CORTIMENT 9mg, prolonged release tablets

budesonide

1 PRODUCT NAME

CORTIMENT® 9 mg, prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 9 mg of budesonide.

Excipients with known effect:
Lactose monohydrate
Contains lecithin, derived from soya oil.

For a full list of excipients, see section 6.1.

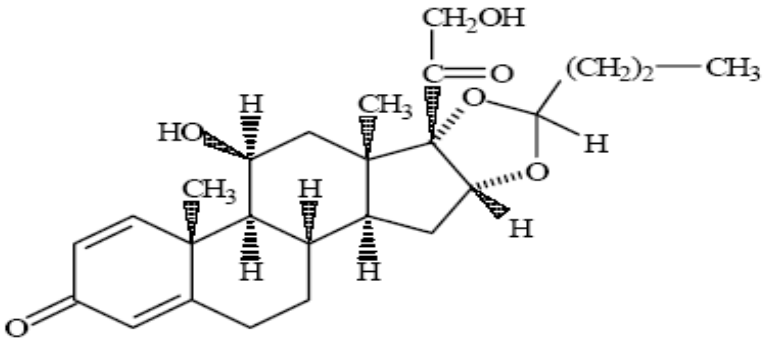
3 PHARMACEUTICAL FORM

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”.

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 16α, 17-[(1RS)-butylidenebis(oxy)]-11β, 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 $C_{25}H_{34}O_6$ and molecular weight is 430.5.
CAS No. 51333-22-3.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

Adults

The recommended daily dose for induction of remission is one 9 mg tablet in the morning, for up to 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 (see section 4.4).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance, to peanut oil or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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 section 4.8).

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 have 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 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 section 4.5).

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.

Visual disturbances

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.

Use in special populations
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.

4.5 Interaction with other medicines and other forms of interaction

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 (including cobicistat-containing products) and grapefruit juice. Co-treatment with CYP3A inhibitors is expected to increase systemic exposure to budesonide several times and the risk of systemic side effects (see sections 4.4 and 5). 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 treatments are combined,, the period between dosing of the combined 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.

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

4.6 Fertility, pregnancy and lactation

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.

Breastfeeding
Budesonide is excreted in breast milk.
Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability.

Budesonide concentrations in infant plasma samples were all less than the limit of quantification.
Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the suckling child is anticipated to be low. These data support continued use of budesonide, oral and rectal administrations, during breastfeeding.
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.

4.7 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 Section 4.8).

4.8 Undesirable effects

Adverse drug reactions reported in clinical trials with Cortiment are presented in Table 1 & 2. Adverse drug reactions reported for the therapeutic class are presented in Table 3. 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 ≥ 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 1: Adverse events with a frequency ≥ 5% observed in phase III clinical trials.

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

Dose: 1 tablet daily

Tabulated summary of adverse reactions

Adverse reactions reported are listed according to the following frequency: 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).

Table 2: Cortiment drug-related adverse reactions reported during clinical trials with more than one case (N=255)

MedDRA System Organ Classification	**Common**	**Uncommon**
Infections and infestations		Influenza
Blood and lymphatic system disorders		Leukocytosis
Psychiatric disorders	Insomnia	Mood altered
Nervous system disorders	Headache	Dizziness

MedDRA System Organ Classification	Common	Uncommon
Gastrointestinal disorders	Nausea Abdominal pain upper Abdominal distension Abdominal pain Dry mouth Dyspepsia	Flatulence
Skin and subcutaneous tissue disorders	Acne	
Musculoskeletal and connective tissue disorders	Myalgia	Back pain, Muscle spasm
General disorders and administration site conditions	Fatigue	Oedema peripheral
Investigations	Blood cortisol decreased	

Table 3: Events reported for the therapeutic class (intestinal anti-inflammatory agents, corticosteroids acting locally, budesonide)

MedDRA System Organ Classification	Common	Uncommon	Rare	Very Rare
Immune system disorders				Anaphylactic reaction
Endocrine disorders	Cushingoid features			Growth retardation in children*
Metabolism and nutrition disorders	Hypokalemia			
Psychiatric disorders	Behavioural changes such as nervousness, insomnia and mood swings Depression	Psychomotor hyperactivity Anxiety	Aggression	
Nervous system disorders		Tremor		
Eye disorders			Cataract including subcapsular cataract Glaucoma Vision, blurred (see also section **4.4**)	

MedDRA System Organ Classification	Common	Uncommon	Rare	Very Rare
Cardiac disorders	Palpitations			
Gastrointestinal disorders	Dyspepsia			
Skin and subcutaneous tissue disorders	Skin reactions (urticaria, exanthema)		Ecchymosis	
Musculoskeletal and connective tissue disorders	Muscle cramps			
Reproductive system and breast disorders	Menstrual disorders			

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 corticosteroid intake, and individual sensitivity

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 https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
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.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Intestinal anti-inflammatory agents, Corticosteroids acting locally, ATC code: A07EA06.

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 section 5.2). 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.

Pharmacodynamic effects

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.

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.

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

Clinical efficacy and safety

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 ≥ 4 and ≤ 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. Remission was defined as an UCDAI score of ≤1, with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥1 point reduction in endoscopy score. In both studies, CORTIMENT 9 mg showed superiority to placebo in inducing remission (Table 4).

Table 4: Effect of CORTIMENT 9 mg prolonged-release tablets on Primary Endpoint:

	Remission n/N (%)		**P value**
Study	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.

5.2 Pharmacokinetic properties

Absorption
Following single oral administration of CORTIMENT 9 mg in healthy subjects, maximum plasma concentration (C_{max}) of budesonide was 1.35 ± 0.96 ng/mL at 13.3 ± 5.9 hours post-dose (T_{max}), and the area under the plasma concentration time curve (AUC) was approximately 13.56 ± 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%.

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

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

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Stearic Acid (E570)
Lecithin (soya) (E322)
Microcrystalline cellulose (E460)
Hydroxypropylcellulose (E463)
Lactose Monohydrate

Silicon dioxide (E551)
Magnesium Stearate (E470b)

Tablet Film-coating
Methacrylic acid copolymer
Talc-purified (E553b)
Titanium Dioxide (E171)
Triethylcitrate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
The tablets are packaged in polyamide/aluminium/PVC blister foil packs with aluminium push through foil, contained in a cardboard carton.

Packs contain 30 tablets.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription Medicine

8 SPONSOR
Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL
21 Dec 2017

10 DATE OF REVISION OF THE TEXT
Feb 2018

(CCDS V2.0, Aug 2017)

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 4.4	Added warning about visual disturbances
Section 4.5	Added statement about potential interaction with the ACTH test.

	Wording about P450 3A4 interaction updated.
Section 4.6	Additional information about breast feeding
Section 4.8	Table numbering updated. Table 2 updated adverse reaction information. Reformat adverse reactions related to therapeutic class into Table format (Table 3). Blurred vision added.