

PRODUCT INFORMATION

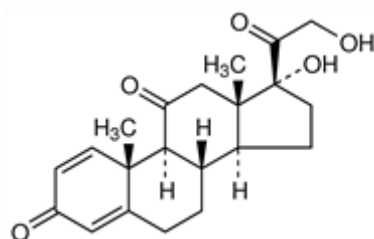
LODOTRA[®] 1 mg, 2 mg and 5 mg modified release tablets

NAME OF THE MEDICINE prednisone

DESCRIPTION

Prednisone is an odourless, white crystalline powder, which is practically insoluble in water, slightly soluble in alcohol and methylene chloride. The melting point is 233-235°C. The octanol-water partition coefficient (log P) is 1.46.

The chemical name is 17 α ,21-dihydroxypregna-1,4-diene-3,11,20-trione, and its molecular weight is 358.4. The molecular formula is C₂₁H₂₆O₅. The structural formula is:



CAS No: 53-03-2

LODOTRA[®] modified release tablet:

The formulation has been designed as a timed-release tablet. The core contains lactose, silica - colloidal anhydrous, croscarmellose sodium, magnesium stearate, povidone and iron oxide red CI77491. The shell contains silica - colloidal anhydrous, calcium hydrogen phosphate, glyceryl behenate, magnesium stearate, povidone and iron oxide yellow CI77492.

PHARMACOLOGY

Actions

The pharmacotherapeutic group is 'glucocorticoids' and the ATC code is H02AB07. Prednisone is a non-fluorinated glucocorticoid for systemic therapy, which has a dose-dependent effect on the metabolism in almost all tissues. Under physiological conditions, these effects are central to maintaining homeostasis of the organism at rest and under stress, and for controlling the actions of the immune system. Prednisone has the same chemical relationship to prednisolone as cortisone has to hydrocortisone. The mechanism of action of corticosteroids is thought to be by control of protein synthesis. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid receptor complex.

In the LODOTRA[®] modified release tablets dosages typically prescribed; prednisone has an immediate anti-inflammatory (antiexudative 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 of LODOTRA[®] modified release tablets results in impaired response of the immune system and the adrenal cortex. The mineralotropic effect that is pronounced with hydrocortisone is still detectable with 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 tumour necrosis factor alpha (TNF α) reach peak plasma levels in the early morning hours (e.g. IL-6 between 7 am to 8 am). Cytokine concentrations decrease after the administration of LODOTRA[®] modified release tablets, and subsequent night-time release of prednisone (with absorption starting between 2 am to 4 am, and C_{max} occurring between 4 am to 6 am).

Pharmacokinetics

Absorption:

LODOTRA[®] modified release tablets are prednisone-containing modified release tablets. Prednisone is released between 4 - 6 hours following ingestion of LODOTRA[®] modified release tablets. Subsequently, prednisone is rapidly and almost completely absorbed.

Distribution:

Peak serum levels are reached approximately 6 - 9 hours following ingestion.

Metabolism:

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 pharmacological effects. Prednisolone is the active metabolite. The conversion from prednisone to prednisolone is rapid so that prednisone has a pre-conversion biological half-life of only about 60 minutes. Both prednisone and prednisolone are reversibly bound to plasma proteins with high affinity for transcortin (corticosteroid binding globulin, CBG) and low affinity for plasma albumin. Prednisolone is 90 to 95% bound to plasma proteins.

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 occupied and more free prednisolone is present. This may result in a faster metabolic elimination. This is observed for prednisone regardless of the dosage form.

Elimination:

Prednisolone is primarily eliminated by hepatic metabolism; approximately 70% by glucuronidation and approximately 30% by sulphation. It is also converted to 11 β , 17 β -dihydroxyandrost-1,4-dien-3-one and to 1,4-pregnadien-20-ol. The metabolites exhibit no hormonal activity and primarily undergo renal elimination. Negligible amounts of prednisone and prednisolone are found unchanged in 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

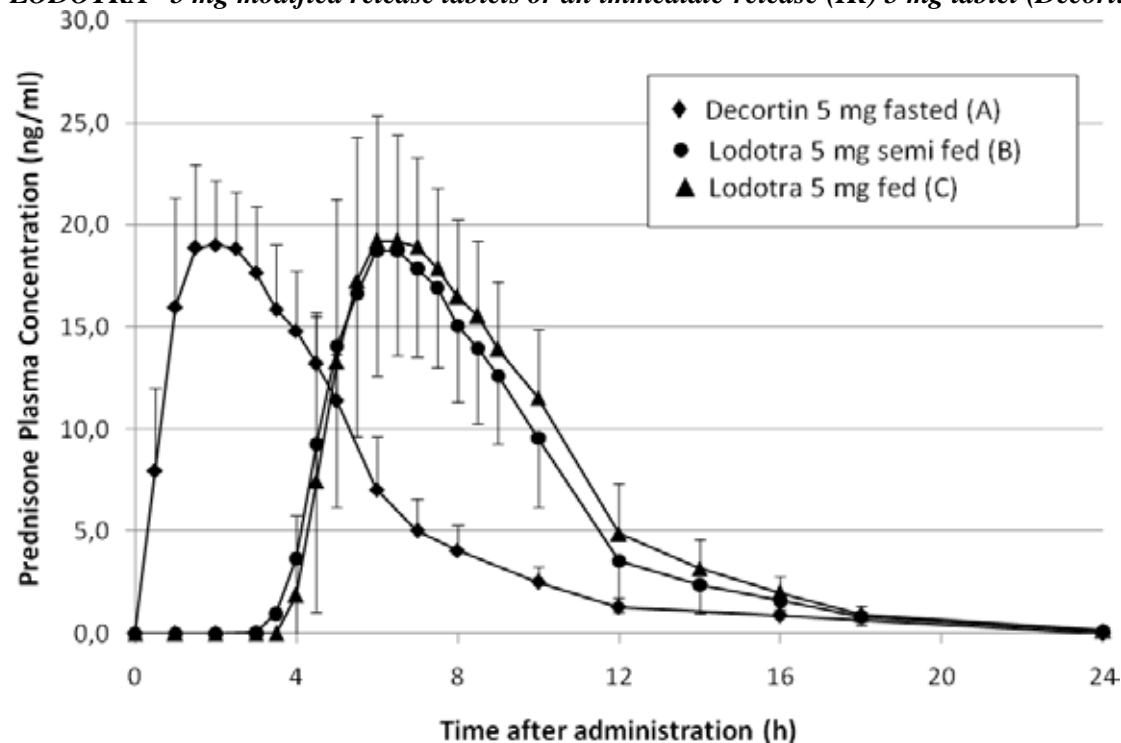
The bioavailability of prednisone from LODOTRA[®] modified release tablets was compared with prednisone immediate release (IR) tablets in 27 healthy subjects, with the following results:

Table 1: Pharmacokinetic parameters for LODOTRA versus IR prednisone

Parameter	LODOTRA [®] 5 mg: 2.5 hours after a light meal	LODOTRA [®] 5 mg: immediately after a full evening meal	Prednisone IR: 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	3.5 (2.0; 5.5)	4.0 (3.5; 5.0)	0.0 (0.0; 0.5)
Area under concentration-time curve (AUC _{0-∞}): ng x h/mL	110 (101; 119)	123 (114; 133)	109 (101; 118)

Values are least-square geometric means and range.

Figure 1: Mean plasma levels of prednisone after single doses of 5 mg prednisone administered as LODOTRA[®] 5 mg modified release tablets or an immediate-release (IR) 5 mg tablet (Decortin[®]).



The immediate release 5 mg tablet was administered fasted, at 2 am (A). LODOTRA[®] 5 mg modified release tablets were administered 2.5 hours after a light evening meal (B), or

immediately after a full evening meal (C). * Decortin is available in Germany (not available in Australia).

The prednisone plasma concentration profiles observed following administration of LODOTRA[®] modified release tablets are very similar to that following administration of an immediate-release tablet; however the LODOTRA[®] modified release tablet profile is delayed 4 – 6 hours after dose administration.

Lower prednisone plasma concentrations have been observed in 6-7% of LODOTRA[®] doses as observed across all pharmacokinetic studies when taken according to recommendations. Such deviating performance was observed to be randomly distributed over treatments and subjects independent of the concomitant administration of food. These observations appear to be primarily caused by individual physiological variability of gastrointestinal transit, such as enhanced gastric emptying or unusually rapid transit of the tablet to distal sites of the gastrointestinal tract.

Dose proportionality was demonstrated for LODOTRA[®] modified release tablets 1 mg, 2 mg and 5 mg based on AUC and C_{max}.

Effect of food

The effect of food was evaluated in an open-label, randomized, 2-period crossover study in healthy male and female subjects. LODOTRA[®] modified release tablets 5mg were administered after a 10 hour fast or after intake of a high-fat meal. The results from this study show that the exposure to both prednisone and prednisolone is increased 3-4 fold when LODOTRA[®] modified release tablets is administered under fed conditions compared to the drug administered under fasted conditions. Additionally, the median lag time (t_{lag}) and t_{max} for both prednisone and prednisolone was 1 hour and 1.5 hours longer in the fasted state. The PK parameters after administration of LODOTRA[®] modified release tablets under fed conditions were comparable with those previously reported in the bioavailability study above under fed or semi-fed conditions.

The results observed under fasted conditions (increases in *in vivo* lag times, and both inter-individual variability and lower values for C_{max} and AUC) indicate that LODOTRA should not be taken under fasting conditions for optimal absorption of LODOTRA[®] in the small intestine. The amount of food is not observed to be relevant, as there was no clinically relevant difference in bioavailability when taken 0.5 hours after a full meal (fed conditions) or 2.5 hours after a light meal (semi-fed conditions). Thus, LODOTRA[®] is recommended to be taken with or up to 2 to 3 hours after the evening meal (see PRECAUTIONS, Important information for patients and caregivers, and DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

CAPRA-1 (12-week study)

In a randomised, 12-week, double-blind study in a total of 288 patients with active rheumatoid arthritis, the primary endpoint was to assess whether the mean relative change in the duration of morning stiffness from baseline was significantly greater for patients treated with LODOTRA[®] modified release tablets than for those treated with immediate release (IR) prednisone in the Intention To Treat population (ITT), using Last Observation Carried Forward (LOCF) methodology. This patient population is used for all the results presented

below. The secondary endpoints compared the two prednisone products on the standard parameters for assessing rheumatoid arthritis, including morning stiffness in terms of mean daily duration per week, recurrence of stiffness during the day, the intensity of pain as a mean daily Visual Analogue Score (VAS) and patient diary per week, quality of sleep as a mean daily VAS score per week, the number of days per week where subjects used analgesics, inflammatory signs (C-reactive protein (CRP) and interleukin-6 (IL-6)), osteocalcin levels, the Disease Activity Score (DAS28), ACR20 response, physician's global assessment of disease activity, the Health Assessment Questionnaire Disability Index (HAQ-DI) and Quality of Life (SF36).

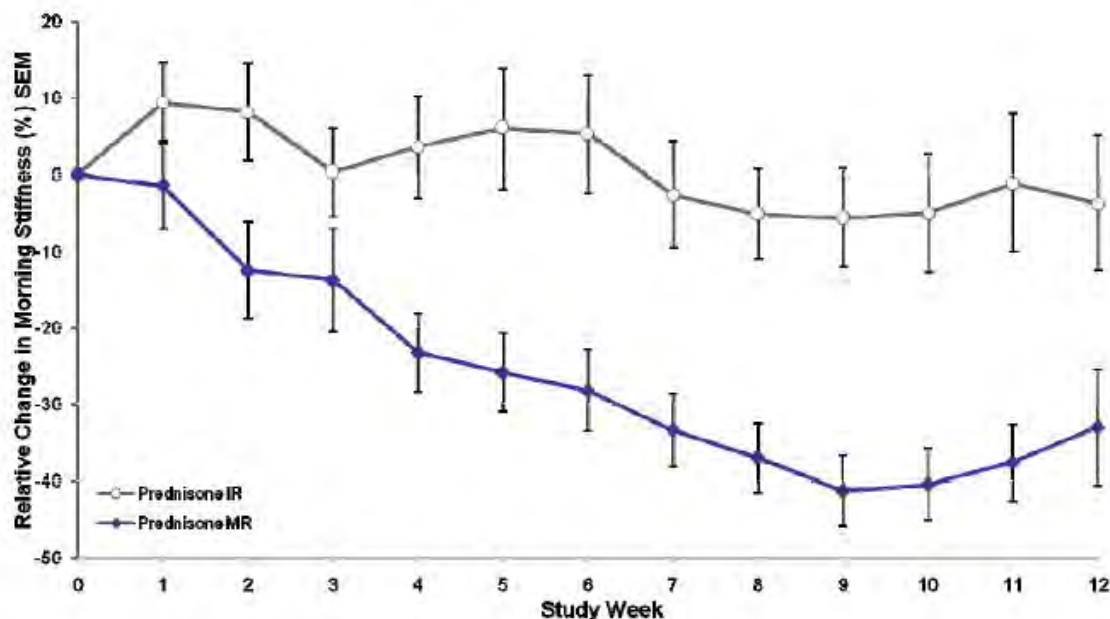
Primary endpoint: Mean relative change in duration of morning stiffness: The mean relative change in the duration of morning stiffness after 12 weeks was -22.7% in the LODOTRA treatment group and -0.4% in the IR prednisone treatment group, making the mean treatment difference 22.4% in favour of LODOTRA[®] (p= 0.0226, one-sided). Morning stiffness is one of the most distressing symptoms for RA patients and thus the observed reduction between baseline and the final week for LODOTRA treatment can be considered a clinically meaningful improvement. The duration of morning stiffness at baseline and after 12 weeks, the relative changes and mean treatment difference are shown in the table, below:

Table 2: Change in duration of morning stiffness after 12-weeks of treatment

	LODOTRA [®] (N=144)				IR prednisone (N=144)			
	Baseline (minutes)	At 12 weeks (minutes)	Absolute change	Relative change	Baseline (minutes)	At 12 weeks (minutes)	Absolute change	Relative change
Mean (SD)	164.1 (101.4)	120.89 (140.53)	-43.96 (136.59)	-22.66% (89.10)	182.5 (125.0)	157.35 (145.63)	-22.68 (138.07)	-0.39% (61.85)
Median (min, max)	146.4 (13.6, 659.3)	79.29 (0.0, 720.0)	-39.29 (-537.62, 600.00)	-33.92% (-100.00, 500.00)	152.9 (32.1, 720.0)	120.0 (0.00, 720.00)	-21.45 (-586.25, 618.57)	-13.48% (-100, 609.86)
Treatment difference	LS mean (SE): 22.4 (11.1)%; 95% CI lower limit: 0.493%; P-value: 0.0226 (one-sided)							

Mean daily duration of morning stiffness per week: The mean daily morning stiffness duration decreased in the LODOTRA[®] group after 2 weeks of treatment, and steadily declined each week, however there was no clear tendency for decreases in the IR prednisone group. The figure below shows the mean relative change in the duration of morning stiffness for each week of the study:

Figure 2: Mean relative change in duration of morning stiffness by week



The reduction of morning stiffness for patients taking LODOTRA[®] was consistently higher than patients taking IR prednisone. A difference of 10% was apparent at week 2 and under continued treatment this difference increased and reached a plateau of 30-40% difference from Week 7 onwards.

The clinically significant secondary efficacy variable, inflammatory signs (IL-6), is discussed below. With regards to all other secondary efficacy end points, there were no significant differences between the LODOTRA[®] group and immediate release prednisone group.

Secondary endpoint: Inflammatory signs (IL-6): A median 28.6% decrease in the pro-inflammatory cytokine IL-6 was seen in the LODOTRA[®] group after 12-weeks of treatment, whereas there was no change in the prednisone IR group. This change was shown to be significant ($p < 0.0001$) in the LODOTRA[®] group but not in the IR prednisone group ($p = 0.2326$) in Post-hoc analyses (Wilcoxon rank-sum test). The differences between the treatment groups at week 12 were also significant ($p = 0.0161$). A 100% reduction in joint stiffness was seen in 16% of LODOTRA[®] patients, and in these patients a 64% reduction in IL-6 levels and a 44% reduction in pain were reported.

Table 3: IL-6 levels at baseline and at week 2, 6 and 12

Inflammatory sign - Cytokine IL-6 (IU/L)	LODOTRA (N = 144) median (min, max)	IR prednisone (N = 144) median (min, max)
Baseline (visit 1)	860 (200, 23000) (n = 142)	1110 (200, 20800) (n = 142)
Final visit	470 (200, 9530) (n = 137)	1080 (200, 22700) (n = 134)
Relative change [%]	-28.6 (-96.8, 2018) (n = 135)	0.0 (-98.1, 3017) (n = 132)

Other Secondary endpoints: After 12 weeks, the two prednisone preparations were similar with respect to all secondary endpoints with the exception of mean daily duration of stiffness and IL-6 levels, where LODOTRA[®] was seen to exhibit superior results with regards to decreasing the duration of morning stiffness and decreasing IL-6 levels.

The number of patients with recurrence of stiffness during the day decreased during the 12-week treatment period in both groups with no notable differences between the two treatments. No notable differences between the two treatments were observed for any other efficacy variables: pain intensity, quality of sleep, DAS28, physician's global assessment of disease activity, HAQ disability index (HAQ-DI) score, Quality of Life (SF-36) scores, CRP, ESR, osteocalcin, or ACR20 response rate.

CAPRA-1 (long-term study)

Of the 251 patients completing the CAPRA-1 12-week study, 249 chose to continue on LODOTRA[®] in a long-term, open-label extension study; either switching from prednisone IR or continuing LODOTRA[®]. The mean duration of morning stiffness was 169.80 (SD 114.38) minutes at the start of the study 87.32 (SD 120.28) minutes after 12 months for all patients. Treatment with LODOTRA[®] resulted in a decrease of about 40% after 3 months, which persisted until the end of the study (9 months for patients previously on prednisone IR and 12 months for patients previously on LODOTRA[®]). In the group switching from prednisone IR treatment to LODOTRA[®], the reduction in morning stiffness was also accompanied by a corresponding decrease in IL-6 levels, from 1050 IU/L to 515 IU/L. The decrease in IL-6 levels seen in the double-blind phase for patients on LODOTRA[®] remained stable after 12 months.

CAPRA-2

In a second randomised, 12 week, double-blind, placebo-controlled study in a total of 350 patients pre-treated with Disease Modifying Anti-Rheumatic Drugs (DMARDs) for 6 months, a significant difference in the proportion of ACR20 responders was seen at 2, 6 and 12 weeks, in favour of the LODOTRA[®] group in the mITT population, using Worst Observation Carried Forward methodology (i.e. patients with missing data are counted as non-responders). ACR20 response, the primary efficacy endpoint, was defined as a 20% minimum reduction in the number of tender or swollen joints, together with a 20% minimum improvement in any one of pain, disability, acute phase reaction, patient global assessment and/or physician global assessment.

Table 4: ACR20 responders in patients already taking DMARDs over 12 weeks

ACR20 responders	Proportion of ACR20 responders		Difference (95% CI)	P-values
	LODOTRA [®] TR (N=231)	Placebo (N=119)		
After 2 wks	23.4% (54)	10.1% (12)	13.3 (4.62; 21.61)	0.0020
After 6 wks	40.7% (94)	24.4% (29)	16.3 (6.76; 26.52)	0.0029
After 12 wks	46.8% (108)	29.4% (35)	17.3 (6.37; 26.91)	0.0016

A significantly greater proportion of LODOTRA[®] patients achieved a 50% improvement (according to ACR50 criteria) after 12 weeks compared to the placebo group, using Last Observation Carried Forward methodology. The proportions of both the ACR50 and the ACR70 responders (patients achieving a 70% improvement) are shown below for LODOTRA[®] patients compared to placebo patients:

Table 5: ACR50 and ACR70 responders in patients already taking DMARDs after 12 weeks

ACR50 and 70 responders	Proportion of ACR50 and ACR70 responders		P-values
	LODOTRA[®] (N=231)	Placebo (N=119)	
ACR50 after 12 weeks	22.1% (51)	10.1% (11)	0.0063
ACR70 after 12 weeks	7.0% (16)	2.5% (3)	0.0955

The key secondary endpoint was to evaluate relative reduction of morning stiffness between LODOTRA[®] patients and placebo patients. The mean relative change in the duration of morning stiffness from baseline after 12 weeks was significantly greater in the LODOTRA[®] group (-42.9%) compared to the placebo group (-22.7%). The difference in the median relative change was -19.6 (95% CI -22.8, -15.8, p=0.0015, using Hodges-Lehmann method).

Table 6: Change in morning stiffness duration in patients already taking DMARDs after 12 weeks

	LODOTRA[®] (N=216)			Placebo (N=107)			P-value
	Value (minutes)	Absolute change	Relative change	Value (minutes)	Absolute change	Relative change	
Mean (SD)	86.0 (101.74)	-64.4 (89.44)	-42.9% (63.58)	114.1 (100.85)	-41.1 (92.04)	-22.7% (67.02)	0.0015
Median (range)	45.6 (0-420)	-55.9 (-473-154)	-55.2% (-100-414)	79.3 (-0-381)	-38.4 (-335-274)	-34.6% (-100-305)	

Additional secondary efficacy endpoints were to compare other measures of clinical efficacy, quality of life and inflammatory markers. LODOTRA[®] was found to be superior to placebo in the majority of other secondary end points, including tender and swollen joint count, patient's assessment of pain, patient's and physician's global assessment of disease activity, time to response, HAQ-DI score, DAS28, EULAR response, severity of morning stiffness, reoccurrence of morning stiffness, patient assessment of morning and evening pain, IL-6 concentration, FACIT-F and SF-36 physical component score.

The maximum dose studied in all rheumatoid arthritis clinical trials was 10 mg. Consequently, there is a lack of data for doses greater than 10 mg, particularly in long-term use greater than 12 months.

INDICATIONS

LODOTRA[®] modified release tablets are indicated for the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness.

CONTRAINDICATIONS

LODOTRA[®] modified release tablets are contraindicated in patients with hypersensitivity to prednisone, prednisolone or to any of the excipients, in children and adolescents and in patients with uncontrolled infections.

PRECAUTIONS

Prednisone-based therapy should only be given when absolutely necessary.

LODOTRA[®] modified release tablets should be used with caution, and accompanied by an appropriate anti-infection treatment, in the presence of the following conditions:

- acute viral infections (e.g. 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
- abscess
- 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 (see PRECAUTIONS, Risk of infection section).

LODOTRA[®] modified release tablets should be used with caution, and should be accompanied if required by appropriate treatment, in the presence of the following conditions:

- gastrointestinal ulcers
- severe osteoporosis and osteomalacia
- hypertension that is difficult to control
- renal insufficiency
- impaired hepatic function (see PRECAUTIONS, Special Patient Groups)
- epilepsy
- uraemia
- severe diabetes mellitus
- psychiatric disorders (also if in patient's history)
- narrow- and wide-angle glaucoma
- corneal ulcers and corneal injuries.

Patients with diabetes mellitus

Patients with diabetes mellitus should be closely monitored, as there may be an increased need for insulin or oral anti-diabetic agents.

Patients with unstable hypertension

During treatment with LODOTRA[®] modified release tablets, regular blood pressure monitoring is required in patients with hypertension that is difficult to control.

Patients with severe cardiac insufficiency

Patients with severe cardiac insufficiency must be closely monitored because of the risk of the condition deteriorating.

Risk of intestinal perforation

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

- nonspecific ulcerative colitis
- severe ulcerative colitis with imminent perforation
- diverticulitis
- entero-anastomoses (immediately postoperative).

Lactose

LODOTRA[®] modified release tablets contain lactose monohydrate. Patients with rare hereditary problems including galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this product.

Indications for acute treatment

LODOTRA[®] modified release tablets should not be given for acute indications in the place of prednisone immediate-release tablets, due to its pharmacodynamic properties.

Substitution, termination, discontinuation

Because of its delayed release properties, LODOTRA[®] modified release tablets should not be substituted by prednisone immediate-release tablets in the same administration regime. In the case of substitution, termination, or discontinuation of prolonged treatment, the following risks must be considered: recurrence of rheumatoid arthritis disease activity, acute adrenal failure (especially in stressful situations e.g. during infections, after accidents, with increased physical strain), and cortisone withdrawal syndrome.

The risk of adrenal suppression depends on a number of factors including the dose and duration of glucocorticoid treatment. When withdrawing treatment with LODOTRA[®], consider tapering the dose as abrupt withdrawal can result in an adrenal crisis/relative adrenocortical insufficiency (see DOSAGE AND ADMINISTRATION section). This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormonal therapy may need to be reinstituted.

Required blood concentrations

LODOTRA[®] modified release tablets will not achieve the desired blood concentration of prednisone if taken under fasting conditions. Therefore, LODOTRA[®] modified release tablets 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[®] modified release tablet doses as observed across all pharmacokinetic studies when taken according to recommendations (see PHARMACOLOGY, Bioavailability). This should be considered if LODOTRA[®] modified release tablets are not sufficiently effective. In these situations a switch to a conventional immediate release formulation may be considered.

Stress

For those patients being treated with LODOTRA[®] modified release tablets who experience high levels of physical stress due to e.g. accidents, surgical procedure etc., during treatment with LODOTRA[®] modified release tablets, a temporary dose increase may become necessary. For mild infections without fever, no increase is necessary.

Sleep disorders

Sleep disorder was documented to occur more frequently with LODOTRA[®] modified release tablets than with conventional immediate release formulations, which are taken in the morning. If insomnia occurs and does not improve, switching to a conventional immediate release formulation is recommended.

Risk of gastrointestinal ulceration and haemorrhage

The risk of gastrointestinal ulceration and haemorrhage is increased when alcohol is used concurrently with glucocorticoids.

Risk of infection

Treatment with LODOTRA[®] modified release tablets can mask the signs and symptoms of an existing or developing infection, making diagnosis more difficult. There may be decreased resistance and inability to localise infection when corticosteroids are used. Susceptibility to infection is not specific for any particular bacterial or fungal pathogen. Long-term use of LODOTRA[®] modified release tablets results in an increased risk of infection, even at low doses, including by microorganisms that rarely cause infection under normal circumstances (opportunistic infections).

Certain viral diseases (e.g. varicella, measles) may be more severe in patients treated with glucocorticoids. Immunosuppressed patients without prior varicella or measles infection are at particular risk. If such patients have contact with persons infected with varicella or measles while taking LODOTRA[®] modified release tablets, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Patients with active or doubtfully quiescent tuberculosis should not be given LODOTRA[®], as reactivation of the disease may occur. Chemoprophylaxis is indicated during prolonged corticosteroid therapy.

Vaccination

Patients should not be vaccinated with live vaccines while on corticosteroid therapy. Vaccination with inactivated vaccines is generally possible in patients being treated with LODOTRA[®] modified release tablets. However, the immune response, and the success of the vaccination, may be impaired when higher doses of glucocorticoids are being taken.

Calcium metabolism

A negative impact on calcium metabolism must be anticipated, depending on the duration of the treatment and the dosage used. 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, and reduced physical activity. Prophylaxis is based on a sufficient supply of calcium and vitamin D, as well as on adequate physical activity and modifying risk factors for osteoporosis. In the case of pre-existing osteoporosis, supplementation therapy should be considered.

Long-term treatment

If long-term treatment with glucocorticoids in patients with rheumatoid arthritis is recommended, the lowest dose possible of glucocorticoids should be used. A risk-benefit

decision must be made in each individual case taking into consideration the adverse effects associated with long-term glucocorticoid use.

During prolonged corticosteroid therapy, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. Duration of treatment and dosage appear to be important factors in determining suppression of the pituitary adrenal axis and response to stress on cessation of steroid treatment. The patient's liability to suppression is also variable. Some patients may recover normal function rapidly. In others, the production of hydrocortisone in response to the stress of infections, surgical operations or accident may be insufficient (see PRECAUTIONS, Substitution, termination, discontinuation section).

Regular medical follow-ups, including ophthalmological examinations, bone mineral density, blood glucose, weight, blood pressure and electrolytes are indicated during long-term treatment with LODOTRA[®] modified release tablets. Fluid retention should be watched for via a fluid balance chart and daily weighing. There is a potential for weight gain with long-term treatment. Enquire about eye symptoms and monitor for cataracts and glaucoma. If comparatively high doses are taken, serum potassium levels should be monitored, dietary sodium restricted and potassium supplements prescribed.

Important information for patients and caregivers

Instruct patients and caregivers that LODOTRA[®] modified release tablets must not be broken, divided, chewed or crushed.

LODOTRA[®] should be taken at bedtime, at about 10pm, with or after the evening meal. If more than 2 to 3 hours have passed since the evening meal, it is recommended that LODOTRA[®] modified release tablets are taken with a light meal or snack. Sub-optimal absorption of LODOTRA[®] modified release tablets is observed when taken under fasting conditions (see PHARMACOLOGY, Pharmacokinetics - Effect of food; and DOSAGE AND ADMINISTRATION).

Patients and caregivers must be instructed not to cease LODOTRA[®] modified release tablets suddenly or substitute LODOTRA[®] with any other types of prednisone tablets unless otherwise instructed to do so by their treating doctor.

Special patient groups

In patients with untreated hypothyroidism, impaired hepatic function or hepatic cirrhosis, comparatively low doses may be sufficient or a dose reduction may be required. In treating chronic active hepatic disease with the drug, major adverse reactions such as vertebral collapse, diabetes, hypertension, cataracts and Cushing's syndrome occur in about 30% of patients.

Use in children

Use in children and adolescents is not recommended as insufficient tolerability and efficacy data are available in this patient population (see CONTRAINDICATIONS).

Use in elderly

Caution is recommended for elderly patients, as they are more susceptible to adverse reactions.

Driving and operating dangerous machinery

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

Carcinogenicity

Carcinogenicity studies of up to two years duration in rats and mice suggested that prednisone/prednisolone did not increase the incidence of tumours in rodents except for an increased incidence of hepatocellular adenoma in rats which appeared to be a glucocorticoid receptor-mediated class effect.

Genotoxicity

Conventional tests for mutagenicity and clastogenicity suggest that prednisone and its metabolites have little or no genotoxic activity.

Effects on fertility

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

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

Use in pregnancy

Australian Categorisation of Drugs in Pregnancy: Category A. Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

LODOTRA[®] modified release tablets should only be used during pregnancy when the benefits outweigh the potential risks. The lowest effective dose of LODOTRA[®] modified release tablets needed to maintain adequate disease control should be used.

Animal studies indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk of foetal 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. There is 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 must be reduced slowly.

The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the fetus or the newborn infant. Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

Use in lactation

Glucocorticoids pass into breast milk in small amounts (up to 0.23 % of an individual dose). At maternal doses up to 10 mg daily, blood levels in the breast feeding infant are below the detection threshold. Harmful effects in infants have not 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 maternal doses above 10 mg/day (e.g. 25% of the serum concentration is present in breast milk following 80 mg prednisone daily dosing), it is recommended to discontinue breastfeeding in such cases.

INTERACTIONS WITH OTHER MEDICINES

Alcohol: Increased risk of gastrointestinal ulceration or haemorrhage

ACE inhibitors: Increased risk of blood count changes.

Aluminium and magnesium antacids: Absorption of glucocorticoids is reduced. However, due to the delayed release mechanism of LODOTRA[®] modified release tablets an interaction between prednisone and aluminium/magnesium antacids is unlikely.

Amphotericin B: Risk of hypokalaemia may be increased.

Antidiabetic agents (oral or insulin): The blood sugar lowering effect is reduced.

Atropine and other anticholinergics: Potential additional increases in intraocular pressure.

Cardiac glycosides: Glycoside effects can be enhanced by potassium deficiency.

Chloroquine, hydroxychloroquine, mefloquine: Increased risk of myopathies, cardiomyopathies.

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

Cyclophosphamide: Effects of cyclophosphamide may be enhanced.

Cyclosporin: Blood levels of cyclosporine are increased. Increased risk of seizures.

Diuretics/laxatives: Potassium excretion is enhanced.

Hypoglycaemic agents: Blood glucose lowering effect is reduced.

Liquorice: Potential inhibition of the metabolism of glucocorticoids.

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

Non-steroidal anti-inflammatory (NSAIDs)/antirheumatic agents, salicylates and indomethacin: Risk of gastrointestinal haemorrhages is increased.

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

Praziquantel: Potential lowering of praziquantel blood concentrations.

Rifampicin, phenytoin, barbiturates, bupropion and primidone: Glucocorticoid efficacy is reduced.

Sodium containing medicines or foods: Increased risk of hyponatremia.

Somatropin: Somatropin efficacy may be reduced.

Vaccines, live viruses and other immunisations: Increased risk of infection (live vaccines) or reduced immune response to vaccines.

Impact on diagnostic methods: Skin reactions caused by allergy testing may be suppressed. TSH increase following protirelin administration may be reduced. Glucocorticoids may produce false-negative results in the nitroblue tetrazolium test for systemic bacterial infection.

ADVERSE EFFECTS

The frequency and severity of the potential adverse reactions listed below depend upon dosage and duration of treatment. In the recommended dose range for LODOTRA[®] modified release tablets (low-dose corticoid therapy with daily doses ranging from 1 to 10 mg), the listed adverse reactions occur less frequently with lower severity compared with doses above 10 mg.

The following adverse reactions may occur for patients on low-dose ($\leq 10\text{mg/day}$ prednisolone equivalent), long-term glucocorticoid, depending upon treatment and dosage:

Blood and lymphatic system disorders:

Common: Moderate leucocytosis, lymphopenia, eosinopenia, polycythaemia

Disorders of the gastrointestinal tract:

Uncommon: Gastrointestinal ulceration, gastrointestinal haemorrhage (without concomitant NSAIDs)

Rare: Pancreatitis

Endocrine disorders:

Common: Adrenal suppression and induction of Cushing's syndrome (typical symptoms include moon-shaped face, upper body obesity, plethora)

Rare: Disturbed sex hormone secretion, resulting in amenorrhoea and impotence, disturbed thyroid function

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

Immune system disorders:

Common: Reduced immune defence, masking of infections, exacerbation of latent infections

Rare: Allergic reactions

Metabolism and nutritional disorders:

Common: Sodium retention with oedema, increased potassium excretion potentially leading to arrhythmia, increased appetite and weight gain, reduced glucose tolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia

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)

Nervous system disorders:

Common: Headache

Rare: Pseudotumor cerebri, manifestation of a latent epilepsy and increased predisposition to develop seizures in cases of manifest epilepsy

Psychiatric disorders:

Common: Insomnia

Rare: Depression, irritability, euphoria, increased impulse, psychosis

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

Vascular disorders:

Uncommon: Hypertension, increased risk of arteriosclerosis and thrombosis, vasculitis (this may also occur as a withdrawal syndrome following long-term therapy)

Frequency:

Very common: $\geq 1/10$; *common:* $\geq 1/100$ to $< 1/10$; *uncommon:* $\geq 1/1000$ to $< 1/100$; *rare:* $\geq 1/10000$ to $< 1/1000$; *very rare:* $< 1/10000$, not known and cannot be estimated from the available data.

DOSAGE AND ADMINISTRATION

LODOTRA[®] modified release tablets must be swallowed whole, and not divided, broken or chewed.

Dividing, breaking or chewing the tablets will damage the delivery system, leading to the immediate release and absorption of the prednisone dose.

LODOTRA[®] modified release tablets are intended for low-dose therapy.

Use in adults

The dose depends on the severity of the condition and the individual response by the patient. In general, 10 mg prednisone is recommended for the initiation of therapy. The initial dose can quickly be reduced to a lower maintenance dose, depending on the clinical symptoms and the patient's response.

When transferring from the standard regimen (glucocorticoid administration in the morning) to LODOTRA[®] modified release tablets administered at bedtime (at about 10 pm), the same dose (up to 10 mg or mg prednisone equivalent) should be maintained. Following the change-over, the dose may be adjusted according to the clinical situation. Depending on the outcome of treatment, the dose can be reduced in steps of 1 mg every 2 to 4 weeks to reach the appropriate maintenance dose.

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, using the appropriate strength of LODOTRA[®] modified release tablets.

The maximum dose studied in all clinical trials was 10 mg. Consequently, there is a lack of data for doses greater than 10 mg, particularly in long-term use greater than 12 months.

In some cases, a higher dose, to a maximum of 20 mg, may be required for the short-term treatment of flares of rheumatoid arthritis (up to one week). Above 10 mg, the doses to be used are 12, 15 and 20 mg. The maximum daily dose to be used is 20 mg.

The daily dose of prednisone must always be made up using the minimum number of tablets required to make up that dose.

To discontinue LODOTRA[®] modified release tablets, the dose should be reduced in steps of 1 mg every 2 to 4 weeks, with monitoring of the pituitary-adrenal axis parameters if necessary.

Method of Administration

LODOTRA[®] modified release tablets must be taken at bedtime, at about 10 pm, with or after the evening meal.

The tablets should be swallowed whole with sufficient liquid.

If more than 2 to 3 hours have passed since the evening meal, LODOTRA[®] modified release tablets must be taken with a light meal or snack.

LODOTRA[®] modified release tablets should not be taken in a fasted state, as this can result in reduced bioavailability (see PHARMACOLOGY, Pharmacokinetics, Effect of Food; and PRECAUTIONS, Important information for patients and caregivers).

LODOTRA[®] modified release tablets are designed to release the active substance approximately 4 to 6 hours after ingestion, allowing the pharmacological effects to commence during the night.

LODOTRA[®] modified release tablets consist of a prednisone-containing core and an inert coating. The delayed release of prednisone is dependent upon the coating remaining intact.

For this reason, the tablets are not to be broken, divided or chewed.

Use in children

Because of insufficient data on tolerability and efficacy, the use of LODOTRA[®] modified release tablets in children and adolescents is not recommended (see CONTRAINDICATIONS).

Use in hypothyroidism and hepatic cirrhosis

In patients with hypothyroidism or hepatic cirrhosis, comparatively low doses of LODOTRA[®] modified release tablets may be sufficient or a dose reduction may be necessary.

OVERDOSAGE

Acute intoxications with LODOTRA[®] modified release tablets are not known. An increase in undesirable effects, especially endocrine, metabolic and electrolyte-related effects, can be expected in overdosage. There is no known antidote for prednisone.

Contact the Poisons Information Centre on 13 11 26 for management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

LODOTRA[®] modified release tablets are available in 1 mg*, 2 mg and 5 mg strengths, and pack sizes of 30 and 100* tablets. The tablets are coloured almost white to yellow and are cylindrical-shaped, with the following letters and numerals embossed on one side:

- 1 mg tablet: “NP” over “1” (pale yellowish white)*
- 2 mg tablet: “NP” over “2” (yellowish white)
- 5 mg tablet: “NP” over “5” (light yellow).

*Not available in Australia.

LODOTRA[®] modified release tablets are packaged in white plastic bottles with a desiccant (white, capsule shaped) fitted into the inside of each bottle cap. This capsule is not to be eaten.

Storage Conditions

Store below 25°C. Keep container tightly closed to protect from moisture.

POISONS SCHEDULE OF THE MEDICINE

S4

SPONSOR

Mundipharma Pty Limited, ABN 87 081 322 509
50 Bridge Street, SYDNEY NSW 2000

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF
THERAPEUTIC GOODS**

7 August 2012

DATE OF MOST RECENT AMENDMENT

13 September 2012

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