Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cortiment 9 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 9 mg of budesonide.

Excipients with known effect:
Lactose monohydrate 50 mg
Contains lecithin, derived from soya oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

White to off-white, round, biconvex, film-coated, gastro-resistant tablet, approximately 9.5 mm diameter, approximately 4.7 mm thickness, debossed on one side with “MX9”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cortiment is indicated in adults for:

- induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient
- induction of remission in patients with active microscopic colitis (MC)

4.2 Posology and method of administration

Posology

Adults

Ulcerative colitis and microscopic colitis:
The recommended daily dose for induction of remission is one 9 mg tablet in the morning, for up to 8 weeks.

When treatment is discontinued, it may be useful to gradually reduce the dose (for more details on treatment discontinuation, see section 4.4).

Paediatric population

The safety and efficacy of Cortiment tablets in children aged 0-18 years have 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 in the elderly is limited.

Hepatic and renal impairment population

Cortiment 9 mg 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 9 mg 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cortiment tablets should be used 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.

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.

Reduced liver function may affect the elimination of glucocorticoids including budesonide, causing higher systemic exposure. Be aware of possible systemic side effects. Potential systemic effects include glaucoma.

When treatment is to be discontinued, it may be useful to gradually reduce the dose at the discretion of the treating physician.

Treatment with Cortiment 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. Some patients may feel unwell in a non-specific way during the withdrawal phase, e.g., pain in muscles and joints. 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.

As corticosteroids are known to have immunological effects the co-administration of Cortiment tablets is likely to reduce the immune response to vaccines.

Concomitant administration of ketoconazole or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the Cortiment dose could also be considered (see also section 4.5). Following significant intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased by approximately twofold. As with other drugs primarily being metabolised through CYP3A4, 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 CYP3A4 activity). See also section 4.5.

Cortiment tablets contain lecithin (soya oil). If a patient is hypersensitive to peanut or soya, this medicine should not be used.

Cortiment 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.

The following warnings and precautions have been generally identified for corticosteroids:

- Adrenocortical suppression has been observed when patients are transferred from systemic corticosteroid treatment with higher systemic effect.
- Suppression of the inflammatory response and immune system increases the susceptibility to infections.
- Corticosteroids may cause suppression of the HPA axis and reduce the stress response. Where patients are subject to surgery or other stresses, supplementary systemic corticosteroid treatment is recommended.

- 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 infected or suspected of being infected, consider reduction or discontinuation of glucocorticosteroid treatment at the discretion of the treating physician.
- 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).
- 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. Replacement of high systemic effect corticosteroid treatment sometimes unmasks allergies, e.g. rhinitis and eczema that were previously controlled by the systemic drug.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

Budesonide is primarily metabolized by cytochrome P450 3A4 (CYP3A4). Inhibitors of this enzyme are 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 section 4.4). 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 metabolized 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 heart 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 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 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

Data on use of inhaled budesonide in a very large number of exposed pregnancies indicate no adverse effects. Although there are no data of outcomes of pregnancies after oral administration, the bioavailability after oral administration is low. In animal experiments, at high exposures, corticosteroids proved to be harmful (see section 5.3). Cortiment should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

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 breast-feeding.

Fertility

There is no data on the effect of Cortiment on fertility in humans. There were no effects on fertility in rats after treatment with budesonide.

4.7 Effects on ability to drive and use machines

No studies on the effects of Cortiment 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. Adverse drug reactions reported for the therapeutic class are presented in Table 2. In Phase II and III clinical trials, the incidence of adverse events for Cortiment tablets, at the recommended dose of 9 mg/day, was comparable to placebo. Most adverse events were of mild to moderate intensity and of a non-serious nature.

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

MedDRA System Organ Classification	**Preferred Term of Adverse Drug Reaction**	
	Common	**Uncommon**
Infections and infestations		Influenza
Blood and lymphatic system disorders		Leukocytosis
Psychiatric disorders	Insomnia	Mood altered
Nervous system disorders	Headache	Dizziness
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 spasms
General disorders and administration site conditions	Fatigue	Oedema peripheral
Investigations	Blood cortisol decreased	

Table 2 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)	
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			

* Note that Cortiment is not recommended for use in children (see 4.2)

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

Side effects typical of systemic corticosteroids (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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Due to the low systemic availability of Cortiment 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, Corticosteroids acting locally

ATC code: A07E A06

Mechanism of action

The exact mechanism of action of budesonide in the treatment of UC and MC 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 significantly less HPA axis suppression and has a lower impact on inflammatory markers.

Data from clinical pharmacology and pharmacokinetic studies indicate that the mode of action of Cortiment tablets is based on a local action in the gut.

Pharmacodynamic effects

MMX extended release technology is characterised by a multi-matrix structure covered by a gastro-resistant coating that dissolves in intestinal fluids having a pH greater than 7.
When the dosage form is administered, the gastro-protective layer protects the dosage form during transit through the stomach and duodenum up to the lower part of the intestine. When the protective layer is lost, the 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 then released into the intestinal tract at a controlled rate throughout the colon.

Budesonide is a glucocorticoid used in the treatment of inflammatory bowel disease. It has a topical anti-inflammatory activity, but does not reduce cortisol levels to the same extent as systemic glucocorticoids.

Clinical efficacy

Ulcerative colitis:

Two randomised, controlled phase III clinical trials including 1022 patients with mild to moderate active UC have been performed in adult patients. Two hundred fifty five (255) patients were treated for 8 weeks with Cortiment 9 mg per day. Patients included were either treatment naïve (42% ITT) or had failed on 5-ASA (58% ITT). Both studies included a reference arm, mesalazine (Asacol) and budesonide (Entocort), respectively to show assay sensitivity. The definition of remission applied in both studies was UCDAI score of $\leq$1, with 0 score for rectal bleeding and stool frequency, normal mucosa (no friability) and $\geq$1 point reduction in endoscopy score.

Effect of Cortiment 9mg tablet on Primary Endpoint:

Study	Cortiment 9 mg Remission (%)	Placebo Remission (%)	P=
Study CB-01-02/01	17.9	7.4	0.0143
Study CB-01-02/02	17.4	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 were not available. Therefore, the place in the therapeutic work-up remains to be established. Some patients may benefit from treatment initially with Cortiment.

Evidence for the indication microscopic colitis (collagenous colitis and lymphocytic colitis) is presented below. This evidence comes from studies on budesonide product Entocort. The systemic availability of this product is similar to that of budesonide product Cortiment (see section 5.2).

Collagenous colitis:
Two randomised, double-blind, placebo-controlled induction studies of six and eight weeks duration investigated the clinical and histological effects of budesonide 9 mg/day in the treatment of collagenous colitis. In the first study, 23 patients were randomised to budesonide 9 mg/day and 22 patients to placebo for 6 weeks. The rate of clinical remission was significantly higher ($p<0.001$) in the budesonide group than in the placebo group 86.9% vs. 13.6%. Histologic improvement was observed in 14 patients of the budesonide group (60.9%) and in one patient of the placebo group (4.5%; $p<0.001$). In the second study, 10 patients were randomised to budesonide for 8 weeks (9 mg/day 4 weeks, 6 mg/day 2 weeks, and 3 mg/day 2 weeks) and ten to placebo. All 10 patients receiving budesonide had a clinical response compared with two in the placebo group ($p<0.001$). Two open-label studies (run-in phase of randomised, double-blind, placebo-controlled maintenance studies) investigated the efficacy of budesonide 9 mg/day during 6 weeks. In the first study, 46 patients (96%) achieved clinical remission within 2–30 (mean 6.4) days, with marked improvements in stool consistency. In the second study, of the 42 patients who commenced the study, 34 patients (81%) were in clinical remission (mean stool frequency of three or fewer per day) at week 6.

Lymphocytic colitis:
Evidence for this indication is limited. One randomised, double-blind placebo-controlled study was carried out in 15 lymphocytic colitis patients. Eleven subjects were treated with budesonide 9 mg/day and four patients received placebo for 8 weeks. A clinical response (defined as at least 50% improvement in the frequency of bowel movements) was seen in 25% of the placebo group vs. 91% in the budesonide group ($p=0.03$).

Paediatric Population

Cortiment was not studied in the paediatric population.

5.2 Pharmacokinetic properties

Absorption

After oral dosing of plain micronised compound, absorption seems to be complete. A large proportion of the unformulated drug is absorbed from the ileum and ascending colon.

Systemic availability of Budesonide following a single administration of Cortiment tablets in healthy volunteers was compared to that of Entocort and the result was similar, about 10%, due to first pass metabolism in the liver. Maximum plasma concentrations of budesonide are approximately 1.3-1.8 ng/ml at 13-14 hours post administration. Concomitant administration of Cortiment tablets with food had no clinically relevant effect on absorption. It has been shown that there is no potential for drug accumulation on repeated dosing.

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).

Paediatric Population

No data or experience is available with respect to the pharmacokinetics of Cortiment tablets in the paediatric population.

5.3 Preclinical safety data

A preclinical toxicology and toxicokinetic bridging study, comparing Cortiment tablets with an existing prolonged release budesonide formulation (Entocort® EC 3 mg capsules, AstraZeneca) in cynomolgous monkeys has confirmed that Cortiment tablets result in a delayed peak exposure and reduced total exposure compared to the existing formulation of budesonide, while maintaining a superimposable toxicological profile.

Preclinical data have shown that budesonide produces effects less severe or similar to other glucocorticoids, such as weight increase, atrophy of the adrenal glands and thymus and effects on the leucocyte count. As with other glucocorticosteroids, and dependent on the dose and duration and the diseases concerned, these steroid effects may also be relevant in man.

Budesonide had no effect on fertility in rats. In pregnant rats and rabbits, budesonide, like other glucocorticosteroids, has been shown to cause foetal death and abnormalities of foetal development (smaller litter size, intrauterine foetal growth retardation and skeletal abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The relevance of these findings to man has not been established (see also section 4.6).

Budesonide had no mutagenic effects in a number of in vitro and in vivo tests. A slightly increased number of basophilic hepatic foci were observed in chronic rat studies with budesonide, and in carcinogenicity studies an increased incidence of primary hepatocellular neoplasms, astrocytomas (in male rats) and mammary tumours (in female rats) were observed. These tumours are probably due to the specific steroid receptor action, increased metabolic burden and anabolic effects on the liver, effects which are also known from rat studies with other glucocorticosteroids and therefore represent a class effect in this species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Stearic Acid (E570)
Lecithin (soya) (E322)
Microcrystalline cellulose (E460)
Hydroxypropylcellulose (E463)
Lactose Monohydrate
Silica, Colloidal Hydrated (E551)
Magnesium Stearate (E470b)

Tablet Film-coating
Methacrylic acid – methyl methacrylate copolymer (1:1)

Methacrylic acid – methyl methacrylate copolymer (1:2)
Talc (E553b)
Titanium Dioxide (E171)
Triethyl citrate

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 foil blister 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.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd
United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1009/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th December 2014Date of last renewal: 28th February 2018

10 DATE OF REVISION OF THE TEXT

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