Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pinacort 3 mg modified release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 3 mg 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

Hard modified release capsule

Approximately 19 mm gelatine capsules, light grey opaque body and swedish orange opaque cap

The capsules are filled with white to off-white pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate Crohn's disease of the ileum and ascending colon.

Active microscopic colitis.

Maintenance treatment of severe, recurrent microscopic colitis. See also 4.2.

4.2 Posology and method of administration

For patients experiencing difficulty swallowing, the capsule can be opened, and the contents swallowed mixed with a tablespoon of apple purée. The capsule contents must not be broken into pieces or chewed.

Posology
Adults
The dose should be adjusted to the disease activity.

Crohn's disease: The recommended dosage in active mild to moderate Crohn's disease is 9 mg (equivalent to 3 modified release capsules) daily for 8 weeks.
The full effect is usually achieved within 2-4 weeks. The modified release capsules should be taken in the morning. The modified -release capsules should be swallowed whole.
The recommended dosage for disease remission is 6 mg (equivalent to 2 modified release capsules) daily. Long-term use is not recommended.
When replacing prednisolone in steroid-dependent patients, 6 mg daily is recommended. When commencing treatment with Pinacort, the prednisolone dosage should be reduced.

Microscopic colitis:
Induction of remission: The recommended dosage in the active disease is 9 mg (equivalent to 3 capsules) once daily for 8 weeks.
Maintenance of remission in patients with microscopic colitis: Maintenance of remission therapy should be used only in patients who have already had a recurrence after discontinuation of induction therapy. The recommended dose is 2 capsules per day (i.e. 6 mg budesonide) taken as a single dose in the morning.

The lowest effective dose should be used. The treatment should be evaluated regularly to assess if continued treatment is necessary.

Discontinuation of treatment should be done gradually by decreasing the dose.

The modified release capsules should be taken in the morning.

The elderly
Dosage as for adults. Experience is limited in respect of treatment of the elderly with Pinacort

Paediatric population
Children ≥ 8 years, with a body weight exceeding 25 kg: The recommended dosage for active, mild to moderate Crohn's disease is 9 mg (equivalent to 3 modified release capsules) daily for 8 weeks. The full effect is usually achieved within 2-4 weeks. The modified release capsules should be taken in the morning, see sections 4.8, 5.1 and 5.2.
No experience is available with respect to courses of treatment longer than 12 weeks.

Patients suffering from diseases of the liver
Hepatic impairment increases the systemic availability of budesonide.
Where patients are subject to surgery, fever or other stress situations, the dose may need to be increased, or supplementary systemic glucocorticoid treatment is recommended. People with diabetes may need an increase in their dose of insulin.
The treatment should not be stopped abruptly, but withdrawn gradually (tapering doses), see section 4.4.

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 may arise that are typical of systemic corticosteroids. Possible systemic effects include glaucoma.

Caution is required when treating patients with infections, hypertension, diabetes mellitus, osteoporosis, gastric ulcer, glaucoma or cataracts, or with a heredity proclivity toward diabetes or glaucoma or other conditions, since corticosteroids may produce adverse effects.

When patients are transferred from higher systemic corticosteroid therapy to Pinacort, they may develop adrenal suppression.

Chickenpox and measles may worsen in patients treated with oral glucocorticosteroids. Special care should therefore be taken with regard to exposure in patients who have not had or lack protection against these diseases. Treatment with VZIG (Varicella zoster immunoglobulin) or IVIG (pooled intravenous immunoglobulin) may be indicated. If chickenpox develops, antiviral therapy may be undertaken.
The dosage should be discontinued gradually as the patient's own ACTH secretion may be reduced following prolonged treatment with Pinacort. Some patients generally feel unwell during the discontinuation phase with, for example, pain in muscles and joints. A generally insufficient steroid effect should be suspected if, in rare cases, symptoms such as fatigue, headache, nausea and vomiting occur. In these cases, a temporary increase in the systemic glucocorticoid dosage may be required.

When Pinacort replace a systemic steroid treatment, allergies such as rhinitis and eczema, which were previously controlled with the systemic treatment, sometimes re-emerge.

Budesonide may reduce the response of the HPA axis to stress. Where surgery or other stressful situations occur, the addition of a systemic glucocorticoid is recommended.

Hepatic impairment affects the elimination of corticosteroids, leading to lower elimination rates and increased systemic exposure. Be aware of any systemic side effects.

The metabolism of budesonide is mediated mainly by CYP3A. Concomitant treatment with CYP3A inhibitors, including ketoconazole or medicinal products containing cobicistat, is expected to increase the risk of systemic adverse reactions. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, and if so, patients should be monitored for said systemic corticosteroid side effects. If this is not possible, the time interval between

dosages of the products should be as long as possible and a reduction of the budesonide dosage should also be considered (see also section 4.5).

After abundant intake of grapefruit juice (which inhibits CYP3A4 activity mainly in the intestinal mucosa), the systemic exposure to oral budesonide increases approximately twofold. As with other drugs that are primarily metabolised by CYP3A4, the regular intake of grapefruit or grapefruit juice in conjunction with the administration of budesonide should be avoided (other juices, such as orange juice or apple juice, do not inhibit CYP3A4). See also section 4.5.

With long-term use of high-dose Pinacort, systemic glucocorticoid effects, such as hypercorticism and inhibition of adrenal cortex function may occur.
Experience with the use of budesonide or other glucocorticoids in relapsing Crohn's disease after prolonged treatment is limited.
Direct comparative studies of efficacy/side effects between long-term treatment with budesonide compared with pulsatile treatment with glucocorticoids are lacking.

Visual disturbances
Visual disturbances may be reported during systemic and topical use of corticosteroids. If a patient presents with symptoms such as blurred vision or other visual disorders, consideration should be given to whether the patient should be referred to an ophthalmologist for investigation of the possible causes of these symptoms. These may include cataracts, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR), which have been reported following the use of systemic and topical corticosteroids.

Paediatric population
Caution when treating growing individuals. Control of height growth is recommended in children and adolescents.

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

4.5 Interaction with other medicinal products and other forms of interaction

At recommended dosage levels, omeprazole does not affect the pharmacokinetics of oral budesonide, whereas cimetidine has a weak but clinically insignificant effect.
Metabolism of budesonide is mainly mediated by CYP3A4.
Inhibitors of this enzyme, e.g., ketoconazole, itraconazole and HIV protease inhibitors, may therefore increase the systemic exposure to budesonide several times, see section 4.4. Since there is no data available to support a dosage recommendation, the combination should be avoided. If this is not possible, the time interval between dosages of the products should be as long as possible and a reduction of the budesonide dosage should also be considered.
Budesonide is unlikely to inhibit the metabolism of other drugs via CYP3A4, as budesonide has a low affinity for this enzyme.
Concomitant treatment with CYP3A4 inducers, such as carbamazepine, may reduce budesonide exposure, and this which may require a dosage increase.
Elevated plasma concentrations and increased 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 low-dose combined contraceptive pill.
Because adrenal function may be impaired, an ACTH stimulation test to diagnose pituitary insufficiency may show erroneous results (low values).

4.6 Fertility, pregnancy and lactation

Pregnancy
In pregnant animals, administration of budesonide, like other corticosteroids, is associated with abnormalities in foetal development. The relevance of these findings to humans has not been established. As with other medicines, administration of budesonide during pregnancy requires that the benefits to the mother be weighed against the risks to 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 pharmacokinetic properties within the therapeutic dosage ranges after inhaled, oral and rectal administration, the exposure of the breast-fed infant is expected to be low.

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

4.7 Effects on ability to drive and use machines

Pinacort has zero or negligible influence on the ability to drive vehicles and use machines.

4.8 Undesirable effects

The side effects observed with Pinacort capsules are shown in the table below.

The following definitions apply to the occurrence of side effects:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), no known frequency (cannot be calculated from the available data).

Organ system	Common	Uncommon	Rare	Very rare
Immune system:				Anaphylactic reaction.
Endocrine system:	Cushing's syndrome-like symptom picture.			Growth inhibition.
Metabolism and nutrition:	Hypokalaemia.			
Mental disorders:	Behavioural changes such as nervousness, insomnia, mood swings and depression.	Anxiety.	Aggression.	
Central and peripheral nervous system:		Tremors, psychomotor hyperactivity.		
Eyes:			Glaucoma, cataract including subcapsular cataract, blurred vision (see also section 4.4).	
Heart:	Palpitations.			
Gastrointestinal tract:	Dyspepsia.			
Skin and subcutaneous tissue:	Skin reactions (urticaria, exanthema).		Ecchymosis.	
Musculoskeletal and connective tissue disorders:	Muscle cramps.			
Reproductive system and mammary glands:	Menstrual disorders.			

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

Description of selected adverse events
Typical side effects such as systemic glucocorticosteroids (e.g., Cushing's syndrome-like symptoms and growth retardation) may occur. These side effects depend on the dosage, duration of treatment, concomitant and/or previous intake of glucocorticosteroids and individual sensitivity.
Clinical studies have shown that the frequency of glucocorticosteroid-related adverse reactions is lower (approximately halved) when using Pinacort compared to prednisolone at the same therapeutic doses.

Paediatric population
Systemic therapy and inhalation therapy with corticosteroids, including Pinacort, may cause a decreased growth rate in children. No long-term studies have been performed in children treated with Pinacort. Based on available data from short-term studies (see section 5.1), the overall observed safety profile of Pinacort in paediatric patients is consistent with the safety profile in adults.

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

Reports of acute toxicity or death from a glucocorticosteroid overdose are rare. Acute overdosing, even at high dose levels, is not expected to cause any clinical problems. No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticosteroid for local treatment, ATC code: A07EA06

Mechanism of action
The mechanism of action of glucocorticosteroids in the treatment of Crohn's disease is not fully understood. Anti-inflammatory effects such as inhibition of the release of inflammatory mediators and inhibition of cytokine-mediated immune systems are likely to be important.

Clinical efficacy and safety
Clinical data indicate that budesonide has a strong local anti-inflammatory effect. Compared with prednisolone 40 mg, budesonide has an equivalent clinical frequency of remission in patients with a mild to moderate disease (CDAI score < 450), but at recommended doses significantly less effect on the HPA axis (both on morning plasma cortisol and 24-hour plasma and urinary cortisol) and systemic inflammatory markers, blood glucose and serum alkaline phosphatase.
ACTH tests have shown a significantly reduced effect on adrenal function at the recommended dosage than after treatment with prednisolone 40 mg.
In a subgroup analysis of adult steroid-naïve patients, in which bone density was monitored for two years, treatment with budesonide showed significantly less bone calcification than with prednisolone treatment. In previously steroid-treated patients, no difference was detected between the treatment groups.
The estimated dosage of budesonide needed to suppress cortisol plasma concentrations as much as 20 mg prednisolone did, is 29 mg – 3 times the maximum daily dose of budesonide.

Paediatric population
Long-term studies have not been carried out in children treated with budesonide. In a study evaluating the effect of budesonide on cortisol suppression in 8 children (in a range of 9-14 years) and 6 adults, 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 compared with baseline values. No clinically relevant safety findings have been reported. (Study 08-3044). A study undertaken in children with mild to moderate Crohn's disease (CDAI ≥ 200) compared the effect of budesonide capsules at a dosage of 9 mg once daily with the effect of prednisolone given in tapering doses starting at 1 mg/kg. Twenty-two patients were treated with budesonide capsules and 26 were treated with the reference drug prednisolone. After 8 weeks of treatment, 70.8% of patients treated with prednisolone achieved the efficacy measure (CDAI ≤ 150) compared with 54.5% of patients treated with

budesonide. The difference was not statistically significant (p = 0.13). During the study, adverse reactions were observed in 96% of patients treated with prednisolone and in 91% of patients treated with budesonide. The nature of these side effects was similar in both study arms, but the incidence of glucocorticoid-related side effects (such as acne and Cushing's syndrome – "moon face") was lower in patients treated with budesonide.
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 in the ileum and/or ascending colon. Median treatment time with budesonide was 58 days (range: 5 days to 90 days). Patients were treated with budesonide orally once daily, dosage depending on body weight – 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 treatment weeks, a decrease in the mean (± SD) of PCDAI values was seen from 19.1 (± 10.1) to 9.1 (± 8.5), indicating an improvement in disease activity; with an improvement in mean (± SD) for IMPACT 3 values from 132.1 (± 18.8) to 140.9 (± 16.9). Side effects were observed at a similar frequency and severity as in adults, and were mainly related to Crohn's disease, puberty and possible glucocorticosteroid-related side effects.
Study D9422C00002 was an open-label, non-comparative study designed to evaluate budesonide, 6 mg once daily as maintenance therapy in 50 paediatric patients (children and adolescents, aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease in ileum and/or ascending colon that was in clinical remission (PCDAI ≤ 10). The treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily and a 2-week phase-out phase of 3 mg once daily. The median duration of treatment with budesonide was 98.5 days (range: 11 days to 135 days). Most patients remained in clinical remission because there were no major changes in mean PCDAI values or IMPACT 3 values. The mean (± SD) for PCDAI was 4.85 (3.62) initially and 6.89 (8.08) after 12 weeks of maintenance treatment with budesonide, 6 mg daily. At the same time, the mean IMPACT 3 values were 145.62 (12.43) and 146.98 (15.48), respectively.
Side effects were observed at a similar frequency and severity as in adults, and were mainly related to Crohn's disease, puberty and possible glucocorticosteroid-related side effects.

Collagen colitis:
Two randomised, double-blind, placebo-controlled induction studies with six and eight weeks of treatment, respectively, examined the clinical and histological effects of budesonide, 9 mg/day in the treatment of collagen colitis. In the first study, 23 patients were randomised to budesonide 9 mg/day and 22 patients to placebo for 6 weeks. The clinical remission frequency was significantly higher (p < 0.001) in the budesonide group compared with the placebo group, 86.9% and 13.6%, respectively. Histological improvement was observed in 14 patients in the budesonide group (60.9%), and in one patient in the placebo group (4.5%; p < 0.001). In the second study, 10 patients were randomised to budesonide for 8 weeks (9 mg/day for 4 weeks, 6 mg/day for 2 weeks and 3 mg/day for 2 weeks) and ten to placebo. All 10 patients receiving budesonide responded clinically compared with two in the placebo group (p <0.001).
Two open-label studies (the induction phase of randomised, double-blind, placebo-controlled maintenance studies) examined the effect of budesonide, 9 mg/day for 6 weeks. In the first study, 46 patients (96%) achieved clinical remission within 2-30 days (mean 6.4), with marked improvement in stool consistency. In the second study, 34 patients (81%) of the 42 patients who began the study were in clinical remission (average bowel movements, three or fewer per day) at week 6.

Lymphocytic colitis:
A randomised, double-blind, placebo-controlled study was performed in 15 patients with lymphocytic colitis. Eleven subjects were treated with budesonide, 9 mg/day and four patients received placebo for 8 weeks. A clinical response (defined as a minimum 50% improvement in the frequency of bowel movements) was seen in 25% in the placebo group compared with 91% in the budesonide group (p = 0.03).

5.2 Pharmacokinetic properties

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

Children appear to have slightly higher plasma concentrations of budesonide than adults at recommended dosage.

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 (approximately 90%) 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. The metabolites are excreted unchanged or in conjugates form, mainly through the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (about 1.2 L/min), and the plasma half-life after intravenous dosing is on average 2-3 hours.

Linearity
The pharmacokinetics of budesonide is proportional to the dose in the therapeutic dose range.

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 (C_{max}) 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 C_{max} ± SD: children 5.99 nmol/L ± 3.45; adults 3.97 nmol/L ± 2.11.)

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Ethyl cellulose
Methacrylic acid-ethyl acrylate copolymer
Oleic acid
Polysorbate 80
Sugar spheres (maize starch, sucrose)
Talc
Triethyl citrate
Triglycerides, medium chain

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

Store in original bottle in order to protect from light and moisture.

This product does not require any special temperature storage restrictions.

6.5 Nature and contents of container

HDPE bottles with PP screw cap including silica desiccant packsizes containing 20, 45, 50, 90 or 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/251/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th June 2022

10 DATE OF REVISION OF THE TEXT

August 2023