



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Prednisone

Proprietary Product Name: Lodotra

Sponsor: Mundipharma Pty Limited

June 2013

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of Abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ACR	American College of Rheumatology
AUC	Area Under the Curve
ATC	Anatomical Therapeutic Classification (WHO drug classification)
BMI	Body Mass Index
CI	Confidence intervals
C _{max}	Peak (or maximum) concentration
CrCl	Creatinine clearance
CRP	C-Reactive Protein
CTX I	C-Terminal Telopeptide Type I Collagen
DMARD	Disease Modifying Anti-Rheumatic Drug
EULAR	European League Against Rheumatism
ICH GCP	International Conference on Harmonisation and Good Clinical Practice
GMT	Geometric Mean Titre
HPA	Hypothalamic Pituitary Axis
IL	Interleukin

Abbreviation	Meaning
IM	Intramuscular
IR	Immediate Release
Ig	Immunoglobulin
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LS	Least Square
MCID	Minimal Clinically Important Difference
MR	Modified Release
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
QOL	Quality of Life
SAE	Serious adverse event
SE	Standard Error
SF-36	Short Form-36 Questionnaire
TEAE	Treatment Emergent Adverse Event
TNF	Tissue Necrosis Factor
T-lag	Absorption Lag Time
T _{max}	Time to peak (maximum) concentration
TR	Timed Release
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Major Variation -New dosage form
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	17 July 2012
<i>Active ingredient(s):</i>	Prednisone
<i>Product Name(s):</i>	Lodotra
<i>Sponsor's Name</i>	Mundipharma Pty Limited
<i>Dose form(s):</i>	Tablets - modified release
<i>Strength(s):</i>	1 mg, 2 mg and 5 mg
<i>Container(s):</i>	High-density polyethylene (HDPE) bottles
<i>Pack size(s):</i>	30's, 100's
<i>Approved Therapeutic use:</i>	<i>Lodotra modified release tablets are indicated for the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness.</i>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	See Product Information (PI) and Product Background below.
<i>ARTG Number (s)</i>	183793, 183794, 183795

Product background

Rheumatoid arthritis is an inflammatory condition with signs and symptoms that include joint stiffness, pain and swelling which is often the subject of circadian variations. The mechanism responsible for the circadian variation of rheumatoid arthritis symptoms are complex. However, inflammation causes increased production of pro-inflammatory cytokines. Research into the circadian rhythms of these cytokines show a higher plasma level concentration of some cytokines prior to waking and this may influence symptoms such as morning stiffness.

This AusPAR describes the application to register Lodotra tablets containing prednisone in a modified-release (delayed or timed release) formulation (TR) for the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness. The tablets are designed to be taken at bedtime (approximately 10 pm) and to release the active ingredient within 4-6 h of ingestion. Peak plasma levels of prednisone are reached 6-9 h after ingestion. Lodotra is proposed by the sponsor as an efficient way to counteract the circadian rhythm of pro-inflammatory cytokines such as IL-6 and timed to address the symptoms of morning stiffness. 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 peak plasma concentration (C_{max}) occurring between 4 am to 6 am).

Prednisone is a non-fluorinated glucocorticoid. It is metabolised to prednisolone which is also an active glucocorticoid. Prednisone is used for systemic therapy and has a dose-dependent effect on metabolism in almost all tissues. It has an immediate anti-

inflammatory (anti-exudative and anti-proliferative) effect and a delayed immunosuppressive effect.

Lodotra is a modified (delayed or “timed”) release formulation of prednisone. The active drug sits within a core surrounded by an inactive shell, the dissolution of which delays the release of prednisone by approximately 4 h. It is not a sustained release preparation; when the prednisone is finally released from Lodotra, the release occurs in a manner similar to that from an immediate release tablet. Drug release is triggered by penetration of water and is mostly independent of the gastrointestinal tract (GIT) environment.

There are three immediate-release products containing prednisone on the Australian Register for Therapeutic Goods (ARTG) namely:

- Predsone 1 mg tablets (Aspen Pharmacare Australia Pty Ltd),
- Sone 5 mg and 25 mg tablets (Valeant Pharmaceuticals Australasia Pty Ltd) and
- Panafcort 1 mg, 5 mg and 25 mg tablets (Aspen Pharmacare Australia Pty Ltd).

The current approved wording of the indications in Australia for Sone tablets is very broad and brief, namely “*Wherever corticosteroid therapy is indicated*”. The current approved wording of the indications in Australia for Panafcort tablets is also very broad, beginning with the words “*Wherever corticosteroid therapy is indicated*”. However, in the latter case, this wording is followed by a list of over 20 conditions, including rheumatoid arthritis, where corticosteroid therapy is used.

The sponsor has requested the following indications for Lodotra:

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

Although the requested indications for Lodotra are much more restrictive than those approved for the immediate release prednisone medicines on the ARTG, the Delegate for this application sought the opinion of the Advisory Committee on Prescription Medicines (ACPM) as to whether the indication which is sought is consistent with the already approved indication for rheumatoid arthritis.

According to the Product Information document (PI), the initial daily dose is 10 mg and this may be titrated down in steps of 1 mg. In some cases short-term higher treatments of 12, 15 or 20 mg are required and thus the maximum daily dose is 20 mg. It follows from this and the tablets strengths being supplied, that the daily dose (apart from doses of 5 mg and 2 mg) will be made up of more than one tablet. The PI also gives specific instructions in relation to the timing compared to food intake: they should be taken at ~10 pm with or after the evening meal but if more than 2-3 h have passed since the evening meal, the tablets should be taken with a light meal or snack.

The relevant TGA adopted European Union (EU) guidelines to this application include:

pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)

Clinical Investigation of Medicinal Products for Long-Term Use

Replaces: pp. 163 - 165 of Rules 1989

Effective: 12 February 2002

See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

CPMP/EWP/556/95 Rev 1 (pdf,176kb)

Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis

Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001)

Published: TGA Internet site

Effective: 29 January 2007

pp. 257 - 261 of Rules 1998 (3C) - 3CC17a (pdf,25kb)
 Medicinal Products (Non-Steroidal Anti-Inflammatory Compounds) for the Treatment of
 Chronic Disorders

Replaces: pp. 175 - 176 of Rules 1989

Effective: 12 February 2002

CPMP/EWP/280/96 (pdf,90kb)

Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II
 (Pharmacokinetic and Clinical Evaluation)

Replaces: pp. 181 - 192 of Rules 1998 (3C) - 3CC11a

Published: TGA Internet site

Effective: 14 March 2001

Adopted by TGA with the following conditions:

"For multiple strengths of generic TDDS products, bioequivalence studies should be performed at least on the lowest and highest strengths versus the corresponding innovator products. If an applicant considers that this is unnecessary in a particular case, a justification for not submitting bioequivalence data should be submitted in accordance with Section 4 of Appendix 15 (Biopharmaceutic studies) of the ARGPM."

Regulatory status

Lodotra 1, 2 and 5 mg modified release tablets were registered on the ARTG on 7 August 2012. The following table summarises the international regulatory status for Lodotra indicated for *the treatment of moderate to severe, active rheumatoid arthritis in adults particularly when accompanied by morning stiffness.*

Table 1. Summary of International regulatory status of Lodotra

Country/Region	Registration Status	Approval Date (s)
EU	Approved	Belgium, Denmark, Germany and, Portugal in March 2009; United Kingdom in April 2009; France and Sweden in May 2009; Luxembourg in June 2009; Austria, Finland, Netherlands and Poland in July 2009; Spain in August 2011; Norway in October 2009; Italy in November 2010;
Switzerland	Approved	August 2011
New Zealand	Approved	20 September 2012
USA	Approved	26 July 2012

Lodotra has also been approved in Israel (3 March 2011) and South Korea (16 January 2013).

Product Information

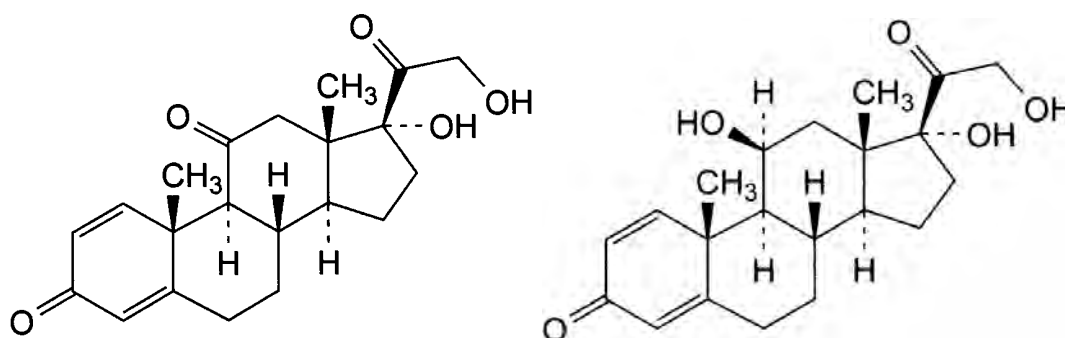
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Introduction

Figure 1 describes the chemical structures of prednisone and its active metabolite prednisolone.

Figure 1. Chemical structures



prednisone

$C_{21}H_{26}O_5$ MW = 358.4

CAS # = [53-03-2]

Practically insoluble in water {<0.1 mg/mL}

prednisolone

$C_{21}H_{28}O_5$ MW = 360.4

CAS # = [50-24-8]

Drug substance

The prednisone is to be manufactured at two sites.

In both cases, a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability was provided indicating compliance with the European Pharmacopoeia (EP)/ British Pharmacopoeia (BP) monograph for Prednisone.

Note that the related substance prednisone-21-aldehyde gave a positive Ames test. It is controlled to no more than (NMT) 0.25%¹, which equates to a maximum daily intake of 50 mg. The advice from the Toxicology Section of TGA's Office of Scientific Evaluation (OSE) was that this was initially not acceptable (see *Drug Product* below for more detail).

The particle size distribution is satisfactorily controlled.

The residual solvents methanol, dichloromethane and acetone are controlled to levels equal to or less than prescribed by International Conference on Harmonization (ICH) guidance.

Drug product

The tablets are to be manufacture at two sites.

¹ Sponsor comment: "0.25% is the limit which P21A is controlled by the drug substance manufacturer and is also the limit stated in the European Pharmacopoeia for impurities."

The cores of the three strengths are all the same mass with the amount of lactose present being adjusted to compensate for the different amounts of prednisone present.

The shells of the three strengths are all the same mass but the three strengths have different shades of yellow.

The manufacturing process involves two wet granulation steps.

- The shell coating acts to delay the release of the prednisone from the tablets. It has pH independent dissolution properties and, once the shell has dissolved or worn away, the core acts as an immediate release tablet.
- There are controls on the particle size distributions of the excipients glyceryl behenate and calcium hydrogen phosphate dihydrate.
- The position of the core within the outer shell is controlled by three independent procedures.

Data was provided to demonstrate that ethanol (up to 40%) did not decrease the *in vitro* lag time.

The control of the tablets was initially considered as **not** acceptable in that:

- The proposed lower limit for assay of the 1 mg and 2 mg tablets (but not the 5 mg tablets) at expiry does not comply with Therapeutic Goods Order No. 78 (TGO 78): a limit of no less than (NLT) 90.0% is proposed, but TGO 78 stipulates a limit of NLT 92.5% or higher must be used.

Note the stability data provided on batches stored in the proposed container system indicate that the limit of NLT 92.5% can be met at the end of the proposed shelf life when the proposed lower limit for assay at release of NLT 95.0% is met. Thus, if this if the lower assay limit at expiry was tightened to NLT 92.5%, approval could be granted on this issue.

The sponsor agreed to the tighter limits and this issue is resolved.

- If the *in vivo* lag-time is too long a tablet could reach the colon before the modified release coating is fully eroded/dissolved. Absorption in the colon is less than in the higher GI tract. Therefore if this occurs, the absorption will be less. Bioavailability data indicated that tablets with mean *in vitro* lag time of 4.9 h and maximum *in vitro* lag time of 5.5 h was bioequivalent to batches of tablets with earlier *in vitro* lag times (for example, tablets with mean *in vitro* lag time of 3.9 h and maximum *in vitro* lag time of 4.5 h and tablets with mean *in vitro* lag time of 3.2 h and maximum *in vitro* lag time of 3.5 h). However the proposed expiry specifications for all strengths allow for the *in vitro* lag time to be as long as 6.0 h for some tablets due the proposal of Stage 2 and Stage 3 testing. No data has been provided to demonstrate that tablets with an *in vitro* lag time of 6 h will not reach the colon prior to the erosion/dissolution of the modified release coating.

Therefore, the proposed dissolution limits for the in vitro lag time have not been justified.

Note the stability data provided on batches stored in the proposed container system indicate that neither Stage 2 nor Stage 3 testing are required over the proposed shelf life and products will still comply if removal of these parts of the Stage 2 and Stage 3 limits are deleted from the expiry specifications. The removal of the related parts of the Stage 2 and Stage 3 limits would also have to be deleted from the release specifications to ensure compliance with any tighter expiry specifications. Thus if the Stage 2 and Stage 3 dissolution limits at both release and expiry were amended to remove the possibility that some tablets could have longer *in vitro* lag times than those allowed at Stage 1, approval could be granted on this issue.

The sponsor has agreed to the tighter limits and this issue is resolved.

- The products have a degradant prednisone-21-aldehyde (P21A) that gave a positive Ames test and it is therefore potentially carcinogenic. As such, without further justification it should be controlled to the threshold of toxicological concern (TTC, 1.5 µg/day). However P21A is only controlled to NMT 0.25% in the specifications of the drug substance and not at all in the specifications of the drug product. According to Appendix 18 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), the limit may be qualified in three ways. The sponsor provided a justification for their approach but this justification has not fully addressed any of these three ways: (i) there is no transparent EP, BP or US Pharmacopeia (USP) monograph published since it was found that the material has a positive Ames test which states a limit of NMT 0.25% is qualified; (ii) no data has been provided on the levels of this degradant in the prednisone products currently registered in Australia and no postmarket data to support that cancer is not an adverse reaction of these registered products²; and (iii) sufficient toxicological data have not been provided to qualify the proposed limit. In particular, the Toxicological Section of OSE evaluation concludes, 'in the absence of further supportive non-clinical evidence *in vivo* (such as testing of P21A for clastogenicity *in vivo*), the ICH principle of controlling impurities to a low as reasonably practicable (ALARP) should be followed, and therefore P21A should be routinely tested for in the drug product and controlled to expiry limits that are consistent with the actual stability data'.³ Therefore the finished product release and expiry specifications are unacceptable as they do not include a qualified limit for the degradant P21A and the drug substance specifications are unacceptable as the proposed limit for P21A has not been qualified.

It is noted the data stability indicates that an expiry limit of NMT 0.1% in the finished product specifications for the degradant P21A could be met and if the sponsor was to adopt this limit approval could then be granted on this issue so long as the sponsor also added the same limit of NMT 0.1% for P21A to the finished product release specifications and the drug substance specifications to ensure compliance at expiry.⁴ In relation to this the related substances test methods used with the finished product and drug substance have been shown to be able to quantify the amounts of P21A present but these test methods would require amendment with any necessary changes following the change to the limit.

The sponsor has proposed an expiry limit of NMT 0.2% and provided further toxicological argument and quality data to support this limit.⁵ As per the current Streamlined Submission Process this has not been evaluated and approval can only be

²Sponsor comment: "No data had initially been provided on the levels of this degradant in the prednisone products currently registered in Australia. In further correspondence with the TGA, the applicant provided data on P21A contained in marketed products in Australia. Although no postmarket data was provided to support that cancer is not an adverse reaction of these registered products, the applicant cannot comment on post-market data from other products."

³ Sponsor comment: ". However, the guideline "does not need to be applied retrospectively to authorised products" (and prednisone is approved for decades), "if a manufacturing procedure for API remains essentially unchanged" (EMA 2010). Then "a re-evaluation with respect to the presence of potentially genotoxic impurities is generally not needed."

⁴ Sponsor comment: "The sponsor tested prednisone containing products marketed in Australia (see above) for P21A and found 0.1 to 0.2 % (with more than 1 year remaining shelf-life) with the analytical method developed for the testing of Lodotra. It is further noted that the batch release data for Lodotra indicates that a limit of NMT 0.1% in the finished product release specifications for the degradant P21A could be met, if the sponsor was to select API batches with the same limit of NMT 0.1% for P21A (instead of 0.25% as specified by the API manufacturers).

⁵ Sponsor comment: "The sponsor later agreed to the limit of NMT 0.1% and proposed an expiry limit of NMT 0.2% for P21A. The sponsor will provide quality data to support this limit when more stability data is available."

recommended if the expiry limit for P21A is tightened to NMT 0.1% (which the evaluator believed could be met) and a similar limit is adopted for the release limit and the limit in the drug substance.

- The other tests and expiry limits are acceptable and there are appropriate release limits to ensure compliance throughout the shelf life. This includes:
 - The possibility of Stage testing for the amount dissolved after the *in vitro* lag time, and the possibility of Stage testing for *in vitro* lag times.
 - The degradant expiry limits are strength specific (different for the three strengths).
 - The known and unknown degradant expiry limits are different for the three strength tablets. Given that the dose may range between 1 and 20 mg and a combination of 1, 2 and 5 mg tablets will be required for each dose, the sponsor has added a comment to the PI that '*The daily dose of prednisone must always be made up using the minimum number of tablets required to make up that dose.*' These instructions ensure that the maximum daily intake of any one degradant remains below the ICH threshold. The expiry limits for total degradants are also strength specific.
 - The limits for appearance, hardness, friability, and water content.
- Stability data was provided on tablets stored in bottles with a desiccant attached to the closure and in bottles without desiccant. Only bottles with the desiccant will be supplied in Australia.
 - In bottles with desiccant, there was a strength dependent and temperature dependent degradation.
 - The degradation in bottles with desiccant was less than in bottles without desiccant indicating that the degradation is also humidity dependent.
 - The data supported a shelf life of 2 years when stored below 25°C with the additional storage condition of 'keep container tightly closed to protect from moisture'.
 - Data was also provided to support an in-use shelf life of 14 weeks (100 days). For example, 1 tablet from the 100 tablet pack per day.

The chemistry and quality control aspects of the draft PI have been finalised to the satisfaction of the PCS evaluator. As have the carton and blister foil labels and the Provisional ARTG Records.

Biopharmaceutics

Bioavailability

The pivotal Phase III efficacy studies were performed with the proposed products. The PI states that patients may be started directly on the proposed products or switched from an immediate release prednisone tablet currently registered in Australia. It also gives specific instructions in relation to the timing compared to food intake: tablets should be taken at ~10 pm with or after the evening meal but if more than 2-3 h have passed since the evening meal, the tablets should be taken with a light meal or snack.

Data provided

To support registration, nine (9) bioavailability studies were provided together with a number of justifications for not providing bioavailability data. In all studies the levels of prednisone and its active metabolite prednisolone in plasma were determined using appropriately validated test methods.

Results

Study EMR 62215-001 compared 4 experimental formulations to “Decortin” immediate release prednisone tablets registered in Germany. None of the test formulations were as proposed and this was not evaluated by the Pharmaceutical Chemistry Section (PCS) at TGA.

Study EMR 62215-002 compared a further experimental formulation to “Decortin” immediate release prednisone tablets registered in Germany in both fed and fasted states. As the test formulation was not as proposed, this was not evaluated by PCS.

Study EMR 62215-005 compared the proposed 5 mg tablet administered at 8 pm in the semi-fasted state (2½ h after a snack, 9.9 g fat, ~2000 kJ, Treatment B) and in the fed state (30 minutes after a high fat meal, 26 g fat, ~4700 kJ, Treatment C) to “Decortin” 5 mg immediate release prednisone tablets registered in Germany administered at 2 am the next day in the fasted state (Treatment A) and also determine the effect of a high fat meal on the proposed 5 mg tablet. The results indicate: (i) similar time to peak plasma concentration (T_{max}) results even though the immediate release tablet was administered 4 h later; (ii) a mean *in vivo* lag time for the proposed tablets of 6 h which was not influenced by the timing and type of meal; and (iii) close to bioequivalence of the three treatments (*the lower 90% confidence interval for C_{max} was only 74% in one case, the upper 90% confidence interval for C_{max} was 131% in one case, and the upper 90% confidence interval for AUC was between 126 and 128% in five cases*). These results were brought to the attention of the Clinical Delegate to consider in relation to the use of the product.

Study NP01-006 compared the proposed 5 mg tablet administered after a fast and after a high fat meal. The results indicate: (i) a 3-4 fold increase in the bioavailability with food; (ii) a longer T_{max} when fasted.

Study NP01-008 studied single doses of the proposed 1 mg, 2 mg and 5 mg tablet administered in the fasted state. This was therefore a pharmacokinetic study rather than a bioavailability study and as such it was not evaluated by PCS. However, for completeness, dose proportionality was observed.

Study NP01-009 compared four 5 mg tablets with different *in vitro* lag times in the fasted state with the object of generating an *in vitro*, *in vivo* correlation (IVIVC). These were all of the proposed formulation and generated by using different compression forces during the tablet manufacture. As the PI does not allow dosing in the fasted state and the same four tablets were compared in the fed state in study NP01-010, this study was not evaluated in detail. The sponsor concluded that: (i) the formulations were not bioequivalent due to high variability in the individual results; (ii) there was a close to linear relationship between the *in vitro* lag time and the *in vivo* lag time and between the *in vitro* lag time and the *in vivo* T_{max} ; and (iii) the results for the reference tablets were consistent with the fasted results in study NP01-006.

Study NP01-010 compared four 5 mg tablets with different *in vitro* lag times administered 1 h after a high fat meal (26 g fat, ~4700 kJ) as per the instruction in the PI, with the object of generating an IVIVC. The four batches had mean *in vitro* lag times of 3.2, 3.9, 4.4 and 4.9 h and maximum individual *in vitro* lag times of 3.5, 4.5, 5.0 and 5.5 h. All four batches were bioequivalent and there were correlations between *in vitro* lag time and the *in vivo* lag time and between the *in vitro* lag time and the *in vivo* T_{max} . The *in vivo* lag time, the *in vivo* T_{max} were 0.9 h and 3.1 h after the *in vitro* lag time. There were no correlations between any of the *in vitro* lag time, the *in vivo* lag time or the *in vivo* T_{max} and either C_{max} or AUC.

Study NP01-013 compared the proposed 5 mg tablet administered at 10 pm, 1 h after a light meal (28 g fat, ~3300 kJ), as per the instruction in the PI to the “Decortin” 5 mg immediate release prednisone tablets registered in Germany administered at the 8 pm, 30 minutes after a breakfast (27 g fat, ~3250 kJ). The *in vivo* lag time and *in vivo* T_{max} results

were obviously very different but 90% confidence interval results for the AUCs prednisone and prednisolone were within the criterion of 80.0-125.0%. The 90% confidence interval for the C_{max} of prednisolone was also within 80.0-125.0% but that for the C_{max} for prednisone was not. This C_{max} was ~22% higher with a confidence interval of 116.1-127.7%. These results were brought to the attention of the Clinical Delegate to consider in relation to the use of the product.

Study NP01-014 compared the proposed 5 mg tablets from the two proposed sites of manufacture administered at 8 am after a standard high fat breakfast. The results indicated bioequivalence.

Important Note: A number of low bioavailability results were observed in all the bioavailability studies using the proposed tablets (for examples from study NP01-010). Thus from bioavailability studies EMR 62215-005, NP01-006, NP01-009, NP01-010, NP01-013 and NP01-014 there were 21 low results out of a total of 362 relevant datasets (that is, about 6% of results are low). These instances appeared to be totally random and not related to subject or, in the case of study NP01-010, to the *in vitro* lag time.

The sponsor stated that these low results only occur when the tablets are given fasted or with a light meal but their criterion for a low result was that the AUC must be <30% of the mean AUC. However in study EMR 62215-005 there was one result after a full fat dinner which was only 33% of the mean AUC and the next lowest results was 77% of the mean AUC and the PCS evaluator has taken this result to be a low result.

The sponsor has put forward an argument that the low results are due to a random and unexplained enhanced gastrointestinal transit time and in the absence of any data to suggest manufacturing errors, this was accepted. Although the 1 mg tablets showed a 1 hr increase in the *in vitro* lag time on storage, no unusual *in vitro* lag time or dissolution results were noted from greater than 1300 individual tablet results. This fact of randomly low bioavailability was brought to the attention of the Clinical Delegate to consider in relation to the use of the product.

Justification for not generating bioavailability data on the 1 mg and 2 mg tablets

All bioequivalence studies were performed using the 5 mg tablets only.⁶ A justification was provided to extrapolate to the 1 and 2 mg tablets. The chemical and physical aspects of this justification were acceptable which included comparative dissolution profiles generated in a large variety of media (water, pH 1.2, acetate buffer pH 4.5, simulated intestinal fluid pH 6.8, fasted state simulated intestinal fluid and fed state simulated intestinal fluid). The clinical aspects included that the dose response was linear over 1-5 mg and that prednisone was BCS class 1. The clinical aspects should have been assessed by the clinical evaluator.

Justification for the use of an overseas prednisone comparator rather than an Australian prednisone comparator

Given that the PI states that patients may be switched from an immediate release prednisone tablet currently registered in Australia, a justification for not comparing the proposed product to an Australia product was provided. This compared the two Australian immediate release tablets to the "Decortin" 5 mg immediate release prednisone tablets registered in Germany use in the biostudies. Although the qualitative formulations of these three tablets were all different, none of the excipients in any of the formulations are likely to affect gastric emptying times. In addition the dissolution profiles in water, pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 indicated very fast dissolution with both Australian products >85% dissolved in 15 minutes in all media. Although the German product had slightly less than 85% dissolved in 15 minutes at pH 4.5 and 6.8, the sponsor

⁶Sponsor comment: "Study NP01-008 showed dose-linearity between 1, 2 and 5 mg (see above)."

provided the dissolution profiles for a second German immediate release 5 mg prednisone (viz: Galan®) which like the Australian products had >85% dissolved in all four media and a closer qualitative formulation to “Decortin” than the Australian products. As “Decortin” and Galan® are listed as interchangeable in Germany, it was accepted that the chemical and physical aspects of this justification were acceptable. As above, the clinical aspects included that the dose response was linear over 1-5 mg and that prednisone was BCS class 1⁷. The clinical aspects should have been assessed by the clinical evaluator. If the clinical evaluator agrees that the justification is acceptable, the results of bioavailability Study NP01-013 can be extrapolated in relation to this issue.

Justification for the lack of a study at steady state

This was based on the fact that the product is not designed to be sustained release but delayed release and thus the PK profile will be the same as an immediate release tablet only shifted in time. It is accepted that this is the case and further noted that at a dose of 5 mg at least the profiles of both prednisone and the metabolite prednisolone show a drop to undetectable levels in a mean of 20 h due to the half lives being only 2-4 h. The clinical aspects should have been assessed by the clinical evaluator.

Bioavailability in relation to the Product Information document (PI)

The pharmacokinetics subsection is based on the bioavailability data provided and in particular the results of Study EMR 62215-005 have been presented. This is acceptable to PCS. However, the Clinical Delegate may wish to include a statement that low bioavailability is observed randomly after dosing in ~6% of cases.

Advisory committee considerations

Previous consideration by the Pharmaceutical Subcommittee of ACPM (PSC)

This application was presented to the 142nd meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on prescription Medicines (ACPM) in November 2011. The PSC had no objections to approval of the submission provided all outstanding issues were addressed to the satisfaction of the TGA (which was not the case), and did not require to review this submission again. In particular the Committee:

- agreed that there was a logical explanation as to why the T_{max} for the prednisolone metabolite is earlier than the T_{max} for prednisone as this observation was confirmed by the result obtained from a simulation conducted by the Sponsor.
- considered the removal of outliers in Study NP01-010 inappropriate. The Committee supports the evaluator’s conclusion that outliers can only be removed from statistical analyses if supported by a satisfactory clinical explanation. It has since been accepted that there is a clinical reason for the low results (fast, but random, gastrointestinal transit times) and that the omission of the outliers is acceptable.
- considered that the increased variability in C_{max} and AUC⁸
- observed with the proposed product compared to the immediate release product in Study NP01-013 could be attributed to the measurement of the drug substance and its metabolite. *It has since been attributed mainly to the random low results.*

⁷ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

⁸ AUC=Area under the plasma concentration time curve

- agreed that it was not clear that the data supports the drug release limits for lag-time and percent dissolved 1.5 h after lag-time.
- considered the sponsor's justification for not providing bioavailability data on all strengths of the tablet formulation proposed for registration acceptable.
- The PSC considered that the sponsor should be asked to:
- provide batch analysis data on three recent consecutive process re-validation batches of the drug substance manufactured at both manufacturing sites.
- ensure that drug substances from both nominated manufacturing sites are included in the protocol for future validation batches at one of the proposed finished product manufacturers.

These issues have been resolved.

The Committee considered that the Delegate should assess the clinical implication in relation to the observed differences in the dissolution profile of prednisone from the immediate release (IR) tablet formulation registered for supply in Australia and the overseas sourced IR tablet formulation used in the bioavailability studies provided in support of this submission. This has been mentioned above and the clinical aspects of the justification should have been assessed by the clinical evaluator.

Quality summary and conclusions

Recommendations

Approval of this submission cannot be recommended with respect to chemistry and manufacturing control as:

- The proposed lower limit for assay of the 1 mg and 2 mg tablets (but not the 5 mg tablets) at expiry does not comply with Therapeutic Goods Order No. 78 (TGO 78).

This issue was later resolved.

- The proposed dissolution limits for the *in vitro* lag time have not been justified. This issue was later resolved.
- The finished product release and expiry specifications are unacceptable as they do not include a qualified limit for the degradant P21A and the drug substance specifications are unacceptable as the proposed limit of NMT 0.25% for P21A has not been qualified. This issue had not been resolved by the time this application was presented to the ACPM.

Conclusions with respect to bioavailability:

- The proposed products have an *in vivo* lag time compared to the immediate release products on the market and there was a correlation between the *in vitro* lag time and the *in vivo* lag time and between the *in vitro* lag time and the *in vivo* T_{max} .
- The *in vivo* T_{max} is 6-7 h when the tablets are taken as directed in the PI. Thus T_{max} will occur at 4-5 am given that the PI instructs that the tablets be taken at 10 pm.
- Compared to the fasted state, the bioavailability from the proposed tablets is 3-4 times when given with a high fat meal. The bioavailability was also 10% higher 30 minutes after a high fat meal compared to 2½ h after a light meal. The PI recommends that the tablets should be taken at ~10 pm with or after the evening meal, but if more than 2-3

h have passed since the evening meal, the tablets should be taken with a light meal or snack. Difference brought to the attention of Clinical Delegate.

- Compared to an immediate release tablet from Germany, the proposed tablet was bioequivalent with respect to the AUCs of prednisone and prednisolone, the C_{max} of prednisolone but not the C_{max} for prednisone. This C_{max} was ~22% higher. Difference brought to the attention of Clinical Delegate.
- Tablets manufactured at different sites were bioequivalent.
- Randomly 6% of the bioavailability results are low, probably due to unexplained fast gastrointestinal transit times. Brought to the attention of Clinical Delegate.

The chemical and physical aspects of the justifications for not providing certain bioavailability data and for the use of the German immediate release comparator rather than an Australian immediate release comparator were acceptable. The clinical aspects should have been assessed by the clinical evaluator.

III. Nonclinical findings

Introduction

No new nonclinical data were supplied with this application. This is acceptable as there are no toxicological implications related to the delay in T_{max} observed with the new prednisone formulation and there are no novel excipients.

The sponsor presented a literature-based submission in support of Lodotra® tablets, comprising both review articles and descriptions of original research, that were of relevance to understanding the mode of action and safety of prednisone use in humans.

Pharmacology

Glucocorticoids such as prednisolone are able to induce cellular responses via both genomic and non-genomic mechanisms. Genome-based responses are initiated by diffusion of glucocorticoid through the cell membrane and binding to, and activation of, cytosolic glucocorticoid receptor. Activated glucocorticoid receptor can then enter the nucleus and bind glucocorticoid response elements, resulting in upregulated transcription of various genes involved in anti-inflammatory/immunosuppressive action. Alternatively, activated glucocorticoid receptor can exert anti-inflammatory/immunosuppressive (and other) effects by binding pro-inflammatory transcription factors, such as NF κ B and AP1, and blocking upregulation of the transcription of their target genes. Non-genome-based responses to glucocorticoids may be mediated by a membrane-bound form of the glucocorticoid receptor, which may be coupled to signalling proteins via a G-protein.

Pharmacokinetics

Absorption: pharmacokinetics of prednisone/prednisolone are complex and can vary substantially between different laboratory animal species, reflecting factors such as non-linear plasma protein binding, non-linear first-pass biotransformation, non-linear renal elimination and saturable tissue binding.

Distribution: prednisolone binds to the plasma proteins transcortin (corticosteroid binding globulin) and albumin; binding to transcortin is high affinity but low capacity, whereas albumin binding is low affinity but high capacity; the affinity of prednisone for transcortin is 10 fold lower than that of prednisolone.

Metabolism and excretion: prednisone is a pro-drug that is converted to its active form, prednisolone, by the HSD11B1 isoform of 11 β -hydroxysteroid dehydrogenase in the liver; further metabolism of prednisone/prednisolone involves initial addition of oxygen or hydrogen atoms followed by glucuronidation or sulphation; the latter hydrophilic inactive metabolites are excreted by the kidneys.

Pharmacokinetic drug interactions

Prednisolone is a substrate of P-glycoprotein, suggesting that cellular levels of prednisolone might be increased in the presence of P-glycoprotein inhibitors.

Toxicology

Acute toxicity

Subcutaneous (SC) injections of prednisolone in mice and rats produced death associated with generalised infection and consistent with immune suppression.

Repeat - dose toxicity

Rats receiving a daily SC injection of prednisolone at 18.7 mg/kg died or were sacrificed in extremis during the period from the second to tenth week of dosing. Death was associated with inflammation, immune suppression and infection. Four of the five studies supplied by the sponsor examined the effects of repeat, topical application to the skin of rats or dogs of a gel containing prednisolone farnesylate. The changes seen in dosed animals were generally reversible and were consistent with the known action of glucocorticoids, they included: decreased white blood cell (WBC) counts, atrophy of thymus, lymph nodes, spleen, and adrenal cortex, and thinning of skin.

Genotoxicity

Prednisolone farnesylate, which is metabolised to prednisolone, was tested for genotoxicity in bacterial reverse mutation and *in vitro* and *in vivo* chromosomal aberration assays. The mutation and *in vivo* chromosomal aberration assays gave negative results; however, a low level of chromosomal aberrations was detected in the *in vitro* assay when cells were incubated with a very high concentration of drug and a source of metabolic activation. These results suggest that prednisolone may have very weak clastogenic activity.

Carcinogenicity

Three studies involving repeat oral dosing of rodents with prednisone or prednisolone were presented: mice dosed at up to 5 mg/kg/day for 18 months; rats dosed at 3 mg/kg at up to 9 doses per month for 18 months; and rats dosed at 0.4 mg/kg/day for 2 years. The mouse and rat (18 months) studies showed no significant increase in the incidence of tumours. The rat (2 years) study suggested a significant increase in the incidence of hepatocellular adenoma. Using conversion factors (mg/kg to mg/m²) of 3 (mouse), 6 (rat), and 37 (human – 70 kg) and comparing with a human dose of 10 mg daily, the exposure ratios for the high dose (HD) in the mouse (18 months), rat (18 months), and rat (2 years) studies are around 3, 1, and 0.5, respectively. These results suggest possible weak carcinogenic activity by prednisone/prednisolone.

Reproductive toxicity

Possible reproductive toxicity of prednisolone farnesylate was examined in four studies (three using rats and one using rabbits). Daily SC injection of test article at up to 1 mg/kg had no effect on fertility or reproductive performance of male and female rats, although dams showed decreased weight gain. Similarly, daily SC dosing of rats from Day 7 to 17 of pregnancy, at up to 25 mg/kg/day, had no effect on parturition, lactation, numbers of live newborns or fetal deaths, or on the incidence of developmental abnormalities, although dams showed decreased weight gain even at the low dose (LD). Daily SC dosing of rats from Day 17 of pregnancy to Day 21 after parturition, at up to 5 mg/kg/day, had no significant effects on F1 or F2 offspring⁹. Rabbits received a daily SC dose of prednisolone farnesylate from Day 6 to Day 18 of pregnancy. At 10 mg/kg/day, dams died or miscarried, and at 1 mg/kg/day, most dams miscarried. There were no effects on body weight gain or fetuses for rabbits dosed at 0.05 mg/kg/day.

Using conversion factors (mg/kg to mg/m²) of 6 (rat), 15 (rabbit), and 37 (human – 70 kg), comparing with a human dose of 10 mg daily, correcting for the molecular weight difference between prednisolone and prednisolone farnesylate (approximately 358 versus 581) and assuming that the effects of prednisolone and prednisolone farnesylate are comparable, it can be calculated that the exposure ratios at the doses producing no effect on dams or fetuses are: 0.1 (0.2 mg/kg, rat, pre- and post-mating), <0.7 (< 1 mg/kg, rat, Day 7 to 17 of pregnancy), 0.03 (0.05 mg/kg, rat, Day 17 of pregnancy to Day 21 after parturition), 0.09 (0.05 mg/kg, rabbit, Day 6 to 18 of pregnancy).

The exposure ratios producing no effect on dam or fetus, in the reported laboratory animal studies, are all low. Nevertheless, teratogenic effects were not reported even at much higher doses. Similarly, a study of lupus erythematosus patients, who were treated with prednisone during pregnancy, suggested a lack of teratogenic effect in humans.¹⁰ Glucocorticoids, including prednisolone, are known to readily cross the human placenta.^{11, 12} It is thought, however, that the fetus is largely protected from prednisolone in the maternal circulation by the presence of the HSD11B2 isoform of 11 β -hydroxysteroid dehydrogenase in the placenta (where it acts to oxidise prednisolone to prednisone) and by the lack of the HSD11B1 isoform (converts prednisone to prednisolone) in the fetal liver (see references in Spielman et al., 1992¹³).

Studies of breast-feeding women, given oral prednisolone for medical or experimental purposes, showed that prednisone and prednisolone were present in milk and that there was relatively rapid bidirectional exchange of unbound drug between serum and milk;

⁹ The parental generation is the first set of parents crossed. The F1 (first filial) generation consists of all the offspring from the parents, that is, their children. The F2 (second filial) generation consists of the offspring from allowing the F1 individuals to interbreed, hence the grandchildren of the parental generation.

¹⁰ Fine L.G., Barnett E.V., Danovitch G.M., Nissenson A.R., Conolly M.E., Lieb S.M. and Barrett C.T. (1981) Systemic lupus erythematosus in pregnancy. *Annals of Internal Medicine*, **94**: 667-677.

¹¹ AMA (1983) Adrenal corticosteroids in endocrine dysfunction, pp. 873-886. Adrenal corticosteroids in nonendocrine diseases. pp. 887-911. In: AMA Drug Evaluations, 5th ed. American Medical Association: Chicago, Illinois.

¹² Gerner R. and Halberstadt E. (1979) Studies on placental transfer of 16-methylene prednisolone (Decortilen) (author's transl.). *Zeitschrift für Geburtshilfe und Perinatologie*, **183**: 272-274.

¹³ Spielman H., Steinhoff R., Schaefer C. and Bunjes R. (1992) Glucocorticoids. In: *Handbook of Pharmacotherapy during Pregnancy and Lactation. A Reference Book for Daily Practice*. pp. 49-51. 4th ed. Gustav Fischer: Stuttgart, Jena, New York.

although drug levels were low and were not considered a significant risk to nursing infants.^{14,15, 16}

Pregnancy classification

The sponsor has proposed Pregnancy Category A, which is consistent with the nonclinical and clinical data for prednisone.

Paediatric use

Lodotra® tablets are not recommended for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- No new nonclinical data were supplied with this application. This is acceptable as there are no toxicological implications related to the delay in T_{max} observed with the new prednisone formulation and there are no novel excipients.
- The sponsor presented a literature-based submission in support of Lodotra® tablets, comprising both review articles and descriptions of original research, that were of relevance to understanding the mode of action and safety of prednisone use in humans.
- Prednisone is a pro-drug that is converted to its active form, prednisolone, by the HSD11B1 isoform of 11 β -hydroxysteroid dehydrogenase in the liver. Prednisolone binds irreversibly to the glucocorticoid receptor (expressed by various cell types), resulting in receptor activation. Activated glucocorticoid receptor induces various cellular responses, including the upregulation of transcription of genes involved in anti-inflammatory/immunosuppressive action and the down-regulation of pro-inflammatory genes, via both genomic and non-genomic mechanisms.
- The pharmacokinetics of prednisone/prednisolone are complex and can vary substantially between different laboratory animal species.
- Mortality following a single SC injection of prednisolone in rodents was preceded by generalised infection and was apparently the result of immune suppression.
- The changes seen in rats and dogs exposed to repeat, non-lethal doses of prednisolone were generally reversible and were consistent with the known action of glucocorticoids, including decreased WBC counts, atrophy of thymus, lymph nodes, spleen and adrenal cortex, and thinning of skin.
- The weight of evidence from genotoxicity assays with prednisone and prednisolone suggests a low potential for genotoxicity.
- 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.

¹⁴ Greenberger P.A., Odeh Y.K., Frederiksen M.C. and Atkinson A.J. (1993) Pharmacokinetics of prednisolone transfer to breast milk. *Clinical Pharmacology and Therapeutics*, **53**: 324-328.

¹⁵ Reynolds J.E.F. (1996) Prednisolone, pp. 1054-1056. Prednisone, p. 1056. In *Martindale: The Extra Pharmacopoeia*, 31st ed. Royal Pharmaceutical Society: London.

¹⁶ Schaefer C. and Spielman H. (2001) Corticosteroids. In: *Drug Prescription in Pregnancy and Lactation*, pp. 503-504. Urban and Fischer: Munich, Jena.

- Relatively low doses of prednisolone farnesylate induced decreased weight gain in pregnant rats and rabbits. Nevertheless, teratogenic effects were not reported even at much higher doses.

Conclusions and recommendation

- The nonclinical safety profile of Lodotra® tablets was adequately covered by the extensive nonclinical data and literature available for prednisone and prednisolone.
- There are no nonclinical objections to the registration of Lodotra® tablets.
- Amendments to the draft Product Information were recommended to the Delegate but these are beyond the scope of this AusPAR.

IV. Clinical findings

Introduction

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2 of this AusPAR.

Clinical rationale

Rheumatoid arthritis is a chronic autoimmune disorder which affects approximately 1% of the population. Glucocorticoids have been used since 1955 to manage the condition and remain an important therapy in contemporary practice as an adjuvant treatment with disease modifying anti-rheumatic drugs.^{17,18} Glucocorticoids have a broad spectrum of anti-inflammatory and immunosuppressive effects. They inhibit leucocyte trafficking; modify the functions of leucocytes, fibroblasts and endothelial cells; and suppress the synthesis and actions of pro-inflammatory cytokines such as interleukin (IL)-6.¹⁹ In addition to controlling symptoms of active RA such as morning stiffness, there is increasing evidence that low dose glucocorticoid treatment (equal to or less than 10 mg/day of prednisone or equivalent) may have disease modifying effects.²⁰ Some of the main symptoms of RA, such as joint pain and morning stiffness are typically most prominent in the morning upon awakening. It is known that the mechanism underpinning this observation relates to circadian rhythms involving both the hypothalamic-pituitary-adrenal axis as well as endogenous inflammatory mediators such as IL-1, IL-6 and TNF (Tumour Necrosis Factor). The levels of these pro-inflammatory cytokines in patients with RA are known to exhibit a circadian rhythm with peak concentrations observed between 2

¹⁷ Da Silva JAP, Jacobs JWG, Kirwan JR, Boers M, Saag KG, Ines LBS, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006; 65(3): 285-293.

¹⁸ Bijlsma JWJ and Jacobs JWG. Glucocorticoid chronotherapy in rheumatoid arthritis. *Lancet* 2008; 371(9608): 183-184.

¹⁹ Buttgerit F, Burmester GR and Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. *Lancet* 2005; 365(9461): 801-803.

²⁰ Kirwan JR, Bijlsma JWJ, Boers M and Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database of Systematic Reviews* (online; published 2007): number 1 CD006356.

am and 6 am. Furthermore, the serum concentration of IL-6 has been observed to correlate with morning stiffness and other clinical symptoms.^{21,22}

Lodotra is a modified (delayed or “timed”) release formulation of prednisone. The active drug sits within a core surrounded by inactive shell which delays the release of prednisone until approximately 2 am, when the drug is ingested at about 10 pm. The maximal concentration of prednisone is achieved at approximately 4 am. Drug release is triggered by penetration of water and is mostly independent of the gastrointestinal tract environment. The overnight timed release of prednisone is proposed to be an efficient manner in which to counter-act the circadian rhythm of pro-inflammatory cytokines such as IL-6 and thus reduce the symptoms of RA associated with these phenomena. Although administration of immediate release (IR) prednisone at low dose (5 or 7.5 mg/day) taken at 2 am versus 7.30 am has been shown in a single study involving 26 RA subjects treated for 4 days to improve morning stiffness and joint pain, such a regimen in the long term would be inconvenient and likely to result in disturbed sleep with reduced drug adherence.²³ Lodotra was developed as modified release formulation of prednisone which could be taken prior to bedtime (at around 10 pm) but achieve the same drug exposure and profile after a 4 h delayed release as compared to a standard IR prednisone tablet ingested at 2 am.

Formulation

Formulation development

Three, open label, Phase I studies (EMR 62215-001, -002 and -005) were performed in healthy male volunteers to evaluate the PK profile and oral bioavailability of 8 potential MR formulations of prednisone compared to the reference IR formulation, Decortin®. The principal aim of these studies was to identify a MR formulation that could be taken in the evening (~10 pm) and which releases the prednisone about 4 h after ingestion (at approximately 2 am to coincide with the circadian rise of pro-inflammatory cytokines, particularly IL-6) and which has a similar PK profile to the reference IR prednisone formulation once released. A dose of 5 mg was given for all formulations in these studies. Standard conditions relating to diet, fluid intake and physical activity were adhered to. On the days of study drug ingestion, participants received standard meals at breakfast, lunch and dinner. For Studies EMR 62215-002 and -005, subjects were also given an afternoon snack. All of the 3 initial studies had a randomised, crossover design with 7 day wash-out periods between single doses of study drug. No formal statistical power calculations were done but at least 12 subjects were required in each study to meet the relevant regulatory guideline. The number of volunteers involved in each study was 12 in EMR 62215-001, 28 in EMR 62215-002 and 27 in EMR 62215-005. All subjects were aged between 18-60 years (mean age of 32 years) with a normal body mass index (BMI) (mean body weight of 75 kg), no history of drug or alcohol abuse and had no chronic health problems.

The pilot study EMR 62215-001 investigated 2 press-coated and 2 film-coated MR formulations administered at 8 pm after a meal. The 2 film-coated formulations were unsuitable for further investigation as they showed insufficient median lag times (1-1.5 hs). The press-coated formulations showed better PK profiling and 1 formulation in particular had a median lag time of 4 h and a relative bioavailability (AUC) compared to

²¹ Straub RH and Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis and Rheum* 2007; 56(2): 399-408

²² Perry MG, Kirwan JR, Jessop DS and Hunt LP. Overnight variations in cortisol, Interleukin-6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68(1): 63-68.

²³ Arvidson NG, Gudbjornsson B, Larsson A and Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1997; 56(1): 27-31.

Decortin® for both prednisone and prednisolone of 85%. Consequently, press coating was chosen as the preferred manufacturing process for further investigation.

The next development study (EMR 62215-002) then tried to develop a MR tablet with a longer *in vitro* dissolution time of 6 h, so that if it was ingested at 8 pm it would produce a similar drug exposure to IR prednisone taken at 2 am. In this trial, the MR formulation was taken at 8 pm after a light meal at 5.30 pm or a normal dinner at 7.30 pm. The median *in vivo* lag time was 6.8 h after ingestion in the semi-fed state but with limited bioavailability (35-39% for prednisone and prednisolone, respectively) compared to Decortin®. Subsequently, the formulation with an *in vitro* lag time of 6 h was abandoned and a target formulation with a lag time of 4 h was desired. Optimisation of the lag time kinetics was achieved by adapting the outer shell mass. The final MR formulation (thereafter known as Lodotra®) with an *in vitro* lag time of 4 h was initially evaluated in Study EMR 62215-005 and then subsequently in the latter Phase I and also Phase III clinical trials.

Excipients

All of the proposed excipients are commonly used in tablet formulations. The concentration of glyceryl behenate used in Lodotra tablets is relatively high compared with other approved modified release tablets but the substance itself can be used in food without limitation.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

Clinical data

- 9 biopharmaceutical studies, including 3 that provided data about the selection and development of the commercial formulation (Studies EMR 62215-001, -002 and -005), 1 study (NP01-006) that examined the effect of food on bioavailability, 1 study (NP01-008) that assessed dose proportionality, 2 bioavailability studies to support the product specification (NP01-009 and -010), 1 study (NP01-014) evaluating bioequivalence for tablets produced by 2 different manufacturers, and 1 comparative bioavailability study (NP01-013) of Lodotra with a commonly used immediate release formulation of prednisone (Decortin®) in humans under therapeutic dosing conditions.
- 2 pivotal efficacy/safety studies (EMR 62215-003 and NP01-007). Both of the Phase III studies were of 12 weeks duration and designed as superiority trials for the main efficacy outcome.
- Study EMR 62215-003 also had a 9-month, open-label follow-up phase which provided supportive evidence in relation to the maintenance of efficacy and safety.

Paediatric data

The submission did not include any paediatric data and there is no current intention to develop such a program.

Good clinical practice

All studies in the Lodotra clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements were met. However, major protocol deviations potentially affecting the robustness of the efficacy analysis involved at least 20% of subjects in the 2 pivotal Phase III trials. Protocol deviations were clearly articulated and similarly distributed among the active and control treatment groups.

Pharmacokinetics

Studies providing pharmacokinetic data

The pharmacokinetic (PK) studies supporting the current application for the licensing of Lodotra in Australia consist of 9 Phase I trials which can be summarised as:

Studies EMR 62215-001, -002 and -005 were primarily conducted to investigate the bioavailability and PK characteristics of various experimental MR formulations with the aim to select a MR tablet formulation with the appropriate PK profile for evening ingestion,

Study NP01-006 mainly evaluated the effect of food on bioavailability,

Study NP01-008 assessed the dose proportionality of 1, 2 and 5 mg tablets of Lodotra,

Studies NP01-009 and -010 evaluated the bioavailability of batches with different *in vitro* lag times under fasted and fed conditions,

Study NP01-013 (performed as a post-approval commitment to the initial licensing in Germany) compared the relative bioavailability of 5 mg Lodotra tablets (given at 10 pm after a light evening meal) to a commonly used IR prednisone formulation in Europe (Decortin, 5 mg and taken at 8 am in a fed state after breakfast), and

Study NP01-014 which evaluated the bioequivalence of single oral doses of Lodotra 5 mg produced by 2 different manufacturing sites.

All the PK studies have been conducted in healthy subjects (male and female) between the ages of 18 and 45 years, who were predominately of Caucasian ethnicity. No multi-dose PK studies have been performed and the sponsor justifies this approach on the basis that the likelihood of accumulation of prednisone or prednisolone is negligible due to the short elimination half-lives of the active components (< 3 h) and the recommended dosage regimen is once daily.

Summary of pharmacokinetics

The information outlined below is a summary of data derived from the 8 single dose PK studies conducted as part of the Lodotra clinical development program, all of which recruited healthy volunteers. No PK studies involving patients with RA have specifically been performed.

Evaluator's overall conclusions on pharmacokinetics

In total, 9 Phase I PK studies involving healthy volunteers (mainly, young males) have been conducted as part of the clinical development program and 6 of these trials used Lodotra tablet formulations identical to the commercially proposed product. Study EMR 62215-005 evaluated the PK behaviour of the final Lodotra formulation (5 mg) with an *in vitro* lag time of 3.5 h to the reference IR prednisone product of Decortin and demonstrated similar PK characteristics with the exception of an *in vivo* lag time of 3.5-4 h.

Dose proportionality for a limited range of Lodotra dosing (1, 2 and 5 mg) was shown in Study NP01-008. Studies NP01-009 and -010 demonstrated that batches of Lodotra with different *in vitro* lag times showed comparable and acceptable bioavailability.

A consistent finding from the studies (in particular, EMR 62215-005 and NP01-006) is that fasting conditions significantly alter the PK of Lodotra with increased *in vivo* lag time and T_{max} with fasting versus fed state and C_{max} and AUC considerably lower with fasting. In

addition, inter-individual variability of C_{max} and AUC is significantly higher under fasting administration.

Study NP01-013 which was conducted under Summary of Product Characteristics (SmPC) conditions revealed comparable PK profiles for Lodotra and Decortin in terms of C_{max} and AUC. This trial also confirmed the expected MR formulation behaviour with the estimated differences between Lodotra and Decortin being 4.5 h for T-lag and 3.5 h for T_{max} .

Pharmacodynamics

Evaluator's overall conclusions on pharmacodynamics

The PD properties for Lodotra were only assessed from data collected in the 2 pivotal Phase III clinical trials involving samples from 600 adult patients with RA (354 of whom had received Lodotra, 132 had been given IR prednisone and 114 had received placebo tablets). Most subjects were middle-aged Caucasian females. The sponsor had nominated changes in IL-6 levels with treatment as the pivotal PD marker to support the biological plausibility for the benefits of MR prednisone in improving symptomatic control of RA, particularly morning stiffness. Other supportive PD markers were serum inflammatory markers (especially CRP as it has a link with IL-6 production), other cytokines (TNF) and bone turnover markers.

In both of the Phase III studies, the median or mean baseline levels of IL-6 showed statistically significant improvements following treatment with Lodotra compared to IR prednisone (in the CAPRA-1 Study) and placebo (in the CAPRA-2 Study). However, the clinical relevance of these changes is unclear, and the result was additionally clouded by large inter-individual variability in IL-6 values. Furthermore, none of the supportive PD markers (in particular CRP) were significantly different between any of the treatment groups (MR or IR prednisone, and placebo) in either of the Phase III studies.

Dosage selection for the pivotal studies

Both pivotal Phase III studies investigated prednisone doses at the low end of the dose range (3-10 mg daily in Study EMR 62215-003 and a fixed 5 mg/day in Study NP01-007) in patients receiving concurrent DMARD therapy. Low dose concurrent prednisone therapy (< 10 mg/day) is frequently prescribed for adult patients with RA, and its efficacy in controlling symptoms and having disease modifying characteristics is reported in the literature.^{24,25,26,27}

With ingestion of the modified release formulation of prednisone at approximately 2200 h (+/- 30 minutes), the dosage regimen chosen in the 2 pivotal Phase III studies allowed for the release of the active drug to achieve optimal concentration prior to the early morning circadian rise of various cytokines (in particular, IL-6) which is thought to trigger the characteristic morning symptoms of stiffness and pain associated with active RA.

²⁴ ACR Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis and Rheum* 2002; 46(2): 328-346.

²⁵ Conn DL. Low dose prednisone is indicated as a standard treatment in patients with rheumatoid arthritis. *Arthritis and Rheum* 2001; 45(5): 462-467.

²⁶ Hoes JN, Jacobs JWG, Boers M, Boumpas D, et al. EULAR evidence based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007; 66(12): 1560-1567.

²⁷ Saag KG. Low dose corticosteroid therapy in rheumatoid arthritis: balancing the evidence. *Amer J Med* 1997; 103(6): 31S-39S.

Efficacy

The sponsor is seeking a single indication- “for the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness.”

The efficacy data pertaining to the indication sought by the sponsor was evaluated in 2 pivotal, Phase III studies (EMR 62215-003 and NP01-07) of 12 weeks duration. As the study populations and outcome measures were different, the trials will be considered individually. Furthermore, no integrated efficacy analysis was provided in the submission. Supportive efficacy data was provided by the 9 month, open-label extension (OLE) phase of Study EMR 62215-003, although this trial predominately aimed to collect longer-term safety information. None of the earlier phase clinical studies provided efficacy data to the sought indication.

Evaluator’s conclusions on clinical efficacy “for the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness”

The sponsor has provided the efficacy data from 2 pivotal, randomised, multicentre, double blind trials to support the efficacy of Lodotra in treating adult patients with active RA, particularly when morning stiffness is a prominent symptom. Supportive evidence of efficacy is provided by the 9-month open label extension phase of 1 of the Phase III studies (CAPRA-1). In general, the trials were of adequate design to evaluate the proposed indication, and they both had a clear and appropriate plan of analysis. The biological rationale for the use of modified release prednisone in RA is plausible and the low dose used in both of the pivotal studies (3-10 mg/day) is appropriate to the literature, including international treatment guidelines. In both Phase III studies, patients continued on their background DMARD, as well as NSAID for most subjects.

In the CAPRA-1 study, 2 treatment groups (each consisting of 144 subjects) were randomised to receive either Lodotra 3-10 mg/day or a common formulation of immediate release prednisone (Decortin) used in Europe. In the CAPRA-2 Study, patients were randomised to receive either a fixed 5 mg/day dose of Lodotra (n=231) or placebo tablets (n=119) while continuing their background treatment for RA at stable doses (DMARD, and often concurrent NSAID). The majority of patients (at least 84%) in all treatment groups completed the 12 weeks of follow-up in both pivotal studies. However, there was high number of protocol violations in the CAPRA-1 Study affecting both treatment groups (52% for MR and 42% for IR prednisone) which may have potentially affected the validity of the efficacy analysis. In the CAPRA-2 Study, protocol violations affected 20-21% of subjects in each of the 2 treatment groups.

The populations examined in the Phase III studies are partly similar in demographics to patients that would be treated in Australian clinical practice. The trials were conducted mainly in Germany and Poland and mostly recruited middle-aged Caucasian women. The background treatments for RA are consistent with Australian treated patients but the incidence of co-morbid illness was less than expected. The baseline disease characteristics of the study cohorts are consistent with a group of patients with moderately to severely active RA, which is congruent with the proposed indication wording. However, the generalisability of the study results to a broader RA population in Australia has limitations. As stated in the Lodotra RMP for Australia, the background incidence of co-morbid disease in the RA population include cardiovascular disease (12-22%), depression (19%), diabetes (5-7%), peptic ulcer disease (3-9%) and renal disease (3%). In the study populations, most of these conditions were usually under-represented (a history of peptic ulcer was an exclusion in the CAPRA-1 Study).

The primary efficacy outcome in the CAPRA-1 Study was the duration of morning stiffness and main efficacy endpoint in the CAPRA-2 Study was the ACR20²⁸ responder rate at 12 weeks. The CAPRA-2 trial also had the change in the duration of morning stiffness as a key secondary parameter. In addition, there were several other secondary efficacy endpoints in both studies, some of which were dependent on subjective assessments done by either the subject or physician (such as, stiffness variables and pain intensity). Nonetheless, the efficacy endpoints were appropriate for evaluating the proposed indication for Lodotra.

In the controlled period of both Phase III studies the primary efficacy measure was achieved in favour of Lodotra over comparator treatment. In the CAPRA-1 Study, the relative improvement from baseline to Week 12 in the duration of morning stiffness for Lodotra compared to IR prednisone was 22.7%, which although statistically significant represents a modest clinically relevant difference. In the CAPRA-2 Study, the ACR20 responder rate after 12 weeks of treatment was higher in the Lodotra group (47.2%) compared to placebo (28.6%). This outcome in favour of Lodotra was supported by a higher proportion of Lodotra treated subjects (22.5%) achieving an ACR50 response at 12 weeks compared to placebo (9.2%; $p=0.0026$). Furthermore, the mean decrease in morning stiffness from baseline to 12 weeks was -56.5% for Lodotra and -33.3% for placebo. Overall, the primary efficacy results of the 2 pivotal studies indicate a treatment effect with Lodotra in active RA beyond placebo (and of moderate clinical relevance) and modestly better than standard IR prednisone.

The results for the secondary efficacy endpoints were inconsistently achieved. In the CAPRA-1 Study, none of the secondary efficacy outcomes demonstrated a treatment difference between MR or IR prednisone except when the primary variable (duration of morning stiffness) was assessed on a per week basis instead of a change from baseline to 12 weeks (as for the primary analysis). In particular, the objective endpoints of clinical relevance such as DAS28 and HAQ-DI score showed no difference in treatment effect (MR or IR prednisone). In the CAPRA-2 Study when Lodotra 5 mg/day was compared to placebo + background DMARD, some but not all of the secondary efficacy endpoints were met. These results confirm that the addition of low dose prednisone to standard care for patients with active RA has a clinical benefit of moderate magnitude.

The CAPRA-1 Study also had an open label extension phase for participants to either continue receiving Lodotra (as per the double blind period) or be switched to Lodotra from IR prednisone. The treatment switch patients achieved an improvement in the duration of morning stiffness similar to those initially treated with Lodotra, while the continuing Lodotra maintained their response to MR prednisone. However, for many of the secondary endpoints of clinical relevance such as those subjects able to alter their baseline dose of prednisone, no result in favour of Lodotra was observed.

In summary, the data in this submission appears to support the efficacy of Lodotra in treating adult patients with active RA, particularly with respect to improving the duration of morning stiffness. The 2 pivotal studies are appropriately different in design to understand the relative effect of Lodotra in comparison to alternative management approaches such as IR prednisone or placebo + background DMARD. The open label experience provides limited information on the durability of response up to 12 months of treatment.

²⁸ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a $\geq 20\%$ improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) $\geq 20\%$ improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

Safety

Patient exposure

During the double blind phase of Study EMR 62215-003, all randomised patients were either exposed to either Lodotra (n=144) or IR prednisone (n=144) at a daily dose of 3-10 mg (according to individual patient requirements). The mean, median and range for the duration of exposure were similar between the 2 treatment groups as was the mean daily dosage of 6.4-6.8 mg/day (as per Table 2). When entering the OLE of Study EMR 62215-003, all patients from the IR prednisone group were switched to Lodotra. Table 15 also displays the duration of exposure and the mean daily dose (6.79 mg) for the combined dataset (double blind and open label, follow up phases).

Table 2. Extent of exposure to prednisone in CAPRA-1 Study

	Double- blind Phase		Total (double-blind + open Follow-up)
	Lodotra (N = 144)	IR prednisone (N = 144)	Lodotra (N = 249)
Duration of exposure (days)			
Mean	75.4	79.5	297
Median	83.0	83.0	281
Range	5.0 – 112.0	11.0 – 99.0	56-406
Mean daily dose (mg/day)			(n=248)
Mean	6.38	6.80	6.79
Median	5.1	6.02	6.37
Range	0.0* – 11.1	3.0 – 10.4	1.89-21.88

Table 3 summarises the number of patients exposed to Lodotra for specific time periods (incremental 3 month periods to 12 months).

Table 3. Treatment duration with Lodotra in CAPRA-1 Study

	Number of patients
Total	288
At least 3 months of Lodotra exposure	245
At least 6 months of Lodotra exposure	232
At least 9 months of Lodotra exposure	192
At least 12 months of Lodotra exposure	48

Table 4 summarises the overall exposure to Lodotra in the second pivotal Phase III study (NP01-007). In this trial, all subjects receiving Lodotra were given it at a fixed 5 mg/day dose and the median duration of exposure was 84 days. However, 70.6% (163/231) of subjects took the therapy for at least 84 days.

Table 4. Exposure to Lodotra in Study NP01-007

Exposure	Statistic	Value
Number of Lodotra patients	N	231
Overall exposure		
Mean (SD)	days	80.4 (15.70)
Median (range)	days	84.0 (5-96)
Categories		
<14 days	n (%)	5 (2.2%)
≥14 days to <28 days	n (%)	5 (2.2%)
≥28 days to <42 days	n (%)	1 (0.4%)
≥42 days to <56 days	n (%)	3 (1.3%)
≥56 days to <70 days	n (%)	0
≥70 days to <84 days	n (%)	54 (23.4%)
≥84 days	n (%)	163 (70.6%)

Table 5 provides a summary of the total exposure to prednisone (including test and reference formulations) for 8 of the earlier phase clinical studies. Study NP01-014 is not represented in Table 18. It involved 52 subjects receiving up to 2 single oral doses of 5 mg of prednisone. In total, 247 subjects were exposed to study treatment in the 9 early phase trials. All of these studies were single dose only in design. The dose of prednisone varied from 2-20 mg but the most commonly examined doses were 5 and 10 mg.

Table 5. Summary of prednisone exposure in Phase 1 Studies (NP01-014 not shown)

Study	Number of subjects	Prednisone (mg) administered as test formulation	Prednisone (mg) administered as Decortin
EMR 62215-005	26	10	5
	1 ^b	0	5
EMR 62215-001	2 ^c	10	5
	2 ^d	10	0
	8	15	10
	2	20	5
EMR 62215-002	28	10	10
NP01-006	24	10	n.a.
NP01-008	17	8	n.a.
	1	2	n.a.
NP01-009	27	20	n.a.
	1	5	n.a.
NP01-010	27	20	n.a.
	1	5	n.a.
NP01-013	27	5	5
	1	5	0

Postmarketing experience

Lodotra is marketed in 7 European countries (Austria, Denmark, Finland, Germany, Norway, Poland and the United Kingdom). The tablet is available in strengths of 1, 2 and 5

mg. A total of 17, 213, 400 mg of prednisone has been distributed as of the data lock date of 17 October 2010. Based on the sponsor's assumption that an adult patient takes a daily dose 10 mg (which seems higher than the trial data information), the patient exposure is estimated to be approximately 4716 patient-years since the initial marketing authorisation of Lodotra in the European Union (EU). This exposure includes the subjects enrolled in the Lodotra Non-Intervention Studies (NIS). The NIS program is being conducted by Merck Pharma GmbH Germany to assess the change in activity status and quality of life for RA patients, as well as the safety and tolerability of Lodotra. Enrolment into the program was ceased in late 2009 upon obtaining the desired recruitment numbers of approximately 3000 RA patients. A study report for the NIS is not included with the current submission but the sponsor states it should be available in the second quarter of 2011.

The submission contained 4 Periodic Safety Update Reports. No new safety concerns have been identified in the adverse drug reports (serious and non-serious) obtained from spontaneous reporting sources and the scientific literature for Lodotra as well as the active substance, prednisone.

Evaluator's overall conclusions on clinical safety

The data presented in this submission concerning the safety profile of Lodotra in adult subjects is of sufficient volume for assessment of the short to medium term risks. In total, 375 patients with RA have received at least 1 dose of Lodotra (3-10 mg) in the pivotal Phase III trials. Regarding the extent of exposure, 192 of these subjects received Lodotra for at least 9 months. Collectively, the safety data in the Phase I studies involved 247 healthy men and women, who were mostly given single doses of Lodotra ranging from 2-20 mg.

Key safety conclusions identified by the clinical development program include:

- During the 12 week, double blind periods of the Phase III studies, Lodotra was generally well tolerated with the overall incidence and most types of common adverse events (AEs) being similar in patients receiving comparator treatment (either IR prednisone or placebo with background DMARD for RA);
- Overall serious AEs (SAEs) occurred at a low and similar frequency in the prednisone treatment groups, as well as the comparison between Lodotra and placebo;
- Discontinuations due to AEs were similar in incidence and type between MR and IR prednisone (CAPRA-1 Study) but numerically higher for Lodotra compared with placebo (CAPRA-2 Study);
- The 9 month, open label extension phase of the CAPRA-1 Study demonstrated that although the overall incidence of AEs remained within expectations, AEs of special interest for longer-term follow-up became evident (such as gastrointestinal ulcers/gastritis, weight gain, mood and sleep disorders, hypertension and glaucoma);
- Collectively, there were 7 cases of significantly impaired glycaemic control with Lodotra in the Phase III trials, and the incidence of elevated total cholesterol levels was higher for those receiving Lodotra (12.5-15.6%) compared to both IR prednisone (10.4%) and placebo (7.6%);
- The effect of extended treatment with Lodotra compared with IR prednisone (both in low dose) on the hypothalamic-pituitary axis was investigated in a sub-study of EMR 62215-003 using a CRH test and showed no significant difference in HPA axis suppression between the 2 prednisone formulations; and
- The AE profile observed in the Phase I studies was characteristic of early phase trial reporting with most of the observed AEs judged as unrelated or consistent with the

known side effect profile of prednisone (primarily headache and gastrointestinal disorders).

In summary, the safety data indicates that the administration of Lodotra to subjects with RA (mainly middle-aged women) is generally safe and well tolerated and has a comparable short to medium term safety profile as standard immediate release formulations of prednisone as well as placebo tablets in patients receiving background DMARD treatment for RA. However, some significant potential safety concerns will require on-going pharmacovigilance. These risks include osteoporosis, cardiovascular safety (hypertension and an increased risk of atherosclerosis), ophthalmic conditions (cataracts and glaucoma), gastrointestinal ulcers and metabolic consequences (weight gain and HPA suppression).

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The main benefits of Lodotra in the proposed usage pertaining to the requested indication are:

- Improvements in the duration of morning stiffness for adult patients with moderately to severely active RA over 12 weeks compared to IR prednisone (relative mean change of 22.7%), or placebo + background standard of care (relative mean change of 23.2%).
- Improvements in the ACR20 (46.8% versus 29.4%) and ACR50 response rates (22.5% versus 9.2%) at 12 weeks compared to placebo + background DMARD treatment.
- Maintenance of improvements in the duration of morning stiffness with treatment for up to 12 months.

First round assessment of risks

The risks of Lodotra in the proposed usage are:

- Discontinuations to AEs are numerically higher for Lodotra (2.2%) versus placebo (0.8%) but similar in incidence and type between MR and IR prednisone (8.3% versus 6.9%, respectively).
- In total, 7 cases of significantly impaired glycaemic control were observed with Lodotra in the Phase III trials.
- The incidence of elevated total cholesterol levels was higher for those given Lodotra (12.5-15.6%) compared to both IR prednisone (10.4%) and placebo (7.6%).
- AEs of special interest became evident in the longer term follow-up study with cases of gastrointestinal ulcers, gastritis, weight gain, mood and sleep disorders, hypertension and glaucoma being reported.

First round assessment of benefit-risk balance

The benefit-risk balance of Lodotra for the proposed indication and dosing regimen is favourable.

First round recommendation regarding authorisation

The evaluator recommended acceptance of the sponsor's proposed indication for Lodotra subject to amendments of the PI, provision of data for the Non-Intervention Study and regular periodic safety update reports.

Second round evaluation of clinical data submitted in response to questions

The sponsor has submitted a response dated 25 January, 2012 to the TGA consolidated Section 31 request for information. From the clinical evaluation perspective, the response included an update with respect to prescribing information for Australia. Responses to quality questions were also included but were not specifically considered as part of the second round clinical evaluation.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to efficacy. Accordingly, the benefits of Lodotra® in the proposed usage are unchanged from those identified in the first round assessment.

Second round assessment of risks

As requested, the sponsor has provided a safety report (dated 6 July 2011) for the Non-Intervention Study (NIS) which was an uncontrolled, multicentre study undertaken in Germany involving adult patients with RA. After consideration of the new clinical information, the risks of Lodotra® in the proposed usage are unchanged from those identified in the first round assessment.

The NIS was conducted in 461 centres between April 2009 and October 2010. The safety population included 2676 patients who had at least 1 on-study assessment. The trial was prematurely terminated so that the results could be made available by the end of 2010 as a post approval commitment to the European reference member state regulatory authority (BfArM, Germany). Patients were eligible for inclusion if they had active RA with accompanying morning stiffness and were either already receiving or about to commence low dose oral corticosteroids. All patients were commenced on Lodotra at a starting dose of 5 mg/day. At 9 months of follow-up, the mean dose of Lodotra was 4.1 mg/day. The study population was consistent with expectations; predominately female (72.0%) and middle-aged (median of 60 years; range 18-97 years). The mean duration of RA was 7.9 years. In total, 158 patients (5.9%) experienced 218 AEs leading to withdrawal. The most common types of AEs by system organ class (SOC) resulting in cessation were Gastrointestinal disorders (54 cases, 2.02%), Psychiatric (29 subjects, 1.08%) and Nervous system problems (17 patients, 0.64%). The most frequent individual types of AEs leading to withdrawal were nausea (n=22), upper abdominal pain (n=18), sleep disorders (n=16), headache (n=9), dizziness (n=6) and impaired glucose metabolism (n=6).

A total of 22 patients (0.82%) experienced 35 SAEs. Half (11 subjects, 0.41%) of the SAE patients had events that were considered to be treatment related. These included 8 Gastrointestinal SAEs (in particular, various types of GIT bleeding and symptoms relating to gastritis); and singular reports of sleep disturbance, tachyarrhythmia and ruptured Achilles tendon. Four deaths occurred during the observation period and none were considered to be treatment related. Two of the deaths were for unclear reasons (69 and 82 year old women), one patient died following a fall (75 year old female) and another subject (81 year old female) suffered a fatal myocardial infarct.

In summary, the incidence and type of adverse events observed in the NIS are consistent with the expected safety profile of continued low dose corticosteroid treatment.

Second round assessment of benefit-risk balance

The benefit-risk balance of Lodotra® for the proposed indication and dosing regimen is favourable.

Second round recommendation regarding authorisation

The evaluator recommended acceptance of the sponsor's proposed indication for Lodotra subject to regular periodic safety update reports.

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 6.

Subject to the evaluation of the nonclinical aspects of the Safety Specification by the toxicology area of the OSE and the clinical aspects of the Safety Specifications by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 6. Summary of Ongoing Safety Concerns

Important identified risks	No new risks compared to known class effects of glucocorticoids (osteoporosis, hyperglycaemia, ophthalmic disorders, cardiovascular disorders, gastrointestinal disorders and increased risk of infections, suppression of the HPA axis) and hypersensitivity to prednisone or to any of the excipients were identified.
Important potential risks	Adrenocortical suppression Sleep disorders/insomnia Impaired glycaemic control
Important missing information	Long-term safety data with the modified release formulation

Adrenocortical suppression

Due to the circadian rhythm of cortisol, it was hypothesised that night-time administration of Lodotra may lead to an increased risk of adrenocortical suppression compared with IR prednisone. No cases of adrenocortical suppression were detected during the clinical development program and no cases have been reported following marketing authorisation in Europe.

Insomnia/sleep disorders

Data from the double-blind phase of the CAPRA-1 trial was suggestive that the modified formulation of Lodotra administered at night might increase sleep disorders compared with IR prednisone administered in the morning. CAPRA-1 was a 12 week, randomised, double-blind, active-controlled (IR prednisone), parallel group study in 288 RA patients. Three patients in the Lodotra group reported sleep disorders (n=1) or insomnia (n=2) leading to withdrawal of study medication. There were no reports in the IR group. In the open-label follow-up phase of the study there no withdrawals due to sleep disorders.

There were no withdrawals in the CAPRA-2 trial. CAPRA-2 was a randomised double-blind, placebo-controlled trial in RA patients pre-treated with DMARDs for 6 months. In addition to the events leading to withdrawal, insomnia as a treatment emergent adverse event with Lodotra was reported in the CAPRA-1 trial (n=1), the CAPRA-1 open-label extension (n=1), and the CAPRA-2 trial (n=2). There have been 8 spontaneously reported adverse events since market authorisation in Europe up until 17 October 2011.

Impaired glycaemic control

During the double-blind phase of CAPRA-1 there were 2 cases of clinically relevant abnormal blood glucose values reported in each of the groups. During the open-label follow-up phase there were 4 case reports. One patient treated with Lodotra in the CAPRA-2 trial who had a history of diabetes recorded a non-fasting elevated blood glucose reading (patient was noted to have not taken insulin during the morning of blood draw). No spontaneous case reports have been received by the sponsor since approval in the EU.

OPR reviewer comment:

The sponsor acknowledges that the list of potential safety concerns are actually identified risks that are well known adverse effects of glucocorticoids. The sponsor has used the term 'Potential risk' to refer to the possibility of an increased risk with Lodotra versus IR prednisone. While the rationale behind this is acknowledged, it is recommended that the sponsor considers reclassifying the '*Important potential risks*' as '*Important identified risks*' for consistency in future RMPs.

The following is stated in the *Precautions* section of the draft PI (April 2011) under the sub-heading *required blood concentrations*: "*low plasma concentrations have been observed in 6% - 7% of Lodotra®TR modified release tablet doses taken according to recommendations, and this should be considered if Lodotra®TR modified release tablets are not sufficiently effective.*" While the data relating to this statement in the PI are not being evaluated by the OPR, the sponsor is asked to provide information on the potential safety implications of low plasma concentrations in 6% - 7% of tablet doses particularly with regard to the risk of precipitating acute adrenal insufficiency in patients switching from long-term IR prednisone. In the sponsor's response to s31 request for information, it is stated that results from the clinical trial CAPRA 1 showed similar profiles in hypothalamic pituitary adrenal (HPA) axis suppression when comparing Lodotra and the IR prednisone formulation. In addition, it is stated that data from the two Phase III clinical trials, CAPRA 1 and CAPRA 2 and spontaneous reporting did not find a higher risk in adrenal insufficiency with Lodotra. Although the sponsor did not specifically address the question on the safety impact of adrenal insufficiency in patients who switched from long-term IR prednisone to Lodotra, it is acknowledged that the clinical trial CAPRA 1 included a 9-month open-label extension phase to evaluate the response of patients who switched from IR prednisone to Lodotra (PI January 2012 draft, *Clinical Trials – CAPRA-1 (long-term study)* section). Based on the available information, it can be deduced that there has not been a report on acute adrenal insufficiency precipitated by low plasma prednisone concentration in patients who switched from long-term IR prednisone. The inclusion of precautionary statement under the *Precautions – Substitution, termination, discontinuation* section in the PI remains appropriate.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance (PhV) activities²⁹, consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, are proposed to monitor all the specified ongoing safety concerns. The sponsor states that additional safety data will be generated by the evaluation of the NIS-Lodotra. This is a non-interventional study assessing activity status/quality of life outcomes in RA patients, and to further investigate safety and tolerability of Lodotra. Enrolment was stopped by the end of 2009 in order to have the results available by the end of 2010. The sponsor states that the estimated total cases for evaluation was approximately 3000 and that a report of the study will likely be available in 2Q 2011.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

No protocol or protocol summary for the non-interventional study has been provided with the RMP, nor could any be located on a search of the submission contents. As such it is not possible to comment on the adequacy of the study design to further characterise the Ongoing Safety Concerns particularly with regards to the potential increased risk with Lodotra versus IR prednisone for the risk of adrenocortical suppression, sleep disorders and impaired glycaemic control and the long-term safety of Lodotra. The PSUR for the period 18 April 2010 to 17 October 2010 was included with the initial submitted dossier. It is noted from this document that the NIS-Lodotra was intended to add information on Lodotra under real life conditions. Further information was requested from the sponsor in the s31 request for information to provide a summary of the study protocol and to state how the results of the study will be made known to the TGA and, if the study analysis has been completed, whether there are any safety implications that need to be addressed in the RMP. A full protocol for evaluation was not requested as the study is completed or near completion.

The NIS-Lodotra final summary report has been provided in response to the s31 request for information. This study was an uncontrolled, multicentre, non-interventional evaluation of Lodotra on the activity status and quality of life (specifically on reduction of morning arthritis symptoms), and safety in RA patients ≥ 18 years old who had symptoms of joint morning stiffness and were already on or would be stabilised on glucocorticoid therapy. Two groups of patients were included: those under the care of a primary care physician (3 month observational period, with follow-up initially, at 6 weeks and 3 months) and those under the care of a rheumatologist (9 month observational period, with follow-up initially, at 6 weeks, 3 months, 6 months and 9 months). Mean study initiation daily dose was 5 mg. Caveats: all parameters were recorded only if data were collected during routine medical check-ups and study monitoring and source data verification were not conducted. Section 9.7.1.12 *Safety variables* of the NIS report states that serious AEs were evaluated and collected at each visit, AEs leading to withdrawal were evaluated and collected (in case of withdrawal) and other AEs evaluated only if reported by investigators. The total targeted patient numbers were 8000 however, enrolment was stopped at 2730 patients (940 at General Practice (GP) sites, 1790 at rheumatologist sites)

²⁹ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

in 2009 in order for the company to complete data analysis by the end of 2010 to meet post market commitments in Germany. The safety population included 2676 patients who had at least one on-study visit (929 at GP sites, 1747 at rheumatologist sites). A total of 218 adverse events (AEs) were reported involving 158 patients (5.9%) who subsequently withdrew from the study. The list of most frequently reported events include nausea (0.82%), upper abdominal pain (0.67%), sleep disturbances (0.6%), headache (0.34%), dizziness (0.22%) and disturbances in blood glucose metabolism (0.11%) (which appeared to correspond to AEs leading to withdrawal, as discussed in Section 12.7 *Safety Conclusions* on page 44 of the NIS report). It is unclear then why the NIS synopsis, *Summary – Conclusion* (p.4) section of the report stated that “Severity, outcome and causality were not documented for adverse events leading to withdrawals and were not evaluated”. Serious AEs were reported in 22 patients (0.82%), with 11 cases (including GI bleeding, haemorrhagic proctitis, stomach pain/ache and skin red) considered to be possibly or probably related to Lodotra. Four patients (0.15%) died during the study but none was considered to be attributed to Lodotra. The sponsor concluded that the distribution and type of reported AEs were consistent with those identified in the randomised Phase III trials and published studies for low dose prednisone therapy, and did not reveal any new or a change in safety signals.

With respect to the EU-RMP, it is noted on page 29 of the PSUR (period 18 April 2010 to 17 October 2010) submitted with the application that close monitoring was implemented as part of the EU-RMP for sleep related disorders and impaired glycaemic control. The sponsor was asked to identify what was meant by close monitoring and provide justification if such additional PhV measures were not planned for the post-market monitoring of Lodotra in Australia. The sponsor’s response to s31 request for information clarifies that this “close monitoring” refers to routine pharmacovigilance activities conducted by the company to evaluate monthly cumulative spontaneous reports and literature cases that will include data from Australia. Any increased frequency in sleep related disorders and impaired glycaemic control will be subjected to risk benefit review and any change to safety profile will be reported to the sponsor for communication (with suggested risk mitigation strategy) to regulatory agencies. The sponsor has also stated that the main differences between the EU and Australian RMP are the inclusion in Annex 6 of the updated EU-RMP (version 5) two newly available study reports: *In vitro* nonclinical studies on “prednisone 21-aldehyde deriviate and NIS-Lodotra final abbreviated study report (discussed above). The *in vitro* nonclinical study was done to address FDA’s recommendations to characterise the presence of prednisone 21-aldehyde derivative (previously referred to as UDP 1) as an impurity of the drug. The sponsor found that the amount of prednisone 21-aldehyde present in Lodotra was consistent with other commercially marketed prednisone products in Europe (Decortin and Hexal), and concluded that there was no change in the overall risk-benefit assessment for Lodotra. The sponsor did not find an increase in mutagenic effect in Ames test using spiked prednisone batch samples of concentrations of up to 5000 µg/dish (spiked batch sample contained 95.1% prednisone and 3.87% related substances), suggesting that amount of impurities present in samples under normal manufacturing process were not associated with a mutagenic potential. However, Ames test performed using isolated prednisone 21-aldehyde and one of its hydrated form (upon FDA’s recommendation) showed positive results suggesting that enriched (and high) amount of this impurity might have mutagenic potential. The sponsor argued that the results from the Ames test using enriched amount of prednisone 21-aldehyde should be viewed with some caution in relation to clinical safety as there is no current evidence from published nonclinical and clinical studies to suggest a carcinogenic potential for prednisone. The company also stated that it intends to minimise the amount of degradation products (UDP 1) by the addition of desiccants in the bottles, which have been shown to decrease the amount of UDP 1 (to be submitted as a variation to marketing authorisation).

Annex 2, 'Synopsis of Ongoing & Completed Clinical Trial Programme' could not be found in the dossier. However, the sponsor has provided this missing information as Annex 3 of the EU-RMP version 5 in response to the s31 request for information. In summary, the current PhV plan is considered acceptable, pending any additional issues raised by the clinical and/or non-clinical evaluator(s).

Risk minimisation activities

The sponsor proposes routine risk minimisation³⁰ by way of labelling information.

OPR reviewer comment

Unless the clinical and/or nonclinical evaluation report(s) raises additional safety concerns for which additional risk minimisation strategies may be required, the implementation of routine risk minimisation for all the Ongoing Safety Concerns is considered acceptable. In regard to the proposed routine risk minimisation activities, the evaluator commented that a number of suggested revisions to the draft PI document had been satisfactorily incorporated by the sponsor in the updated draft PI (January 2012). :

In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) is considered satisfactory.

Summary of recommendations

The final RMP may need to be updated if any additional safety concerns are identified by the clinical and/or nonclinical evaluator(s). If no additional safety concerns are identified, the OPR provides this recommendation in the context that the submitted RMP is supportive to the application: the implementation of the Australian Risk Management Plan for Lodotra, that identified as version 2 (dated January 2012), and any subsequent versions, be implemented as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The proposed lower limit for assay of the 1 mg and 2 mg tablets (but not the 5 mg tablets) at expiry was found not to comply with Therapeutic Goods Order No. 78 (TGO 78). A limit of NLT 90.0% had been proposed but TGO 78 stipulates a limit of NLT 92.5% or higher. As noted by the pharmaceutical chemistry evaluator, the stability data provided in the submission indicated that the limit of NLT 92.5% could be met at the end of the proposed shelf life when the proposed lower limit for assay at release of NLT 95.0% is met. The sponsor agreed to the tighter lower assay limit at expiry, namely NLT 92.5%.

As noted by the pharmaceutical chemistry evaluator, if the *in vivo* lag-time is too long, a tablet could reach the colon before the modified release coating is fully eroded/dissolved. Absorption in the colon is less than in the higher GI tract. Therefore if this occurs, absorption will be less. No data was provided to demonstrate that tablets with an *in vitro* lag time of 6 h will not reach the colon prior to the erosion/dissolution of the modified

³⁰ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

release coating. The evaluator proposed a strategy under which approval could be granted, namely that Stage 2 and Stage 3 dissolution limits³¹ at both release and expiry were amended to remove the possibility that some tablets could have longer *in vitro* lag times than those allowed at Stage 1. Once again the sponsor agreed to the tighter limits.

The products have a degradant, prednisone-21-aldehyde (P21A), which gave a positive Ames test and which is therefore classified as potentially carcinogenic. As such, without further justification, it should be controlled to the threshold of toxicological concern (TTC = 1.5 µg/day). However, the P21A is only controlled to NMT 0.25% in the specifications of the drug substance and not at all in the specifications of the drug product. The sponsor was requested to clarify the relationship between the TTC level of 1.5 µg/day and the NMT value of 0.25%. The sponsor provided a justification for its approach but, as demonstrated by the evaluator, did not address any of the requirements as laid down in App 18 of the ARGPM. Furthermore, the advice of the nonclinical evaluator was that, in the absence of further supportive nonclinical evidence *in vivo* (for example, testing of P21A for clastogenicity *in vivo*), the ICH principle of controlling impurities to as low as reasonably practicable (ALARP) should be followed and therefore P21A should be routinely tested for in the drug product and controlled to expiry limits that are consistent with the actual stability data. Therefore the pharmaceutical chemistry evaluator concluded that the finished product release and expiry specifications were unacceptable as they did not include a qualified limit for the degradant P21A and that the drug substance specifications were unacceptable as the proposed limit for P21A had not been qualified. The sponsor responded by proposing an expiry limit of NMT 0.2% and provided further toxicological argument and quality data to support this limit. Under the current Streamlined Submission Process, such data cannot be evaluated and approval can only be recommended if the expiry limit for P21A is tightened to NMT 0.1% (which the evaluator believed could be met) and a similar limit is adopted for the release limit and the limit in the drug substance. Given that Lodotra is intended to be taken long-term, the Delegate fully supports this recommendation by the pharmaceutical chemistry evaluator. The ACPM was asked to comment on this issue.

Bioavailability

The pivotal Phase III efficacy studies were conducted with the proposed products. To support registration, nine (9) bioavailability studies were provided along with a number of justifications for not providing certain bioavailability data. In all studies the levels of prednisone and its active metabolite prednisolone in plasma were determined using appropriately validated test methods.

The Delegate will focus on the issues of concern raised by the quality evaluator in relation to his evaluation of the biopharmaceutical component of the dossier:

- Study EMR 62215-005 compared the proposed 5 mg tablet administered at 10 pm in the semi-fed state and in the fed state to Decortin 5 mg immediate release prednisone tablets registered in Germany administered at 2 am the next day in the fasted state. The results showed (i) similar T_{max} results even though the immediate release tablet was administered 4 h later, (ii) a mean *in vivo* lag time for the proposed tablet of 6 h which was influenced neither by the timing nor by the type of meal and (iii) something close to bioequivalence of the 3 treatments. The evaluator expressed some concern about a lower limit of the 90% CI for C_{max} in one case being 74%, about an upper limit of the 90% CI for C_{max} being 131% in one case and finally about the upper limit of the 90% CI for AUC being between 126 and 128% in five cases. Given the need for careful

³¹ Sponsor Comment; "The possibility of Stage 2 and 3 lag time limits at both release and expiry were amended to remove the possibility that some tablets could have longer *in vitro* lag times than those allowed at Stage 1."

and slow dose titration of prednisone, the delegate does not view these deviations from the recommended guidelines as clinically significant.

- Study NP01-013 compared the proposed 5 mg tablet administered at 10 pm, 1 h after a light meal as per the instruction in the PI for the Decortin 5 mg IR prednisone tablet registered in Germany administered at 8 pm. The 90% CI results for the AUCs of prednisone and prednisolone and of the C_{max} of prednisolone were all within the prescribed interval of 80.0-125.0%, while that for the C_{max} of prednisone was not. The latter C_{max} was approximately 22% higher with a 90% CI of [116.1-127.7]. Actually the latter interval only fails by a small amount at its upper end. Also, given the satisfactory AUC results and the need for careful and slow dose titration, the Delegate does not view this deviation as clinically significant.
- The quality evaluator observed a number of low bioavailability results spread across all the bioavailability studies using the proposed tablets. From these 5 studies there were 21 low results out of a total of 362 relevant individual patient datasets or about 6% of the results. These results appeared to be random and related neither to the subject nor to the *in vitro* lag time. For the most part, these low results appeared to occur when the tablets were given fasted or with a light meal and the sponsor has reasoned that these low results are due to a random and unexplained, enhanced gastrointestinal transit time. In the absence of any data to implicate manufacturing errors/problems, the quality evaluator agreed. The Delegate also agrees that the sponsor's explanation is likely to be true. However, the Delegate will recommend that there be discussion and acknowledgement of this issue under both the *Pharmacology* and *Dosage and Administration* sections of the proposed PI. The ACPM is asked to comment on this issue.
- All bioequivalence studies were conducted using the 5 mg tablets only. A justification was included in the dossier to enable extrapolation of the data for the 5 mg tablets to the 1 and 2 mg tablets. The chemical and physical aspects of this justification, including appropriate dissolution profiles conducted in a wide variety of media, were found to be acceptable. The clinical part of the justification included data to support linearity of dose response over the range 1-5 mg and data to show prednisone was BCS class 1. The clinical component of the justification is acceptable to the delegate.
- Given that the proposed PI states that patients may be switched from an immediate release prednisone tablet currently registered in Australia, a justification for not comparing the bioavailability of the proposed product to that of an Australian-registered product was provided. Again a wealth of data comparing dissolution profiles was part of the justification. The clinical parts of the justification included data similar to that described under the previous dot point and are acceptable to the delegate.
- There was also a justification for not submitting a study at steady state. This was based on the fact that the product is not designed to be sustained release but a delayed or "timed" release; hence the "TR" in Lodotra. The PK profile will be the same as for the immediate release tablet only shifted in time. The clinical aspects of the justification are acceptable to the Delegate.

The conclusions of the quality evaluator with respect to bioavailability were as follows:

- The proposed products have an *in vivo* lag time compared to the immediate release products on the market and there was a correlation between the *in vitro* lag time and the *in vivo* lag time and between the *in vitro* lag time and the *in vivo* T_{max} .
- The *in vivo* T_{max} is 6-7 h when the tablets are taken as directed in the PI. Thus T_{max} will occur at 4-5 am if the tablets are taken in accordance with the instructions in the PI, that is, at 10 pm.

- Compared to the fasted state, the bioavailability from the proposed tablets is 3-4 times higher when given with a high fat meal. The bioavailability was also 10% higher 30 minutes after a high fat meal compared to that 2.5 h after a light meal. The PI recommends that the tablets should be taken at about 10 pm with or after the evening meal but if more than 2-3 h have passed since the evening meal, the tablets should be taken with a light meal or snack. This recommendation would appear to be the only rational one given the circumstances. However, the Delegate recommends that the PI should make it quite clear that the preferred option is the former.

The quality evaluator's final recommendation is that the product cannot be approved due to an unacceptable proposed expiry limit for the degradant, prednisone-21 aldehyde (P21A). The Delegate concurred with this recommendation. However, the Delegate is of the opinion that if the sponsor were able to come to an agreement with the quality evaluator concerning all the latter's requests regarding the specifications of the product, then the application could be approved.

Nonclinical

No new non-clinical data were supplied with this application. This was judged to be acceptable to the nonclinical evaluator as there are no toxicological implications related to the delay in T_{max} observed with the new prednisone formulation and there are no novel excipients.

The sponsor presented a literature-based submission in support of Lodotra tablets, comprising both review articles and descriptions of original research, that were of relevance to understanding the mode of action and safety of prednisone use in humans.

The nonclinical evaluator was of the opinion that the non-clinical safety profile of Lodotra was adequately covered by the extensive nonclinical data and literature available for prednisone and prednisolone.

There are no nonclinical objections to the registration of Lodotra tablets.

The nonclinical evaluator made a number of recommendations for amendment of the proposed PI. These recommendations are supported by the Delegate.

Clinical

The contents of the Module 5 have been outlined earlier. The clinical evaluator has recommended that the benefit-risk balance of Lodotra for the proposed indication and dosing regimen is favourable.

Pharmacokinetics

A total of 9 Phase I PK studies involving healthy, mainly young male volunteers were conducted as part of the clinical development program and 6 of these trials used Lodotra tablet formulations identical to the commercially proposed product. Study EMR 62215-005 evaluated the PK behaviour of the final Lodotra formulation (5 mg) with an *in vitro* lag time of 3.5 h to the reference IR prednisone product of Decortin and demonstrated similar PK characteristics with the exception of an *in vivo* lag time of 3.5-4 h.

For a limited range of Lodotra dosing, namely 1, 2 and 5 mg, dose proportionality was shown in Study NP01-008. Studies NP01-009 and -010 demonstrated that batches of Lodotra with different *in vitro* lag times showed comparable and acceptable bioavailability.

A consistent finding from the studies, in particular EMR 62215-005 and NP01-006 was that fasting conditions significantly alter the pharmacokinetics of Lodotra. Both the *in vivo* lag time and T_{max} are increased in the fasting compared with the fed state while both C_{max} and AUC are considerably lower with fasting. In addition, inter-individual variability of C_{max} and AUC is significantly higher when the drug is administered under fasting conditions. The Delegate requested that the sponsor ensures that all these issues are explained fully in the relevant section of the proposed PI. The ACPM was asked to comment.

Study NP01-013 revealed comparable PK profiles for Lodotra and DECORTIN in terms of C_{max} and AUC. This trial also confirmed the expected modified release formulation behaviour with the estimated differences between Lodotra and Decortin being 4.5 h for T-lag (absorption lag time) and 3.5 h for T_{max} .

Pharmacodynamics (PD)

None of the early phase or biopharmaceutic studies evaluated PD data. However, the 2 Phase III trials, including the OLE phase of the EMR 62215-003 or CAPRA-1 study did collect data on PD endpoints as part of their analyses. The PD endpoints selected for study were ESR, CRP & IL-6 (in both Phase III trials with changes in IL-6 nominated by the sponsor as the pivotal PD marker) and $TNF\alpha$ (in the Phase III trial NP01-007 or CAPRA-2).

In both the Phase III studies, the median or mean baseline levels of IL-6 showed statistically significant improvements following treatment with Lodotra compared to the immediate release prednisone (in the CAPRA-1 Study) and placebo (in the CAPRA-2 Study). However, the clinical relevance of these changes is unclear, made more so by large inter-individual variability in IL-6 values. None of the supportive PD markers, particularly CRP, were significantly different between any of the treatment groups (modified release or immediate release prednisone or placebo) in either of the Phase III studies.

Efficacy

The efficacy data for the indication sought by the sponsor was evaluated in 2 pivotal, Phase III studies (EMR 62215-003 or CAPRA-1 and NP01-007 or CAPRA-2), each of 12 weeks' duration. The study populations and the outcome measures were different in each trial and so no integrated efficacy analysis was performed. Supportive efficacy data was provided by the 9 month, open-label extension (OLE) phase of EMR 62215-003 (CAPRA-1) although the principal aim of the latter was the collection of safety data.

Study EMR 62215-003 (CAPRA-1)

This trial was a randomised, double-blind, active-controlled, double-dummy, parallel-group study of 12 weeks' duration with an option for 9 months of open-label follow-up in adult patients with active RA carried out at 17 centres in Germany and 12 centres in Poland.

The primary objective was to demonstrate that 12 weeks of treatment with modified release prednisone (Lodotra) administered in the evening (9.30-10.30 pm) was superior to standard morning administration (6-8 am) of immediate release prednisone in reducing the duration of morning stiffness. There were a number of secondary objectives involving the comparison of standard RA efficacy parameters.

Eligible patients had to have received a daily dose of 2.5-10 mg of prednisone for at least 3 months prior to entry with a stable dose for at least 1 month prior to screening and also had to have taken DMARD treatment for at least 3 months.

The study treatments involved a total daily dose of 3-10 mg prednisone, corresponding to the individual patient's pre-study dose. Lodotra tablets were supplied in the 1 mg and 5

mg dose strengths. The reference product was a common commercial formulation of immediate release prednisone used in Europe, Decortin (1 and 5 mg strengths). Compliance with study medication was high in both treatment groups with only 9 patients out of 144 (6.3%) in the Lodotra and 5 out of 144 (3.5%) in the immediate release prednisone group taking less than 80% of their study medication.

The sample size calculation was based on the primary efficacy variable. Assuming a standard deviation of 64% in the relative change from baseline to Week 12 in the duration of morning stiffness, 120 subjects were required in each of the groups if the treatment difference between modified release and immediate release prednisone was 27%. It was also estimated that 15% of recruited subjects may not be evaluable in the primary analysis and so approximately 140 patients had to be randomised per treatment group.

The primary analysis of the relative change from baseline of morning stiffness was performed on the Intent to Treat (ITT) population with a supportive analysis using the Per Protocol (PP) population. Analysis of the secondary efficacy variables was also carried out on the ITT population.

Disposition of subjects in the CAPRA-1 study: Of the 288 subjects randomised, 251 (87.2%) completed the double-blind treatment phase, 121/144 (84.0%) of the modified release prednisone group and 130/144 (90.3%) of the immediate release prednisone group.

Subjects with major protocol deviations, defined as likely to affect the validity of the data for duration of morning stiffness, were excluded from the PP analysis. A total of 135 out of 288 subjects (46.9%) showed major protocol deviations; 75/144 (52.1%) in the modified release prednisone group and 60/144 (41.7%) in the immediate release prednisone group. The three most common reasons for such exclusions were duration of therapy “out of range” (that is, final assessment outside the period 84 ± 3 days), baseline morning stiffness < 45 min duration and timing of evening medication “out of range”. Each of the latter three was reasonably evenly balanced between treatment groups.

The distribution of baseline demographic characteristics was balanced between treatment groups. Most patients were female (247/288 or 85.8%) and middle-aged (45-65 years). The mean age was 55.0 years (standard deviation (SD) 11.2 years, range 20-79 years). The mean patient weight was 70.6 kg (range 43-115 kg). Similarly, the distribution of baseline disease characteristics was balanced between treatment groups. The mean duration of RA was 9.6 years with nearly 40% of subjects having had RA for more than 10 years. Patients had evidence of high disease activity at baseline with a mean DAS28 score of 5.9. Co-morbidities at baseline were similarly distributed between the 2 treatment groups.

The results for the primary efficacy outcome are summarised in Table 7 below:

Table 7. Duration of Morning Stiffness after 12 weeks in Study EMR 62215-003, CAPRA-1 (Intention-to-Treat)

Duration of morning stiffness	Prednisone TRT (N = 144) mean (SD) median (min., max.)	Prednisone Standard (N = 144) mean (SD) median (min., max.)
Baseline [min]	164.1 (101.4) 146.4 (13.6, 659.3) (n = 125)	182.5 (125.0) 152.9 (32.1, 720.0) (n = 129)
Final week [min]	120.9 (140.5) 79.3 (0.0, 720.0) (n = 127)	157.4 (145.6) 120.0 (0.0, 720.0) (n = 131)
Relative change [%]	-22.66 (89.1) -33.92 (-100.0, 500.0) (n = 125)	-0.39 (89.0) -13.48 (-100.0, 609.9) (n = 129)
Treatment difference LS mean (SE) [%] Lower limit of 95% CI p-value	22.4 (11.1) 0.493 0.0226 (one-sided)	

Source: Section 14.2, Tables 14.2.1.1a to 14.2.1.4a. (Note: The statistical tests were performed two-sided at a significance level of 5%. One-sided p-values were transformed from the two-sided p-values.)

LS = least square, SE = standard error

According to the CER, the relative mean change in the duration of morning stiffness after 12 weeks of treatment was -22.7% (baseline mean of 164 minutes to a final mean value of 121 minutes) for Lodotra and was -0.4% (baseline of 182.5 minutes to a final mean of 157.4 minutes) for the immediate release prednisone. Using an analysis of variance accounting for treatment and centre effects, the treatment difference was shown to be 22.4% with the lower limit of the associated 95% CI being 0.49%, giving a statistically significant result, $p = 0.0226$. The Delegate has two concerns about these results. Firstly, there is a relatively large difference at baseline between the mean duration of morning stiffness between the groups, 164.1 minutes for the modified or timed release prednisone group and 182.5 minutes for the immediate release group. This could indicate that the patients in the latter group had worse disease at baseline. The sponsor is requested to comment on this difference. Secondly, if one looks at the results in the above table, the absolute difference between the baseline and final values of the mean duration of morning stiffness in the timed release prednisone group was 43.2 minutes (164.1 – 120.9), giving an apparent relative reduction of 43.2/164.1 or 26.3% which is at least reasonably close to the value of 22.66% in the above table. However, the absolute difference between the baseline and final values of the mean duration of morning stiffness in the immediate release prednisone group was 25.1 minutes (182.5 – 157.4), giving an apparent relative reduction of 25.1/182.5 or 13.75% which is not at all close to the value of 0.39% in the above table. Of course what the Delegate has calculated here are the relative changes in the mean durations of morning stiffness in each group over the study period. These may not necessarily be the same as relative mean changes. However, one would have thought they would have been at least of the same order of magnitude. Interestingly, the 13.75% reduction in the mean duration of morning stiffness as calculated by the Delegate for the immediate release group is close to the value of 13.48% for the relative reduction in the median duration of morning stiffness. The sponsor is asked to provide a detailed commentary on this apparent discrepancy in its pre-ACPM response, showing step by step all its working in arriving at the relative change values of -22.66% and -0.39% in the above table.

Improvements in the mean daily duration of morning stiffness (assessed on a weekly basis) were seen as early as 2 weeks and continued to improve to Week 9, thereafter plateaued to Week 12. For the immediate release prednisone group there was no clear

trend of any change over the 12 week study period. The numbers 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 treatment groups at any assigned visits (Weeks 2, 6 and 12). No statistically significant differences between the two treatment groups were observed for any other secondary efficacy variables.

Study NP01-007 (CAPRA-2)

The CAPRA-2 Study was a randomised, double-blind, parallel-group, placebo-controlled trial conducted in 62 centres in 4 countries in Europe (Poland, Germany, Hungary and UK) and 2 in North America (USA and Canada). Patients with a history of RA who were on DMARD treatment for at least 6 months (with a stable dose for at least 6 weeks prior to screening) and had a duration of morning stiffness of at least 45 minutes were eligible for inclusion.

The primary objective of the study was to show that 12 weeks of treatment with 5 mg of modified or timed release prednisone (Lodotra) when administered in the evening was superior to placebo with respect to the ACR20 responder rate. Patients continued their background RA therapy at the same dose for the duration of the study. The overall compliance with study medication was high and comparable between the two treatment groups.

The primary efficacy outcome was the difference in the proportions of ACR20 responders between the 2 groups at 12 weeks. The key secondary efficacy variable was the relative % change from baseline in the duration of morning stiffness at Week 12. There were a number of other secondary efficacy outcomes.

The sample size calculation was based on the comparison of 2 proportions using the chi-squared test and a randomisation ratio of 1:2 (placebo: Lodotra). Superiority for Lodotra compared with control therapy was defined as an ACR20 response rate at least 20% higher. The published literature indicates a typical placebo ACR20 response rate of 25-30%. With an assumed ACR20 response rate of 25% in the control group, a total of 294 subjects (98 placebo, 196 Lodotra) were required to provide 90% power to detect an ACR20 response rate of 45% in the Lodotra group at a significance level of 0.05. It was then estimated that a minimum of 350 patients would have to be enrolled in the study to obtain 294 evaluable subjects.

The main efficacy endpoint of the % ACR20 response rate after 12 weeks of treatment was analysed using the safety population with a logistic regression model incorporating treatment and geographic area, age category and gender as factors with a 2-sided significance level of 0.05.

Of the 350 subjects randomised, 323 (92.3%) completed the double-blind treatment phase; 217/231 (93.9%) in the modified or timed release prednisone group and 106/119 (89.1%) in the placebo arm. A total of 71 subjects (20.3% of 350) showed major protocol deviations; 46/231 (19.9%) of the Lodotra group and 25/119 (21.0%) of the placebo group. The 4 most common reasons for exclusion from the PP analysis were receipt of prohibited medications (mainly NSAIDs), failure of adherence to study medications, mis-randomisation and failure to meet inclusion, exclusion etc. criteria.

Baseline demographic characteristics were distributed in a balanced fashion between the 2 treatment groups. Most patients were female (84.0%, 294/350) and middle-aged (45-65 years of age) with a mean age of 57.2 years (SD 9.76 years). Almost all patients were white (98.3%, 344/350). Likewise baseline disease characteristics were distributed in a balanced manner between the 2 treatment groups. The mean duration of RA was 8.0 years. Patients had evidence of high disease activity at baseline with a mean DAS28 score of 5.2. Co-morbidities at baseline were similar between the groups.

The primary efficacy endpoint [ITT] was achieved since Lodotra 5 mg daily demonstrated a statistically significantly higher ACR20 responder rate (46.8%, 108/231) after 12 weeks of treatment compared to that achieved by placebo (29.4%, 35/119). The treatment difference was 17.3% (95% CI [6.37, 26.91]) and was significant using different imputation methods for missing values and was confirmed by analysis of the results in the safety and PP populations). The relevant table from the CER is reproduced below.

Table 8. ACR20 Response rate at Visit 4 in NP01-007 (CAPRA-2) Study (different imputation methods)

Imputation scheme	Lodotra n/N (%)	Placebo n/N (%)	% Difference in proportions ^a (95% CI ^b)	Odds ratio (95% CI ^c)	P-value ^d
Primary analysis					
Worse case ^e	108/231 (46.8%)	35/119 (29.4%)	17.3 (6.37, 26.91)	2.16 (1.34, 3.48)	0.0016
Secondary analysis					
Observed case	108/224 (48.2%)	35/116 (30.2%)	18.0 (6.83, 27.78)	2.21 (1.36, 3.58)	0.0013
LOCF ^f	110/229 (48.0)	35/119 (29.4%)	18.6 (7.66, 28.22)	2.30 (1.42, 3.72)	0.0007
Withdrawal ^g	108/230 (47.0%)	35/119 (29.4%)	17.5 (6.58, 27.16)	2.18 (1.35, 3.51)	0.0014

Source: Section 14.2, Table 14.2.1.2.1.2.

N = total number of patients per treatment group, n = number of responders.

Note: Visit 4 includes early withdrawal patients.

^a The observed difference between treatments was reported.

^b The 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link with treatment, geographic region, gender and median age class as factors.

^c Asymptomatic 95% CIs based on asymptotic normality of the estimated odds ratio.

^d The p-value was based on logistic regression with treatment, geographic region, gender and median age class as factors.

^e Worse case imputation: all missing values were imputed as non-responders.

^f LOCF imputation: last observation (post-baseline) was carried forward.

^g Withdrawal imputation: missing values for withdrawn patients were imputed as non-responders.

The relative % change from baseline to Week 12 in the duration of morning stiffness was a key secondary efficacy variable with direct relevance for the indication sought by the sponsor. The median baseline duration of morning stiffness was comparable between the 2 groups; 128.6 minutes for Lodotra and 138.6 minutes for placebo. At 12 weeks, the median duration of morning stiffness was 45.2 minutes in the Lodotra group and 85.0 minutes in the placebo group which corresponded to a median percentage decrease from baseline of 56.5% for Lodotra and 33.3% for placebo (p = 0.0008). Sensitivity analyses using different imputation methods and populations (ITT, PP) confirmed the result. Not all of the secondary efficacy endpoints were met. For example, while the ACR50 response rate achieved statistical significance at Week 12 (22.5% Lodotra versus 9.2% placebo), the ACR70 response rate at Week 12 did not achieve statistical significance, although the latter was numerically higher in the Lodotra group (6.9%) than in the placebo group (2.5%). On the whole, the secondary efficacy outcomes were supportive of the primary outcome.

Open Label Extension phase of EMR 62215-003 (CAPRA-1)

A total of 249 of 251 eligible patients (120 from the original Lodotra group and 129 from the immediate release prednisone group) entered the OLE study phase and 219 patients (88.0%) completed the 9 months of follow-up.

For patients who initially received treatment with modified or timed release prednisone, the mean reduction in the duration of morning stiffness was maintained over the extended treatment period (that is, over the extra 9 months to a total of 12 months). The group formerly on the immediate release prednisone showed a notable reduction in the duration of morning stiffness after 3 months of Lodotra with a relative reduction of 46% (absolute change from 150 to 85 minutes). The treatment effect in this group who switched remained relatively stable over the 9 months of follow-up. The other secondary efficacy outcomes were somewhat variable but generally supportive.

Safety

During the double-blind phase of Study EMR 62215-003, all randomised patients were either exposed to Lodotra (n = 144) or immediate release prednisone (n = 144) at a daily dose of 3-10 mg. The mean, median and range for the duration of exposure were similar between the two treatment groups as was the mean daily dosage of 6.4-6.8 mg/day. When entering the open label extension of Study EMR 62215-003, all patients from the immediate release prednisone group were switched to Lodotra. In the other pivotal trial, NP01-007, all subjects receiving Lodotra were given it at a fixed 5 mg/day dose and the median duration of exposure was 84 days.

With regard to the frequencies of all adverse events (irrespective of relationship to study treatment), an integrated summary of safety for the CAPRA-1 and -2 studies was performed and showed that the safety profile was comparable across both Phase III studies. The overall incidence of AEs across the 2 Phase III studies was slightly higher in the placebo group (48.7%, 58/119) compared to Lodotra (41.9%, 157/375) or standard IR prednisone (39.6%, 57/144). Drug-related AEs occurred more frequently for IR prednisone (30.6%, 44/144) than Lodotra (16.8%, 63/375) and placebo (8.4%, 10/119). Drug-related AEs leading to withdrawal were most frequently reported for IR prednisone (4.2%, 6/144), followed by Lodotra (2.9%, 11/375) and placebo (0.8%, 1/119). The incidence of SAEs and drug-related SAEs was low and comparable for all 3 treatments. There was correlation between prednisone dose (above or below 5 mg/day) and the incidence of AEs for either prednisone formulation (modified release or IR).

The most commonly reported AEs (occurring in >2% of patients in any treatment group) did not reveal any statistically significant differences between Lodotra and placebo, or Lodotra and IR prednisone, except for RA flare being more frequently reported for placebo than for either formulation of prednisone (26.1% [31/119] for placebo versus 12.8% [48/375] for Lodotra and 9.7% [14/144] for immediate release; $p < 0.05$ for both pairwise comparisons); and a statistically significant difference in the incidence of diarrhoea, which was reported for a higher proportion of patients receiving immediate release prednisone than Lodotra (2.8% [4/144] versus 1.1% [4/375]; $p = 0.0444$), although there were very low numbers of patients with diarrhoea in both groups.

With regard to the frequencies of treatment-related adverse events in the CAPRA-1 Study, such drug-related AEs were reported in 35 of 288 patients (12.2%). These were made up of 19 (13.2% of 144) subjects in the Lodotra group and 16 (11.1% of 144) patients in the immediate release prednisone arm. During OLE treatment, 27 patients (10.8% of 249) were recorded to have suffered a drug related AE. The most frequently reported drug-related AEs were gastrointestinal complaints (MedDRA³² Preferred Term “abdominal pain

³² MedDRA or Medical Dictionary for Regulatory Activities is a clinically validated international [medical terminology](#) used by regulatory authorities and the regulated biopharmaceutical industry during the regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation. In addition, it is the [adverse event](#) classification dictionary endorsed by the [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use](#) (ICH).

upper” and “gastritis”), “nausea” and “headache” (overall, 6 patients [2.1% of 288] for each of the last 2 AE types in the double blind phase). The incidences of drug-related AEs were similar in both prednisone treatment groups, which is to be expected because of the study design. Furthermore, all patients had received prednisone before the study for at least 3 months and in light of the RA disease duration (mean 10 years) it can be assumed that the majority of patients had probably received prednisone for a long time. With longer treatment duration, weight increases were observed in 6 cases (2.4% of 249) in the OLE phase. Otherwise, no significant or clinically relevant changes in the AE profile were observed under open label treatment. Although the duration of the open label follow-up was considerably longer (up to 3 fold) than the duration of the double-blind phase, the incidence of most AEs was lower which may be contributed to by under-reporting because of the longer visit intervals.

With regard to the frequencies of treatment-related adverse effects in the CAPRA-2 Study, 28 patients in all (8.0% of 350) reported AEs that were considered to be related to study treatment; 18 (7.8% of 231) in the Lodotra group and 10 (8.4% of 119) in the placebo group. The most commonly reported treatment-related AE by preferred term was headache (4 patients overall, 1.1% of 350 with 3/231 (1.3%) in the Lodotra group and 1/119 (0.8%) in the placebo group). All treatment-related AEs were mild or moderate in severity with the exception of 1 AE (severe headache in a patient receiving placebo who withdrew because of the AE).

No subject died while receiving study treatment in any of the trials. However, 1 patient (a 64 year old female with treated RA for 14 years) involved in the CAPRA-1 Study suddenly died 18 days after receiving her last dose of immediate release prednisone. The death was assumed to be due to myocardial infarction and the patient had a significant past history of coronary artery disease. The death was judged to be unrelated to prednisone. In addition to the death, 11 SAEs were reported in 7 patients (2.4%) in the CAPRA-1 Study; 6 SAEs in 4 patients (2.8%) receiving Lodotra and 5 SAEs in 3 subjects (2.1%) given immediate release prednisone. All patients with SAEs recovered from their events but 2 patients had sequelae (OA-related thumb surgery for a patient receiving Lodotra and a shoulder tendon rupture for a subject administered immediate release prednisone). Most patients (249 of 251) who completed the double-blind phase of the CAPRA-1 study entered the OLE period and all subjects received Lodotra then. Of these, 34 patients experienced 52 SAEs. Only 2 of the SAEs that occurred during the 12 months of treatment were assessed as possibly related to Lodotra: gastric ulcer perforation in 1 patient and gastrointestinal haemorrhage in another subject. In both of these patients, concomitant medications (Non-Steroidal Anti inflammatory drugs (NSAID):diclofenac and ketoprofen) may have contributed to the events. During the CAPRA-2 Study, 4 SAEs were reported for 3 patients; 1 patient [0.4%] in the Lodotra group and 2 patients [1.7%] in the placebo group. The patient in the Lodotra group experienced 2 SAEs (palpitations and chest discomfort). In the placebo group, 1 patient experienced an SAE of ischemic heart disease and the other had abnormal cervical cytology reported. None of the SAEs were considered to be related to study medication.

During the double-blind treatment phase of the CAPRA-1 Study, a total of 22 patients (7.6% of 288) experienced 34 AEs leading to the discontinuation of prednisone. Ten patients received immediate release prednisone (6.9% of 144) and 12 patients received Lodotra (8.3% of 144). During the 9 OLE months of CAPRA-1, an additional 14 patients (5.6% of 249) treated with Lodotra withdrew due to AEs. The most common AEs leading to discontinuation of prednisone were worsening of RA (16 patients in total; 10 in the controlled period and 6 in the OLE) followed by upper abdominal pain, nausea, and insomnia (each AE type reported in 2 patients). Over 12 months of follow-up, 3 patients developed infections that led to discontinuation of Lodotra; 1 case each of sepsis (onset on study day 59), pneumonia (Study Day 220) and tuberculosis (exact date unknown). The latter 2 patients were taking a daily dose of Lodotra of 3-5 mg and the sepsis case was

taking 7-10 mg. All of the infectious related withdrawals, and all but 1 of the insomnia cases were rated as either unlikely to be related or not related to Lodotra, an appraisal which the clinical evaluator did not find convincing. The sponsor is asked to comment on this issue, particularly with regard to the withdrawals related to infection. In the CAPRA-2 Study, 6 patients developed AEs leading to withdrawal; 5 subjects (2.2% of 231) treated with Lodotra and 1 person (0.8% of 119) in the placebo group. Four of the Lodotra withdrawal patients had their AE attributed to study medication. The events included single patients experiencing hypertension (with associated headache and anxiety), glaucoma exacerbation, vomiting and headache. The patient in the immediate release prednisone who withdrew did so because of headache.

In both of the Phase III studies, the incidence of developing new increases of serum transaminases (from normal baseline values) with Lodotra was 2.6-6.3%, which is comparable to those given immediate release prednisone in the CAPRA-1 Study (incidence 3.5-4.9%) and placebo in CAPRA-2 (frequency 5.0-7.6%).

The pivotal studies showed no consistent trend to increased blood urea or creatinine levels between any of the study treatments (modified release versus immediate release prednisone in CAPRA-1, and modified release prednisone versus placebo in the CAPRA-2 Study).

During the double blind phase of the CAPRA-1 Study, 2 cases of clinically relevant, abnormally increased blood glucose concentrations were reported in each of the prednisone treatment groups (1.4% of 144 for each group). During the OLE phase of CAPRA-1, 4 cases of significantly raised blood glucose levels were reported (1.6% of 249). During the CAPRA-2 Study, 1 patient treated with Lodotra recorded significantly increased blood glucose. This was a known, long-standing diabetic subject who had not yet administered her regular morning dose of insulin prior to the study blood tests being taken.

The incidence of raised total cholesterol levels (from a normal baseline value) with Lodotra was 12.5% (18/144) in the CAPRA-1 and 15.6% (36/231) in the CAPRA-2 Study compared with 10.4% (15/144) for immediate release prednisone in CAPRA-1 and 7.6% (9/119) for placebo in the CAPRA-2 trial. However, the incidence of newly elevated serum triglyceride levels was similar (4.8-6.7%) in the 2 pivotal studies regardless of study treatment (modified release or immediate release prednisone or placebo).

There were no significant trends for changes in serum chemistry (such as sodium and potassium) across the treatment groups (modified release or immediate release prednisone or placebo).

Consistent with the known effects of prednisone, the CAPRA-2 Study demonstrated a significant difference in 2 haematological variables (baseline to Visit 4) when Lodotra was compared to placebo. The incidence of subjects developing baseline normal to high neutrophil counts with Lodotra was 17.7% (41/231) versus 8.4% (10/119) for placebo. The incidence of patients developing baseline normal to low monocyte counts was 10.0% (23/231) for Lodotra compared with 6.7% (8/119) for placebo. The CAPRA-1 Study showed no significant difference between modified release and immediate release prednisone for the incidences of abnormalities in any haematology parameter.

The effect of extended treatment with Lodotra compared with immediate release prednisone (both in low dose) on the hypothalamic-pituitary axis (HPA) was investigated in a sub-study of EMR 62215-003 using a corticotrophin releasing hormone (CRH) test, and showed no significant difference in HPA axis suppression between the 2 prednisone formulations.

As noted by the clinical evaluator, the current dataset for Lodotra has an exposure limited to 12 months of therapy. Some of the important side effects of prednisone therapy (even in

low dose) are only associated with long term use (many years of treatment). In particular, assessments regarding the potential impact of Lodotra on the incidence of osteoporosis, cardiovascular safety and certain ophthalmic conditions (primarily cataracts and glaucoma) cannot, in the opinion of the evaluator, be made from the current drug exposure dataset. With this, the Delegate would agree.

The AE profile observed in the Phase I studies was characteristic of early Phase trial reporting with most of the observed AEs judged as unrelated or consistent with the known side effect profile of prednisone (primarily headache and gastrointestinal disorders).

First round benefit-risk assessment

The clinical evaluator was of the opinion that the benefit-risk balance for the proposed indication and dosing regimen was favourable.

At the end of the first round assessment, the clinical evaluator had some questions related to the proposed Product Information document. The sponsor in turn accepted all the recommendations regarding the PI which were implicit in the evaluator's questions.

Second round benefit-risk assessment

In answer to a question from the RMP evaluator, the sponsor provided for the second round assessment a copy of the final summary report for the Non-Intervention Study (NIS)-Lodotra. This was evaluated by both the clinical and RMP evaluators. This study was an uncontrolled, multicentre, non-interventional evaluation of Lodotra on the activity status, quality of life (specifically on reduction of morning arthritis/stiffness symptoms) and safety in RA patients aged at least 18 years who had symptoms of morning stiffness of joints and were already on or would be stabilised on glucocorticoid therapy. All patients were commenced on Lodotra at a starting dose of 5 mg/day. At the 9 month follow-up point, the mean dose of Lodotra was 4.1 mg/day. The total targeted patient numbers were 8000 but enrolment was stopped at 2730 patients in 2009 so that the results could be made available by the end of 2010 as a post-approval commitment to the regulatory authority of the relevant EU reference member state which, in this case, was Germany.

As noted by the clinical evaluator, the NIS-Lodotra study population was consistent with expectations; predominately female (72.0%) and middle-aged (median of 60 years; range 18-97 years). The mean duration of RA was 7.9 years. In total, 158 patients (5.9%) experienced 218 AEs leading to withdrawal. The most common types of AEs by SOC resulting in cessation were gastrointestinal disorders (54 cases, 2.02%), psychiatric (29 subjects, 1.08%) and nervous system problems (17 patients, 0.64%). The most frequent individual types of AEs leading to withdrawal were nausea (n=22), upper abdominal pain (n=18), sleep disorders (n=16), headache (n=9), dizziness (n=6) and impaired glucose metabolism (n=6).

In the NIS-Lodotra Study, a total of 22 patients (0.82%) experienced 35 SAEs. Half (11 subjects, 0.41%) of the SAE patients had events that were considered to be treatment related. These included 8 gastrointestinal SAEs (in particular, various types of GIT bleeding and symptoms relating to gastritis) and single reports of sleep disturbance, tachyarrhythmia and ruptured Achilles tendon. Four deaths occurred during the observation period and none was considered to be treatment related.

The clinical evaluator was of the opinion that the incidence and type of adverse events observed in the NIS are consistent with the expected safety profile of continued low dose corticosteroid treatment. The RMP evaluator did have one comment which was that it was unclear why the NIS-Lodotra synopsis, *Summary – Conclusion*, stated that severity, outcome and causality were not documented for adverse events leading to withdrawal and were not evaluated. In total, 158 patients (5.9%) experienced 218 AEs leading to withdrawal. The sponsor was requested to provide a detailed comment on this issue.

The clinical evaluator concluded, at the end of the second round assessment that the benefit-risk balance for Lodotra for the proposed indication and dosing regimen was still favourable.

Risk management plan

The sponsor accepted all recommendations to update the Safety Specification in the draft RMP after the first round evaluation. In particular, the sponsor made changes relating to the risk of adrenal suppression, the need for ophthalmological follow-up, prophylaxis of osteoporosis and dosing administration instructions.

The RMP evaluator was of the opinion that the submitted RMP was supportive of the application and made one recommendation, that the Australian Risk Management Plan for Lodotra, version 2, dated 2 January 2012 and any subsequent versions, be implemented as a condition of registration.

Risk-benefit analysis

Delegate considerations

Risk benefit discussion

As noted by the clinical evaluator, the main benefits of Lodotra with regard to the requested indication are:

- Improvements in the duration of morning stiffness for adult patients with moderately to severely active RA over 12 weeks compared to immediate release prednisone (relative mean reduction of 22.7%), or to placebo + background standard of care (relative mean reduction of 23.2%).
- Improvements in the ACR20 response rate (46.8% versus 29.4%) and ACR50 response rate (22.5% versus 9.2%) at 12 weeks compared to placebo + background DMARD treatment.
- Maintenance of improvements in the duration of morning stiffness with treatment for up to 12 months.

As noted by the clinical evaluator, the principal risks associated with the proposed usage of Lodotra are:

- Discontinuations due to AEs were numerically higher with Lodotra (2.2%) versus placebo (0.8%) but similar in incidence and for the same types of AEs as between Lodotra and the immediate release prednisone (8.3% versus 6.9%, respectively).
- As noted by the clinical evaluator, the current dataset for Lodotra has an exposure limited to 12 months of therapy. Some of the important side effects of prednisone therapy (even in low dose) are only associated with long term use (many years of treatment). In particular, assessments regarding the potential impact of Lodotra on the incidence of osteoporosis, cardiovascular safety and certain ophthalmic conditions (primarily cataracts and glaucoma) cannot, in the opinion of the evaluator, be made from the current drug exposure dataset. One would have to assume that the risks of all the latter would no less with Lodotra than they are with the currently registered immediate release products.

Another current risk, this time one identified by the quality evaluator, is that to do with the application of appropriate specifications for the degradant prednisone-21 aldehyde (P21A). The Delegate is of the opinion that if the sponsor were able to come to an

agreement with the quality evaluator concerning all the latter's requests regarding the specifications of the product, then the application could be approved.

Indication

The requested indications are acceptable, particularly given that they actually match the target population studied in the clinical trials. The wording is:

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

As noted previously by the Delegate, these indications are much more limited in scope than the corresponding indications for the approved immediate release prednisone medicines and do actually match the target population studied. Does the ACPM have any concerns about any apparent lack of consistency between the indications which are sought by the sponsor and the indications already approved for RA for the immediate release dosage forms? The sponsor is also asked to comment on this issue.

Recommendation

The Delegate proposed to approve this submission by Mundipharma Pty Limited to register the new dosage form Lodotra 1 mg, 2 mg and 5 mg modified or timed release tablets based on the safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above in the Risk / Benefit Discussion.

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

This approval will be contingent upon amendment of the Product Information document to the satisfaction of the TGA and satisfactory answers to the questions below as well as satisfactory resolution of the specifications issue for the degradant P21A. A specific condition of registration will be imposed relating to the implementation of the Australian Risk Management Plan for Lodotra, version 2, dated 2 January 2012 and any subsequent versions as may be agreed with the Office of Product Review.

The sponsor was asked to address the following issues in the Pre-ACPM response:

- a. With regard to the degradant, prednisone-21-aldehyde (P21A), the sponsor was requested to clarify the relationship between the TTC level of 1.5 µg/day and the NMT value of 0.25% and to indicate whether it is prepared to accept the recommendation of the quality evaluator in relation to the specifications for P21A.
- b. The sponsor was requested to comment on the difference in the baseline mean durations of morning stiffness of the Lodotra and immediate release prednisone groups in the Study EMR 62215-003.
- c. The sponsor was requested to provide a detailed commentary, showing all necessary working, which explains the apparent discrepancy observed by the delegate between the relative changes of -22.66% and -0.39% in the results for the primary efficacy outcome.
- d. The sponsor was requested to comment on the fact that the clinical evaluator found unconvincing the claim of the CAPRA-1 investigators that the infection-related withdrawals in the study were either unlikely to be related or were not related to Lodotra.
- e. The RMP evaluator did have one comment which was that it was unclear why the NIS-Lodotra synopsis, *Summary – Conclusion*, stated that severity, outcome and causality

were not documented for adverse events leading to withdrawal and were not evaluated. The sponsor was requested to respond to this observation and explain why such AEs were not evaluated.

- f. The sponsor was asked to comment on the basis on which the proposed PI was constructed and the sponsor has been asked to comment on a number of issues detailed in the reports (above). These issues are beyond the scope of this AusPAR.
- g. The sponsor was asked for a comment on the issue of consistency between the indication which has been sought and the already approved indication for RA for the immediate release dosage forms.

ACPM's advice was requested on the following issues

- Does the ACPM agree with both the quality evaluator and the Delegate that, unless the sponsor agrees to the tighter expiry limits for the degradant, prednisone-21-aldehyde (P21A) as proposed by the evaluator, then the application must be rejected?
- Does the ACPM accept the sponsor's explanation for the observation that about 6% of the individual patient AUC results in the bioavailability studies were very low? Does the ACPM agree with the Delegate that there must be acknowledgement of this issue in the proposed PI?
- Is the ACPM satisfied that there is satisfactory discussion of the pharmacokinetic properties of the drug in the relevant section of the PI, in particular in relation to the fasting vs. fed profiles as exemplified by the high inter-individual variability of both C_{max} and AUC under fasting conditions?
- Is the ACPM satisfied that there is sufficiently strong wording in the PI that this medicine is to be taken consistently with food and never on an empty stomach?
- Does the ACPM agree with the Delegate that there must be more detailed reporting in the PI of the primary efficacy outcomes in each of the pivotal studies, particularly with regard to baseline and final values of the relevant parameters and with regard to any related absolute changes of these parameters?
- Is the ACPM satisfied that the requested indication is consistent with the already approved indication for RA which applies to the immediate release prednisone medicines?
- The ACPM is asked to comment on what would appear to be the decision of the sponsor to base the construction of the proposed PI on the approved EU SmPC rather than on the already approved PIs for the immediate release dosage forms. To what extent should the proposed PI be consistent with, draw from or mirror the already approved PIs?

Response from sponsor

The sponsor response addressed the issues outlined in “Recommendation” of the Delegate’s Overview.

a.) Clarify the relationship between the TTC level of 1.5µg/day and the NMT value of 0.25% and indicate if Mundipharma will accept the recommendation in relation to the specifications for P21A

The CHMP proposes a TTC level of 1.5µg/day is to be implemented for an impurity with potential genotoxic risk (positive Ames test). However, P21A (previously the unknown impurity UDP1) is an impurity present not only in both the drug substance prednisone from the two proposed drug substance manufacturers, but also in prednisone tablets marketed in the EU, USA and Australia. Results for P21A are at similar levels to Lodotra and show that the TTC level of 1.5µg/day is exceeded for all prednisone product marketed in the EU, USA and Australia. Moreover, there is no proper basis to apply the TTC level of 1.5µg/day retrospectively, given that there is no discernible safety concern –positive Ames test results have not been confirmed by published preclinical carcinogenicity studies or clinical experience for the use prednisone. The assessment of risk undertaken is consistent with the guidelines set out in the EU Questions and Answers on the “Guideline on the limits for Genotoxic Impurities” (23 September 2010), which states “if a manufacturing procedure for API remains essentially unchanged, a re-evaluation with respect to the presence of a potentially genotoxic impurity is generally not needed.” Thus, to apply retrospectively the TTC of 1.5µg/day to Lodotra and to all marketed Australian prednisone- containing products is not reasonable, considering that: (i) both proposed active pharmaceutical ingredient (API) sources have been granted Certificates of Suitability (CEPs) by the EDQM; (ii) the maximum allowable limit for P21A as stipulated in the latest CEP for prednisone from [one of the proposed API manufacturers] is 0.25%; and (iii) the EP monograph for prednisone states that the limit for each impurity is NMT 0.25%. Until such time that the EDQM re-evaluate P21A in the monograph for prednisone, it is unlikely that API sources will be controlled to tighter P21A limits.

Mundipharma is unable to accept the recommendation for an expiry limit of NMT 0.1% for the impurity P21A (identified in Lodotra tablets as prednisone-21 aldehyde hydrate). The limit of NMT 0.1% at expiry cannot be met for the following reasons:

1. As discussed above, current API sources of prednisone are currently only controlled to NMT 0.25% of P21A. A P21A-free source is to our knowledge not available.
2. Stability results in the originally proposed packaging (without desiccant) showed levels of P21A of NMT 0.4%.
3. Stability results in the proposed packaging with desiccant (introduced as a result of implementing the ALARP principle applied for all degradation products) indicate that P21A is now controlled to a significantly lower level. The updated stability data including 24-months provided to the TGA shows P21A levels in Lodotra tablets at levels of 0.2% for the 2 mg tablet at 24 months when stored at 30°C/75 % RH. Although levels of 0.2% are observed only when stored at a higher storage conditions (30°C/75 % RH), the proposed expiry limit of 0.2% is recommended, and requested for the following reasons:
4. PAL-hydrate is difficult to quantify and unstable in solution. A re-validation of the related substances test method with regard to P21A was only possible with wider acceptance criteria. This information was provided to the evaluator by 19 April 2012 and accepted in his response in the revised Quality evaluation dated 23 April 2012: “It is stated that the relative response factor (rrf) of P21A is 1.1495 and the validation data has been updated to include a derivation of the rrf. These changes are acceptable”. The difficulty in quantifying PAL-hydrate allows for reporting of results to single digits

(one decimal place). However, the highest level observed at 25°C/60%RH was 0.11% (2 mg at 24 months).

5. Due to the difficulty in quantifying PAL-hydrate (see 4); during stability testing fluctuating results have been observed with no clear trend to higher P21A levels at expiry. These results were also provided to the TGA. Stability results indicate that P21A may be controlled to a level of $\leq 0.1\%$ (with one exception: 2 mg at 24 months, see (3)), however this is considered the borderline in that results above 0.1% could occur due to variability of results observed.

It is concluded that the manufacturers would be unable to supply Lodotra to the Australian market as it cannot be guaranteed that Lodotra will be able to meet with an expiry limit of NMT 0.1%, recalling that no other prednisone containing products in Australia or, indeed elsewhere, are required to meet this impractical expiry specification.

In addition, the TGA must consider the following:

6. Testing of Australian marketed prednisone immediate release solid oral dosage forms is now complete and shows that P21A levels are comparable to that for other prednisone oral dosage forms marketed worldwide, including Lodotra. Furthermore, the data indicates that Australian marketed prednisone immediate release tablets have P21A levels at around 0.1% when tested with another 2 years remaining of the product shelf life. Notably, these Australian products do not contain a desiccant to enhance stability. With the possible fluctuation of the results, single values of up to 0.2% are also very likely to be observed during storage. Very importantly, with 0.1% PAL hydrate in Sone 25 mg tablets, the total daily exposure would be 25µg/day, and with 0.2% the total daily exposure would be 50µg/day. This strongly suggests that the proposal for a release limit of 0.1% and expiry limit of 0.2% is reasonable for Lodotra and supported by relevant guidelines and should be acceptable to the TGA.

Mundipharma is aware that no new data is to be submitted (with the exception of safety related data) as the evaluation is considered completed. However, the information provided in points 3 (updated stability data) and 6 (P21A results for Australian IR prednisone products) was of importance in addressing the TGA's chemistry and manufacturing control questions, and to justify the proposed P21A limits. The above information was explained to the TGA Senior Case Manager via telephone on 19 April 2012 before submission. Confirmation via email from the Case Manager was received on the same day that the submission of this data would be accepted as the changes to be made were safety-related, given that P21A was considered potentially genotoxic. However, Mundipharma was advised by email on 20 April 2012 that the data would not be evaluated in relation of the expiry limit for P21A, as the submission of additional/new unrequested data is not allowed as part of the Streamline Submission Process. In the revised Quality evaluation report dated 23 April 2012, the quality evaluator also stated: "As the data assessed indicated that the limits of NMT 0.1% can be met this is a quality issue and not a safety issue". From the data presented above, this limit cannot be secured. If the TGA considers P21A not to be a safety concern, ICH guideline clearly defines limits for unidentified and identified impurities/ degradation products (for New Chemical Entities) which are much higher than 0.1%. A limit of NMT 0.2% for P21A should therefore be reasonable and neither of a quality, nor of a safety concern. If the TGA considers that P21A should be controlled according to the ALARP principle, then it should not be acceptable that the TGA should dismiss the data described above, particularly in relation to the P21A results for Australian prednisone tablets. The TGA has an obligation to review all data considered relevant to the safety of LODOTRA, and if the only reason for the dismissal of data is because of the Streamlined Submission Process, then all prednisone products registered in Australia should be withdrawn from the market as they also pose a safety concern in relation to levels of P21A. On the basis of the currently available and submitted data, it is proposed that: for the API only batches with NMT 0.1% P21A will be

used (instead of the NMT 0.25% as per CEP); for Lodotra tablets, the batch release and expiry limit for P21A are NMT 0.1% and 0.2% for all strengths, respectively. In addition, Mundipharma is committed to reviewing further stability data when available and to revise the specification if possible.

b.) Comment on the difference in baseline mean durations of morning stiffness of the LODOTRA and immediate release prednisone groups in the study EMR 62215-003.

Prior to randomisation, the patients were required to complete the two week screening period and meet all enrolment criteria. Randomisation was blinded to the baseline results. Although the mean baseline duration of morning stiffness (baseline values were collected by daily diary entry during the last week of the screening period) was somewhat higher for the immediate release prednisone group compared to the Lodotra group, it should be noted that the standard deviation is quite large for both groups and the median values between the two groups are comparable as shown below in Table 9 (taken from Clinical Study Report ER Table 11.8).

Table 9. Duration of morning stiffness at baseline

Duration of morning stiffness	Prednisone TRT (N = 144) mean (SD) median (min., max.)	Prednisone Standard (N = 144) mean (SD) median (min., max.)
Baseline [min]	164.1 (101.4) 146.4 (13.6, 659.3) (n = 125)	182.5 (125.0) 152.9 (32.1, 720.0) (n = 129)

All the other disease characteristics for the two treatment groups were highly comparable with no indication that one group had worse disease than the other group. The groups were balanced regarding baseline disease.

c.) Provide detailed commentary, showing all necessary working, which explains the apparent discrepancy observed by the delegate between the relative changes of -22.66% and -0.39% in the results for the primary efficacy outcome.

All calculations for change from baseline and percent change from baseline were done on an individual patient basis prior to calculation of any by treatment group means. The baseline value for each patient was calculated as the average of the values collected for that patient during the previous week. The final week value was calculated similarly, for example, as the average of the values collected for that patient during the final week. Change from baseline was calculated as [final week value] - [baseline value] for each patient individually, and percent change from baseline was calculated as $(\text{[final week value]} - \text{[baseline value]}) / \text{[baseline value]} * 100$. For this study, it can be seen when taking into account all the descriptive statistics that while the standard deviations, minimum, and maximum values are similar between treatment groups, the medians are similar at baseline but are different at the final week. This is an indication that more patients in the TRT group are having improvement of a larger magnitude than those in the Standard group. Further exploration of the individual patient data shows that 72% of patients had a decrease (of any size) in morning stiffness in the TRT group but that only 60% of patients in the Standard group had a decrease. If a criterion of decrease of 50% or more is used, then 41% of patients in the TRT group versus 25% of patients in the Standard group had a decrease of that magnitude. The smaller number of patients in the Standard group who had a decrease, along with the smaller decreases seen in that group, account for the mean relative change from baseline being so small in the Standard group. An example calculation for one patient is provided below.

Table 10. Results for Subject X:

	Baseline Week Values	Final Week Values
Day 1	50	25
Day 2	80	30
Day 3	105	30
Day 4	75	15
Day 5	95	30
Day 6	55	15
Day 7	60	25

Calculations for Morning Stiffness:

Baseline Analysis Value:
 $(50+80+105+75+95+55+60)/7 = 74.28571$

Final Week Analysis Value:
 $(25+30+30+15+30+15+25)/7 = 24.28571$

Change from Baseline:
 $24.28571 - 74.28571 = -50.0$

Percent Change from Baseline:
 $(24.28571 - 74.28571)/74.28571 * 100 = -67.3077$

d.) Comment on the fact that the clinical evaluator found unconvincing the claim that the infection-related withdrawals in the CAPRA-1 study were either unlikely to be related or were not related to LODOTRA

The distributor of Lodotra in Germany (Merck) was sponsor of CAPRA 1. The study protocol, as for most studies, allows the treating investigator to decide if an adverse event is related or not. This is not uncommon as it is expected that the treating investigator, who has close contact with the patient and their progress, would be in the best position to determine whether adverse events are related/not related.

e.) Respond to the observation from the RMP evaluator that it was unclear why the NIS-LODOTRA synopsis stated that severity, outcome and causality were not documented for AEs leading to withdrawal and were not evaluated and explain why such AEs were not evaluated

The distributor of Lodotra in Germany (Merck) was sponsor of the non-interventional study NIS LODOTRA and conducted the study according to the study protocol. The study protocol intended to reflect daily practice of treating patients and to limit intervention into the routine practice. It was not planned to document severity, outcome and causality for AEs leading to withdrawal and therefore participating sites did not report the information. Due to this lack of documentation an evaluation could not be done either.

g.) Comment on the issue of consistency between the indication which has been sought and the already approved indication for RA for the immediate release dosage forms

The indication sought for Lodotra is supported by the clinical benefits and favourable safety profile observed in two clinical studies (CAPRA 1 and 2) for daily low-dose prednisone in patients with moderate to severe active rheumatoid arthritis, particularly in relation to morning stiffness. The studies provided data in patients in up to 12 months. The request to comment on the issue of consistency between the indication between Lodotra and approved IR dosage forms for RA is not clear, particularly since after both the first and second round risk-benefit assessments: "The clinical evaluator was of the opinion that the benefit-risk balance for the proposed indication and dosing regimen was favourable." (see the Delegate's report section titled "Request for Pre-ACPM Advice".

Nevertheless, a review of the current Therapeutic Guidelines states that IR dosage forms of prednisone in Australia are currently indicated in RA for:

- short-term use for rapid symptom relief
- while waiting for a response to DMARDs and

- may be useful for patients where other treatments have failed or are contraindicated³³.

The dose recommended for the above indications is prednisolone 5-10mg daily, each morning.

It is important to note that the Lodotra dose range is in line with the current recommended dosage range stated in the Therapeutic Guidelines. Lodotra is also similar with regards to 'rapid symptom relief' as beneficial effects on reducing morning stiffness are observed in patients taking Lodotra as early as two weeks. In addition, the PI states the following:

"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."

The wording in the PI allows physicians to consider the use of Lodotra for patients where other treatments are not suitable, and more particularly in light of the latest clinical strategies for the use of low-dose daily glucocorticoids in the appropriate patient to provide better quality of life for RA patients experiencing morning stiffness.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit-risk profile for the indication:

For the treatment of moderate to severe, active rheumatoid arthritis in adults, particularly when accompanied by morning stiffness.

The ACPM agreed with the Delegate that the amendments to the Product Information (PI) and Consumer Medicine Information (CMI) should include the following:

- all statements in *Clinical Trials* section of the PI to ensure the accurate reflection of the modest efficacy and limitations as evidenced by the primary outcomes of each of the trials, with specific attention to:
 - referencing the outcomes for improvements in morning stiffness in absolute and not percentage terms.
 - highlighting the low bioavailability in 6% of the patient population
- a statement in the *Dosage and Administration* section of the PI and relevant section of the CMI to ensure the detail of the significant clinical impact of inconsistently dosing with or without food is clearly understood by prescribers and consumers.
- a statement in the *Contraindication* section of the PI and CMI to ensure awareness of the significant safety risks of use in children.
- a statement in the *Dosage and Administration and Clinical trial* sections of the PI to reflect the absence of data on dosing above 10 mg.

³³ Therapeutic Guidelines – Rheumatology. Version 2, 2010

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lodotra modified release tablets containing prednisone 1 mg, 2 mg and 5 mg, indicated for:

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

Specific conditions applying to these therapeutic goods

1. The Australian Risk Management Plan for Lodotra, version 2, dated 2 January 2012 and, and any subsequent revisions as agreed with the Office of Product Review, is to be implemented.
2. For the API only batches with NMT 0.1% P21A are to be used.
3. The batch release and expiry limits for P21A will be NMT 0.1% and NMT 0.2%, respectively, for all strengths of Lodotra.
4. Within 12 months of the date of the letter of approval of this submission, the sponsor will provide to the TGA a document outlining the estimated date by which new stability data will become available in the proposed packaging for marketing. As soon as possible after that estimated date, the sponsor will provide a summary of the stability data in relation to P21A and advise whether the data supports the revision of the corresponding specification.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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Reference/Publication #