Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lodotra 2 mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One modified-release tablet contains 2 mg of prednisone.

Excipient with known effect: lactose

Each modified-release tablet contains 41.80 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet

Yellowish-white, cylindrical modified-release tablet, 5 mm in height and 9 mm in diameter, with “NP2” embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lodotra is indicated for the treatment of moderate to severe, active rheumatoid arthritis, particularly when accompanied by morning stiffness, in adults.

4.2 Posology and method of administration

Posology
The appropriate dose depends on the severity of the condition and the individual response of the patient. In general, for the initiation of the therapy 10 mg prednisone is recommended. In certain cases, a higher initial dose might be required (e.g. 15 or 20 mg prednisone). Depending on the clinical symptoms and the patient’s response, the initial dose can be reduced in steps to a lower maintenance dose.

When changing over from the standard regimen (glucocorticoid administration in the morning) to Lodotra administered at bedtime (at about 10 pm), the same dose (in mg prednisone equivalent) should be maintained. Following the change-over, the dose may be adjusted according to the clinical situation.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available. For long-term therapy of rheumatoid arthritis, the individual dose of up to 10 mg prednisone daily should be adjusted according to the severity of the course of the disease.

Depending on the treatment result, the dose can be reduced in steps of 1 mg every 2 - 4 weeks to reach the appropriate maintenance dose.

In order to discontinue the therapy with Lodotra, the dose should be reduced in steps of 1 mg every 2 − 4weeks, with monitoring of pituitary-adrenal axis parameters if necessary.

Paediatric population

Because of insufficient data on tolerability and efficacy, the use in children and adolescents is not recommended.

Method of administration

Lodotra should be taken at bedtime (at about 10 pm), with or after the evening meal and be swallowed whole with sufficient liquid. If more than 2 - 3 hours have passed since the evening meal, it is recommended to take Lodotra with a light meal or snack (e.g. a slice of bread with ham or cheese). Lodotra should not be administered in the fasted state. This could result in a reduced bioavailability.

Lodotra is designed to release the active substance with a delay of approximately 4 - 6 hours after intake, the release of the active substance and the pharmacological effects will start during the night.

Lodotra modified-release tablets consist of a prednisone-containing core and an inert coating. Delayed release of prednisone is dependent on an intact coating. For this reason, the modified-release tablets are not to be broken, divided or chewed.

In patients with hypothyroidism or hepatic cirrhosis, comparatively low doses may be sufficient or a dose reduction may be necessary.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

A prednisone-based pharmacotherapy should only be given when absolutely necessary and should be accompanied by appropriate anti-infectious therapy in the presence of the following conditions:

- Acute viral infections (herpes zoster, herpes simplex, varicella, herpetic keratitis),
- HBsAg-positive chronic active hepatitis,
- Approximately 8 weeks before and 2 weeks after immunisation with live vaccines,
- Systemic mycoses and parasitoses (e.g. nematodes),
- Poliomyelitis,
- Lymphadenitis following BCG inoculation,
- Acute and chronic bacterial infections,
- History of tuberculosis (caution: reactivation!) Due to their immunosuppressive properties glucocorticoids can induce or aggravate infections. Such patients should be monitored carefully e.g. by performing a tuberculin test. Patients at special risk should receive a tuberculostatic treatment.

In addition, a prednisone-based pharmacotherapy should only be given when necessary and should be accompanied if required by appropriate therapy in the presence of the following conditions:

- Gastrointestinal ulcers,
- Severe osteoporosis and osteomalacia
- Hypertension that is difficult to control,
- Severe diabetes mellitus,
- Psychiatric disorders (also if in patient’s history),
- Narrow- and wide-angle glaucoma,
- Corneal ulcers and corneal injuries.

Because of the risk of intestinal perforation, prednisone may only be used if absolutely necessary and with adequate monitoring in cases of:

- Severe ulcerative colitis with imminent perforation,
- Diverticulitis,
- Entero-anastomoses (immediately postoperative).

Lodotra cannot achieve the desired blood concentration of prednisone if taken under fasting conditions.

Therefore, Lodotra should always be taken with or after the evening meal in order to ensure sufficient efficacy. In addition, low plasma concentrations may occur in 6% -7% of Lodotra doses as observed across all pharmacokinetic studies and 11% in a single pharmacokinetic study when taken according to the recommendations. This should be considered if Lodotra is not sufficiently effective. In these situations a switch to a conventional immediate-release formulation may be considered.

Lodotra should not be substituted by prednisone immediate-release tablets in the same administration regime because of Lodotra's delayed release mechanism.

In case of substitution, termination, or discontinuing prolonged treatment, the following risks must be considered: Recurrence of the rheumatoid arthritis disease activity, acute adrenal failure (especially in stressful situations, e. g. during infections, after accidents, with increased physical strain), cortisone withdrawal syndrome.

Lodotra should not be given as for acute indications instead of prednisone immediate-release tablets due to its pharmacological properties.

During the use of Lodotra, a possibly increased need for insulin or oral anti-diabetics should be considered. Patients with diabetes mellitus should therefore be treated under close monitoring.

During the treatment with Lodotra, regular blood pressure checks are required in patients with hypertension that is difficult to control.

Patients with severe cardiac insufficiency have to be closely monitored because of the risk of deterioration of the condition.

Caution is necessary when corticosteroids, including prednisone, are prescribed to patients with recent myocardial infarction due to the risk of myocardial rupture.

Caution is necessary when corticosteroids, including prednisone, are prescribed to patients with renal insufficiency.

Sleep disorder is documented to occur more frequently with Lodotra than with conventional immediate release formulations which are taken in the morning. If insomnia occurs and does not improve, a switch to a conventional immediate release formulation may be advisable.

The treatment with Lodotra can also mask signs and symptoms of an existing or developing infection and thus may render diagnostic efforts more difficult.

Even with low doses, long-term use of Lodotra results in an increased risk of infection. These possible infections may also be brought about by microorganisms that rarely cause infection under normal circumstances (so-called opportunistic infections).

Certain viral diseases (varicella, measles) may take a more severe course in patients treated with glucocorticoids. Immunosuppressed individuals without prior varicella or measles infection are at particular risk. If such individuals, while being treated with Lodotra, have contact with persons infected with varicella or measles, a preventive treatment should be initiated, if required.

In patients with known or suspected Strongyloides (threadworm) infestation glucocorticoids may lead to Strongyloides hyperinfection and dissemination with widespread larval migration.

Vaccinations with inactivated vaccines are generally possible. However, it has to be taken into account that the immune response and consequently the success of the vaccination may be impaired with higher doses of glucocorticoids.

In case of long-term therapy with Lodotra, regular medical follow-ups (including ophthalmologic examinations at three month intervals) are indicated; if comparatively high doses are given, sufficient supply of potassium supplements and restriction of sodium have to be ensured and serum potassium levels have to be monitored.

If during the treatment with Lodotra high levels of physical stress are caused by certain events (accidents, surgical

procedure etc.), a temporary dose increase may become necessary.

Depending on the duration of the treatment and the dosage used, a negative impact on calcium metabolism must be expected. Osteoporosis prophylaxis is therefore recommended and is particularly important if other risk factors are present (including familial predisposition, advanced age, postmenopausal status, insufficient intake of protein and calcium, excessive smoking, excessive alcohol consumption, as well as reduced physical activity). The prophylaxis is based on a sufficient supply of calcium and vitamin D, as well as on physical activity. In case of pre-existing osteoporosis, an additional therapy should be considered.

The medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

When using high doses of prednisolone for an extended period of time (30 mg/day for a minimum of 4 weeks), reversible disturbances of spermatogenesis were observed that persisted for several months after discontinuation of the medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac glycosides: The effect of the glycosides can be enhanced by potassium deficiency.

Saluretics/laxatives: Potassium excretion is enhanced.

Antidiabetic agents: The blood sugar lowering effect is reduced.

Coumarin derivatives: The efficacy of coumarin anticoagulants may be reduced or enhanced.

Non-steroidal antiphlogistic/antirheumatic agents, salicylates and indomethacin: The risk of gastrointestinal haemorrhages is increased.

Non-depolarising muscle relaxants: Muscle relaxation may be prolonged.

Atropine and other anticholinergics: The concurrent use of Lodotra may result in additional increases in intraocular pressure.

Praziquantel: Glucocorticoids may lower the praziquantel concentrations in the blood.

Chloroquine, hydroxychloroquine, mefloquine: There is an increased risk of occurrence of myopathies, cardiomyopathies.

Somatropin: The efficacy of somatropin may be reduced.

Oestrogens (e.g. oral contraceptives): May enhance the efficacy of glucocorticoids.

Liquorice: Inhibition of the metabolism of glucocorticoids is possible.

Rifampicin, phenytoin, barbiturates, bupropion and primidone: The efficacy of glucocorticoids is reduced.

Cyclosporine: The blood levels of cyclosporine are increased. There is an increased risk of seizures.

Amphotericine B: The risk of hypokalaemia may be increased.

Cyclophosphamide: The effects of cyclophosphamide may be enhanced.

ACE inhibitors: Increased risk of occurrence of blood count changes.

Aluminium and magnesium antacids: The absorption of glucocorticoids is reduced. However, due to the delayed

release mechanism of Lodotra an interaction between prednisone and aluminium/magnesium antacids is unlikely.

Impact on diagnostic methods: Skin reactions caused by allergy testing may be suppressed. The TSH increase following the administration of protirelin may be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy

During pregnancy, Lodotra should only be used when the benefits outweigh the potential risks. The lowest effective dose of Lodotra needed to maintain adequate disease control should be used.

Animal studies indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the foetus risk of intrauterine growth retardation, adult cardiovascular and/or metabolic disease and may have an effect on the glucocorticoid receptor density, and neurotransmitter turnover or neurobehavioural development.

Prednisone has caused cleft palate formation in animal experiments (see section 5.3). There is an ongoing discussion on the possibility of an increased risk of oral cleft formation in the human foetus as a result of the administration of glucocorticoids during the first trimester.

If glucocorticoids are administered towards the end of pregnancy, there is a risk of atrophy of the foetal adrenal cortex, which may necessitate replacement therapy in the newborn, which has to be slowly reduced.

Breastfeeding

Glucocorticoids pass in small amounts into breast milk (up to 0.23 % of an individual dose). For doses up to 10 mg daily, the amount taken via breast milk lies below the detection threshold. So far, no damage to infants has been reported. Nevertheless, glucocorticoids should only be prescribed when the benefits to mother and child outweigh the risks.

Because the milk/plasma concentration ratio increases with doses above 10 mg/day (e.g. 25 % of the serum concentration are found in the breast milk with 80 mg prednisone daily), it is recommended to discontinue breastfeeding in such cases.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The frequency and severity of the undesirable effects listed below depend on dosage and duration of treatment. In the recommended dose range for Lodotra (low-dose corticoid therapy with daily doses ranging from 1 to 10 mg), the listed undesirable effects occur less frequently with lower severity compared to doses above 10 mg.

The following undesirable effects may occur depending on the duration of treatment and the dosage:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders:
Common: Moderate leucocytosis, lymphopoenia, eosinopoenia, polycythaemia

Cardiac disorders:
Not known: Tachycardia

Immune system disorders:
Common: Reduced immune defence, masking of infections, exacerbation of latent infections

Rare: Allergic reactions

Infections and infestations
Common: Increases susceptibility to and severity of infections

Endocrine disorders:
Common: Adrenal suppression and induction of Cushing's syndrome (typical symptoms: moon-shaped face, upper body obesity and plethora)
Rare: Disturbed sexual hormone secretion (amenorrhoea, impotence), disturbance of the thyroid function

Metabolism and nutrition disorders:
Common: Sodium retention with oedema, increased potassium excretion (caution: arrhythmias), increased appetite and weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia
Not known: Reversible epidural, epicardial or mediastinal lipomatosis, hypokalaemic alkalosis

Psychiatric disorders:
Common: Insomnia
Rare: Depression, irritability, euphoria, increased impulse, psychosis

Nervous system disorders:
Common: Headache
Rare: Pseudotumor cerebri, manifestation of a latent epilepsy and increased predisposition to develop seizures in cases of manifest epilepsy

Eye disorders:
Common: Cataract, especially with posterior subcapsular opacity, glaucoma
Rare: Aggravation of symptoms associated with corneal ulcer, promotion of viral, fungal and bacterial eye inflammations
Not known: Central serous chorioretinopathy

Vascular disorders:
Uncommon: Hypertension, increased risk of arteriosclerosis and thrombosis, vasculitis (also as withdrawal syndrome following long-term therapy)

Gastrointestinal disorders:
Uncommon (no concomitant NSAIDs): Gastrointestinal ulcerations, gastrointestinal haemorrhages
Rare: Pancreatitis
Not known: Nausea, diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common: Striae rubrae, atrophy, telangiectasia, increased capillary fragility, petechiae, ecchymoses
Uncommon: Hypertrichosis, steroid acne, delayed healing of wounds, rosacea-like (perioral) dermatitis, changes in skin pigmentation
Rare: Hypersensitivity reactions, e.g. drug exanthema
Not known: Hirsutism

Musculoskeletal and connective tissue disorders:
Common: Muscular atrophy and weakness, osteoporosis (dose-related, may occur even with short-term use)
Rare: Aseptic osteonecrosis (humeral and femoral head)
Not known: Steroid myopathy, tendon rupture, vertebral and long bone fractures

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

Acute intoxications with Lodotra are not known. In case of overdosing, an increase in undesirable effects, especially endocrine, metabolic and electrolyte-related effects, can be expected (see section 4.8).

There is no known antidote for prednisone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB07

Prednisone is a non-fluorinated glucocorticoid for systemic therapy.
Prednisone shows a dose-dependent effect on the metabolism of almost all tissues. Under physiological conditions, these effects are vital to maintain homoeostasis of the organism at rest and under stress, as well as for the control of the activities of the immune system.

In doses typically prescribed for Lodotra, prednisone has an immediate anti-inflammatory (antiexsudative and antiproliferative) effect and a delayed immunosuppressive effect. It inhibits chemotaxis and the activity of immune cells as well as the release and effect of mediators of inflammatory and immune reactions, e.g. of lysosomal enzymes, prostaglandins and leucotrienes.

Prolonged therapy with high doses results in impaired response of the immune system and of the adrenal cortex. The mineralotropic effect that is pronounced in hydrocortisone is still detectable in prednisone and may require monitoring of serum electrolyte levels.

In patients with rheumatoid arthritis, pro-inflammatory cytokines such as the interleukins IL−1 and IL−6 and tumor necrosis factor alpha (TNFα) reach peak plasma levels in the early morning hours (e.g. IL− 6 between 7 to 8 am). Cytokine concentrations were shown to decrease after administration of Lodotra and subsequent night-time release of prednisone (with start of absorption between 2 - 4 am and C_{max} between 4 - 6 am).

The efficacy and safety of Lodotra was assessed in two randomised, double-blind controlled studies in patients with active rheumatoid arthritis.

In the first study, a multi-centre randomised double-blind phase III study of 12 week duration in a total of 288 patients pre-treated with prednisone or prednisolone, the group switching to Lodotra at the same dose showed a mean reduction of 23% in the duration of morning stiffness whereas the duration in the reference group did not change. Details are presented in the following table.

Relative change in the duration of morning stiffness after 12 weeks of treatment:

Relative change [%]	Lodotra (n = 125)	Prednisone IR (n = 129)
Mean (SD) Median (min, max)	–23 (89) –34 (–100, 500)	0 (89) –13 (–100, 610)

In a subsequent open label extension phase (9 months treatment) the mean relative change in the duration of morning stiffness compared to baseline was about −50 %.

Change in the duration of morning stiffness after 12 months treatment with Lodotra:

Duration of Morning stiffness [min]	Lodotra	
	Mean (SD)	N
0 months Start of the study	156 (97)	107
12 months End of open label phase	74 (92)	96

In the same study, after 12 weeks of treatment, a median decrease of the pro-inflammatory cytokine IL−6 of 29 % was observed in the group treated with Lodotra, whereas no change was observed in the comparator group who received standard prednisone. After 12 months of treatment with Lodotra the IL−6 level remains stable.

Change in the IL-6 level after 12 months:

IL-6 [IU/L]	Lodotra	
	median (min, max)	N
0 months Start of the study	860 (200, 23000)	142
12 months End of open label phase	470 (200, 18300)	103

Values < 200 IU/L were set to 200 IU/L for statistical analyses

The efficacy of Lodotra given on top of a DMARD was confirmed in a second randomised, placebo-controlled trial in patients insufficiently responding to DMARD therapy alone. At 12 weeks the Lodotra patients had a significantly higher ACR20 and ACR50 response rate (46.8% and 22.1%, respectively) compared to placebo patients (29.4% and 10.1%, respectively). There was also a greater mean change in DAS 28 scores from baseline (5.2 for the Lodotra group and 5.1 for the placebo group) to week 12 in the Lodotra group (−1.2 points) as compared with that seen in the placebo group (−0.7 point change).

In addition, after 12 weeks of therapy the mean duration of morning stiffness was 86.0 minutes (-66 minutes change) in the Lodotra group and 114.1 minutes (-42.6 minutes change) in the placebo group. Lodotra could be safely used in combination with other DMARDs.

5.2 Pharmacokinetic properties

Absorption
Lodotra are prednisone-containing modified-release tablets. Prednisone is released between 4 − 6 hours following intake of Lodotra. Subsequently, prednisone is rapidly and almost completely absorbed.

Distribution
Peak serum levels are reached approximately 6 - 9 hours after intake.

Biotransformation
More than 80 % of the prednisone is converted to prednisolone by first-pass hepatic metabolism. The ratio of prednisone to prednisolone is approximately 1:6 to 1:10. Prednisone itself exerts negligible pharmacologic effects. Prednisolone is the active metabolite. The compounds are reversibly bound to plasma proteins with high affinity for transcortin (corticosteroid binding globulin, CBG) and low affinity for plasma albumin.
In the low dose range (up to 5 mg), approximately 6% of free prednisolone is present. Metabolic elimination is dose linear in this range. In the dose range above 10 mg, the binding capacity of transcortin is increasingly exhausted and more free prednisolone is present. This may result in a faster metabolic elimination.

Elimination

Prednisolone is primarily eliminated by hepatic metabolism, to approximately 70 % by glucoronidation and to approximately 30 % by sulphatation. There is also conversion to 11ß,17ß−dihydroxyandrosta-1,4-dien-3-one and to 1,4-pregnadien-20-ol. The metabolites exhibit no hormonal activity and undergo primarily renal elimination. Negligible amounts of prednisone and prednisolone are found unchanged in the urine. The plasma elimination half-life of prednis (ol)one is approximately 3 hours. In patients with severe hepatic dysfunction the half-life may be prolonged and a dose reduction should be considered.

The duration of the biological effects of prednis(ol)one exceeds the duration of the presence in the serum.

Bioavailability

A bioavailability study in 27 healthy subjects conducted in 2003 revealed the following results in comparison with a prednisone immediate-release tablet:

Parameter	Lodotra 5 mg: 2.5 hours after a light meal	Lodotra 5 mg: Immediately after a meal	Reference preparation 5 mg fasted
Maximum plasma concentration (C_{max}): ng/ml	20.2 (18.5; 21.9)	21.8 (20.0; 23.7)	20.7 (19.0; 22.5)
Time of maximum plasma concentration (t_{max}): h	6.0 (4.5; 10.0)	6.5 (4.5; 9.0)	2.0 (1.0; 4.0)
Duration of the delay of drug release (t_{lag}): h	4.0 (3.5; 5.0)	3.5 (2.0; 5.5)	0.0 (0.0; 0.5)
Area under the concentration-time curve ($AUC_{0-\infty}$): ng x h/ml	110 (101; 119)	123 (114; 133)	109 (101; 118)

Values are least-square geometric means and range

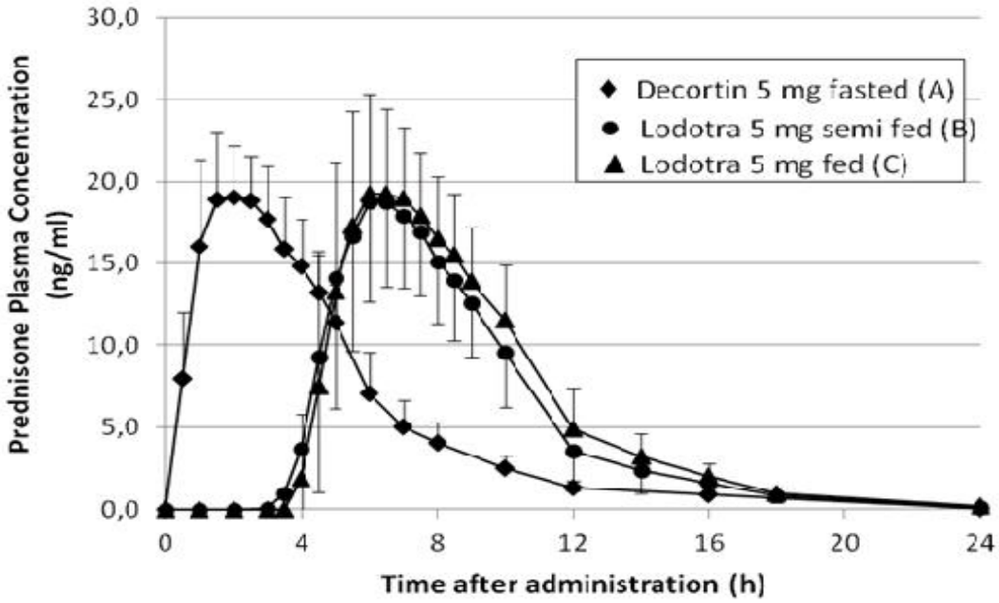

Figure: Mean plasma levels of prednisone after a single dose of 5 mg prednisone administered as Lodotra 5 mg or an immediate release tablet. 5 mg immediate release tablet (A: fasted, intake at 2 am), Lodotra 5 mg (B: 2.5 hours after a light evening meal) and Lodotra 5 mg (C: immediately after a full evening meal).

The plasma concentration profiles of Lodotra are very similar to an immediate-release tablet, with the important difference that the Lodotra profile is delayed with 4 – 6 hours after drug intake. Lower plasma concentrations have been observed in 6-7% of doses.

Dose proportionality was demonstrated for Lodotra 1 mg, 2 mg and 5 mg based on AUC and C_{max}.

5.3 Preclinical safety data

Subchronic/chronic toxicity

Light and electron microscopic changes in the Langerhans' islet cells of rats were observed following daily intraperitoneal administration of 33 mg/kg bw over 7 to 14 days in rats. In rabbits, experimental liver damage could be produced by administering 2 to 3 mg/kg bw/day for 2 to 4 weeks. Histotoxic effects (myonecroses) were reported following several weeks of administration of 0.5 to 5 mg/kg bw in guinea pigs and 4 mg/kg bw in dogs.

Mutagenic and tumour-forming potential

The toxicity observed in animal studies with prednisone was associated with exaggerated pharmacological activity. No genotoxic effects of prednisone have been observed in conventional genotoxicity tests.

Reproductive toxicity

In animal reproduction studies, glucocorticoids such as prednisone have been shown to induce malformations (cleft palate, skeletal malformations). With parenteral administration, minor anomalies of skull, jaw and tongue were found in rats. Intrauterine growth retardation was observed (also see section 4.6).

Similar effects are considered unlikely to occur in patients at therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Povidone K 29/32
Red ferric oxide E 172

Tablet shell:
Colloidal anhydrous silica
Calcium hydrogen phosphate dihydrate
Glycerol dibehenate
Magnesium stearate
Povidone K 29/32
Yellow ferric oxide E 172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years
Shelf life after first opening of the bottle: 14 weeks.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Container with 30 and 100 modified-release tablets:
White bottle made of high-density polyethylene (HDPE). Screw cap (including a desiccant capsule) with three elevated points arranged around the rim to facilitate easy opening made of HDPE.

Container with 500 modified-release tablets:
White bottle made of high-density polyethylene (with a small amount of LDPE). Screw cap (without three elevated points) made of polypropylene.

Pack sizes:	Bottles with 30 and 100 modified-release tablets
Hospital packs:	Bottles with 30, 100 and 500 modified-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
Millbank House,
Arkle Road,
Sandyford,
Dublin 18,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th May 2013

Date of last renewal: 4th Mach 2014

10 DATE OF REVISION OF THE TEXT

September 2014