SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Budesonide 3 mg prolonged-release capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains approximately 3 mg of budesonide.

Excipient(s) with known effect

- Each 3 mg capsule contains approximately 285 mg of sucrose

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release capsule

Swedish-orange opaque cap and light-grey opaque body prolonged-release hard gelatine capsules. Size approximately 19 mm length filled with white to off-white gastro-resistant prolonged-release pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn's disease - Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon.

Microscopic colitis - Induction of remission in patients with active microscopic colitis. Maintenance of remission in patients with microscopic colitis.

4.2 Posology and method of administration

Posology

Adults

Active Crohn's disease: The recommended daily dose for induction of remission is 9 mg once daily in the morning, for up to eight weeks. The

full effect is usually achieved within 2–4 weeks.
When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy.

Paediatric population
There are limited data on the use of budesonide in children (see Sections 5.1 and 5.2). The available data are insufficient to support safety and efficacy in the paediatric population, therefore such use cannot be recommended until further data become available.

Older people
No special dose adjustment is recommended. However, experience with budesonide in older people is limited.

Method of administration
For oral use. Capsules should be swallowed whole with water and should not be sucked, chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

Side effects typical of systemic corticosteroids may occur. Potential systemic effects include glaucoma.

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 serious chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use 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 glucocorticosteroids may have unwanted effects.

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

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).

Treatment with budesonide 3 mg prolonged-release capsules results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy. When patients are transferred from systemic glucocorticosteroid treatment with higher systemic effect to budesonide 3 mg prolonged-release capsules, they 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.

Replacement of high systemic effect glucocorticosteroid treatment with budesonide capsules sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic drug.

Chicken pox and measles can have a more serious course in patients on oral glucocorticosteroids. 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 glucocorticosteriods treatment and immediately consult a physician. Glucocorticosteroids may cause suppression of the hypothalamus-pituitary-adrenal (HPA) axis and reduce the stress response. Where patients are subject to surgery or other stress situations, supplementary systemic glucocorticoid treatment is recommended.

Reduced liver function affects the elimination of glucocorticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects. The pharmacokinetics after oral ingestion of budesonide was affected by compromised liver function as evidenced by increased systemic availability in patients with moderately severe hepatic cirrhosis.

When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy. Some patients 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 should occur. In these cases a temporary increase in the dose of systemic glucocorticosteroids is sometimes necessary.

Co-treatment with CYP3A inhibitors, including ketoconazole and cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects. If this is not possible, the period between treatments should be as

long as possible and a reduction of the budesonide dose could also be considered (see also Section 4.5).

After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. As with other drugs primarily metabolised through CYP3A4, regular ingestion of grapefruit or its juice, should be avoided in connection with budesonide 3 mg prolonged-release capsules administration (other juices such as orange juice or apple juice do not inhibit CYP3A4). See also Section 4.5.

When budesonide 3 mg prolonged-release capsules are used chronically in excessive doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear.

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

Paediatric population

It is recommended that the height of children receiving prolonged treatment with glucocorticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated. The benefits of the glucocorticosteroid therapy and the possible risks of growth suppression must be carefully weighed. Long-term studies have not been performed in children treated with budesonide 3 mg prolonged-release capsules.

4.5 Interaction with other medicinal products and other forms of interaction

Although not studied, concomitant administration of colestyramine may reduce budesonide uptake, in common with other drugs.

Raised plasma concentrations of and enhanced effects of corticosteroids have been reported in women also treated with oestrogens and contraceptive steroids.
However, a low-dose combination oral contraceptive that more than doubled the plasma concentration of oral prednisolone, had no significant effect on the plasma concentration of oral budesonide.

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

The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome P450 enzymes.

Inhibitors of this enzyme, e.g. ketoconazole, itraconazole, HIV protease inhibitors and grapefruit juice, can therefore increase systemic exposure to budesonide several times (see Sections 4.4 and 5.2). 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. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide. Inhibition by budesonide on other drugs metabolism via CYP3A4 is unlikely, 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.

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

The ability of corticosteroids to cross the placenta varies between individual drugs, however, in mice, budesonide and/or its metabolites have been shown to cross the placenta.

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities in foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

As with other drugs the administration of budesonide 3 mg prolonged-release capsules during pregnancy requires that the benefits for the mother are weighed against the risk for the foetus.

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.

Infants of mothers taking higher than recommended doses of budesonide may have a degree of adrenal suppression.

These data support continued use of budesonide, oral and rectal administrations, during breast-feeding.

4.7 Effects on ability to drive and use machines

Budesonide 3 mg prolonged-release capsules has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Adverse drug reactions by frequency and system organ class (SOC)

SOC	**Frequency**	**Reaction**
Immune system disorders	Very rare	Anaphylactic reaction
Endocrine disorders	Common	Cushingoid features
	Very Rare	Growth retardation
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	Glaucoma, 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
Reproductive system and breast disorders	Common	Menstrual disorders

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

Description of selected adverse events

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.

In clinical studies, at recommended doses, the incidence of adverse events was comparable to placebo.

Clinical studies showed the frequency of steroid associated side effects for budesonide 3 mg prolonged-release capsules to be approximately half that of conventional prednisolone treatment, at equipotent doses. In studies of patients with active disease, receiving budesonide 9 mg daily, the incidence of adverse events was comparable to placebo. Very rarely a wide range of psychiatric/ behavioural effects may occur, when systemic steroids are prescribed at high doses and for prolonged periods (See Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the 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 United Kingdom (Northern Ireland) Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Reports of acute toxicity or death following overdosage of glucocorticosteroids are rare. Thus, acute overdosage with budesonide even in excessive 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.

Chronic overdosage may lead to systemic corticosteroid effects, such as Cushingoid features. If such changes occur, the dose of budesonide should be gradually reduced until treatment is discontinued, in accordance with normal procedures for the discontinuation of prolonged oral glucocorticosteroid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids acting locally, ATC code: A07EA06.

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.

The exact mechanism of budesonide in the treatment of Crohn´s disease is not fully understood.

Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of budesonide is based, at least partly, on a local action in the gut. Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. At doses clinically equivalent to prednisolone, budesonide gives significantly less HPA axis suppression and has a lower impact on inflammatory markers.

At recommended doses, budesonide 3 mg prolonged-release capsules caused significantly less effect than prednisolone 20–40 mg daily on morning plasma cortisols; on 24 hour plasma cortisol (AUC 0–24 h) and on 24 hour urine cortisol levels.

ACTH tests have shown budesonide to have significantly less effect than prednisolone on adrenal functions.

Paediatric population

HPA axis function. At recommended doses, budesonide cause significantly less effect than prednisolone 20-40 mg daily on morning plasma cortisol, on 24-hour plasma cortisol (AUC 0-24 h) and on 24-hour urine cortisol. Also, ACTH tests have shown that budesonide, compared with prednisolone, have significantly less

impact on the adrenal function. Children with Crohn's disease have a slightly higher systemic exposure and cortisol suppression than adults with Crohn's disease.

Long-term studies have not been performed in children treated with budesonide capsules. In a study evaluating the effect of budesonide on cortisol suppression in 8 children (range 9–14 years) and 6 adults, the oral administration of 9 mg budesonide for 7 days induced a mean cortisol suppression (± SD) of 64% (± 18%) in children and 50% (± 27%) in adults with respect to baseline values. No clinically relevant findings in terms of safety have been reported. (Study 08-3044)

A study performed in children with mild to moderate Crohn's disease (CDAI ≥ 200) compared the activity of budesonide at the dose of 9 mg once daily with that of prednisolone, administered at tapering doses, starting from 1 mg/kg. 22 patients were treated with budesonide and 26 patients were treated with the reference drug prednisolone. After 8 weeks of treatment, 70.8% of patients treated with prednisolone reached the endpoint (CDAI ≤ 150), as compared to 54.5% of subjects treated with budesonide, the difference was not statistically significant (p =0.13). In the course of the study, adverse events were observed in 96% of patients treated with prednisolone and 91% of patients treated with budesonide. The nature of these adverse events was similar in both study arms, but the incidence of glucocorticoid-related side-effects (such as acne and moon face) was lower in patients treated with budesonide. (Study SD-008-3037)

Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Budesonide in 108 paediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of budesonide of 58 days (range: 5 days to 90 days). Patients were dosed with oral budesonide once daily according to bodyweight, patients weighing ≤25 kg received 6 mg once daily for 8 weeks; patients weighing >25 kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean (±SD) PCDAI score from 19.1 (±10.1) to 9.1 (±8.5), indicating an improvement in disease activity; with an improvement in mean (±SD) IMPACT 3 score from 132.1 (±18.8) to 140.9 (±16.9). AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

Study D9422C00002 was an open-label, un-comparative study designed to evaluate budesonide 6 mg once daily as maintenance treatment in 50 paediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI ≤10). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of budesonide was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with budesonide 6 mg daily. At the same points in time the mean IMPACT 3 score was
145.62 (12.43) and 146.98 (15.48), respectively. AEs were observed at a similar

frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

5.2 Pharmacokinetic properties

Absorption

After oral dosing of plain micronised compound, absorption is rapid and seems to be complete. A large proportion of the drug is absorbed from the ileum and ascending colon. Systemic availability in healthy subjects is approximately 9–12% for budesonide. This is similar to the systemic availability of plain micronized budesonide, indicating complete absorption. In patients with active Crohn's disease systemic availability is approximately 12–20% at the start of treatment.

Distribution

Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85–90%. In healthy volunteers mean maximal plasma concentrations of 5–10 nmol/L were seen at 3–5 hours following a single oral dose of budesonide 9 mg.

Biotransformation

Budesonide then undergoes extensive biotransformation in the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid 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 is rate limited by absorption. The average terminal half-life is 4 hours. Budesonide has a high systemic clearance (about 1.2 L/min).

Paediatric population

In a study comparing the pharmacokinetics of budesonide in 8 children (range 9–14 years) and 6 adults, budesonide 9 mg for 7 days induced a systemic exposure (AUC) that was 17% higher in children than in adults, with maximum concentrations (Cmax) 50% higher in children than in adults (mean AUC ± SD: children 41.3 nmol/L ± 21.2; adults 35.0 nmol/L ± 19.8. Mean Cmax ± SD: children 5.99 nmol/L ± 3.45; adults 3.97 nmol/L ± 2.11.) (Study 08-3044).

5.3 Preclinical safety data

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe or similar to those observed after administration of other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

Budesonide, evaluated in six different test systems, did not show any mutagenic or clastogenic effects.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide as well as the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

The toxicity of Budesonide, with focus on the gastro-intestinal tract, has been studied in cynomolgus monkeys in doses up to 5 mg/kg after repeated oral administration for up to 6 months. No effects were observed in the gastrointestinal tract, neither at gross pathology nor in the histopathological examination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sugar spheres (Maize starch & Sucrose),
Ethylcellulose,
Polysorbate 80,
Methacrylic acid-methyl methacrylate copolymer (1:1),
Triethyl citrate,
Talc

Capsule shell
Black iron oxide
E172 Red Iron
Oxide E172
Titanium dioxide
E171 Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original container in order to protect from light/moisture

6.5 Nature and contents of container

Budesonide are available in packs containing 20, 45, 50, 60, 90 or 100 capsules in HDPE bottles. 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

Laboratorios Liconsa S.A
Dulcinea s/n,
28805 Alcalá de Henares
Madrid
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 23218/0264

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/01/2022

10 DATE OF REVISION OF THE TEXT

13/10/2023