide was found to cross the placental barrier. In pregnant rats and rabbits, administration of budesonide, like other glucocorticosteroids, has been shown to cause fetal death, fetal adrenal suppression, and abnormalities of fetal development (reductions in fetal/pup growth and litter size, and skeletal and visceral abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The relevance of these findings to humans has not been established, and there are limited data on pregnancy outcomes after oral administration of budesonide.

However, as with other drugs the administration of CORTIMENT prolonged-release tablets during pregnancy requires that the benefits for the mother are weighed against the risks for the fetus. CORTIMENT prolonged-release tablets should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

### **Use in Lactation**

Budesonide is excreted in breast milk. Due to first-pass metabolism in the liver on theoretical grounds, the amount of drug present in milk, and consequent exposure of the suckling infant is expected to be low. However, there are no study data on the use of oral budesonide by nursing mothers or effects on their infants. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from budesonide therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

### **Use in Children**

Safety and efficacy of CORTIMENT prolonged-release tablets in children aged 0-18 years have not yet been established. No data are available; therefore, the use in paediatric population is not

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recommended until further data become available.

### **Use in Elderly**

No special dose adjustment is recommended. However, experience of the use of CORTIMENT prolonged-release tablets in the elderly is limited.

### **Use in special populations**

CORTIMENT prolonged-release tablets were not studied in patients with hepatic and renal impairment; therefore, caution should be exercised in the administration and monitoring of the product in these patients (see PRECAUTIONS).

CORTIMENT prolonged- release tablets contain lactose monohydrate and should not be taken by patients with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

### **Carcinogenicity**

The carcinogenic potential of budesonide has been assessed in mice and rats at respective oral doses up to 200 and 50 µg/kg/day. No oncogenic effect was noted in mice. One study showed an increased incidence of malignant gliomas in male Sprague-Dawley rats given budesonide 50 µg/kg/day; however this was not confirmed in further studies in male Sprague-Dawley and Fischer rats. 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; however this was also observed in rats treated with prednisolone and triamcinolone acetonide, thus indicating a class effect of corticosteroids in rats.

### **Genotoxicity**

Budesonide had no mutagenic effects in a number of in-vitro and in-vivo tests.

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

No studies on the effects of CORTIMENT prolonged-release tablets on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or tiredness may occur (see ADVERSE EFFECTS).



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### **INTERACTIONS WITH OTHER MEDICINES**

No interaction studies have been performed.

Budesonide has a lower systemic bioavailability compared to other glucocorticoids, so drug-drug interactions may be reduced compared to many glucocorticoids. Patients with an increased risk of drug interactions include the elderly and those with impaired renal or hepatic function.

Budesonide is primarily metabolised by cytochrome P450 3A4 (CYP3A4). Inhibitors of this enzyme, e.g. ketoconazole, itraconazole, HIV protease inhibitors and grapefruit juice, can therefore increase systemic exposure to budesonide several times (see PRECAUTIONS and PHARMACOLOGY). Since there is no data to support a dosage recommendation, the combination should be avoided. 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. Budesonide is unlikely to inhibit other drugs metabolised via CYP3A4, since budesonide has low affinity to the enzyme.

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

Corticosteroid interactions that may present a significant hazard to selected patients are those with cardiac glycosides (increased effect due to reduced potassium levels) and diuretics (increased elimination of potassium).

Increased plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no such significant effect has been observed with budesonide and concomitant intake of low-dose combination oral contraceptives.

Although not studied, concomitant administration of cholestyramine or antacids may reduce budesonide uptake, in common with other drugs. Therefore, these preparations should not be taken simultaneously, but at least two hours apart.

At recommended doses, omeprazole does not affect the pharmacokinetics of oral budesonide, whereas cimetidine has a slight but clinically insignificant effect.

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### ADVERSE EFFECTS

In phase II and III clinical trials, the incidences of adverse events for CORTIMENT prolonged-release tablets, at the recommended dose of 9 mg/day, were comparable to placebo. Most adverse events were of mild to moderate intensity and of a non-serious nature. Because clinical trials are conducted under different conditions, the incidences of adverse events in these clinical trials cannot be directly compared to the incidences in other clinical trials of another product and may not reflect the incidences observed in practice.

The treatment-emergent adverse events occurring in  $\geq 5.0\%$  of patients reported for CORTIMENT prolonged-release tablets and placebo during the phase III clinical trials can be seen in Table 2:

Table 2: Adverse events with a frequency  $\geq 5\%$  observed in phase III clinical trials.

Adverse event	CORTIMENT 9 mg, prolonged-release tablets N = 255 (%)	Placebo N = 258 (%)
<b>Gastrointestinal</b>		
Colitis ulcerative	34 (13.3)	36 (14.0)
Nausea	13 (5.1)	11 (4.3)
Abdominal pain	9 (3.5)	15 (5.8)
<b>Nervous system disorders</b>		
Headache	29 (11.4)	27 (10.5)

Dose: 1 tablet daily

A summary of the CORTIMENT drug-related adverse reactions reported during phase III clinical trials can be seen in Table 3:

Table 3: Adverse reactions observed in phase III clinical trials.

	Common ( $\geq 1/100$ to $<1/10$ )	Uncommon ( $\geq 1/1,000$ to $<1/100$ )	Rare ( $\geq 1/10,000$ to $<1/1000$ )
Gastrointestinal disorders	Nausea Abdominal pain upper	Abdominal distension Abdominal pain Diarrhoea Dyspepsia	
Nervous system disorders	Headache	Somnolence	
Psychiatric disorders	Insomnia Mood altered		
Skin and subcutaneous tissue disorders		Acne	Pruritus
General disorders and administration site conditions		Drug ineffective	Fatigue Peripheral oedema
Musculoskeletal and connective tissue disorders		Pain in extremity	
Investigations	Blood cortisol decrease		
Endocrine disorders		Cushingoid syndrome	



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Infections and infestations	Influenza Upper Respiratory Tract viral infection		
Blood and lymphatic system disorders		Anaemia	

Occasionally, side effects typical of systemic glucocorticosteroids may occur. These side effects depend on the dosage, duration of treatment, concomitant or previous treatment with other glucocorticosteroids and individual sensitivity. Steroid class side effects include:

*Skin and subcutaneous tissue disorders:*

Allergic exanthema, red striae, petechiae, ecchymosis, steroid acne, delayed wound healing, contact dermatitis.

*Musculoskeletal, connective tissue and bone disorders:*

Aseptic necrosis of bone (femur and head of the humerus)

*Eye disorders:*

Glaucoma, cataract.

*Psychiatric disorders:*

Depression, irritability, euphoria.

*Gastrointestinal disorders:*

Stomach complaints, duodenal ulcer, pancreatitis.

*Metabolism and nutrition disorders:*

Cushing's syndrome, moon-face, truncal obesity, reduced glucose tolerance, diabetes mellitus, sodium retention with oedema formation, increased excretion of potassium, inactivity and/or atrophy of the adrenal cortex, growth retardation in children, disturbance of sex hormone secretion (e.g. amenorrhoea, hirsutism, impotence).

*Vascular disorders:*

Hypertension, increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy).

*Immune system disorders:*

Interference with the immune response (e.g. increase in risk of infections).

**Paediatric population**

No data available.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Australian Adverse Drug Reaction Reporting System.

## DOSAGE AND ADMINISTRATION

### Dosage

*Adults*

The recommended daily dose for induction of remission is one 9 mg tablet in the morning, for up to

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8 weeks.

### *Paediatric population*

The safety and efficacy of CORTIMENT prolonged-release tablets in children aged 0 - 18 years has not yet been established. No data are available, therefore the use in paediatric population is not recommended until further data become available.

### *Elderly*

No special dose adjustment is recommended. However, experience of the use of CORTIMENT prolonged-release tablets in the elderly is limited.

### *Hepatic and renal impairment population*

CORTIMENT was not studied in patients with hepatic and renal impairment, therefore caution should be exercised in the administration and monitoring of the product in these patients.

### *Method of administration*

One tablet of CORTIMENT is taken orally in the morning, with or without food. The tablet should be swallowed with a glass of water and must not be broken, crushed or chewed as the film coating is intended to ensure a prolonged release.

## **OVERDOSAGE**

Due to the low systemic availability of CORTIMENT prolonged-release tablets, acute overdosage even at very high doses is not expected to lead to an acute clinical crisis. In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

## **PRESENTATION AND STORAGE CONDITIONS**

The tablets are packaged in polyamide/aluminium/PVC blister foil packs with aluminium push through foil, contained in a cardboard carton.

Packs contain 10, 20, 30, 50, 60 or 80 tablets. Not all pack sizes may be marketed in Australia.

### **Storage conditions**

Store below 30°C.

### **NAME AND ADDRESS OF THE SPONSOR**

Ferring Pharmaceuticals Pty Ltd  
Suite 2, Level 1, Building 1  
20 Bridge Street  
Pymble NSW 2073  
Australia

### **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (S4)

### **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)**

31 August 2015

### **DATE OF MOST RECENT AMENDMENT**

11 November 2015