Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pralatrexate

Proprietary Product Name: Folotyn

Sponsor: Mundipharma Pty Ltd

August 2013
Updated August 2017

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.
- The 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 <http://ww.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.

Contents

List of Abbreviations

Abbreviation	Meaning
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
BCRP	breast cancer resistance protein
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CER	clinical evaluation report
CR	complete response
CRu	complete response unconfirmed
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DHAP	dexamethasone, cisplatin and cytarabine
DHF	dihydrofolate
DHFR	dihydrofolate reductase
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPOCH	infusional etoposide, doxorubicin, vincristine plus bolus cyclophosphamide and prednisone
EU	European Union
FPGS	folylpolyglutamyl synthetase
GARFT	glycinamide ribonucleotide formyltransferase
GCP	good clinical practice
hERG	human ether-a-go-go-related gene
Hcy	homocysteine

Abbreviation	Meaning
IC_{50}	the concentration of an inhibitor causing 50% inhibition
ICE	ifosfamide, carboplatin and etoposide
IND	investigational new drug (USA)
LC/MS/MS	liquid chromatography–tandem mass spectrometry
LLOQ	lower limit of quantification
MMA	methylmalonic acid
MRP	multidrug resistance-associated protein
MTD	maximum tolerated dose
NSCLC	non small cell lung cancer
NHL	non-Hodgkin's lymphoma
OAT	organic anion transporter
OCT	organic cation transporter
OS	overall survival
pB-LBL	precursor B-cell lymphoblastic lymphoma
PDX	pralatrexate
PET	Positron-emission tomography
PFS	progression-free survival
P-gp	P-glycoproteins
PIP	paediatric investigation plan
PPF	pre-submission planning form (TGA)
PTCL	peripheral T-cell lymphoma
PR	partial response
PR interval	time from the beginning of the P wave to the QRS complex of an ECG
QT interval	time between the beginning of the Q wave and the end of the T wave of an ECG
QTcF	Fridericia's rate-corrected QT interval

Abbreviation	Meaning
QTcB	Bazett's rate-corrected QT interval
RR interval	time duration between two consecutive R waves of an ECG
RFC-1	reduced folate carrier 1
RT-PCR	reverse transcription combined with polymerase chain reaction
SCT	stem cell transplant
TCC	transitional cell carcinoma
TGA	Therapeutic Goods Administration
T-LBL	T-cell lymphoblastic lymphoma
THF	tetrahydrofolate
TS	thymidylate synthase
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
TGA Decision:	Rejected
Date of TGA Initial Decision:	20 December 2012
Date of Final TGA Decision:	17 May 2013
[1]AAT decision:	Approved
Date of AAT decision:	23 December 2014
Date of entry onto ARTG	26 February 2015
Active ingredient(s):	Pralatrexate
Product Name(s):	Folotyn
Sponsor's Name and Address:	Mundipharma Pty Ltd
Dose form(s):	Injection solution
Strength(s):	20 mg in 1 mL 40 mg in 2 mL
Container(s):	Carton with vial
Pack size(s):	Single vial
Approved Therapeutic use:	*Folotyn is indicated for the treatment of adult patients with peripheral T-cell lymphoma (PTCL) (nodal, extra nodal and leukaemic/disseminated) who have progressed after at least one prior therapy*.
Route(s) of administration:	Intravenous (IV)
Dosage:	30 mg/m^2 once weekly
ARTG Number (s):	192493 and 192492

Product background

This AusPAR describes the application by Mundipharma Pty Ltd to register Folotyn, an intravenous infusion of pralatrexate. Pralatrexate is a close methotrexate analogue and a new chemical entity. It acts as a folate analogue, inhibiting folate metabolism by binding to and inhibiting dihydrofolate reductase. It is polyglutamylated by folylpolyglutamyl synthetase and this prolongs its intracellular retention and is important for cytotoxicity. Pralatrexate is internalised by reduced folate carrier 1, which has higher expression in

[1] AAT=Administrative Appeals Tribunal

leukocytes and tumour cell lines[2]. It is proposed for use in the treatment of T-cell lymphoma.

This AusPAR describes the application by the sponsor to register pralatrexate for the indication:

> *"Folotyn is indicated for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic / disseminated) who have progressed after at least one prior therapy."*

Pralatrexate is an orphan drug in Australia for "*treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (nodal, extranodal and leukaemic / disseminated)*".

Peripheral T cell lymphoma (PTCL) comprises 10-15% of Non-Hodgkin Lymphomas[3]; "peripheral" refers to maturity of the neoplastic T cell (it is post-thymic, peripheral to the thymus). Outcome is generally poor but exceptions exist (for example, patients with ALK-positive anaplastic large cell lymphoma).

There are no registered treatments for PTCL in Australia. There is no 'standard of care' treatment but a commonly cited first-line treatment is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Stem cell transplantation (SCT) is curative in a small subgroup.

Regulatory status

The FDA granted USA approval for the Folotyn NDA under accelerated conditions on 24 September 2009.

The European MAA for Folotyn 20 mg/mL solution for injection was issued with a negative Opinion by majority vote (not consensus) by the Committee for Medicinal Products for Human Use (CHMP) on 19th January 2012. In the absence of established benefits due to the single arm pivotal study and despite the manageable safety profile, a positive benefit-risk balance could not be considered as established.

The KFDA granted South Korean approval for the Folotyn NDA on 12 July 2012.

A dossier has been submitted to Switzerland and conditional pre-approval has been granted.

Product Information

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

II. Quality findings

Drug substance (active ingredient)

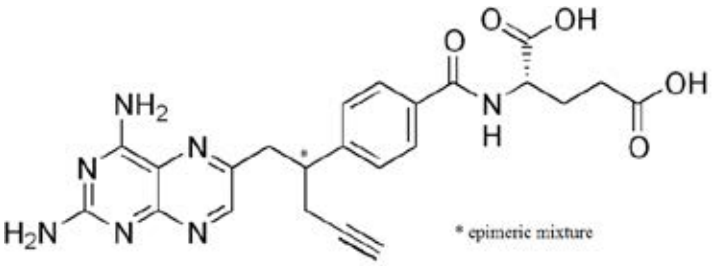
Pralatrexate is synthetic. Pralatrexate has two chiral centres and the drug substance is a mixture of two diastereomers ['PDX-10a' = (2S)(1S) and 'PDX-10b' = (2S)(1R)]. The amino

[2] Nonclinical Evaluation Report: RFC-1, DHFR and FPGS are polymorphically expressed; impact on pharmacodynamic response is unclear. For example, G80A polymorphism in RFC1 (*SLC19A1*) is related to outcome in ALL treated with methotrexate.

[3] CER and O'Connor OA et al. Pralatrexate in patients with relapsed or refractory peripheral T cell lymphoma: results from the pivotal PROPEL study. JCO 10.1200/JCO.2010.29.9024

acid moiety has defined chirality matching methotrexate [≥ 98%], but there are propynyl epimers at the benzylic carbon [ca 50:50]):

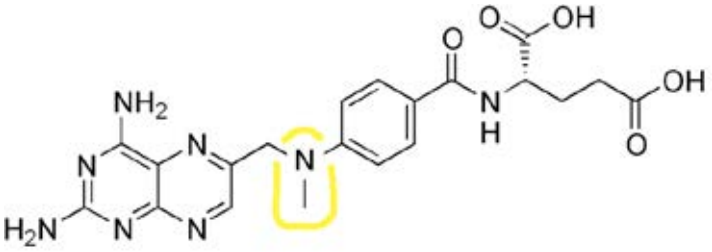
Figure 1. Chemical structure of pralatrexate



(2S)-2-[[4-[(1R or S)-1-[(2,4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid

C23H23N7O5; MW 477.5

Figure 2. Chemical structure of methotrexate



Thus pralatrexate is a diastereomeric mixture (but not a racemate as it is sometimes described in the submission).

Development of a diastereomeric mixture, as here, is generally discouraged. It is not clear how feasible it would be to selectively make each diastereomer on a commercial scale. Mundipharma claims that "*the specified ratio of C10 diastereomers [50:50 (± 4%)] is qualified by the nonclinical toxicology and clinical programs*" and that the diastereomers do not interconvert in solid drug or in solution (which is chemically plausible). The diastereomers are claimed to have similar cytotoxic activity *in vitro*. There are some differences in the rates of clearance of the two diastereomers.

Pralatrexate contains both acidic and basic functionality (pKa values are 3.25, 4.76, and 6.17). The drug substance is crystalline (melting point is about 216°C). The aqueous solubility of pralatrexate in water depends strongly on pH; it is very soluble in alkaline solution (pH > 7). The injection solution is formulated to pH 7.5-8.5 to give reasonable solubility.

There are no pharmacopoeial monographs (as is the usual case for a new chemical entity).

The manufacture and control of the drug substance is considered acceptable.

Drug product

Mundipharma seeks to register pralatrexate 20 mg in 1 mL and 40 mg in 2 mL vials. The injection is a simple aqueous solution formulated with 0.6 % sodium chloride for isotonicity and sodium hydroxide or hydrochloric acid to adjust the pH. (The 20 and 40 mg injections are just different fill volumes.) Packs of one vial are proposed.

The recommended dose is 30 mg/m^2 administered as an intravenous injection over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles. The injection is administered undiluted as an intravenous infusion over 3-5 minutes via the side port of a free flowing 0.9 % sodium chloride intravenous line.

Some minor changes in finished product formulation during clinical trials are not clinically significant.

The injection solution is sterilised by filtration. Chemistry, sterility etc aspects of the finished product are acceptable.

Biopharmaceutics

Bioavailability data are not normally reviewed by the Pharmaceutical Chemistry Section for an intravenous formulation. Population pharmacokinetic analyses are not evaluated by the Section.

There is reasonable evidence that epimerisation *in vivo* is negligible.

Advisory committee considerations

The application was considered at the 145th (2012/3) meeting of the Pharmaceutical Subcommittee (PSC), which recommended (excerpt follows below):

1. The PSC endorsed all the questions raised by the TGA in relation to quality and pharmaceutic aspects of the submission by Mundipharma Pty Ltd to register FOLOTYN solution for infusion containing 20 mg/1 mL and 40 mg/2 mL of pralatrexate. In particular, the PSC supported the questions in relation to specifications of the drug substance and agreed that issue of in vivo epimerisation should be clarified.
2. The Committee advised that all outstanding issues should be addressed to the satisfaction of the TGA.
3. In relation to the population pharmacokinetic analysis, the PSC:
   - Agreed that the results from the population pharmacokinetic analyses could have been confounded by the exclusion of a large number of samples that were below the lower limit of quantification (<LLOQ) from the dataset. The impact on the analysis of this exclusion can only be explored in a formal review of the population analysis. The PSC advised that there are a variety of well-established techniques for handling the <LLOQ data other than excluding them.
   - Noted that the impact of combinations of common covariates on the dose required to achieve various percentages of patients above the effective concentration of 50% (EC_{50}) or EC_{80} was not explored with the chosen population pharmacokinetic model. The PSC agreed that information on this would provide an insight on the patients at the margins who would usually require special attention.
4. There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

[Recommendation No. 2271]

The Quality issues have been resolved.

Quality summary and conclusions

Registration was recommended with respect to chemistry and quality control aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical data were in general accordance with the International Conference on Harmonisation (ICH) guideline on the nonclinical evaluation of anticancer pharmaceuticals (ICH S9[4]); however, the data set was not extensive and there were some major deficiencies. Most notably, there was a lack of adequate comparative pharmacodynamic and pharmacokinetic data to determine if the chosen species for toxicity testing are appropriate animal models. This limits the interpretation of the animal data for a risk assessment.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Folates are members of the B vitamins and are involved in the synthesis of purines, pyrimidines, serine and methionine, and therefore are important for deoxyribonucleic acid (DNA) synthesis. Pralatrexate is a folate analogue that is internalised by the reduced folate carrier 1 (RFC-1) protein, and polyglutamylated by the enzyme folylpolyglutamyl synthetase (FPGS), resulting in accumulation of the antifolate. Pralatrexate, a methotrexate analogue, is intended as an inhibitor of dihydrofolate reductase (DHFR), an enzyme which catalyses the reduction of dihydrofolic acid to tetrahydrofolic acid. Inhibition of DHFR leads to a depletion of intracellular reduced folate stores, thereby leading to a disruption of DNA synthesis. RFC-1 shows differential gene expression with high levels in certain tissues (including leukocytes) and tumour cell lines.[5] The high uptake of pralatrexate into leukocytes, combined with the high proliferative rate of tumour cells, prompted the sponsor to investigate pralatrexate for efficacy in patients with haematological malignancies.

In vitro studies

In vitro, pralatrexate inhibited human DHFR but with 2.5 times lower potency than methotrexate (dissociation constant (Ki) 13.4 pM compared to 5.4 pM for methotrexate). However, pralatrexate was a better substrate than methotrexate for RFC-1-like activity and FPGS-like activity in a human leukaemia cell line (Vmax[6]/Km[7] 10−14 times greater for pralatrexate than for methotrexate). Pralatrexate inhibited the growth of various tumour cell lines (such as head and neck, breast and various lung cancer cell lines). The 50% inhibitory concentration (IC_{50}) for pralatrexate on several leukaemia cell lines was ~40 nM (~100 times lower than the maximum clinical free plasma level).

Pralatrexate is a 1:1 racemic mixture of S- and R-diastereomers at the C10 chiral centre (referred to as PDX-10a and PDX-10b, respectively). The individual diastereomers of pralatrexate appeared to be equipotent in terms of cytotoxicity and therefore both are expected to contribute to the cytotoxic activity.

[4] http://www.tga.gov.au/pdf/euguide/swp64610708enfin.pdf
[5] Whetstine, J.R., R.M. Flatley and L.H. Matherly. (2002) The human reduced folate carrier gene is ubiquitously and differentially expressed in normal human tissues: identification of seven non-coding exons and characterization of a novel promoter. *Biochem. J.* 367: 629–640.
[6] Vmax=maximum rate
[7] Km= is the concentration of the substrate that gives rise to a half-maximal reaction rate

No studies were conducted to compare the potency of pralatrexate across species (humans and species used in toxicity studies). As dogs were more sensitive to pralatrexate toxicity than rats, it is uncertain which one is the more relevant species.

In vivo studies

The efficacy of pralatrexate was assessed in mouse xenograft tumour models. While four sponsor commissioned studies were submitted, none of these examined leukaemia or lymphoma models. The models examined in these studies included lung cancer, breast cancer and SCC. One submitted published paper examined the efficacy of pralatrexate in 3 non-Hodgkin's (B-cell) lymphoma (NHL) models. At 60 mg/kg IP pralatrexate (180 mg/m^2; ~6 times the proposed clinical dose) twice weekly for 14 days, reduced tumour growth and even tumour regression (54–99%) was seen in mice bearing NHL tumours. Complete regression was seen in 3 to 5 animals per group (n=9–10). In comparison, while some tumour growth inhibition was seen with methotrexate (40 mg/kg intraperitoneally (IP) twice weekly), there was no obvious tumour regression and no animals that showed complete regression.

Unfortunately, no *in vivo* efficacy studies were conducted in an appropriate animal model of peripheral T-cell lymphoma, and therefore no comment can be made in regard to efficacy to support the proposed indication.

Resistance development

No nonclinical studies were submitted to assess resistance development to pralatrexate. As pralatrexate is a substrate for the efflux transporters, BCRP, MRP3 and MRP2, overexpression of MRPs or BCRP could confer resistance to tumour cells.[8] Pralatrexate was not a substrate for P-glycoprotein, and over-expression of this transporter has little effect on pralatrexate efficacy.[9] Some pralatrexate-resistant cell lines have been shown to have altered (anti)folate transporter/enzyme expression. Decreases in RFC-1 and FPGS expression have been seen in pralatrexate-resistant cell lines.9 While pralatrexate-resistant cell lines appeared to show partial resistance to methotrexate, there was no significant effect on pemetrexed (another antifolate) activity. There is no information on whether cancer cells resistant to other antifolate agents are also resistant to pralatrexate.

Secondary pharmacodynamics

No nonclinical studies were submitted that examined the potential for pralatrexate to have off-target effects. This is considered a major deficiency.

Safety pharmacology

Specialised safety pharmacology studies examined the central nervous system, the cardiovascular and respiratory systems. In a tissue distribution study and a specific brain penetration study, there was no evidence that pralatrexate crossed the blood-brain barrier. No notable effects were seen on neurobehavioural function in rats treated with ≤ 25 mg/kg IV pralatrexate. The estimated maximum plasma concentrations achieved were up to 2 times in females and 7 times in males, the anticipated clinical peak plasma concentration (C_{max}). As the maximum tested plasma concentrations are only marginally above the maximum anticipated clinical plasma levels, no firm conclusions can be drawn from the negative findings.

In vitro, a concentration-dependent inhibition of hERG potassium (K+) channel current was seen with pralatrexate concentrations ≥ 0.8 mg/mL. The no effect concentration

[8]Assaraf, Y.G. (2006) The role of multidrug resistance efflux transporters in antifolate resistance and folate homeostasis. *Drug Resist. Updates* 9: 227–246.

[9] Serova, M., I. Bieche, M.-P. Sablin, G.J. Pronk, M. Vidaud, E. Cvitkovic, S. Faivre and E. Raymond. (2011) Single agent and combination studies of pralatrexate and molecular correlates of sensitivity. *Br. J. Cancer* 104: 272–280.

(NOEC) was 0.4 mg/mL (~200 times the clinical C_{max} free fraction). A concentration-dependent decrease in Vmax (11% at the highest concentration) and an increase in action potential duration (a 12% increase in action potential duration to 60% repolarisation (APD60) at the highest concentration) were seen in dog Purkinje fibres at pralatrexate concentrations ≥0.34 mg/mL (~170 times the clinical C_{max} free fraction). A NOEC was not established. As the *in vitro* effects only occurred at concentrations far exceeding the clinical C_{max} or were only mild in nature at these high concentrations, effects on QT interval prolongation[10] are not predicted to occur during clinical use. No treatment-related effects were seen on cardiovascular or respiratory parameters in dogs treated with ≤ 0.7 mg/kg IV pralatrexate. However, the maximum plasma concentrations achieved at these doses based on C5min after the first IV dose in the 9 month repeat dose toxicity study are well below the anticipated clinical C_{max} and therefore, no firm conclusions can be drawn from the negative findings.

Pharmacokinetics

Following IV administration, the plasma kinetics of PDX-10a and PDX-10b in rats and dogs showed a biphasic disposition pattern with an initial rapid decline and a more gradual terminal decline with variable terminal elimination half-lives (t½; 0.5 to 21 h) depending on dose. The t½ generally increased with dose in both rats and dogs, suggesting saturation of an elimination process. Because the half-lives varied considerably with dose, a species difference in this parameter could not be discerned. In rats, pralatrexate exposure appeared to consist of approximately equal levels of PDX-10a and PDX-10b while exposure to PDX-10a tended to be ~1.5 times higher than exposure to PDX-10b in dogs and the reverse was the case for humans (PDX-10b exposure was almost 2 times higher than PDX-10a exposure). As the diastereomers were apparently equipotent in cytotoxicity, at least against human cells, this species difference in PDX-10a/PDX-10b exposure ratios is not considered to be toxicologically significant. Following a single IV dose, exposure to pralatrexate was ~2 times higher in male rats compared to their female counterparts, which correlated with a lower clearance rate. This sex difference was not seen after repeated dosing. No consistent sex differences were seen in dogs. Renal excretion was less than 5% of total clearance in rats, while a saturation of renal elimination was indicated at higher doses in dogs. There was no evidence of accumulation with weekly dosing in dogs. There appeared to be some accumulation with weekly dosing in rats but as there was only one toxicokinetic study it is difficult to be certain.

Protein binding in human plasma was moderate (65% bound) and independent of concentration. Human serum albumin was the main protein involved in binding. Based on protein displacement studies, drug interactions involving plasma protein binding are not predicted to occur. No studies were submitted that examined protein binding in the plasma of animals used in toxicity studies. This is considered a major deficiency. Relative exposure comparisons between animal and human data are difficult to interpret in the absence of this information. No significant partitioning into red blood cells was seen. The volume of distribution of the PDX-10a diastereomer was greater than total body water in rats, dogs and human subjects (generally >2 L/kg). The volume of distribution of the PDX-10b diastereomer was similar to PDX-10a in rats and dogs but was consistently less than total body water in human subjects (0.4 L/kg). The reason for the diastereomeric difference in humans (and not other species) is unknown. Following IV administration of radioactively carbon labelled (^{14}C)-pralatrexate to pigmented rats, tissue distribution was extensive. The highest concentrations were initially observed in the gastrointestinal tract

[10] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

contents, suggestive of biliary excretion. Aside from organs involved in excretion, there was no specific accumulation or affinity of drug-related radioactivity to particular organs. There was no evidence of specific affinity for melanin containing tissues or that radioactive material crossed the blood-brain barrier.

No *in vivo* metabolism studies in animal species or humans or *in vitro* metabolism studies in rat or dog hepatic microsomes were submitted. This is considered a major deficiency. It cannot be determined if the animals chosen for toxicity studies are appropriate animal models based on pharmacokinetic parameters. The sponsor conducted a number of *in vitro* studies with human hepatocytes and liver microsomes to suggest that pralatrexate was metabolically stable. In these studies, there was no evidence of a loss of pralatrexate or formation of metabolites. No significant loss (≤ 9%) of pralatrexate was seen with microsomes expressing human cytochrome P450 isozymes CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 or monoamine oxidase (MAO-A and MAO-B). These studies effectively examined the potential oxidative metabolism and conjugation (glucuronidation, sulfation or formation of glutathione adducts) reactions mediated by hepatic enzymes. However, oxidation and conjugation reactions are uncommon reactions for methotrexate analogues[11,12,13] and unfortunately methotrexate was not used as a comparative control. The hepatic enzyme, aldehyde oxidase, generally forms 7-hydroxy derivatives of methotrexate analogues.[11,12]This reaction is unlikely to have been seen in microsome incubations. Assays using human liver cytosols with confirmed reactivity to methotrexate should have been considered.

Pralatrexate is an effective substrate of folylpolyglutamyl synthetase which forms polyglutamylated substrates. It is unusual that polyglutamyl pralatrexate derivatives were not observed in the hepatocyte incubations. Polyglutamylated methotrexate has been observed in rat and rabbit hepatocyte preparations[14,15] and polyglutamylated pralatrexate would be expected. Therefore, there are some concerns regarding the negative findings.

Deglutamylation of the pralatrexate analogues, methotrexate (10-methyl version) and edatrexate (10-ethyl version), have been shown to occur in animals and human subjects.[16, 13] Several lines of evidence suggest this deglutamyl version of antifolates is formed by bacterial enzymes in the lumen of the gut[13,16,17] and reaches the systemic circulation following intestinal absorption. The *in vitro* studies submitted by the sponsor are not designed to examine this type of metabolism, therefore highlighting the limitations of the submitted *in vitro* studies.

According to a pharmacokinetic study in rats, urinary excretion of the parent drug was less than 5% of total clearance; however, a mass balance study indicated urinary excretion of drug-related material of 20–30% of the dose. Also in a mass balance study in rats, radioactive carbon labelled (^{14})-CO_2 was released in expired air following administration of radiolabelled pralatrexate. Taken together, these data indirectly suggest some metabolism occurs in rats. Therefore, the *in vitro* studies with pralatrexate (and the negative findings

[11]Kitamura, S., K. Sugihara, K. Nakatani, S. Ohta, T. Oh-hara, S.-i. Ninomiya, C.E. Green and C.A. Tyson. (1999) Variation of hepatic methotrexate 7-hydroxylase activity in animals and humans. *Life* 48: 607–611.

[12]Johns, D.G. and D.M. Valerino. (1971) Metabolism of folate antagonists. *Ann. N. Y. Acad. Sci.* 186: 378–386.

[13]Fanucchi, M.P., J.J. Kinahan, L.L. Samuels, C. Hancock, T.-C. Chou, D. Niedzwiecki, F. Farag, P.M. Vidal, J.I. DeGraw, S.S. Sternberg, F.M. Sirotnak and C.W. Young. (1987) Toxicity, elimination, and metabolism of 10-ethyl-10-deazaaminopterin in rats and dogs. *Cancer Res.* 47: 2334–2339.

[14]Fabre, G., I. Fabre, D.A. Gewirtz and I.D. Goldman. (1985) Characteristics of the formation and membrane transport of 7-hydroxymethotrexate in freshly isolated rabbit hepatocytes. *Cancer Res.* 45: 1086–1091.

[15] Gewirtz, D.A., J.C. White, J.K. Randolph and I,D. Goldman. (1979) Formation of methotrexate polyglutamates in rat hepatocytes. *Cancer Res.* 39: 2914–2918.

[16]Kris, M.G., J.J. Kinahan, R.J. Gralla, M.P. Fanucchi, M.S. Wertheim, J.P. O'Connell, L.D. Marks, L. Williams, F. Farag, C.W. Young and F.M. Sirotnak. *Cancer Res.* 48: 5573–5579.

[17]Valerino, D.M., D.G. Johns, D.S. Zaharko and V.T. Oliverio. (1972) Studies of the metabolism of methotrexate by intestinal flora – I. *Biochem. Pharmacol.* 21: 821–831.

observed) are not considered an appropriate or adequate substitute for in vivo metabolism studies. If in the future, the sponsor conducts *in vivo* metabolism studies, pralatrexate containing the radiolabel on the pteridine portion of the compound would be more suitable than on the glutamate side as deglutamylated metabolites would be detected using this form.

Excretion of drug-related material was predominantly in the faeces in rats. The composition of excreted drug-related material was not characterised. A mass balance study was not conducted in dogs, the other animal species used in toxicity studies. Also, a mass balance study in human subjects was not submitted but it was stated that unchanged pralatrexate excreted in urine constituted 25–38% of the administered dose. Given the extensive role of the kidney in the clearance of pralatrexate, greater exposure may be seen in patients with renal impairment. In the absence of a complete data set for humans and animals, it is unclear if the chosen animal species are adequate models in terms of the extent and route of excretion.

Biliary excretion was not examined. However, both methotrexate and edatrexate undergo biliary excretion.[18,13] Biliary excretion of methotrexate occurs via the cMOAT/MRP transporter.[18] As pralatrexate is also a substrate for MRP2 and MRP3 (but not P-glycoprotein) it may also undergo biliary excretion. Enterohepatic recirculation was not examined.

Due to the lack of certain key pharmacokinetic studies (comparative plasma protein binding, comparative in vivo metabolism studies, comparative mass balance studies), the adequacy of the chosen animal species for toxicity studies cannot be determined.

Pharmacokinetic drug interactions

Pralatrexate was not metabolised by CYP450 isozymes and pralatrexate is not a substrate for P-glycoprotein or the renal transporters, OAT1, OAT3 or OCT2. Therefore, inducers or inhibitors of these enzymes and transporters are not expected to alter the plasma kinetics of pralatrexate. Pralatrexate was a substrate of MRP3, BCRP, MRP2, OATP1B1 and OATP1B3. Therefore, inducers/inhibitors of these transporters may alter the disposition of pralatrexate.

There was no clinically-relevant inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 or 3A4 activity or the activity of the transporters, P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1 or OATP1B3 in a heterologous expression system. *In vitro*, pralatrexate inhibited CYP2C19 with 100% inhibition at 50 μM (12 times the clinical C_{max} free fraction) and a Ki 545–985 μg/mL (at least 260 times the clinical C_{max} free fraction). This inhibitory activity is unlikely to have clinical relevance. Pralatrexate showed some inhibitory activity on the hepatic transporters MRP2 (IC_{50} 43.5 μM; 3.6 times the clinical C_{max}) and MRP3 (IC_{50} <0.3 μM; 0.02 times the clinical C_{max}). The inhibitory activity on MRP3, in particular, is clinically-relevant. *In vitro*, there was no clinically-relevant induction of CYP1A2, 2C19 or 3A4 activity. Therefore, pralatrexate is unlikely to alter the plasma kinetics of co-administered drugs via interactions with CYP450 isozymes or P-glycoprotein. Pralatrexate is likely to alter the kinetics of co-administered drugs that are substrates of MRP3.

[18]Masuda, M., Y. I'izuka, M. Yamazaki, R. Nishigaki, Y. Kato, K. Ni'inuma, H. Suzuki and Y. Sugiyama. (1997) Methotrexate is excreted into the bile by canalicular multispecifc organic anion transporter in rats. *Cancer Res.* 57: 3506–3510.

Toxicology

Acute toxicity

Only one single dose toxicity study, using the clinical (IV) route was submitted. This study was designed to investigate the toxicity profile of one pralatrexate batch containing high levels of impurities. Group sizes were small (1/sex) and no gross pathological examinations were conducted. All animals died or were euthanised prematurely (<6 days after dosing) due to a high degree of toxicity. Perimortem clinical signs indicated severe gastrointestinal disturbances (bloody diarrhoea and haematemesis). The lowest tested dose, which resulted in 100% mortality, was 3 mg/kg IV (60 mg/m^2; 2 times the intended clinical dose), suggesting a high order of toxicity for pralatrexate. There was no significant difference between batches.

Repeat-dose toxicity

The submitted repeat-dose toxicity package was limited. Six studies were submitted and consisted of studies in rats (up to 6 months duration) and dogs (up to 9 months duration). Only the two pivotal studies were GLP-compliant and reporting in the remaining studies was limited. Comprehensive histopathological analyses were only conducted in the pivotal studies, with only the high dose and control animals examined in the pivotal rat study. Likewise, toxicokinetic data only accompanied these pivotal studies. The duration of the pivotal studies, group sizes used and the use of both sexes are consistent with ICH guidelines. The proposed clinical route of administration (IV) was used in all studies and the clinical dosing regimen (once weekly for 6 weeks followed by a week off) was used in the pivotal studies. As stated previously, it is unknown if the chosen species (rat and dog) are suitable animal models based on pharmacodynamic and pharmacokinetic parameters. Dogs appeared to be more sensitive than rats to pralatrexate with the maximum tolerated dose (MTD) being 0.3 mg/kg/week in dogs and 25 mg/kg/week in rats. It is unknown which species is the more appropriate species, but the MTD in dogs was subclinical.

In the pivotal studies, the maximum doses used were considered acceptable, based on the reduced body weight gain and other toxicity findings in rats and up to the MTD in dogs. Exposure comparisons have been based on combined PDX-10a and PDX-10b area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) (as the diastereomers are equipotent) averaged for both sexes and all time points (excluding Day 1). Exposures in rats were several fold greater than the clinical exposure, while exposures in dogs were subclinical (Table 1). However, the exposure comparisons are difficult to interpret in the absence of comparative protein binding studies.

Table 1. Relative exposure in pivotal repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg)	$AUC_{0-\infty}$ (µg.min/mL)	Exposure ratio[#]
Rat (SD)	6 months	5	313	1.2
		10	737	2.8
		25	1804	6.7
Dog (Beagle)	9 months	0.1	15.4	0.058
		0.3	41.3	0.15
		0.7	73	0.27
Human (PTCL patients)	7 week cycle	30 mg/m^2	268	–

[#] = animal: human plasma $AUC_{0-\infty}$

Major toxicities

The toxicity profile of pralatrexate was generally consistent with other antifolates (methotrexate and pemetrexed) with the haematological and gastrointestinal systems as target organs for toxicity[19,13,20] These toxicities showed a trend to reversion after a 2–4 week treatment-free period.

Haematological effects

Anaemia (megaloblastic in rats) was consistently seen in both rats (at ≥5 mg/kg/week; ERAUC 1.2) and dogs (at ≥0.3 mg/kg/week; ERAUC 0.15). An increase in reticulocytes was also seen, probably as a compensatory mechanism. This observed anaemia is likely a result of an effect on erythropoiesis in the bone marrow and is consistent with effects for drugs of this pharmacological class.[21] Bone marrow hypocellularity was seen in both rats and dogs. Effects on white blood cell groups were only seen at higher doses; 25 mg/kg/week to rats and 0.7 mg/kg/week to dogs. Secondary to these haematological effects was splenomegaly in rats with increased haematopoiesis seen in the spleen and liver, probably a compensating effect, and thymic atrophy in dogs (3/5 females at 0.7 mg/kg/week). The haematological changes did not appear to be a dose-limiting toxicity.

Gastrointestinal effects

Gastrointestinal disturbances were seen in both rats and dogs but the latter species was clearly more sensitive. Dogs treated with ≥0.3 mg/kg/week (ERAUC 0.15) had reduced food consumption, appetite loss, lower body weight gain, emesis and diarrhoea. Gross and histopathological changes in the gastrointestinal tract consisted of red discolouration with minimal to moderate diffuse villus fusion in the duodenum, ileum and jejunum with infrequent dilation and crypt epithelial necrosis. These findings are consistent with those seen with other antifolates. The gastrointestinal effects were the dose-limiting toxicity in dogs, and likely to be dose-limiting clinically, and was the reason for premature termination of some animals (at subclinical exposures). Supplementation with vitamin B12 and oral folic acid in the pivotal dog study helped alleviate these gastrointestinal symptoms. It is noted that supplementation with folic acid and vitamin B12 is mentioned in the draft product information. Therefore, the reduced toxicity findings with supplementation are likely more clinically relevant. However, the deaths and severe toxicity seen in the absence of supplementation, suggest a cause for concern if these vitamins are not included during clinical use.

Other effects

Testes weights were significantly decreased in rats at 25 mg/kg, suggesting testicular atrophy but no histological lesions were reported for this organ. Histological examination was not conducted in an 8 week repeat dose study at higher doses (up to 75 mg/kg). Similar testicular effects have also been reported for another antifolate, pemetrexed.

Genotoxicity and carcinogenicity

The potential genotoxicity of pralatrexate was assessed in the standard battery of tests. An appropriate set of strains was used in the bacterial mutagenicity assay and adequate concentrations were tested in the in vitro assays. The maximum dose in the mouse micronucleus test resulted in bone marrow toxicity but estimated exposures were subclinical (C30 min, the only plasma concentration data in mice, 0.13 times the clinical

[19]Philips, F.S., J.B. Thiersch and F.C. Ferguson. (1950) Studies of the action of 4-aminopteroylglutamic acid and its congeners in mammals. *Ann. N. Y. Acad. Sci.* 52: 1349–1359.

[20] Pemetrexed pharmacology/toxicology review and evaluation NDA 21-462 [FDA redacted report]

[21]Kushawa, S., D.N. Tripathi, A. Vikram, P. Ramarao and G.B. Jena. (2010) Evaluation of multi-organ DNA damage by comet assay from 28 days repeated dose oral toxicity test in mice: A practical approach for test integration in regulatory toxicity testing. *Regulat. Toxicol. Pharmacol.* 58: 145–154.

C_{max}; the maximum dose was 0.3 times the clinical dose based on body surface area). Very low concentrations (up to 2.5 µg/mL) could be tested in the *in vitro* chromosome aberration assay due to cytotoxicity. Negative results were seen in all studies. However, based on its pharmacology and similar to others in its class, pralatrexate would be expected to be genotoxic. The low level of available dTTP and purine nucleotides that occurs as a result of pralatrexate (and other antifolate) treatment are expected to affect the ability of a cell to repair strand breaks arising from spontaneous DNA lesions, thereby leading to positive genotoxicity findings. Both methotrexate and pemetrexed were shown to be clastogenic. [21,22,23]Interestingly, pemetrexed was only clastogenic *in vivo* and negative results were seen in *in vitro* tests. Dosing in the mouse micronucleus test with pralatrexate may not have been adequate to assess clastogenicity *in vivo*. Therefore, based on its mode of action, pralatrexate must be considered potentially clastogenic.

No carcinogenicity studies were conducted, which is considered acceptable given the intended patient group (ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals4).

Reproductive toxicity

Reproductive toxicity studies were restricted to embryofetal development in rats and rabbits, which is considered acceptable considering the intended patient group (ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals4). Adequate animal numbers were used in the pivotal studies with dosing occurring daily during the period of organogenesis. Toxicokinetic data were collected in the pilot studies at higher doses than the main studies and given the linear pharmacokinetics of pralatrexate in rats, were used to estimate exposure at the lower doses used in the pivotal rat study. Exposure in rabbits at 0.1 mg/kg was estimated based on the AUC from the 1 mg/kg/day dose. The estimated exposures are shown in Table 2.

Table 2. Estimated relative exposure in embryofetal toxicity studies

Species	Study	Dose (mg/kg/day IV)	AUC_{last} (ng·h/mL)*	Exposure ratio#
Rat (SD)	PDX-T-07050-R	0.01	1.47	0.005
		0.03	4.42	0.016
		0.06	8.84	0.03
Rabbit (NZW)	PDX-T-07051-B	0.03	388	1.4
		0.1	ND	-
		1	1461	5
Human (PTCL patients)	7 week cycle	30 mg/m²	268	–

* PDX-10a and PDX-10b combined; # = animal:human plasma AUC

Estimated exposures in rats were subclinical, although exposures 5 fold the clinical AUC were achieved in rabbits. Similar to the general toxicity studies, the interpretation of the relative exposure data is difficult in the absence of adequate comparative pharmacology and pharmacokinetic (plasma protein binding and *in vivo* metabolism) studies.

[22]Keshava, C., N. Keshava, W.-Z. Whong, J. Nath and T.-m. Ong. (1998) Inhibition of methotrexate-induced chromosomal damage by vanillin and chlorophyllin in V79 cells. *Teratogen. Carcinogen. Mutagen.* 17: 313–326.

[23]Tweats, D.J., D. Blakey, R.H. Heflich, A. Jacobs, S.D. Jacobsen, T. Morita, T. Nohmi, M.R. O'Donovan, Y.F. Saski, T. Sofuni and R. Tice. (2007) Report of the IWGT working group on strategy/interpretation for regulatory *in vivo* tests II. Identification of *in vivo*-only positive compounds in the bone marrow micronucleus test. *Mutat. Res.* 627: 92–105.

Nonetheless, the exposures were adequate to determine that embryofetal toxicity and maternotoxicity was seen at the highest doses.

Findings in rats and rabbits were similar, with pralatrexate having a negative effect on fetal viability (increased postimplantation loss, a reduced number of viable implants and a decrease in the number of live fetuses) at ≥ 0.06 mg/kg in rats (3% of the clinical exposure) and ≥ 1 mg/kg in rabbits. Total litter loss was seen at ≥ 0.1 mg/kg/day IV in rats and ≥ 1 mg/kg in rabbits (5 times the clinical exposure). The embryofetal lethality findings are consistent with other antifolates and with effects seen in mutants with folate transport defects (Zhao et al., 2001[24]; Pemetrexed pharmacology/toxicology review and evaluation NDA 21-462 [FDA redacted report]). As with other antifolates, pralatrexate treatment to pregnant rats (0.06 mg/kg/day IV) resulted in fetal growth retardation. Some fetal malformations (hindlimb syndactyly, forelimb brachydactyly and hydrocephaly) were seen in 1 to 2 fetuses (each) from female rats treated with 0.06 mg/kg/day IV pralatrexate.

The sponsor claimed that the fetal malformations (hindlimb syndactylyl and forelimb brachydactyly) were not related to treatment. The sponsor used Historical Control Data for the Crl:CD(SD) rat (dated September 1993). The abnormalities of hindlimb syndactyly and forelimb brachydactyly are not specifically listed in these data but the sponsor claims that a number of other conditions describe or may include these malformations, such as: clubbed foot, clubbed hindfoot, micromelia, ectrodactyly and phocomelia. While these broad terms may potentially cover brachydactyly or syndactyly, they also cover other abnormalities. It is recommended that the more recent document dated March 1996, which lists "brachydactyly" and "syndactyly" specifically is a better source for Historical Control Data. According to this source of Historical Control Data, there are no incidences of either brachydactyly or syndactyly as spontaneous alterations in this strain of rat (data from 229 studies). Furthermore, limb malformations (including syndactyly) have been observed with the structurally and pharmacologically related compound, methotrexate.[25,26,27] As the malformations occurred only at the high dose (HD) with an incidence outside of the historical control data, and the nature of the malformations is consistent with those seen with other antifolates, a relationship with treatment cannot be dismissed.

Similar to other antifolates, pralatrexate must be assumed to be embryofetolethal and teratogenic. Pregnancy Category D as proposed by the sponsor seems appropriate given the intended patient group, and it is also consistent with others in the class.

Local tolerance

Dedicated local tolerance studies investigated the irritancy of pralatrexate (20 mg/mL) following intradermal and paravenous administration to rats. No drug-related effects were seen following paravenous injection. Minimal to mild erythema, without microscopic changes, was seen at intradermal injection sites. Red discolouration was seen at a number of the (IV) injection sites in the pivotal repeat-dose toxicity study in dogs, but there were no obvious drug-related histopathological findings. These findings indicate some drug-related redness may be seen at the injection site during clinical use, but drug-related tissue damage at the injection site is not predicted.

[24] Zhao R et al, 'Rescue of embryolethality in reduced folate carrier-deficient mice by maternal folic acid supplementation reveals early neonatal failure of hematopoietic organs', J. Biol Chem (2001) 27, 10224-10228

[25] Schaefer, C., P. Peters and R.K. Miller. (ed.) (2007) Drugs during pregnancy and lactation. Academic Press (Elsevier), California, USA.

[26] Jordan, R.L., J.G. Wilson and H.J. Schumacher. (1977) Embryotoxicity of the folate antagonist methotrexate in rats and rabbits. *Teratol.* 15: 73–79.

[27] Hyoun, S.C., S.G. Običan and A.R. Scialli. (2012) Teratogen update: methotrexate. *Birth Def. Res. (A)* 94: 187–207.

Impurities

Three impurities/degradants in the drug substance/drug product were specified above the relevant ICH qualification threshold. The proposed limits of these impurities/degradants have been adequately qualified by submitted toxicological data. One of the starting materials was shown to be mutagenic in an Ames test. There is, therefore, a need for the Quality evaluator to ensure that the specification for this impurity is ≤ 0.0025%.

Paediatric use

Pralatrexate is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The submitted nonclinical data were in general accordance with the ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals (ICH S9)4; however, the data set was not extensive and there were some major deficiencies.
- *In vitro*, pralatrexate inhibited the growth of various leukaemia cell lines at concentrations well below the clinical C_{max}. Tumour growth inhibition was seen in mouse xenograft models. Unfortunately, no *in vivo* efficacy studies were conducted in an appropriate animal model of peripheral T-cell lymphoma.
- No secondary pharmacology studies were submitted.
- Safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory systems. *In vivo*, CNS function in rats and respiratory and cardiovascular parameters in dogs were unaffected by pralatrexate. However, the maximum tested plasma concentrations were only marginally above the clinical C_{max} in rats and were subclinical in dogs, so no firm conclusions can be drawn from the negative findings. Effects on QT prolongation are not predicted to occur during clinical use, based on *in vitro* cardiovascular assays (hERG K+ inhibition and action potential duration in dog Purkinje fibres).
- Following IV administration, elimination half-lives were dose-dependent in rats and dogs. Protein binding in human plasma was moderate but no studies examined protein binding in the plasma of animals. The volume of distribution in rats and dogs and, for one diastereomer, in humans was greater than total body water and tissue distribution of drug-related material was high in rats. No *in vivo* metabolism studies were submitted. CYP450 enzymes do not appear to be involved in the metabolism of pralatrexate. *In vitro* metabolism studies did not investigate metabolism by enzymes (such as aldehyde oxidase) known to catalyse the metabolism of pralatrexate analogues. Excretion of drug-related material was predominantly in the faeces in rats. Mass balance studies were not performed in dogs or human subjects.
- Inducers/inhibitors of the transporters, MRP3, BCRP, MRP2, OATP1B1 and OATP1B3 may alter the disposition of pralatrexate. Pralatrexate is unlikely to alter the plasma kinetics of co-administered drugs via interactions with CYP450 isozymes or P-glycoprotein. However, pralatrexate is an inhibitor of MRP3, and thus, the kinetics of co-administered drugs that are substrates of MRP3 may be altered.
- The lowest tested dose (60 mg/m^2; 2 times the intended clinical dose) in a single dose toxicity study in dogs resulted in 100% mortality, suggesting a high order of toxicity for pralatrexate.

- Repeat-dose toxicity studies by the clinical route were conducted in rats (up to 6 months) and dogs (up to 9 months). Only the two pivotal studies were GLP-compliant and had adequate reporting. Dogs appeared to be more sensitive than rats with the MTD being 0.3 mg/kg/week in dogs and 25 mg/kg/week in rats. Exposure at the MTD in dogs was subclinical. The toxicity profile of pralatrexate was generally consistent with other antifolates with the haematological and gastrointestinal systems as target organs for toxicity. Decreased testes weights were recorded in rats at 25 mg/kg/day (animal/human exposure ratio based on AUC [ERAUC] 7).
- Megaloblastic anaemia and bone marrow toxicity were seen in both species. Dogs treated with ≥ 0.3 mg/kg/week (ERAUC 0.15) had reduced food consumption, appetite loss, lower body weight gain, emesis and diarrhoea. Gross and histopathological changes consisted of red discolouration in the gastrointestinal tract with minimal to moderate diffuse villus fusion with crypt epithelial necrosis. The gastrointestinal effects were the dose-limiting toxicity in dogs, and likely to be dose-limiting clinically, and was the reason for premature termination of some animals (at subclinical exposures). Supplementation with vitamin B12 and oral folic acid in the pivotal dog study helped alleviate these gastrointestinal symptoms. However, the deaths and severe toxicity seen in the absence of supplementation suggest a cause for concern if these vitamins are not included during clinical use.
- No signs of genotoxicity were observed in the standard battery of tests. However, based on its pharmacology and similar to others in its class, pralatrexate would be expected to be genotoxic. No carcinogenicity studies were submitted, which is considered acceptable.
- Studies on reproductive toxicity were limited to embryofetal developmental studies in rats and rabbits. As with other antifolates, pralatrexate was embryofetotoxic in both of the species with increased postimplantation loss, a reduced number of viable implants and a reduced number of live fetuses. Total litter loss was seen at ≥ 0.1 mg/kg/day IV in both species. Estimated exposures at these doses were similar to or below the clinical exposure. A teratogenic potential cannot be dismissed.
- Minimal to mild erythema was seen at injection sites following IV administration to dogs and intradermal administration to rats, but without any histopathological findings. Some drug-related redness may be seen at injection sites during clinical use but drug-related tissue damage at the injection site is not predicted.
- Three impurities/degradants in the drug substance/drug product were considered qualified at the proposed limits by the submitted toxicological data.

Conclusions and recommendation

In vitro pharmacology studies lend some support to the proposed clinical use. However, the absence of an *in vivo* efficacy study in an animal model of peripheral T-cell lymphoma means that no specific comment can be made in regard to efficacy to support the proposed indication.

The absence of secondary pharmacology studies to assess the potential for off-target site effects is considered a major deficiency.

The lack of comparative pharmacology and pharmacokinetic studies (protein binding, *in vivo* metabolism, mass balance studies) limits the interpretation of the toxicity data, that is, the ability to compare animal to human exposures and the suitability of the animals as models for toxicity assessments. The absence of such studies is considered a critical deficiency of the submitted dossier.

Because of the deficiencies outlined above, the submitted nonclinical data are not considered adequate to support registration. Should registration occur based on clinical data, the Product Information document will need to be amended.
Should a subsequent application for pralatrexate be submitted, the deficiencies in nonclinical identified in this report need to be addressed.

IV. Clinical findings

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

Introduction

Clinical rationale

The sponsor provided a detailed and well argued clinical rationale for the development of pralatrexate as a treatment for peripheral T-cell lymphoma (PTCL). Key elements of the sponsor's rationale are presented below.

Peripheral T-cell lymphoma

PTCL is a rare, heterogeneous group of aggressive non-Hodgkin's lymphomas (NHLs) with a generally poorer prognosis than their B-cell counterparts. The natural history and outcome of PTCL varies widely with various histological subtypes. Patients with anaplastic large cell lymphoma (particularly the subtype positive for anaplastic lymphoma kinase [ALK+]) have better survival that those with other subtypes, with 5-year survival being reported as high as 70%.[28] However, for other subtypes in patients characterised as high risk by the International Prognostic Index (IPI)[29], 5 year survival has been reported to be as low as 6%.[30] Several clinical studies have reported a median survival of less than 2 years for patients with T-cell neoplasms and 5 year survival rates of less than 30%.[31, 32, 33]

Currently available treatment for PTCL

Currently there are no therapies specifically approved for the treatment of PTCL. Given the aggressive clinical course and generally poor outcomes with PTCL, treatment typically involves combination chemotherapy regimens. However, the regimens used have been based largely on their utility and benefit in B-cell diseases. The majority of patients are initially treated with standard regimens of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.[34] A variety of other anthracycline-based combination therapies have also been utilised as first-line treatments.[35] The first-line

[28] Vose J, Harris NM, Harris ME et al. International Peripheral T-cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes. *J Clin Oncol* 2008; 26: 4124 – 4130.
[29] Shipp MA. Prognostic Factors in Aggressive Non-Hodgkin's Lymphoma: Who has "High-Risk" Disease. *Blood* 1994; 83(5): 1165-1173.
[30] Sonnen R, Schmidt W-P, Muller-Hermelink HK & Schmitz N. The International Prognostic Index determines the outcome of patients with nodal mature T-cell lymphomas. *Br J Haematol* 2005; 129: 366-372.
[31] Armitage JO, Weisenberger DD. New approach to classifying Non-Hodgkin's lymphoma: Clinical features of the major histologic subtypes. *J Clin Oncol* 1998; 16: 2780-2795.
[32] Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: Initial features, natural history and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. classification. *Ann Oncol* 1998; 9: 849-855.
[33] Rudiger T, Weisenberger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large cell lymphoma): results from the Non-Hodgkin's: Lymphoma Classification Project. *Ann Oncol* 2002; 12: 140-149.
[34] Savage KJ. Peripheral T-cell lymphomas. *Blood Reviews* 2007; 21: 201-216.
[35] Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a Standard Regimen (CHOP) with Three Intensive Chemotherapy Regimens for Advanced Non-Hodgkin's Lymphoma. *NEJM* 1993; 328: 1002-1006.

response rates for CHOP chemotherapy in patients with PTCL have been reported to range between 50% and 70%. However, patients often relapse soon after responding to first-line treatments.[28]

Also, there have been relatively few studies of potential therapeutic agents for use in relapsed or refractory PTCL - gemcitabine[36], denileukin diftitox[37], deoxycoformycin[38,39,40] and lenalidomide[41]. However, these studies have commonly included indolent tumour types, such as non-transformed mycosis fungoides, and none included more than 30 patients with the more aggressive PTCL subtypes.

The rationale for the clinical development of pralatrexate for use in PTCL

Pralatrexate is a 10-deazaaminopterin analogue of the widely used antifolate/antimetabolite, methotrexate that inhibits the enzyme dihydrofolate reductase (DHFR). Antifolates are well established as effective anticancer agents in the treatment of malignancies such as acute lymphoblastic leukaemia, lymphomas, and breast and lung cancer.[42]

During the preclinical development program a range of in vitro and in vivo pharmacodynamic studies of pralatrexate were performed using model systems of a variety of solid tumour types and haematological malignancies. The sponsor reported these studies demonstrated pralatrexate has a broad and potent cytotoxic activity as a single agent as well as in combination with a variety of currently used chemotherapeutic agents. Of note, *in vitro* studies in CCRF-CEM human leukaemia cells demonstrated that pralatrexate is 14 times more efficiently transported into the cells and 10 times more efficiently polyglutamated than methotrexate.[43] These results were reflected in a 30 fold improvement in cytotoxic activity of pralatrexate compared with methotrexate in these cells. Also, after 5 days of continuous in vitro exposure, pralatrexate demonstrated an 8 to 20 fold greater potency than methotrexate in 5 lymphoma cell lines. It was also reported by the sponsor that this greater efficacy was confirmed by *in vivo* animal studies that used human lymphoma xenografts. A clinical development program was then initiated to determine potential efficacy in patients with refractory Hodgkin's and non-Hodgkin's lymphomas, and solid tumours (including non small cell lung cancer, malignant pleural mesothelioma, metastatic breast cancer and transitional cell carcinoma of the urinary bladder). An early clinical study in which a variety of refractory lymphoma patients were treated with pralatrexate (PDX-02-078) found that PTCL patients responded particularly well. Consequently, in view of the strong clinical need for more effective treatments, a specific clinical development program for PTCL commenced.

[36] Sallah S, Wan JY & Nguyen NP. Treatment of refractory T-cell malignancies using gemcitabine. *Br J Haematol* 2001; 113: 185-187.

[37] Dang NH, Pro B, Hagemeister FB, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non Hodgkin lymphoma. *Br J Haematol* 2006; 136: 439-447.

[38] Dang NH, Hagemeister FB, Duvic M, et al. Pentostatin in T-non-Hodgkin's lymphomas: Efficacy and effect on CD26+ T lymphocytes. *Oncol Rep* 2003; 10: 1513-1528.

[39] Dearden C, Matutes E & Catovsky D. Deoxycoformycin in the treatment of mature T-cell leukaemias. *Br J Cancer* 1991; 64: 903-906.

[40] Mercieca J, Matutes E, Deardon C, et al. The Role of Pentostatin in the treatment of T-Cell Malignancies: Analysis of response Rates in 154 Patients According to Disease Subtype. *J Clin Oncol* 1994; 12: 2588-2593.

[41] Dueck GS, Chua N, Prasad A, et al. Activity of lenalidomide in a phase II trial for T-cell lymphoma; Report on the first 24 cases. *J Clin Oncol* 2009; 27(15S): 8524 (abstract).

[42] Walling J. From methotrexate to pemetrexed and beyond. A review of the pharmacodynamic and clinical properties of antifolates. *Invest New Drugs* 2006; 24: 37-77.

[43] Sirotnak FM, DeGraw JI, Calwell WJ & Piper JR. A new analogue of 10-deazaaminopterin with markedly enhanced curative effects against human tumor xenografts in mice. *Cancer Chemother Pharmacol* 1998; 42: 313-318.

Orphan drug designation

Pralatrexate was granted orphan drug status in Australia for the "*treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (nodal, extranodal and leukaemic/disseminated)*" in September 2011. Although the wording of the proposed indication is slightly different to the wording of the orphan drug designation, the meaning is the same.

It has been estimated that the prevalence of PTCL in Australia in 2010 was approximately 840 patients.

Guidance

The TGA-adopted EU guidelines applicable to this submission are:

- Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr), effective June 2006; and
- Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev. 3) on Confirmatory studies in Haematological Malignancies, effective 17 December 2010;
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005), effective December 2006; and
- Points to Consider on Validity and Interpretation of Meta-analyses, and One Pivotal Study (CPMP/EWP/2330/99), effective 27 March 2002.

Scope of the clinical dossier

The submission contained the following clinical information:

Clinical pharmacology:

- Pharmacodynamic (PD) data from a Phase I/II trial in lymphoma patients (PDX-02-078);
- One study examining effects of pralatrexate on QT interval (PDX-007 QTc);
- One mass balance study in advanced cancer patients (PDX-016);
- One integrated analysis of pharmacokinetic (PK) data derived from three Phase I/II clinical studies (PDX-008, PDX-007 and PDX-99-083);
- One full population PK (POPPK) analysis;
- Protocol for an ongoing open-label, Phase I study to evaluate the safety and PKs of pralatrexate in cancer patients with mild, moderate and severe renal impairment (PDX-019) that is in the earliest stages of enrolment with no data generated as yet.

Efficacy/safety studies:

- One ongoing pivotal Phase II study involving 115 patients with relapsed or refractory PTCL, of whom 111 were treated with pralatrexate (PDX-008, also known as PROPEL). Enrolment was completed and a full clinical study report (CSR) was submitted;
- One Phase I/II study involving 72 adult patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma, of whom 36 (50%) had T/natural killer (NK)-cell lymphoma (PDX-02-078 – also listed under clinical pharmacology studies above). This study was completed and a full CSR was submitted;
- Twelve Phase I/II studies (1 controlled; 11 uncontrolled) in varied stages of completion, conducted in other cancer indications and using treatment regimens other

than that proposed, and which have been evaluated only from a safety point of view in this CER:

  - pralatrexate combined with gemcitabine for treatment of relapsed of refractory lymphoproliferative malignancies (PDX-009 - enrolment ongoing, interim CSR submitted);
  - relapsed or refractory cutaneous T-cell lymphoma (PDX-010 – study ongoing, interim CSR submitted);
  - advanced solid tumours (PDX-97-006, PDX-01-014 - both studies completed, abbreviated CSRs submitted);
  - stage IIIB or IV non small cell lung cancer (PDX 99-053 - study completed, abbreviated CSR submitted; PDX-007 - study completed, full CSR submitted; PDX-012 – comparative ongoing study of PDX vs. erlotinib interim CSR submitted);
  - pralatrexate combined with a taxane (paclitaxel or docetaxel) for treatment of "advanced cancer" (PDX 99-083 - study completed, abbreviated CSR submitted);
  - unresectable malignant pleural mesothelioma (PDX-01-076- study completed, abbreviated CSR submitted);
  - advanced or metastatic relapsed transitional cell carcinoma of the urinary bladder (PDX-011 – enrolment ongoing, interim CSR submitted);
  - advanced or metastatic breast cancer (PDX-014 – enrolment ongoing, synopsis of interim CSR submitted); and
  - relapsed or refractory B-cell NHL (PDX-015 – enrolment ongoing, synopsis of interim CSR submitted).

- Details (but no data) were also submitted for two confirmatory Phase III, controlled clinical studies pertinent to the proposed indication of PTCL:
  - PDX-017 (Protocol submitted) – a randomised, study of sequential pralatrexate vs. observation in patients with previously undiagnosed PTCL who achieved a response after completing at least 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based treatment. The study is open to enrolment in the US, UK and Australia with a target of 549 patients randomised 2:1 to pralatrexate or observation, with follow-up through 7 years post-randomisation.
  - PDX-3501 (Protocol synopsis submitted) – a randomised, comparative, open-label, study of pralatrexate vs. treatment of physician's choice in patients who have progressed after at least one prior therapy for PTCL. This study is currently in the planning and initiation stages. It is planned that 148 adult patients will be enrolled to obtain 108 events (deaths). Subjects will be randomised in a 1:1.
- an Integrated Summary of Safety Tables which comprised a collation of summary safety tables for the various treatment populations in the clinical development program and a document titled Updated Safety Tables, Listings and Narratives that presented supplemental tables and listings generated in response to the European Day 120 List of Questions;
- Postmarketing safety data from seven post-marketing safety update reports (PSURs) covering the period September 2009 to June 2011; and
- 348 literature references.

Evaluator's comment:

The clinical submission also contained 21 *in vitro s*tudies that provided data pertinent to human PKs:

- 4 plasma protein binding studies – PDX-K-06029-U, PDX-K-07043-U, PDX-K-07049-U and PDX-K-08066-U
- 11 studies of hepatic metabolism and cytochrome P450 (CYP450) interaction - PDX-K-06028-U, PDX-K-07030-U, PDX-K-07032-U, PDX-K-07033-U, PDX-K-07044-U, PDX-K-08060-U, PDX-K-08061-U, PDX-K-08062-U, PDX-K-06019-U, PDX-K-11089-U and PDX-K-11090-U; and
- 6 studies of pralatrexate interaction with transporter systems - PDX-K-08059-U, PDX-K-10078-U, PDX-K-10080-U, PDX-K-10081-U, PDX-K-11084-U, PDX-K-11088-U.

The TGA Delegate advised that these studies would be evaluated by the preclinical evaluator and did not require review within this clinical evaluation report (CER).

Study PDX-02-078 and 3 studies sponsored by the MSKCC (PDX-01-014, PDX-97-006, and PDX-99-053) also generated PK data. The PK data from studies PDX-01-014, PDX-97-006, and PDX-99-053 were not included in the sponsor's integrated or POPPK analyses because the HPLC-based pralatrexate assay was not fully validated and did not analyse the individual diastereomers. Likewise, the data from these studies have not been included in the main analysis of the PKs of pralatrexate in this CER. Study PDX-02-078 was not included in the sponsor's pooled analyses because it used a non-chiral, dihydrofolate reductase based assay (normally used for methotrexate and validated for pralatrexate). PK data from study PDX-02-078 were used for population PD modelling of the relationship between the grade of mucositis and total pralatrexate AUC in that study and have been reviewed in this CER as part of the assessment of the PDs of pralatrexate.

Paediatric data

The submission did not include paediatric data. However, the sponsor has, appropriately, developed a paediatric investigation plan (PIP) for pralatrexate. The indications targeted by the PIP are the treatment of paediatric patients aged 3 to 18 years with:

- first relapse or primary refractory mature B-cell NHL;
- peripheral T-cell lymphoma (nodal, other extranodal and leukaemic disseminated); and
- lymphoblastic NHL.

The plan proposes to use 2 pharmaceutical forms; solution for infusion for intravenous use and a solution for injection for intrathecal use (to be developed).

Three clinical studies are proposed in the PIP:

- an open-label multicentre, single arm, dose-finding study to evaluate the safety, pharmacokinetics and activity of high-dose pralatrexate with and without leucovorin in 36 patients aged 3 -18 years with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), T-cell lymphoblastic lymphoma (T-LBL) or precursor B-cell lymphoblastic lymphoma (pB-LBL);
- a randomised, controlled, centrally blinded non-inferiority study comparing the pharmacodynamics, efficacy and safety of high-dose pralatrexate with leucovorin rescue in at least 260 patients aged 3 -18 years with relapsed or primary refractory DLBCL, ALCL, T-LBL or pB-LBL; and
- an open-label dose-finding study to evaluate the pharmacokinetics, safety and maximum tolerated dose (MTD) in patients aged 3 -18 years with CNS involvement of

DLBCL, ALCL, T-LBL or pB-LBL previously treated with one or more systemic treatment that included intrathecal methotrexate.

The PIP was approved by the European Medicines Agency (EMA) in November 2010 but the completion of the studies was deferred until 2021.

Also, waivers were granted on the grounds that clinical studies could not be expected to be of significant therapeutic benefit to or fulfil a need for the following paediatric populations:

- Hodgkin's lymphoma; and
- Children aged less than 3 years with first relapse or primary refractory mature B-cell non- Hodgkin lymphoma, treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic disseminated) and treatment of lymphoblastic non-Hodgkin lymphoma.

Good clinical practice

The PTCL clinical study program for pralatrexate comprised 2 efficacy/safety studies – PDX-02-078 and PDX-008, both of which were conducted in compliance with the principles of ICH Good Clinical Practice (GCP) and the Declaration of Helsinki. The supporting studies undertaken in various other indications were also conducted according to GCP principles and the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the available data relating to each pharmacokinetic (PK) topic and the location of each study summary.

Table 3. Submitted pharmacokinetic data

PK topic	Subtopic	Study ID	*
Healthy adults	General PK	Nil studies	
Target population §	Single dose PKs	PDX-008	
	Multiple dosing PKs	PDX-008	
Other oncology populations	Single dose PKs	PDX-007	
		PDX-99-083	
		PDX-016	*
	Multiple dosing PKs	PDX-99-083	
Special populations	Hepatic impairment	Nil studies	
	Renal impairment	Nil studies	
	Neonates/infants/children/adolescents	Nil studies	
	Elderly	Nil studies	

PK topic	Subtopic	Study ID	*
Genetic/gender PKs		Nil studies	
Drug-drug interaction studies		Nil studies	
Population PK analyses	Healthy subjects Oncology population Integrated PK report Population PK analysis	Nil analyses - POPPK	 * *

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Pralatrexate is a cytotoxic agent, so no studies have been performed in healthy volunteers.

PK data for the two pralatrexate diastereomers PDX-10a and PDX-10b were provided from two Phase I clinical studies (PDX-007 [patients with advanced non-small cell lung cancer] and PDX-99-083 [patients with advanced cancer]) and one Phase II study (PDX-008 [patients with relapsed or refractory PTCL]). Of note, only study PDX-008 included patients from the target population (i.e. the proposed indication of PTCL). These PK data were generated with a fully validated LC/MS/MS assay method that quantified both pralatrexate diastereomers.

In addition, the sponsor provided two pooled PK analyses as follows:

- a pooled, non-compartmental, integrated covariate analysis, comprising all patients from studies PDX-008, -007 and -99-083 who completed a dense PK plasma sampling schedule over 24 - 72 hours (n=54); and
- a POPPK analysis population was performed to estimate population parameters for pralatrexate diastereomers PDX-10a and PDX-10b, including typical values, inter-individual variation, and residual variability after administration of pralatrexate to cancer patients, and to estimate the effects of individual-specific covariate factors that may be predictive of the unexplained random variability in pralatrexate PK. This analysis included all patients from the 3 studies with PK data, including those with sparse PK plasma sampling (n=154).

The contributions of the three clinical studies to these analyses were as follows:

PDX-008 (n=109)

- 10 of the 109 patients provided full plasma PK data and 8 provided urine PK data for the integrated, non-compartmental PK analysis;
- The remaining 99 patients provided sparse plasma PK data;
- All 109 patients provided PK data for the POPPK analysis.

PDX-007 (n=39)

- 38 of the 39 patients provided full plasma PK data and 33 provided urine PK data for the integrated, non-compartmental PK analysis;
- All 39 patients provided PK data for the POPPK analysis.

PDX-99-083 (n=51)

- 6 patients provided full PK data for both non-compartmental PK and POPPK analyses.

Evaluator's overall conclusions on pharmacokinetics

Pralatrexate Solution for Infusion contains pralatrexate as an approximately 1:1 racemic mixture of the *S*- and *R*- configurations at C10 (known as PDX-10a and PDX-10b, respectively). The PKs of these pralatrexate diastereomers have been reasonably well characterised using data from subsets of oncology patients who underwent full plasma profiling in 3 efficacy/safety studies. It has been demonstrated that pralatrexate has stereo-selective pharmacokinetics, the biological cause of which is unknown.

Following IV push over 3-5 minutes there is a multiphasic decline in the levels of both pralatrexate diastereomers, characterised by an initial rapid fall in plasma concentrations followed by a slow terminal phase. The decline of both diastereomers occurs in parallel, with a 2 fold higher plasma exposure of PDX-10b compared with PDX-10a. Approximately one third of pralatrexate clearance is via renal excretion and two thirds by non-renal mechanisms. Of note, a mass balance study is yet to be completed. It is apparent however, that both renal and non-renal clearance of PDX-10b is approximately 50% lower than that of PDX-10a. Also, the volume of distribution indicates that pralatrexate has moderate tissue distribution (with PDX-10a > PDX-10b).

The rapid drop in plasma concentrations is thought to reflect clearance of pralatrexate from the body by renal and non-renal mechanisms, whilst the slow terminal phase could reflect return of pralatrexate from intracellular compartments, after deglutamylation, and/or enterohepatic recycling of drug following biliary excretion into the gastrointestinal tract. The slow terminal phase does not appear to contribute significantly to total exposure to the drug. Furthermore, there was no accumulation of pralatrexate with repeated dosing over the course of a single cycle of treatment in a small number of patients with PTCL. Of note, the effect of repeat dosing beyond the first cycle of treatment was assessed in only one patient who exhibited an increase in both AUC and C_{max} at dose 12 relative to dose 1. The potential for accumulation of pralatrexate in third space compartments (such as pleural effusion and ascites) has not been assessed.

It appears that the PKs of pralatrexate are linear over doses ranging from 30 to 325mg/m^2. However, it is clear from the data submitted that there is considerable inter-individual variability in the PKs of pralatrexate and the observation of linearity needs to be interpreted in that light. It must also be remembered that the data were generated in sick patients taking multiple medications, so it is not entirely clear what the sources of variability in the PKs are. For example, 3 patients were noted to have very low urinary excretion of pralatrexate, despite normal renal function and urinary volumes during the collection period. This raises the possibility of pharmacogenetic issues and/or drug-drug interactions. Specific pharmacogenetic studies of pralatrexate have not been conducted. Furthermore, formal drug-drug interaction studies have not been performed. A population PK analysis of potential drug-drug interactions did not show any significant correlation between pralatrexate and the concomitant administration of diuretics, non-steroidal anti-inflammatory drugs (NSAIDS), sulfonamides and penicillin. However, these analyses were limited by less than optimal data and the sponsor considered that the analyses had not excluded the possibility of underlying drug-drug interactions. Given the significant contribution of renal excretion to the overall clearance of pralatrexate, and the fact that pralatrexate undergoes net renal tubular secretion, the sponsor has appropriately included precautionary statements about the concomitant administration of drugs that affect glomerular filtration and/or renal tubular secretion, and nephrotoxic drugs.

In vitro studies have indicated that, at the doses intended for use in patients with PTCL, there would be low potential for clinically significant drug-drug interactions on the basis of protein

binding displacement, or as a result of interactions affecting the CYP450 system and P-gp transporter system. However, pralatrexate is a potent inhibitor of MRP3 at concentrations readily achieved with the recommended dosing regimen for PTCL. Although pralatrexate is intended for use as a single agent, this finding nevertheless has significance with respect to the potential effects of other oncologic agents, such as etoposide, teniposide, and methotrexate, which are thought to rely on this liver transporter. The proposed PI appropriately includes a cautionary statement about the co-administration of such agents.

No specific population studies have been conducted and, otherwise, only limited PK data are available for such populations. The sponsor's population PK analysis identified creatinine clearance as a covariate for pralatrexate clearance. In particular, it was estimated that the clearances of PDX-10a and PDX-10b would decrease by 21% and 24%, respectively, in a patient with a creatinine clearance of 30 mL/min. After accounting for renal function, age was not a relevant covariate. These findings are appropriately reflected in the proposed PI which cautions that the administration of pralatrexate to patients with moderate to severe renal impairment should be done carefully and that renal function and adverse events should be monitored closely. The draft PI also advises that whilst no dosage adjustments are recommended for age *per se*, age-related decline in renal function could potentially lead to reduced clearance.

Neither the non-compartmental, integrated covariate analysis nor the POPPK analysis identified total bilirubin or transaminase levels as significant covariates for pralatrexate clearance. However, given that 60-70% of pralatrexate is eliminated by non-renal clearance, and that this is likely to be largely via hepatobiliary excretion, a risk for increased exposure in patients with hepatic impairment cannot be excluded. This is adequately reflected in the proposed PI.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 4. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Biomarker–tumour response	PDX-008	
	relationship	PDX-007	
		PDX-99-083	
Secondary Pharmacology	Effect on QT interval	PDX-007 (QT_c)	*
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	Nil studies	
	Effect of age	Nil studies	
PD Interactions	Nil studies		
Population PD and PK-	Healthy subjects	Nil analyses	

PD Topic	Subtopic	Study ID	*
PD analyses	Target population (PTCL) §	PDX-008	
	Oncology (NHL and Hodgkin's lymphoma) patients	PDX-02-078 (Mould et al., 2009)	

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacodynamics

Pralatrexate is an antineoplastic folate analogue that exerts its activity through competitive inhibition of the enzyme dihydrofolate reductase (DHFR) in the folic acid metabolic pathway. As with the PK data, PD data were collected from subsets of oncology patients enrolled in clinical efficacy/safety studies. These data were supplemented by population PK/PD analyses.

No formal analysis of exposure-response for efficacy was performed for patients with PTCL. Also, attempts to examine gene expression of key targets in the folate metabolic pathway as potential markers of tumour response were unsuccessful. Of note, the protocols for some of the more recently initiated studies have allowed for an exploratory evaluation for the presence of a single nucleotide polymorphism for the RFC-1 biomarker in peripheral blood (PDX-010, PDX-011). Interestingly, it has been recently demonstrated that acquired resistance to pralatrexate in human cancer cell lines was associated with decreased RFC-1 expression, in contrast to resistance to methotrexate which was correlated with increased DHFR expression.[44]

Correlations between total pralatrexate AUC and mucosal inflammation were observed in several population PK-PD models, including modelling based on data from patients with PTCL in the pivotal study (PDX-008), and the supportive study in haematological malignancies (PDX-02-078). Results from study PDX-02-078 also suggested there is a correlation between baseline serum methylmalonic acid levels and the risk of developing mucositis. Patients with high levels of methylmalonic and homocysteine who experienced mucositis, who consecutively began vitamin supplementation with folic acid and vitamin B12 and corrected their abnormally high levels of MMA and Hcy, did not experience recurrence of their mucositis on re-challenge with pralatrexate. The latter observation provided evidence for the routine supplementation with vitamin B12 and folic acid with pralatrexate administration.

Effects of pralatrexate on the QT interval were examined in a small sub-study of PDX-007 in patients with non-small cell lung cancer. Given the study population, it was not possible to conduct the study to the standard normally required to examine QT interval effects of new chemical entities. In particular, the study was not placebo controlled and not of a cross over design, such that possible diurnal effects were not accounted for. Although pralatrexate at doses 190mg/m^2 and 230 mg/m^2 were associated with a repolarisation delay in their respective cohorts, when data for all cohorts were combined, the mean changes in QTcF at end-injection, and at 1, 3 and 6 hours post injection and the upper

[44] Serova M, Bieche I, Sabin MP, et al. Single agent and combination studies of pralatrexate and molecular correlates of sensitivity. *British Journal of Cancer* 2011; **104(2)**: 272-80.

bounds of the corresponding 90% CIs were all below the thresholds of 5 ms and 10 ms, respectively. Furthermore, none of the categorical thresholds for concern (that is, QTc interval > 500 ms or increase in QTc interval > 30 m) were observed in any patient. No correlation was observed between either the maximum or mean change in QTcF and pralatrexate exposure (C_{max} and AUC). Of note, the doses used and, consequently the maximum pralatrexate concentrations achieved in the study far exceeded those expected for the target PTCL population. Thus, this evaluator agrees with the sponsor that pralatrexate is unlikely to markedly delay cardiac repolarisation in PTCL patients treated with doses ≤ 30 mg/m^2.

Dosage selection for the pivotal study

The following summary of results from Phase I and II studies gives an understanding of how the dosage regimen for pralatrexate changed over the course of the clinical development program, ultimately leading to dose selection for the pivotal study in patients with PTCL (study PDX-008).

The first Phase I study, PDX-97-006, was conducted exclusively in patients with NSCLC, who had been previously treated with a median of 2 prior chemotherapy regimens. Initially, pralatrexate was administered IV at a dose of 30mg/m2 weekly for 3 weeks out of 4 weeks without vitamin B12/ folate supplementation (n=6). Stomatitis requiring dose reduction and/or delay in the first cycle occurred in 4 of 6 patients treated at the initial dose level (30 mg/m2), making this an intolerable dose of pralatrexate given on this schedule. The dose escalation scheme was modified consequently to a biweekly schedule (every 2 weeks in a 4-week cycle) and dose escalation proceeded from 15 to 30 mg/m^2 and then proceeded in approximately 10 mg/m^2 increments to 170 mg/m^2. Both patients treated at the 170 mg/m^2 dose developed dose limiting toxicities and the 150 mg/m^2 cohort was expanded with 6 additional patients enrolled. Only 1 of these 6 patients developed a dose limiting toxicity. Thus, the 150 mg/m^2 dose was defined as the maximum tolerated dose of the study and the dose recommended for Phase II studies.

A subsequent single-agent Phase II study in patients with Stage IIIB or IV NSCLC (PDX-99-053) used pralatrexate at doses up to 150mg/m^2 every 2 weeks of a 4-week cycle with folate supplementation for patients experiencing significant stomatitis. This study yielded results that were considered to be consistent with the activity of other single agents in this setting (4 partial responses out of 39 treated patients).

Study PDX-02-078 was the first study of pralatrexate as a single agent in patients with relapsed or refractory haematological malignancies (Hodgkin's lymphoma and NHL) and began as a Phase II study using a slightly lower initial starting dose (135 mg/m^2 every other week) than identified in the NSCLC Phase II study because of the greater number of prior therapies these patients had received compared to patients with NSCLC. The protocol was subsequently amended to include inter-patient dose escalation (a Phase I activity) to determine the optimal dose and schedule of pralatrexate, using an initial dose of 30 mg/m^2 weekly for 3 weeks of a 4 week cycle, with subsequent increases in the number of consecutive doses (from 3 to 6 doses) and dose amount (15 mg/m^2 increments). These changes were in response to a higher than anticipated incidence of Grade 3 or 4 stomatitis in patients with Hcy and MMA concentrations > 10 µmol/L and >200 nmol/L, respectively, and because many patients with palpable disease had responses that were suggestive of cytokine failure (that is, they experienced marked reductions in their disease by Day 7 but these grew back to baseline levels by Day 15). Importantly, the study was also amended to include a requirement for normalised Hcy and MMA levels or a 10 day course of folic acid/vitamin B12 repletion prior to study entry. The overall response rate for the study was 33%, including a response rate of 60% among 20 evaluable patients with PTCL. In the Phase I part of the study, 5 dose-limiting toxicities and 2 patient deaths were experienced with 45 mg/m^2 weekly for 6 doses/7 week cycle

treatment group (n = 11 treated patients). The maximum tolerated dose was declared as the dose level below this, that is, 30 mg/m^2 weekly for 6 doses/7 week cycle and it was used in the Phase II part of the study and also used subsequently in Study PDX-008 along with routine supplementation of vitamin B12 and folic acid.

Efficacy

Evaluator's conclusions on clinical efficacy for PTCL

The TGA-adopted EU *Guideline on the Evaluation of Anticancer Medicinal Products in Man*[45] requires that the benefit-risk profile of new chemotherapeutic agents be established with data from well conducted Phase III randomised controlled trials (RCT). However, the guideline also recognises that for rare tumours or very narrow indications it may not be possible to recruit a sufficiently large number of patients to conduct an appropriately powered RCT, in which case the best options available are to either conduct a small randomised reference controlled study and/or conduct a within-patient time-to-progression analysis in which the time-to-progression on last prior therapy is compared to time-to-progression on the new agent.

In this submission, the efficacy of pralatrexate was evaluated in a single non-randomised, open-label Phase II study comprising 109 evaluable patients with relapsed or refractory PTCL. The primary endpoint was based on objective response rate (an accepted marker of activity for cytotoxic agents) determined by independent, adjudicated central review using IWC criteria.[46] The study used standardised treatment conditions and data collection; the study was compliant with GCP requirements; and data were collected prospectively. Key results from the study were:

- an overall response rate (complete response (CR)+ CR unconfirmed (Cru)+ partial response (PR)) of 29% (95% CI: 21 – 39%) by central review;
- 25% of pralatrexate responders had no evidence of response to their most recent prior therapy;
- 19% of pralatrexate responders had no evidence of response to any prior therapy;
- a median duration of response of 306 days (95% CI: 3.4 – NE) or 10.1 months by central review;
- a median progression-free survival of 106 days (95% CI: 51 – 146) or 3.5 months by central review; and
- a median overall survival of 14.5 months (95% CI: 10.6 – 22.5 months) by central review. The most recently available data indicates a survival rate of 56% (95% confidence interval (CI) 46 – 65%) at 1 year; 35% (95% CI 26 – 44%) at 2 years; 29% (95% CI 19 – 39%) at 3 years; and 25% (95% CI 15 – 37%) at 4 years.

Whilst the absence of a randomised controlled design is understandable in the context of PTCL being a rare disease for which there are no standard treatment protocols, there are consequential limitations of the data:

[45] http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

[46] The International Workshop Criteria (IWC) are used for response assessment of non-Hodgkin's lymphoma (NHL).1 These criteria are primarily based on computed tomography (CT), although bone marrow biopsy (BMB) and clinical and biochemical information are also taken into account when assigning a final response designation.

The absence of blinding

This introduces the potential for investigator bias and reader bias in radiographic evaluation which impacts on the reliability and reproducibility of results. Furthermore, diagnosis of PTCL and subtype can be difficult and not always readily reproducible. However, this bias was mitigated as far as possible by requiring that tumour diagnosis, eligibility for study entry and tumour responses be assessed and adjudicated centrally and independently using IWC, with blinding to the investigator's assessment.

The absence of a comparator

The most obvious consequence of the lack of a comparator is that it is difficult to determine whether the magnitude and duration of responses observed in this study will confer a meaningful clinical benefit in the target population. This compromises the reliability of the study and is particularly important given that the response rate was driven largely by partial responses (20/32; 62.5% of responders), and the fact that 9/20 (45%) of partial responders subsequently experienced either disease progression and/or death within 100 days of achieving the response. The revised IWC response criteria for malignant lymphoma recognises that response rates do not necessarily influence other outcomes (especially survival) in lymphoma, but the presence of durable complete responses may be important.[47] In this regard, it is evident from the data that enduring complete responses were seen amongst a subset of patients who achieved a response, including patients with extranodal disease at the time of enrolment in the study. In addition, treatment with pralatrexate allowed bridging to transplant and subsequent ongoing prolonged response in a number of patients.

Other issues of note in the pivotal study were:

Heterogeneity of the study population

There were more than 8 tumour subtypes among patients enrolled in the study. At face value this limits to some extent the internal validity of the study, for different subtypes may have different prognoses and different natural histories following diagnosis. However, it must be remembered that this was a heavily pre-treated, relapsed and refractory population (with a median number of systemic treatments of 3; range 1 to 12). The fact that these patients had experienced disease progression following use of other available treatments would have largely offset the heterogeneity in tumour subtype. For example, it is known that anaplastic large cell lymphoma (ALCL) has a higher chance of cure with initial therapy than other subtypes, especially if it is ALK +ve. However, once this tumour subtype relapses it behaves like the other aggressive PTCL subtypes, with a poor prognosis. Also, where heterogeneity in a study population exists, it is desirable to see similar benefits in all subgroups; in this regard the response amongst patients with angioimmunoblastic subtype was notably lower than with other subtypes. However, the study was not designed to study specific subgroups and the number of patients with angioimmunoblastic PTCL was quite small, so caution is needed in interpreting this result. With regard to the external validity of the study, the proportions of the different subtypes and the demographics of the patients were generally representative of the target population. The prevalence of the various histopathological subtypes reflects that previously reported for patients with PTCL[48,49] with the majority in the safety analysis set

[47] Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25(5)**: 579-86.

[48] Evens AM & Gartenhaus RB. Treatment of T-cell Non-Hodgkin's Lymphoma. *Curr Treat Options Oncol* 2004;**5**: 289-303.

[49] Rodriguez-Abreu D, Filho VB & Zucca E. Peripheral T-cell lymphomas, unspecified (or not otherwise specified): a review. *Haematol Oncol* 2008; **26**: 8-20.

(n = 59, 53%) having PTCL-unspecified according to central review assessment. Furthermore, there were no centre effects evident, so the results can be readily extrapolated to the target population. It is also of some note that the sample size of 100+ patients represents a substantial study in this indication.

Use of PET

The incorporation of PET in the central assessment of response decreased overall response rate (from 29 to 26%) but increased the complete response rate (from 10% to 14%). At the time the study was initiated PET assessment was included as an exploratory analysis. Issues with the use of PET include variability amongst readers and equipment; the potential for false-positive findings due to rebound thymic hyperplasia, infection, inflammation; the potential for false negative findings as a consequence of variable FDG avidity among tumour subtypes and/or variable resolution of PET equipment; and confounding by concomitant administration of haemopoietic growth factors that can cause diffusely increased bone marrow uptake.[47] Thus, the PET based response data should be treated with some caution.

The analysis of efficacy was supplemented by the sponsor with a series of retrospective analyses of data from the pivotal study that employed patients as their own controls, as well as historical controls. Notwithstanding the well-known limitations of retrospective analyses and use of historical controls, the results suggest (but are not conclusive) that pralatrexate may:

- stabilise or reverse an observed trend toward poorer outcomes with progressive lines of treatment in PTCL;
- yield response rates and PFS as good as or better than the immediate prior therapy; and
- alter the natural course of the disease and provide improved survival compared with the currently available treatment options for patients with relapsed/refractory PTCL.

Overall, although the data are less than ideal (which was openly acknowledged by the sponsor), this evaluator is satisfied that the data from the study and its associated retrospective analyses show that pralatrexate has activity against PTCL and that the results are sufficiently compelling to conclude that an acceptable level of efficacy has been demonstrated.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study in PTCL – PDX-008

In the pivotal efficacy study of pralatrexate in PTCL (PDX-008), the following safety data were collected:

General adverse events (AEs) were assessed by asking patients to report all problems, complaints, or symptoms at each study visit during treatment with pralatrexate, as well as at the early termination visit (if applicable), the safety follow-up visit 35 (±5) days after the last dose of pralatrexate, and each routine follow up visit (every 3 months ± 2 weeks) thereafter. AEs regardless of causality were recorded for all patients on-study and events considered possibly, probably, or definitely related to pralatrexate therapy were recorded during the post-treatment period. AEs were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Selected AEs of interest included mucosal inflammation, neutropaenia, leucopaenia, thrombocytopenia, anaemia, abnormalities of liver function (increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), oedema, dry mouth, dyspepsia, odynophagia, pruritus, anorexia and hypokalaemia. These events were summarised and presented separately using the single lowest-level preferred term in order to present each event uniformly. Haematological and mucosal toxicities were closely monitored and formed the basis for pralatrexate dosage reductions.

Laboratory assessments were performed at screening, during the treatment phase of the study (weeks 2-6 of each cycle), at the early termination visit (if applicable), and at the post-treatment safety follow-up visit. All results were converted to standard international (SI) units and flagged as low or high compared to reference normal ranges, markedly low or high (≥ Grade 2 per NCI CTCAE Version 3.0), or clinically significant (≥ Grade 2 per NCI CTCAE Version 3.0, and a shift of ≥ 1 grade from the baseline value). Haematology parameters comprised haemoglobin, haematocrit, white blood cells (WBCs), neutrophils and platelets. Clinical chemistry assessments comprised total bilirubin, creatinine, ALT, AST, and lactate dehydrogenase (LDH levels. Of note, alkaline phosphatase and electrolyte levels were not routinely measured.

Physical examinations were performed at baseline and changes recorded on week 3 of cycle 1, within 7 days of the first dose of each subsequent cycle, at the early termination visit (if applicable), and at the post-treatment safety follow-up visit. An ECG was performed within 21 days prior to the projected start of pralatrexate administration and thereafter if clinically indicated at anytime during the study.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Supporting efficacy study for PTCL – PDX-02-078

In the supporting study of single agent pralatrexate in haematological malignancies, including patients with PTCL (PDX-02-078), the following safety data were collected:

General adverse event data were obtained at every study visit in cycle 1, during week 1 of subsequent cycles, and when the patient went off treatment with pralatrexate. The data were elicited, recorded and assessed in the same manner as used in the pivotal study. Haematological and mucosal toxicities were closely monitored and formed the basis for pralatrexate dosage reductions.

Laboratory assessments were performed at screening, during the treatment phase of the study, and once the patient went off study treatment. Standard haematology parameters were collected at the screening visit; Cycle 1, Dose 1, Cycle 1, Dose 2 (Week 3); subsequent cycles (both Weeks 1 and 3); and once the patient went off study treatment. A broader range of clinical chemistry was assessed in this study compared to the pivotal efficacy study. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, creatinine, glucose, LDH, potassium, total protein, AST, ALT, and sodium levels were assessed at the screening visit and once the patient went off study treatment. Also, a "basal" metabolic panel and hepatic function panel, including tests for sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST/ALT, and total bilirubin, were collected at the screening visit; Cycle 1, Dose 1 and Dose 2; subsequent cycles Dose 1 only; and once the patient went off study treatment. The laboratory results were analysed and presented in the same manner as used in the pivotal study.

A physical examination was performed at the same time as for general adverse events.

This study was initiated in 2002 at MSKCC under an investigator-sponsored IND application. The IND for pralatrexate was transferred to Allos Therapeutics, Inc. from MSKCC in early Feb 2003. Prior to the transfer of the IND to Allos, MSKCC established a process of entering the patient data for PDX 02-078 directly into the MSKCC's research

database without the use of CRFs. After the IND transfer, prospective monitoring of the study was undertaken in accordance with ICH GCP requirements by a contract research organisation on behalf of Allos. An intensive monitoring activity was undertaken in 2008 whereby baseline and safety data collected by the MSKCC were entered on CRFs, reviewed, and entered into the Allos database. These data included (but were not limited to) pralatrexate administration/adjustments, AEs and laboratory results. Laboratory values were not recollected and monitored as part of this process because laboratory data collection in the MSKCC's research database was automated. Overall, it can be accepted that the baseline and the safety information presented in the study report were based on rigorously collected and audited data, with the exception of laboratory values.

Other studies evaluated for safety but not efficacy

The studies undertaken in malignancies other than PTCL were of two general types:

Eight studies (PDX-007, PDX-009, PDX-010, PDX-011, PDX-012, PDX-014, PDX-015 and PDX-016) were initiated by the sponsor and conducted in accordance with GCP requirements. These studies can be considered to provide high quality supportive safety information.

The various elements of monitoring of safety (i.e. AEs, laboratory parameters and physical examination) appeared to be standardised across all the Allos-initiated studies, although the timing was tailored to suit the treatment regimen of each particular study. Therefore, the broad information outlined for the pivotal study (PDX-008) also applies to this group of studies. In study PDX-007 a subset of patients underwent more intensive electrocardiogram (ECG) monitoring as part of the sub-study that examined the effect of pralatrexate on QT interval.

Five studies were initiated by the MSKCC prior to in-licensing of pralatrexate by Allos (PDX-97-006, PDX-99-053, PDX-99-083, PDX-01-014 and PDX-01-076). The data from these studies have not been subjective to rigorous, extensive auditing by the sponsor. Consequently, the quality of the data could not be assured, but the sponsor considered they still provided relevant "contributive" information. This has been accepted by this evaluator.

Somewhat scant descriptions of the monitoring of safety (that is, AEs, laboratory parameters and physical examination) were provided in the abbreviated clinical study reports and protocols submitted for this group of studies. The timing of assessments was tailored to the treatment regimen of the study. Haematology and clinical chemistry testing, physical examination and AE assessments were monitored closely in patients (usually on a weekly basis) following the initiation of treatment, with the frequency reduced during latter doses and cycles. AEs were graded using the NCI Common Toxicity criteria (CTC), Version 2.0. However it was not clear from the information provided as to how the AEs were elicited (that is, whether by direct questioning of patients or reported spontaneously by patients). Also, the laboratory parameters measured across these studies were not standardised. For example, haemoglobin levels were measured across all 5 studies, but leucocyte counts were measured in only 3 studies and platelet counts in 2 studies.

Patient exposure

This evaluator has summarised the study types, indications and treatment combinations under which patients received pralatrexate in Table 5, below. The data are presented by each safety population (1 to 6) and include studies PDX-014 and PDX-015 as at 17 February 2010. As noted above, patients with PTCL were in 3 the populations and these are highlighted by shading. It can be appreciated that:

- As at 17 February 2010, 578 cancer patients had received treatment with pralatrexate;
- 451 patients received pralatrexate as a single agent and 127 patients received pralatrexate in combination with other chemotherapeutic agents that included taxanes (docetaxel and paclitaxel), gemcitabine and probenecid.
- 294 patients had a lymphoproliferative malignancy and, of these, 232 received pralatrexate as a single agent and 62 had received pralatrexate in combination with gemcitabine.
- Specifically with regard to patients with PTCL, 171 patients had been treated and of these 147 received pralatrexate as a single agent (111 patients in study PDX-008 and 36 in study PDX-02-078) and 24 received pralatrexate in combination with gemcitabine as part of a study involving patients with relapsed or refractory lymphoproliferative malignancies (PDX-009).
- 75 patients received pralatrexate without any vitamin supplementation (in PDX-97-006 and the early stages of studies PDX-99-083 and PDX-02-078) and a further 39 received folate supplementation only in the event of "significant" stomatitis (PDX-99-053). With regard to study PDX-02-078, in the first 2 versions of the protocol no patients received vitamin supplementation as part of the study procedures; however, with the second amendment of the protocol (early 2003), patients with ≥ grade 2 stomatitis received vitamin supplementation. After the third amendment of the protocol (mid 2004), all patients received vitamin supplementation. Consequently, 4 patients with PTCL in that study did not receive any vitamin supplementation.

Table 5. Exposure to pralatrexate (PDX) in clinical studies as at 17 February 2010. Table and table footer split across two pages.

Safety population/study/indication		Controlled	Uncontrolled					Total PDX
		PDX only	PDX only	PDX in combination				
				PDX + DOC	PDX + PAC	PDX + GEM	PDX + PRO	Total
Population 1								
PDX-008	*PTCL*		111					111
Subtotal			***111***					***111***
Population 2								
PDX-02-078	*PTCL*		32					32
			4*					4*
	HL, BCNHL		29					29
			7*					7*
PDX-010	*CTCL*		48					48
PDX-015	*BCNHL*		1					1
Subtotal			***121***					***121***
Population 3								
PDX-007	*NSCLC*		39					39
PDX-011	*TCC*		16					16
PDX-012	*NSCLC*	73^						73
PDX-014	*Breast cancer*		1					1
Subtotal		***73***	***56***					***129***
Population 4								
PDX-009	*PTCL*					24		24	24
	HL, BCNHL					38		38	38
Subtotal						***62***		***62***	***62***
Population 5								
PDX-97-006	*NSCLC*		33*						33*
PDX-99-053	*NSCLC*		39#						39#
PDX-99-083	*Mostly lung cancer*			34				34	34
				8*,$	6*,$			14*,$	14*,$
PDX-01-014	*Mostly lung & colon cancer*						17*	17*	17*
PDX-01-076	*Malignant pleural mesothelioma*		16						16
Subtotal			***88***	***42***	***6***		***17***	***17***	***153***
Population 6								
PDX-01	*Mass balance@*		2						2
Subtotal			***2***						***2***
TOTAL		**73**	**378**	**42**	**6**	**62**	**17**	**127**	**578**

* denotes patients who did not receive vitamin B12/folate supplementation. # patients only received folate supplementation for significant stomatitis $ vitamin B12/folate supplementation was implemented part way through study. 14/48 patients did not receive vitamins. @ patients with solid tumour or NHL (to date only solid tumour patients enrolled). ^ the comparator in study PDX-012 is erlotinib.PTCL = peripheral T-cell lymphoma; BCNHL = B-cell non Hodgkin's lymphoma; HL = Hodgkin's lymphoma; CTCL = cutaneous T-cell lymphoma; NSCLC = non-small cell lung cancer; TCC = transitional cell carcinoma; PDX = pralatrexate; DOC = docetaxel; PAC = paclitaxel; GEM = gemcitabine; PRO = probenecid

As at 31 January 2011, 519 patients had received pralatrexate as a single agent and 172 patients received pralatrexate in combination with other chemotherapeutic agents. A total of 355 patients had a lymphoproliferative malignancy and, of these, 248 received pralatrexate as a single agent and 107 had received pralatrexate in combination with gemcitabine. It was not reported how many of the additional 45 patients enrolled in study PDX-009 had PTCL.

Exposure according to dose and duration

The dose of pralatrexate administered to patients across all studies ranged from 10-325 mg/m^2. A variety of administration schedules were also used, ranging from a dose every 2 weeks to weekly doses for 2 of 3 weeks, 3 of 4 weeks, and 6 of 7 weeks (each with 1 week of rest).

In the pivotal study, all 111 patients with PTCL initially received pralatrexate 30 mg/m^2 weekly for 6 weeks in a 7-week cycle. The majority of patients (n = 76; 68%) remained at this dose for the duration of their treatment. The pralatrexate dose was reduced from 30 mg/m2 to 20 mg/m^2 in the remaining 35 (32%) patients. Dose reduction below 20 mg/m^2 was not allowed. The median duration of treatment was 70 days (mean 121; range: 1-696). The median number of cycles administered to patients (based on cycles initiated) was 2.0 (mean 3.0; range: 1-14). Nineteen (17%) patients were treated with pralatrexate for ≥ 6 months and 10 (9%) patients were treated for ≥ 1 year, including 13 (12%) patients treated for ≥ 6 months and 5 (4.5%) patients treated for ≥ 1 year without a dose reduction at any time. A total of 76 (38%) patients required at least one dose omission mainly due to mucositis (n=46; 41%), thrombocytopaenia (n=28; 25%) and neutropaenia (n=14; 13%). Thirty five (32%) patients required a dose reduction and, once again, the most common cause was mucositis (n=25; 23%). Other reasons for dose reduction occurring in 2 or more patients were liver function abnormality, thrombocytopaenia and fatigue (all n=2; 2%). The median total dose of pralatrexate administered over the course of treatment was 208 mg/m^2 (mean: 384; range: 27-2109).

Twenty seven patients in Study PDX-02-078 were treated with the same dose and schedule as in PDX-008, although doses were reduced to 15mg/m^2 rather than 20mg/m^2 in the event of specified toxicities. These patients received a median of 11 doses (range 1-45), with a median duration of treatment of 85 days (mean: 135; range: 1-715). The numbers of doses received by patients in PDX-02-078 were higher than for PDX-008 because the study had been ongoing for significantly longer, with some patients remaining on treatment for long periods. Nineteen of these patients had PTCL. The dose and regimen for patients in the other lymphoproliferative malignancy studies (PDX-010, and the subset of PDX-02-078 patients who did not receive the same dose/schedule as PDX-008) varied by cohort. Treatment doses ranged from 10-270 mg/m^2, and the schedule ranged from once every 2 weeks to weekly for 6 weeks of treatment followed by 1 week of rest. The median number of doses received was 4 for PDX-02-078 and 8 for PDX-010 and the median total dose received was 543 mg/m^2 (range 45-2804) in study PDX-02-078 and 96 mg/m^2 (range 20-1306) in PDX-010. The median duration of treatment range was 36 days (range 1-567) in PDX-02-078 and 71 days (range 7-708) in PDX-010.

The doses in the solid tumour studies (PDX-007, PDX-011, PDX-012) were higher (up to 325 mg/m^2) and given less frequently (every 2 weeks) than those in the

lymphoproliferative studies. The range of the median number of doses received was 3-6. The range of the median duration of treatment was 36-44 days. Overall, the cumulative doses were higher and the duration of treatment shorter in these solid tumour studies compared with the lymphoproliferative malignancies studies.

Evaluator's overall conclusions on clinical safety

The safety profile and risks of pralatrexate have been well elucidated and the main identified risks of pralatrexate can be considered to be related a pharmacological class effect. Although a relatively small proportion of the patients in the pralatrexate clinical development program were from the target population (PTCL) and received pralatrexate as a single agent administered via the proposed regimen, it is clear that the safety profile seen in those patients was generally consistent with that observed across a number of patient populations studied to date. These data have been supplemented by post marketing data generated over a 21 month period during which an estimated additional 985 to 1725 patients with PTCL were exposed to the drug.

The toxicities identified in the clinical development program include:

Mucositis: Mucosal inflammation was observed in 71% patients with PTCL in the pivotal study, with the majority of cases being oral. Serious reactions occurred in 6% patients. In this study 18% patients had Grade 3 toxicity and 4% had Grade 4 toxicity and the median time to onset of ≥ Grade 3 mucosal inflammation was 19 days. Mucosal inflammation/stomatitis was the most common reason for dose reduction and treatment withdrawal in the pivotal study and across the clinical development program.

Myelotoxicity: Thrombocytopaenia, neutropaenia and anaemia were very common toxicities which, along with mucositis, accounted for the majority of treatment-related withdrawals of pralatrexate therapy, dose omissions and dose-reductions. In the pivotal study the median time to onset of thrombocytopenia ≥ Grade 3 was 15 days, with a median duration of 16 days. The median time to onset of ≥ Grade 3 neutropaenia was slightly longer at 22 days, but the median duration was only 8 days which possibly reflects the use of the colony stimulating factors G-CSF and GM-CSF.

Dermatological toxicity: 36% patients with PTCL in the pivotal study and 36% patients across the clinical development program experienced treatment-related dermatological AEs. Grade 3-5 treatment-related dermatological events occurred in 5% PTCL patients in the pivotal study and 3% patients overall. There have been 24 clinically significant dermatological reactions reported in clinical trials and post marketing usage. Severe dermatological reactions occur early in treatment and generally after the first dose. The majority of the important dermatological reactions resolved with supportive therapy and some patients were able to continue pralatrexate therapy. However, of most concern were 6 reactions (skin necrosis, skin exfoliation; skin ulceration; TEN; and bullous eruptions) that occurred after only one or two doses and were associated with a fatal outcome. The fatal and/or life-threatening reactions occurred in patients with extensive skin disease and were generally associated with mucositis, neutropaenia, and/or infection and included extensive skin involvement of the underlying lymphoma. Compromise in the integrity of the skin may also pre-dispose patients to infection and subsequent sepsis in the setting of myelosuppression.

Abnormal liver function: Pralatrexate appears to have a mild potential for hepatotoxicity. In the pivotal study clinically significant abnormalities of AST and ALT were reported in 17% and 16% patients with PTCL, respectively. 9% of patients had clinically significant derangements in total bilirubin levels. Most abnormalities of hepatic function were managed successfully with dose reduction, although in almost all cases the dose reduction was undertaken primarily for other concomitant toxicities such as thrombocytopaenia,

neutropaenia or mucositis. Overall, very few patients had pralatrexate doses omitted or reduced, or therapy withdrawn primarily as a result of adverse effects on liver function.

Infection: Susceptibility to infections such as pneumonia, sepsis and herpes zoster in patients receiving pralatrexate may be increased as the result of myelosuppression (neutropaenia, pancytopaenia), previous chemotherapies and the underlying disease process. In the pivotal study 6% PTCL patients experienced ≥ Grade 3 sepsis; 3% had ≥ Grade 3 herpes zoster infection; and 5% had ≥ Grade 3 pneumonia.

Tumour lysis syndrome: Tumour lysis syndrome was observed in 4 patients with lymphoproliferative disorders across the clinical development program, including 3 patients with PTCL. All cases of tumour lysis syndrome were of grade 3-4 severity, with onset between 3-51 days following initial administration of pralatrexate and duration ranging from 7-14 days. Two patients discontinued pralatrexate because of this ADR. Patients with bulky disease and those responding to pralatrexate may be at higher risk of developing tumour lysis syndrome. Patients experiencing tumour lysis may develop metabolic complications including hyperuricaemia and acute renal failure. The risk of tumour lysis syndrome can be managed through the prophylactic use of allopurinol and ensuring patients are adequately hydrated.

Pulmonary toxicity: Pulmonary toxicity is a known class effect of antifolate therapies. There have been 9 reports of pneumonitis (including 3 Grade 3 cases when pralatrexate was used in combination with gemcitabine) and 1 report of radiation pneumonitis. All but one case of pneumonitis occurred in patients with a lymphoproliferative malignancy (mainly PTCL). Two cases occurred in the pivotal study and were both considered to be treatment-related.

Personal communication between this evaluator and 2 medical officers at the TGA who have haematological expertise confirmed the safety profile for pralatrexate, including dermatological safety, is consistent with the experience of other antifolate cytotoxics available in Australia.

The safety of pralatrexate has not been evaluated in patients with moderate to severe renal impairment or patients with hepatic impairment. Renal toxicity has been identified as a potential risk in the Risk Management Plan.

Also, although there does not seem to be a difference in the overall frequency of AEs between older and younger patients, greater sensitivity of some older individuals cannot be ruled out, especially for the development of mucosal inflammation and thrombocytopaenia. Any propensity for increased frequency of these events in older patients can be mitigated by careful monitoring and dosage adjustment during treatment. Creatinine clearance was found to be a clinically important predictor (representing both renal function and age dependencies) of pralatrexate exposure and therefore potential for adverse effect in population pharmacokinetic modelling. Whilst no dosage adjustments are recommended for age per se, age-related decline in renal function is highlighted appropriately in the proposed PI.

List of questions

Efficacy

Please provide a justification for the censoring of patients 029 and 043 from the Kaplan-Meier analysis of duration of response in Study PDX-008 on the basis of “other cancer treatment”. It appears that for two patients the commencement of another cancer treatment occurred after documentation of the event of interest, that is, progression of disease, as follows:

Patient 1(duration of response censored at 306 days): this patient received pralatrexate for 442 days, having first achieved a response of CR on 1 October 2007. Pralatrexate was last administered on 25 July 2008. On 8 August 2008 treatment was permanently discontinued and the primary reason was documented to be "Other, Progression of Disease". The therapy received subsequent to pralatrexate was combination liposomal doxorubicin and gemcitabine, commenced on 22 August 2008, that is, after the documented date of disease progression;

Patient 2 (duration of response censored at 1 day): this patient received pralatrexate for 246 days and the patient first achieved a response of PR on 4 March 2008. Pralatrexate was last administered on 4 March 2008. On 11 March 2008 treatment was permanently discontinued and the primary reason was documented to be "Other, Progression of Disease". The therapy received subsequent to pralatrexate was methotrexate, aracytine and hydrocortisone, commenced on 13 August 2008, that is, after the documented date of disease progression.

Sponsor's response

Patients were assessed for response and progression by both Investigator assessments and Central Independent Review using IWC criteria. While investigator assessments were used for patient treatment decisions, Central Independent Review was used as the primary efficacy analyses in study PDX-008.

Patient 1

Patient 1 had the last tumour response assessment by the independent review on 1 August 2008 with response of CR (IWC). This was the first assessment of a response (CR) for this patient by independent review. There were not any subsequent scans performed for this patient. Thus, the duration of response by IWC using the independent review was censored at the date of the subsequent therapy according to the statistical analysis plan. On the other hand, this patient had a PD by the investigator on 8 August 2008 and hence the duration of response was not censored, it was considered a PD at the date of the PD for the Kaplan-Meier analysis of duration of response by investigator.

Patient 2

Patient 2 had the last tumour response assessment by the independent review on 4 March 2008 with response of PR (IWC). This was the first assessment of a response (PR) for this patient by independent review. The patient had SD for the previous two assessments. Thus, the duration of response by IWC using the independent review was censored at the date of the subsequent therapy according to the statistical analysis plan. On the other hand, this patient had a PD by the investigator on 11 March 2008 and hence, the duration of response was not censored, it was considered a PD at the date of the PD for the Kaplan-Meier analysis of duration of response by investigator.

Clinical summary and conclusions

First Round Benefit-Risk Balance

First round assessment of benefits

The benefits of pralatrexate in the proposed usage are:

- an overall response rate (CR+CRu+PR) of 29% (95% CI: 21 – 39%) by independent adjudicated (central) review;
- 25% of pralatrexate responders had no evidence of response to their most recent prior therapy;

- 19% of pralatrexate responders had no evidence of response to any prior therapy;
- a median duration of response of 306 days (95% CI: 3.4 – NE) or 10.1 months by central review;
- a median progression-free survival of 106 days (95% CI: 51 – 146) or 3.5 months by central review; and
- a median overall survival of 14.5 months (95% CI: 10.6 – 22.5 months) by central review. The most recently available data indicates a survival rate of 56% (95% CI 46-65%) at 1 year; 35% (95% CI 26–44%) at 2 years; 29% (95% CI 19–39%) at 3 years; and 25% (95% CI 15 – 37%) at 4 years.

There is evidence that suggests that pralatrexate may also:

- stabilise or reverse an observed trend toward poorer outcomes with progressive lines of treatment in PTCL;
- yield response rates and PFS as good as or better than the immediate prior therapy; and
- alter the natural course of the disease and provide improved survival compared with the currently available treatment options for patients with relapsed/refractory PTCL.

However, these latter benefits have been identified from underpowered retrospective analyses.

First round assessment of risks

The risks of pralatrexate in the proposed usage are typical of those associated with antifolate cytotoxic agents and include:

- Mucositis;
- Myelotoxicity;
- Serious skin reactions, including fatal reactions;
- Pulmonary toxicity;
- Infection;
- Abnormal liver function; and
- Tumour lysis syndrome.

First round assessment of benefit-risk balance

The benefit-risk balance of pralatrexate, given the proposed usage, was considered favourable.

In reaching this conclusion this evaluator notes the limitations of the single pivotal study and the difficulty in reaching firm conclusions about the clinical benefit of pralatrexate in the target population. However, it appears that pralatrexate offers durable responses and meaningful survival benefits in a subset of patients with relapsed or refractory PTCL who otherwise have a dismal prognosis from an aggressive disease that has no approved or standard care. On balance, these benefits outweigh the risks associated with the adverse effects of pralatrexate on folate metabolism in that the toxicities are by and large manageable with careful monitoring, vitamin supplementation and dose modification, all of which are emphasised in the proposed product information.

First round recommendation regarding authorisation

The application for the registration of pralatrexate (Folotyn) for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and

leukaemic/disseminated) who have progressed after at least one prior therapy should be approved.

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

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluations (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified in the sponsor's submission is as shown in Table 6.

Table 6. Summary of Ongoing Safety Concerns

Important Identified Risks	Mucosal inflammation
	Thrombocytopenia
	Neutropenia
	Anaemia
	Dermatological reactions (Skin exfoliation, ulceration, TEN)
	Liver function tests abnormal (increases in ALT, AST, ALP)
	Infection (sepsis, herpes zoster, pneumonia)
	Tumour lysis syndrome
	Dyspnoea
Important Potential Risks	*Use in patients with hepatic impairment
	Use in patients with renal impairment (Renal effects)
	*Thromboembolic events
	Drug-drug interactions (NSAIDs, sulfamethoxazole/ trimethoprim/ probenecid)
	*Overdose
	*Third space fluid accumulation
Important Missing Information	*Limited safety data
	*Ethnicity
	*Genetic polymorphisms
	Exposure during pregnancy
	Exposure during lactation
	Paediatric exposure
	#Off-label use

OPR reviewer's comment:

The following changes to the list of identified safety concerns were noted in Section 2.2 *Summary of Safety Concern and Planned Pharmacovigilance Actions* of the RMP Version 2 (as compared to RMP Version 1):

- *Addition of 4 Important potential risks: 'Use in patients with hepatic impairment', 'Thromboembolic events', 'Overdose' and 'Third space fluid accumulation',
- *Addition of 3 areas of Important missing information: 'Limited safety data', 'Ethnicity' and 'Genetic polymorphisms',
- #Re-classification of Important potential risk to Missing information: "Off-label use'.

However, these changes have not been fully updated throughout the RMP document aside from Table 2.1 of the RMP Version 2. It is recommended that the sponsor provides an assurance that this information will be fully and appropriately incorporated in the next available update to the RMP.

In addition, the clinical evaluator has recommended that the Important identified risk 'dyspnoea' should be broadened to capture pneumonitis and pulmonary toxicity. The sponsor was asked to provide information on this issue in a TGA request for information. In brief, the sponsor proposed to use 'dyspnoea' as a broad term to capture respiratory-related adverse events including the potential development of pneumonitis and pulmonary toxicity in their response. This is considered acceptable provided that the sponsor can assure that the appropriate information will be collected for evaluation and the results reported in the Periodic Safety Update Reports (PSURs) as appropriate.

Pursuant to the evaluation of the nonclinical and clinical aspects of the safety specifications of the RMP; the above summary of the Ongoing Safety Concerns is considered acceptable at this stage, with the provisions as discussed above.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Section 2.1.1 *Pharmacovigilance System* of the RMP states that "*a pharmacovigilance system will be introduced.... in accordance with current TGA requirements for pharmacovigilance practices and in accordance with the latest version of Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use*".

Routine pharmacovigilance (PV) activities are proposed for all Ongoing Safety Concerns. In addition, the following are proposed (as stated in Table 2.1 *Planned Actions for Safety Concerns* of the RMP Version 2):

- Enhanced PV (6 questionnaires):
  - Mucosal Inflammation questionnaire for important identified risk 'mucosal inflammation',
  - Haematological questionnaire for important identified risks 'thrombocytopenia', 'neutropenia', and 'anaemia',
  - Dermatological questionnaire for important identified risk 'dermatological reactions',
  - Hepatoxicity questionnaire for important identified risk 'liver function tests abnormal',
  - Thromboembolic events questionnaire for important potential risk 'thromboembolic events',
  - Overdose questionnaire for important potential risk 'overdose',
  - In each of the above questionnaire except for the overdose questionnaire, information on conditions such as effusion will also be requested - for important potential risk 'third space fluid accumulation',

- A postmarket Phase III multicentre, randomised trial (PDX-017):
  - for Important potential risks 'use in patients with hepatic impairment', 'use in patients with renal impairment', and important missing information 'limited safety data', 'ethnicity

  - A search on the Clinicaltrials.gov website (with most recent update verified by the trial sponsoring company in August 2012) indicated that:
    - this study is entitled 'Study of Pralatrexate versus Observation Following CHOP-based Chemotherapy in Previously Undiagnosed Peripheral T-cell Lymphoma Patients',
    - this study commenced in August 2011 with participants being recruited at this stage.
    - study sites include locations in the US, Australia and UK.
    - primary study outcomes: progression-free survival and overall survival of up to 7 years post-randomisation.
    - targeted enrolment: 549 patients
    - estimated primary completion date: December 2016.
- An ongoing mass balance study (PDX-016) for important potential risks 'use in patients with hepatic impairment' and 'use in patients with renal impairment'
- Post-approval confirmatory comparative study for important potential risks 'use in patients with hepatic impairment' and 'use in patients with renal impairment', and important missing information 'limited safety data'
- PTCL registry ("COMPLETE" registry) for important potential risks 'use in patients with hepatic impairment' and 'use in patients with renal impairment', and important missing information 'limited safety data'
- Renal impairment study (PDX-019) for important potential risk 'use in patients with renal impairment'
- Development programme planned for Japan for important missing information 'ethnicity'
- Testing of tumour samples (from post-approval confirmatory comparative study and Japanese study) for expression of components of the folate metabolism pathway using quantitative PCR assay for important missing information 'genetic polymorphisms'.
- Targeted follow-up by named-patient request for important missing information 'paediatric exposure' and 'off-label use'
- European Union (EU) Paediatric Investigation Plan:
  - Nonclinical studies:
    - *In vitro* polyglutamation and retention study,
    - Development of a PDX polyglutamation assay,
    - Preclinical toxicity, toxicokinetic and fertility in juvenile rates,
    - Preclinical pharmacokinetic and intrathecal toxicology study in non-human primates,
  - Clinical studies:
    - Open-label, single-arm, non-controlled, dose-finding accelerated dose escalation/titration, pharmacokinetic, toxicity, sequential combination (PDX-021)
    - Randomised (1:1), active controlled, multi-centre, open-label, centrally-blinded assessment, stratified randomisation, non-inferiority study,
    - Open-label, single-arm, dose-finding/3+3 dose escalation, non-controlled study.

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

A copy of each of the 6 questionnaires was provided by the sponsor with the cover letter dated 20 January 2012 for: mucosal inflammation, haematological events, dermatological reactions, thromboembolic events, overdose and hepatoxicity. These questionnaires are also included in Annex 1 of the RMP Version 2. The sponsor has also clarified in the cover letter dated 20 January 2012 that "*questionnaires will be completed for individual cases when the relevant adverse events are spontaneously reported. The completed questionnaires will be forwarded to the European Drug Safety and Pharmacovigilance Centre, and the information will be collated into Periodic Safety Update Reports for the purpose of signal detection*". The information requested in all of these questionnaires include details of the adverse events, patient's medical and medication history, and reports of any relevant laboratory and/or pathology test results, which are appropriate to monitor and assess these events.

Study PDX-017 entitled 'A *Multi-Center, Randomized, Phase 3 Study of Sequential Pralatrexate versus Observation in Patients with Previously Undiagnosed Peripheral T-cell Lymphoma Who Have Not Progressed Following Initial Treatment with CHOP-based Chemotherapy*' has been initiated to assess efficacy as the primary study outcome. It is stated in Section 2.1.2 *Additional Pharmacovigilance Activities and Action Plan of the Risk Management Plan* that this study "i*s expected to provide comprehensive additional safety data*". However, no further information is provided to detail which safety concerns will be specifically assessed as part of the design of the study. Further information was sought from the sponsor. The following response to the TGA request for information (with the cover letter dated 17 August 2012) was provided by the sponsor:

"*The applicant believes that PDX-017 is an important study that will inform the treatment of patients with PTCL and therefore will be used as an additional study as part of the wider development plan.*

PDX-017 is a single agent study in PTCL patients where pralatrexate is compared to no-treatment. Being a single agent controlled study and enrolling patients who have an earlier stage of disease and therefore are inherently not as ill and less heavily pretreated, one can evaluate the safety profile in a controlled manner and also with a longer duration of treatment.

A summary table of planned pharmacovigilance actions relating to PDX-017 is presented below for each safety concern. The table in Section 2.2 of the RMP (2.2 Summary of Safety Concern and Planned Pharmacovigilance Actions) has been updated with more comprehensive information."

There is no objection to the sponsor's plan to include Study PDX-017 as an additional pharmacovigilance activity for the abovementioned safety concerns. However, it is recommended that the sponsor provides assurance that a copy of the synopsis for Study PDX-017 will be included in the next available update to the RMP.

The below three studies are also proposed as additional pharmacovigilance activities in Table 2.1 Planned Actions for Safety Concerns of the RMP Version 2 but no further information is provided:

- Post-approval confirmatory comparative study for Important potential risks '*Use in patients with hepatic impairment*' and '*Use in patients with renal impairment*', and Important missing information '*Limited safety data*'
- PTCL registry ("COMPLETE" registry) for Important potential risks '*Use in patients with hepatic impairment*' and '*Use in patients with renal impairment*', and Important missing information '*Limited safety data*'.

- Renal impairment study (PDX-019) for Important potential risk '*Use in patients with renal impairment*'.

It is recommended that they sponsor provides a brief draft outline (or study synopsis, if available) for each of the above three studies to inform how each study is adequately designed to monitor the relevant safety concerns, including but not limited to information on the study duration, targeted enrolment and expected milestone(s) for interim (if any) and final study reports.

It is also recommended that the sponsor confirms if the outstanding studies listed as post-marketing commitments requested by the US FDA (Section 3 of this report) are the same as those proposed in Table 2.1 *Planned Actions for Safety Concerns* of the RMP Version 2, or if not, to briefly comment on their applicability to the Australian RMP implementation.

Routine pharmacovigilance is proposed for the Important identified risk dyspnoea. As dyspnoea may be a result of various causes including treatment-related respiratory adverse events such as pneumonitis and pulmonary toxicity, it is unclear whether routine pharmacovigilance activity will be sufficient to fully monitor, evaluate and characterise this broadly term risk, or to provide specific information on treatment-related respiratory events including pneumonitis and pulmonary toxicity. Further information was sought from the sponsor. The sponsor provided a response to a TGA request for information (with the cover letter dated 17 August 2012), with the following conclusion:

"Conclusion

Dyspnoea

A detailed summary of dyspnoea SAEs of special interest identified from the PDS-008 study have been presented. Six SAEs involving 5 patients included 4 events of dyspnoea considered not related to pralatrexate, 1 event of exertional dyspnoea considered possibly related to pralatrexate but likely due to lymphomatous infiltration of the lung, and 1 event of pneumonitis with suspicion of hypersensitivity aetiology.....Multiple potential causes of dyspnoea are recognised in this patient population including underlying disease, infectious sources, and drug toxicity.

The intent of capturing Dyspnoea as an important identified risk in the RMP for pralatrexate is to provide a broad-based means to monitor for the potential development of pulmonary toxicity with pralatrexate. The RMP has been revised to more accurately describe potential mechanisms for dyspnoea, including pulmonary toxicity."

Pneumonitis

The association of interstitial pneumonitis with the administration of methotrexate is also well recognised and monitoring and investigation via pharmacovigilance activities will continue. A statement has been added to the Risk Management Plan regarding the potential risk for the development of interstitial pneumonitis with clinical manifestations of dyspnoea, pulmonary infiltrates or respiratory insufficiency following the administration of pralatrexate. Additional pharmacovigilance will include close monitoring and re-evaluation in the next PSUR."

It is still unclear whether the use of routine pharmacovigilance activity in absence of any other planned or targeted follow-up activities, will allow for a systematic and uniform collection of sufficiently detailed information, to enable further characterisation and evaluation of the broad range of respiratory-related adverse events that may be captured under the broad term 'dyspnoea'. This will be important to distinguish between the potential risks of respiratory-related adverse events associated with drug toxicity versus underlying disease or infections. It is recommended that the sponsor proposes a strategy (for example, targeted follow-up questionnaire) to ensure that the broad range of respiratory-related adverse events including pneumonitis and pulmonary toxicity, that are

intended to be captured under the term 'dyspnoea' will be appropriately and adequately monitored, characterised and reported in the PSURs as appropriate.

Risk minimisation activities

Routine risk minimisation activities, as in the provision of relevant precautionary statements/warnings or adverse events information in the Australian PI and Consumer Medicine Information (CMI), are proposed for all safety concerns.

OPR reviewer's comments:

In regard to the proposed routine risk minimisation activities, the draft Australian PI is considered satisfactory at this stage, however, it is recommended to the Delegate considers the merit of requesting the following statements included under the *Special populations; Renal Impairment* section of the updated draft PI (August 2012 version) to be similarly included under the *Dosage and Administration; Patients with renal impairment* section of the PI:

"*Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly. Avoid FOLYTN use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk*."

In regard to the proposed routine risk minimisation activities, the draft Australian CMI is considered satisfactory at this stage.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

- the implementation of the Australian RMP Version 2 (dated July 2012) and any subsequent versions, is imposed as a condition of registration under the provisions as stated below.

If this submission was approved, it was recommended that the Delegate considers requesting the sponsor to address the following items post registration:

- To propose a strategy (for example, targeted follow-up questionnaire) to ensure that the broad range of respiratory-related adverse events including pneumonitis and pulmonary toxicity, that are intended to be captured under the term 'dyspnoea' will be appropriately and adequately monitored and characterised as part of the pharmacovigilance activity, unless an acceptable justification can be provided. This proposal should be provided to the OPR prior to marketing. The sponsor should also provide assurance that pneumonitis and pulmonary toxicity will be monitored and evaluated as part of the pharmacovigilance commitment, and reported via the PSURs as appropriate.
- To provide a properly updated RMP within 6 months post-registration that will address the deficiencies identified in this report, namely the following or otherwise provide an acceptable justification for why it is not relevant:

To ensure that the updates to the safety concerns and pharmacovigilance plan in Table 2.1 *Planned Actions for Safety Concerns* of the RMP Version 2 are fully and appropriately incorporated in the RMP.

  - To include the synopsis for Study PDX-017 with the RMP.

- To amend the information presented in Table 1.1 *Summary of the Safety Concerns Investigated in Nonclinical Studies and the Relevance of the Findings to Human Usage* of the RMP, as requested by the nonclinical evaluator.
- The following three studies are proposed as additional pharmacovigilance activities in Table 2.1 *Planned Actions for Safety Concerns* of the RMP Version 2 but no further information is provided. A brief draft outline (or study synopsis, if available) for these studies should be provided to inform how each study is adequately designed to monitor the relevant safety concerns, including but not limited to information on the study duration, targeted enrolment and expected milestone(s) for interim (if any) and final study reports:
  - Post-approval confirmatory comparative study for Important potential risks 'U*se in patients with hepatic impairment*' and '*Use in patients with renal impairment*', and Important missing information '*Limited safety data*',
  - PTCL registry ("COMPLETE" registry) for Important potential risks '*Use in patients with hepatic impairment*' and '*Use in patients with renal impairment*' and Important missing information '*Limited safety data*',
  - Renal impairment study (PDX-019) for Important potential risk '*Use in patients with renal impairment*'.

- To confirm if the outstanding studies listed as post-marketing commitments requested by the US FDA are the same as those proposed in Table 2.1 P*lanned Actions for Safety Concerns* of the RMP Version 2, or if not, to briefly comment on their applicability to the Australian RMP implementation.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There are no outstanding issues with chemistry and quality control aspects of the products.

Nonclinical

The non clinical evaluator did *not* support registration, due to deficiencies in the nonclinical submission (absence of secondary pharmacology studies; lack of comparative plasma protein binding/*in vivo* metabolism/mass balance studies that may have allowed a determination about the adequacy of dog and rat species for toxicology studies).

Regarding metabolism, hepatic enzyme aldehyde oxidase generally forms 7-hydroxy derivatives of methotrexate analogues. This reaction would not have been seen in the *in vitro* human hepatocyte/liver microsome studies conducted: "*assays using human liver cytosols with confirmed reactivity to methotrexate should have been considered*". This does not mean the enzyme is necessarily important for pralatrexate metabolism. Other limitations of the submitted *in vitro* studies were identified.

Clinical

The sponsor's response to clinical evaluation report 1 (CER1) has been taken into account in this Overview.

The most influential study was a Phase II, uncontrolled, open-label study of 111 patients with relapsed or refractory PTCL (PDX-008, also known as PROPEL).

Additional evidence came from Study PDX-02-078, a Phase I/II study that included 72 patients, of whom 36 had T- or NK- cell lymphoma.

The overall clinical development program comprised 15 completed or ongoing clinical studies across a range of different cancer types, conducted over a period of 13 years.

Pharmacokinetics (PK)

Key features are:

- pralatrexate is a diastereomeric mixture; there is unexplained 2 fold higher plasma exposure of diastereomer PDX-10b than PDX-10a;
- lack of accumulation to dose 6 of cycle 1; scant data about accumulation over cycles;
- linear dose-concentration relationship in the dose range 30-325 mg/m2;
- volumes of distribution of 105L for PDX-10a and 37L for PDX-10b in Study PDX-008, suggesting moderate tissue distribution;
- evidence from nonclinical studies that pralatrexate does not cross the blood-brain barrier;
- moderate (67-86%) binding to human plasma proteins such as albumin;
- no significant metabolism by hepatic CYP450 isoenzymes or glucuronidases and lack of identified metabolites;
- majority of clearance via hepatobiliary excretion; one mechanism proposed by the sponsor was OATP1B1-mediated sinusoidal hepatocellular uptake then MRP2/BCRP mediated canalicular efflux[50];
- 30% contribution to elimination by renal excretion; net renal tubular secretion, that is, via active transport;
- absence of a reliable mass-balance study
- identification of 3 patients with very low urinary excretion despite normal renal function, all using concomitant proton-pump inhibitors;
- lack of PK studies in hepatic and renal impairment;
- lack of clinical drug-drug interaction studies;
- low risk of inhibition or induction of CYP450 enzymes and P-gp;
- potent inhibition of MRP3
- etoposide, teniposide and methotrexate rely on this liver membrane efflux transporter;
- in patients with Dubin-Johnson syndrome, MRP3 compensates for defective or absent MRP2; theoretically inhibition of MRP3 might in this situation lead to accumulation of bilirubin in hepatocytes
- pralatrexate is a substrate for OATP1B1 and OATP1B3 and BCRP, MRP2 and MRP3
- co-administration with probenecid results in delayed pralatrexate clearance (CER1), probably due to inhibition of renal tubular secretion and inhibition of cellular efflux

[50] Page 35 of EPAR accessed 25.10.2012 at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002096/WC500129886.pdf

Pharmacodynamics (PD)

Key findings are mentioned under efficacy and safety below.

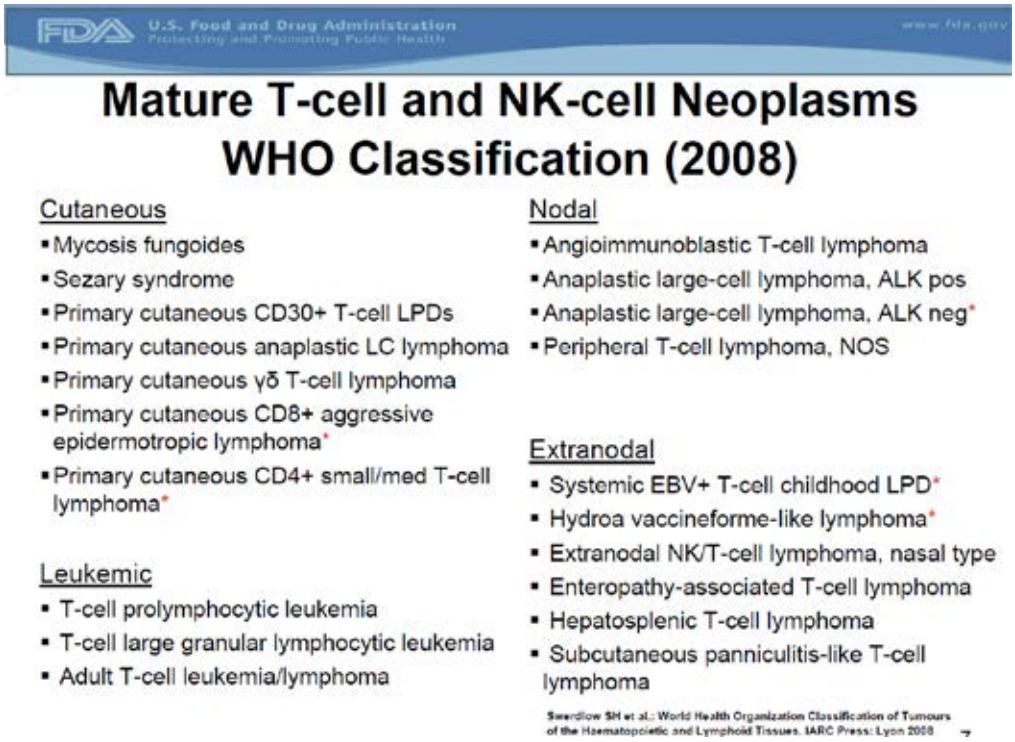
Efficacy

Study PDX-008 (PROPEL)

This was a Phase II, *single arm, open label* study. Database cut-off was 17 August 2009.

Adults could enrol if they had: confirmed PTCL; disease progression after ≥1 previous treatment; ECOG performance status ≤ 2; no marked reduction in neutrophils or platelets; and no significant liver or renal impairment. Highly aggressive PTCL subtypes such as T-cell prolymphocytic leukaemia were excluded, as were indolent subtypes. Cutaneous T cell lymphoma was excluded, apart from transformed mycosis fungoides. The WHO classification of PTCL is shown below in Figure 3.

Figure 3. WHO PTCL classification



Patients received pralatrexate 30 mg/m^2 IV, once weekly for 6 consecutive weeks followed by one rest week, making up a 7 week cycle. If methylmalonic acid levels were >200 nM and/or homocysteine >10 µM, vitamin supplementation was given for ≥10 days prior to first dose of pralatrexate; otherwise, patients received concurrent folic acid (1-1.25 mg PO daily) and vitamin B12 (1 mg IM every 8-10 weeks). Patients were treated for 24 months or until other events (such as disease progression) intervened.

Dose selection is described in the CER1. Use of higher doses in Study PDX-02-078 led to severe stomatitis in patients with high homocysteine and methylmalonic acid levels.

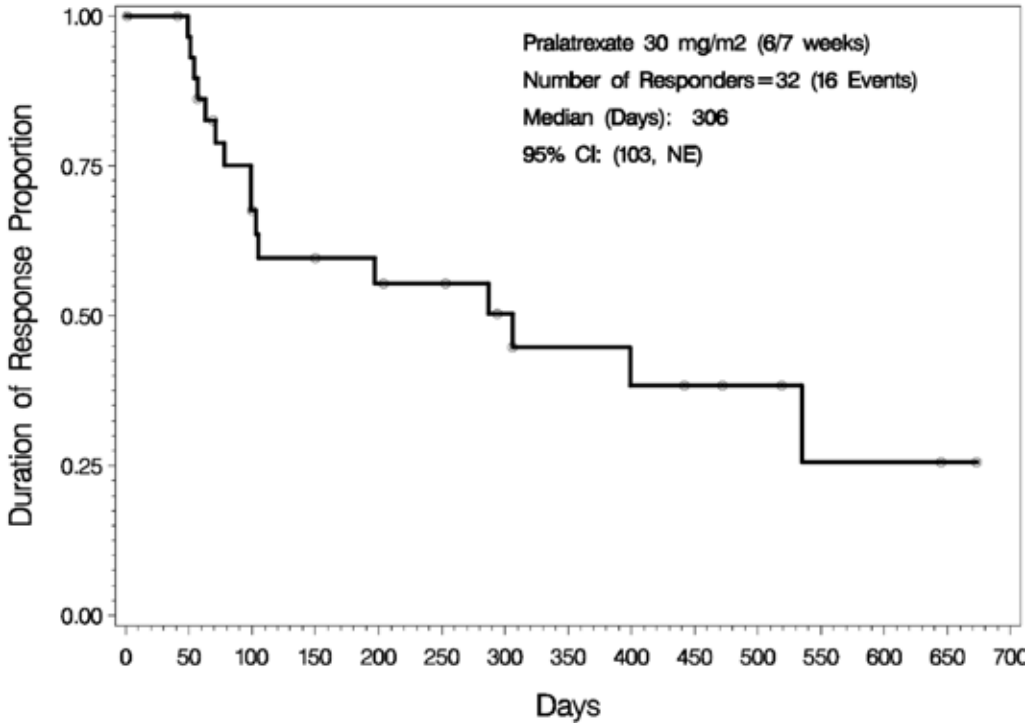
Some 115 patients were enrolled but only 111 received ≥1 pralatrexate dose; 109 had a confirmed diagnosis of PTCL and were included in the efficacy analysis. Most patients were male and White; median age was 59 years (yrs). Patients were heavily pre-treated (with a median of 3 prior therapies, and range 1-12); CHOP was the most commonly used prior systemic therapy, in 70%.

There was central assessment of tumour response, taking into account imaging, clinical data, LDH levels and bone marrow biopsy results.

The primary efficacy endpoint was *overall response rate (ORR)* by central assessment. ORR was 29% (95% CI 21-39%) (32/109, made up of 20 patients with partial responses, 11 with complete responses and 1 with an unconfirmed complete response). Patients with angioimmunoblastic T cell lymphoma had a response rate of 8% (1/13). There were responses in patients refractory to prior therapies (5/26; the 5 patients had received 1-3 prior treatments).

Duration of response is important in a lymphoma study with the primary endpoint of ORR[51]. Figure 4 shows duration of response; the Kaplan-Meier estimate of median duration of response is 10.1 months, but there was considerable censoring. 19 patients had confirmation of response (≥2 tumour response assessments with CR or PR). Duration of response was ≥6 months in 14/32. In 5/32, response was prolonged (20.7-46.9 months).

Figure 4. Duration of response results for Study PDX-008 (PTCL). Efficacy Analysis set. Central Review-IWC



Median *progression-free survival* was 3.5 months.

Median *overall survival* was 14.5 months. With additional follow-up, 24.9% of patients survived to 4 years after starting pralatrexate (with 5/109 patients still alive and having survived >4 years from treatment day 1 at time of last follow-up). Most received other treatment after discontinuing pralatrexate.

Quality of life was not reported.

External / historical comparisons supported efficacy but are subject to significant biases.

The sponsor analysed ORR using *patients as their own controls*, looking at responses with previous treatments. Given the expectation of progressive resistance, results generally supported pralatrexate, although ORR with CHOP used immediately prior to pralatrexate was 58% (versus 35% for pralatrexate). The analyses were "non-prespecified".

[51] Cheson BD et al. Revised Response Criteria for Malignant Lymphoma JCO 2007; 25 (5): 579-586

Study PDX-02-078

In those dosed as proposed, 8/13 evaluable T cell NHL patients has an objective response (including 3/13 with a complete response). In the 45 mg/m^2 (6/7 week) dose group, 2/3 evaluable T cell NHL patients had a complete response, but there were 5 dose-limiting toxicities and 2 deaths in 11 patients.

Study PDX-010

This was a Phase 1 study in relapsed / refractory cutaneous T cell lymphoma (Stage ≥1B mycosis fungoides; Sezary syndrome; primary cutaneous anaplastic large cell lymphoma). The dose chosen to use in an expanded cohort was 15 mg/m^2 once a week for 3 out of 4 weeks, and 23 patients received that dose. The population and dose regimen differed from that proposed in the application, so efficacy outcomes are not directly relevant. However, 10/22 patients given 15 mg/m^2 as above had partial responses based on investigator read.

Efficacy conclusions

There were no efficacy data from randomised, controlled studies in the Dossier. The TGA-adopted *EU Guideline on the Evaluation of Anticancer Medicinal Products in Man*[52] generally requires such data, but in rare tumour types or narrow indications, underpowered controlled studies are one option and within-patient *time to progression (TTP*) analyses are another.

A within-patient TTP analysis was conducted for patients in PDX-008. TTP differs from PFS in that TTP censors for death without progression. The sponsor presented data for PFS and/or TTP, as well as objective response, in within-patient analyses.

PTCL is a rare disease, and the sponsor seeks registration in patients who have progressed on at least one prior therapy. Therefore, within-patient TTP analysis of patients in PDX-008 is an approach consistent with the TGA-adopted EU Guideline. However:

- Randomised studies in PTCL are possible. The sponsor submitted a protocol for a Phase 3 study in less heavily treated PTCL (PDX-017, enrolling subjects who have an objective response to CHOP, randomising to pralatrexate or observation). The randomised study of pralatrexate, PDX-3501, is planned in patients who have progressed after ≥ 1 prior therapy for PTCL. ClinicalTrials.gov reveals that several Phase III controlled studies in PTCL are being conducted. Whether these studies can recruit sufficient numbers to detect relevant differences in anti-tumour activity is unclear.
- Within-patient TTP analysis of patients in PDX-008 was only generally supportive of pralatrexate. In an important comparison (with CHOP), pralatrexate did not have demonstrably better efficacy, although it was used at a more advanced stage of disease.

Over the proposed population, efficacy is not dramatic and durable responses are infrequent. Also, the lack of a control arm hampers interpretation of PTX-008's results.

Safety

Exposure

Patient categories given pralatrexate in trials are described in the CER1. Study PDX-008 provides the most relevant safety information, from 111 subjects exposed to pralatrexate. Some 19/111 patients were treated for≥ 6 months and 10/111 for ≥ 12 months, including 5/111 who did not require any dose reduction. Dose modifications (omissions and dose reductions) were commonly due to mucositis, thrombocytopenia and neutropenia.

[52] http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

Experience with pralatrexate in the postmarketing setting is limited (~985-1725 patients).

Adverse effects

Main toxicities are *mucosal inflammation* (for example, stomatitis and mucositis) and *myelosuppression* (anaemia, neutropenia and thrombocytopenia), in line with disruption of DNA synthesis in rapidly dividing cells.

- Most cases of mucositis were oral but there were pharyngeal and oesophageal cases; some cases required hospitalisation.
- Thrombocytopenia was often severe (Grade 3 in 15/111, Grade 4 in 21/111); epistaxis was common (all reports were Grade 1-2) but there were no Grade 4 bleeding events in patients with the AE of thrombocytopenia.
- Neutropenia was also commonly severe (Grade 3 in 15/111, Grade 4 in 9/111); 'severe and serious' febrile neutropenia and sepsis were reported in 4 and 2 patients respectively.

Skin reactions were common and included rash, blistering and ulceration. In all studies (689 patients) and postmarketing experience (985-1725 patients), the sponsor noted 6 reports of dermatological reactions resulting in death. In 5/6, only one dose was given. In 2 clinical trial cases (one patient from PDX-02-078 and one patient from PDX-009) there was extensive initial skin involvement by PTCL; 3/4 with fatal reactions in the post-marketing setting had skin involvement by PTCL. Compromised skin integrity is problematic in the setting of myelosuppression. See also "*Serious skin reactions*" in the CER1. In Study PDX-010 (cutaneous T cell lymphoma; lower dose) there were some skin reactions sufficient to warrant discontinuation.

One patient in PDX-008 developed *pneumonitis* considered to be an acute hypersensitivity reaction to pralatrexate. There were 8 other cases of pneumonitis across all studies and 6/8 had PTCL. Most cases were considered causally related.

Tumour lysis syndrome was reported as a serious AE in 4 cases across all studies; 3/4 cases were in PTCL patients.

Liver function test derangements were frequent but with no control arm in PDX-008 the contribution of pralatrexate is unclear. Hepatic failure was not mentioned.

There was no routine monitoring of electrolytes in PDX-008, but *hypokalaemia* was reported as an AE in 18/111.

There is a correlation within the PTCL cohort between pralatrexate exposure and severity of mucositis and thrombocytopenia. Study PDS-02-078 also found a correlation between baseline serum methylmalonic acid levels and risk of mucositis (detailed in CER1 with an explanation for use of routine B12 and folic acid supplements).

A sub-study of PDX-007 examined QT prolongation. Only 190-230 mg/m^2 doses were tested; there was a moderate delay in cardiac repolarisation and there were no outlying high values. Only 5 subjects received pralatrexate via intravenous (IV) push over 3-5 minutes and this group experienced the most QTc prolongation but doses were high.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's Office of Product Review (OPR), although the RMP Evaluator requested that, if pralatrexate were to be registered, there should be an improved strategy to characterise cases of pneumonitis/pulmonary toxicity seen in the postmarketing space. Also, it was recommended that several aspects of the RMP be updated within 6 months of registration

and that post marketing commitments in the US be reconciled with those proposed in Australia.

Risk-benefit analysis

Delegate considerations

The pivotal study PDX-008 was not a Phase III, controlled study. Objective response rate was the primary efficacy endpoint. Within-patient time-to-progression comparisons are endorsed by the TGA-adopted EU guideline on anti-cancer medicines in the setting of rare diseases; PTCL is a rare disease. In this case, within-patient comparisons of time to progression were not clearly pre-specified, and did not universally favour pralatrexate (for example, the immediate prior therapy CHOP had a better response rate and equivalent time to progression).

Objective response rates were good in this heavily pre-treated population but responses were not always durable. There was a large benefit in this regard in only a few of the 109 patients studied for efficacy: 5/109 had a prolonged duration of response. In several, a good response allowed bridging to haematopoietic stem cell transplantation.

Possibly, existing treatment of relapsed/refractory PTCL may produce good outcomes such as durable response or bridging to SCT in an equivalent small proportion of subjects; this was not assessed either by a control arm or by within-patient historical analysis (for example, only median PFS and median TTP were presented in such analyses).

While not designed to assess response by histopathological sub-group, there was a signal in Study PDX-008 that response may be limited in angioimmunoblastic T cell lymphoma.

The sponsor writes that the "*focus of any therapeutic intervention for PTCL in the relapsed or refractory setting should be centered on producing a durable disease response in patients while not concurrently adding unmanageable, intolerable, or irreversible toxicity*." There are distinct safety concerns with pralatrexate, including severe mucositis and myelosuppression, potentially fatal skin reactions and pneumonitis. Rare fatal skin reactions are problematic in that they can occur after the first dose.

Quality of life was not assessed in PDX-008. Many common AEs seen with pralatrexate would impact on quality of life.

Allowing registration of pralatrexate in the proposed population trades good outcomes in a few subjects (for example, highly durable response in 5/109) with severe toxicity in many (for example, Grade 3-4 thrombocytopenia, mucositis and neutropenia each in >20%). There is an unmet need for more beneficial treatments in relapsed/refractory PTCL. It is not clear that pralatrexate does provide a net benefit across this population of cancer patients.

Proposed action

The Delegate proposed to reject the application, for reasons described above. If the Advisory Committee for Prescription Medicines (ACPM) advises registration and this advice is accepted, the Delegate would recommend changes to the PI.

The advice of the Committee was requested. Specifically, does the Committee view pralatrexate as providing a net benefit across the proposed patient population (or any other PTCL population)?

Response from sponsor

No new serious unexpected adverse events have been reported since the registration dossier was submitted in Australia.

In a gravely ill, relapsed and refractory patient subset for whom no other treatment is currently available, pralatrexate has produced consistently high and durable response rates across multiple histological subtypes in both the pivotal study (PDX-008) and the supportive Phase I/II study (PX-02-078). Three years of post-marketing experience in the US has shown the safety profile of pralatrexate to be predictable and manageable, and certainly no worse than that of other oncology therapies.

In reaching the conclusion that "*The benefit-risk balance of pralatrexate, given the proposed usage, is favourable*." the clinical evaluator notes the limitations of the single pivotal study and the difficulty in reaching firm conclusions about the clinical benefit of pralatrexate in the target population. However, it appears that pralatrexate offers durable responses and meaningful survival benefits in a subset of patients with relapsed or refractory PTCL who otherwise have a dismal prognosis from an aggressive disease that has no approved or standard care. On balance, these benefits outweigh the risks associated with the adverse effects of pralatrexate on folate metabolism, in that the toxicities are by and large manageable with careful monitoring, vitamin supplementation, and dose modification, all of which are emphasised in the proposed product information.

Regarding the delegate considerations of efficacy

1. The pivotal study PDX-008 was not a Phase III, controlled study.

Sponsor's response: The sponsor recognises the deficiency of the single-arm pivotal trial design. This approach was taken due to the rarity of the studied disorders and the lack of treatment consensus in the relapsed/refractory peripheral T-cell lymphoma (R/R PTCL) setting, that is, the lack of an obvious control arm. This study was the largest, most robustly conducted study ever undertaken in relapsed/refractory PTCL at the time. The efficacy of pralatrexate has been demonstrated in two clinical studies: a Phase I-II study in R/R lymphoma (PDX-02-078), which demonstrated the t-cell specificity of pralatrexate, and the pivotal Phase II study in R/R PTCL (PDX-008), which was a rigorously-conducted, multi-centre study in 109 evaluable patients. These data are further supported by progression-free survival (PFS) analyses using patients as their own controls, comparing pralatrexate to prior therapy, in addition to overall survival (OS) analyses in which pralatrexate outcomes are compared to matched-case comparisons from historical databases. The magnitude of pralatrexate efficacy in this patient population is compelling and clinically meaningful, as evidenced by:

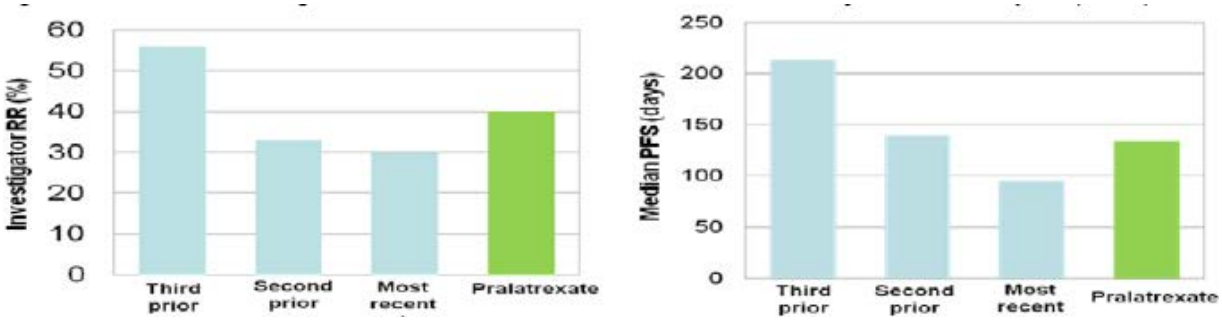
- Consistently high response rates in heavily pretreated patients across multiple histological subtypes demonstrated in both the pivotal study, PDX-008 (39% by investigator and 29% by central review) and supportive Phase I/II study PDX-02-078.
- Clinically significant, durable responses in PDX-008, with a median duration of 12.06 months at the time of submission (based on IWC assessment plus PET in 28 responding patients); a median duration of CR/CR unconfirmed (Cru) of 44.2 months, with 59% (19/109) and 47% (15/109) of responding patients experiencing responses lasting >6 and >12 months, respectively; improved outcomes for patients in comparison to their most immediate prior therapy, using intra-patient control. Ongoing PDX-008 data collection indicates continued extended response durations.
- Matched-control analyses simulating randomised data, that demonstrate the clinical efficacy benefit of pralatrexate with superior survival outcomes (hazard ratio of 0.39 [95% CI: 0.26, 0.60], and median OS of 19.0 months for pralatrexate versus 5.8 months for matched-controls treated with currently-used agents.

2. ***Within-patient time- to-progression comparisons are endorsed by the TGA-adopted EU guideline on anti-cancer medicines in the setting of rare diseases; PTCL is a rare disease. In this case, within-patient comparisons of time to progression were not clearly pre-specified, and did not universally favour pralatrexate (for example, the immediate prior therapy CHOP had a better response rate and equivalent time to progression).***

Sponsor's response: *Pralatrexate improved outcomes in the overall population*

Response rates and progression-free survival (PFS) have been documented as decreasing with successive lines of therapy in patients with malignant diseases, including lymphoma and breast cancer, until resistance occurs. Patients in PDX-008 had undergone a median of three prior systemic therapies and therefore represent a population of patients with R/R PTCL in whom the pattern of "*progressive resistance*" to standard treatments may be examined. Progressive resistance represents the course the disease was following prior to pralatrexate administration; thus, the PFS on pralatrexate would be expected to be lower than the PFS on prior therapy rather than higher. However, pralatrexate provided a clear benefit to the overall population of PDX-008, for both the PFS and response rate (using the response assessed by the investigator for prior therapy and therefore also for pralatrexate). As shown in Figure 5, for the patients who received at least three therapies prior to pralatrexate, the aggressive disease course of PTCL results in progressively lower response rates and PFS with each successive line of treatment, demonstrating progressive resistance in a PTCL population. This trend was reversed with pralatrexate therapy. Thus, pralatrexate, a targeted T-cell anti-neoplastic agent, reversed the trend of decreasing response to successive lines of chemotherapy in the overall population and improved the outcomes that patients would have likely experienced without pralatrexate. This consistency in anti-cancer response is highly unlikely to be a chance finding, and the response rate is further corroborated by PFS analysis to further contextualise the clinical benefit conferred by treatment with pralatrexate in a definable PTCL patient population.

Figure 5. Reversal of Progressive Resistance in Patients with 3 Prior Systemic Therapies (N=57)



Clinically Important Improvement in PFS Ratio of Pralatrexate Compared to Prior Therapy: PFS intra-patient ratios of the PFS on current therapy to the PFS on the most immediate prior therapy have been previously investigated with a threshold of >1.3 being indicative of an effective therapy, as it represents a >30% increase in PFS.[53,54, 55, 56] Using

[53] Bonetti A., Zaninelli M., Leone R., Franceschi T., Fraccon A.P., Pasini F., Sabbioni R., Cetto G.L., Sich D., Brienza S. & Howell S.B. (2001): Use of the ratio of time to progression following first- and second-line therapy to document the activity of the combination of oxaliplatin with 5-fluorouracil in the treatment of colorectal carcinoma. *Ann Oncol* 12, 187-91.

[54] Buyse M., Quinaux E., Hendlisz A., Golfinopoulos V., Tournigand C. & Mick R. (2011): Progression-free survival ratio as end point for phase II trials in advanced solid tumors. *J Clin Oncol* 29, e451-2; author reply e453.

[55] Von Hoff D.D., Stephenson J.J., Jr., Rosen P., Loesch D.M., Borad M.J., Anthony S., Jameson G., Brown S., Cantafio N., Richards D.A., Fitch T.R., Wasserman E., Fernandez C., Green S., Sutherland W., Bittner M., Alarcon

patients as their own controls increases statistical sensitivity and eliminates the inter-patient variability inherent in small studies. When this analysis was applied to the 109 patients in PDX-008, 35 patients (32%, 95% CI: 23.3, 40.9) had a PFS ratio of at least the identified threshold of 1.3 (that is, a >30% improvement in PFS). These results are important since they substantiate pralatrexate as an effective therapy that improved patient outcomes relative to prior therapy by >30% for one-third of patients in PDX-008. Additionally, they reflect a strong correlation between response and PFS, since 27 of the 35 patients (77%) who had a prolonged benefit in PFS relative to prior therapy (that is, ratio >3) had achieved a response to pralatrexate by investigator assessment.

3. ***Objective response rates were good in this heavily pre-treated population, but responses were not always durable.***

Sponsor's response: Table 7 presents the proportion of patients who were still in response and/or had not progressed at 1, 2, 3, and 4 years from the documented date of first response to pralatrexate (duration of response) or from initiation of pralatrexate (PFS), using the updated response data provided by the sponsor (Module 2 Clinical Summary Efficacy Addendum). Although the 3 and 4 year rates are based on small patient numbers, they provide clear evidence that a subset of patients have had durable responses and achieved meaningful survival benefits from pralatrexate treatment. The median time from initial diagnosis at study entry into PDX-008 was 15.6 months (range 0.8-322.3 months). A survival of ≥ 2 years from initiation of pralatrexate must be considered highly significant in the context of heavily-pretreated, relapsed/refractory PTCL.

Table 7. Rates of Duration of Response and PFS for updated PDX-008 Data

	(% of pralatrexate responders) By Central Review			
	1 year	2 years	3 years	4 years
Duration of Response (N = 32)	49.6	34.8	34.8	23.2
Progression-free Survival (N = 109)	27.3	16.9	16.9	11.2
Overall Survival (N = 09)	56.0	38.4	28.5	24.9

(95% Confidence Interval)

Response to Pralatrexate Translated into Extended Progression-free Survival Outcomes: In the 32 patients assessed as responders by central review, PFS outcomes from pralatrexate were nearly doubled when compared with outcomes from these patients' prior therapy (median PFS of 438 versus 242 days). Figure 6 shows each responder's PFS outcomes from pralatrexate versus most recent prior therapy. Using patients as their own controls, the majority of responders (23/32, 72%) experienced a longer PFS with pralatrexate than they did for their most recent prior therapy (that is, PFS ratio >1.0). Since PFS typically decreases with each successive line of therapy (progressive resistance) and 53% of pralatrexate responders (17/32) had not responded to their most recent prior therapy, the improved PFS with pralatrexate demonstrates a reversal of the expected outcomes and reflects the clinical benefit associated with pralatrexate response. Seventeen (17) pralatrexate responders were refractory to their most recent prior therapy, including 5 patients refractory to all prior therapies. In this population the median PFS in these patients nearly quadrupled, from 111 days on their prior therapy to 419 days on pralatrexate (Figure 7). Importantly, pralatrexate responses and PFS were independent of outcomes from patients' most recent prior therapies and a response to pralatrexate did not simply reflect a general responsiveness to chemo-therapy but the differential ability of pralatrexate to induce responses where other therapies had failed.

A., Mallery D. & Penny R. (2010): Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol* 28, 4877-83.

[56] Zalcberg J.R., Verweij J., Casali P.G., Le Cesne A., Reichardt P., Blay J.Y., Schlemmer M., Van Glabbeke M., Brown M. & Judson I.R. (2005): Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer* 41, 1751-7.

Figure 6. PFS in pralatrexate responders versus Most recent Prior Therapy

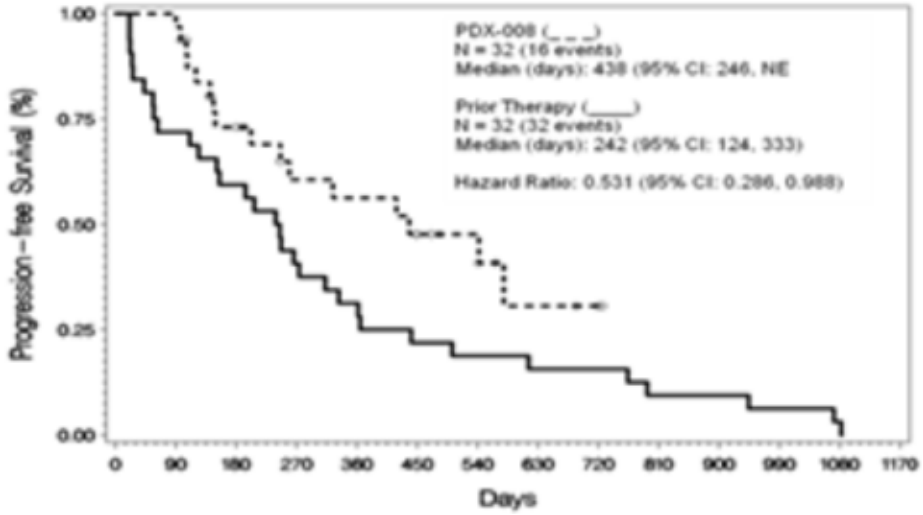
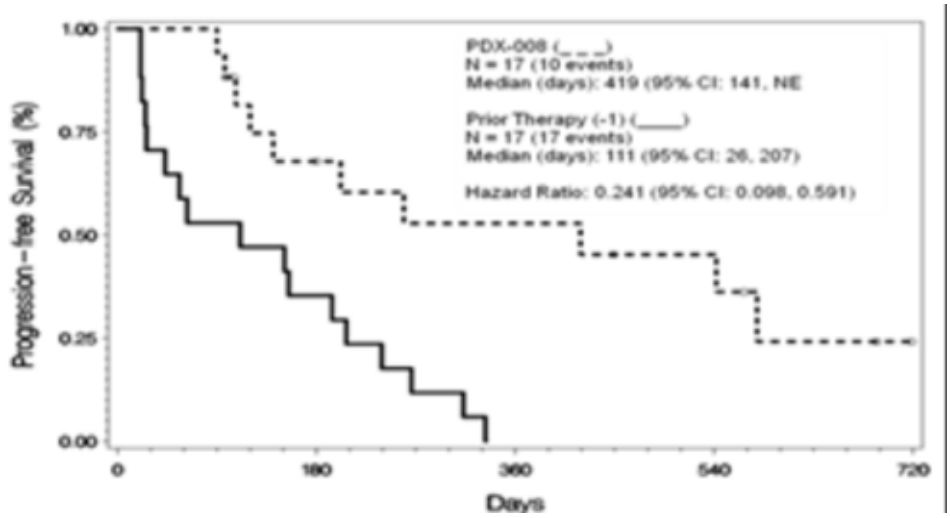


Figure 7. PFS on pralatrexate versus Most recent prior therapy; responders to PDX but not to Most recent prior therapy



4. ***There was a large benefit in this regard in only a few of the 109 patients studied for efficacy: 5/109 had a prolonged duration of response. In several, a good response allowed bridging to haematopoietic stem cell transplantation (SCT).***

Sponsor's response: The role of transplantation in both front line and relapsed disease is still experimental in PTCL. Within the National Comprehensive Cancer Network (NCCN) guidelines, pralatrexate is currently recommended for use in both the transplant-ineligible and transplant-eligible populations. As was seen in PDX-008, 63% of patients were refractory to their previous therapy and 24% of patients had no response to any previous therapy. These patients were not chemo-sensitive and would not have been deemed appropriate for stem cell transplant. However, transplant eligibility is a further treatment option for responders. PDX-008 enrolled heavily pre-treated R/R PTCL patients, all of whom were ineligible for transplant at the time of study entry. The intent of initial PTCL treatment is to induce a durable response and/or a sufficient response to allow the patient to subsequently undergo stem cell transplant. Patients must first achieve a response in order to be eligible for stem cell transplant since transplanting patients with active disease is associated with very poor outcomes. In the European Union and Canada, only 11% and

13% of patients underwent stem cell transplant after initial chemotherapy, respectively.[57] In the R/R setting the SCT option is very limited and the fact that pralatrexate can induce a response durable enough to bridge to SCT is a clear indication of the beneficial effect of pralatrexate in these heavily pre-treated patients.

5. ***Within-patient time to progression (TTP) analysis of patients in PDX-008 was only generally supportive of pralatrexate.***
6. ***Possibly, existing treatment of r/r PTCL may produce good outcomes such as durable response or bridging to SCT in an equivalent small proportion of subjects; this was not assessed either by a control aim or by within-patient historical analysis.***

Sponsor's response: Matched Control Analyses. The Applicant acquired demographic, treatment, and survival outcome data from four historical databases in the US, Europe, and Korea comprising a total of 390 patients who met the following criteria: histologies consistent with the inclusion criteria of PDX-008; Patients who received at least two therapies and were therefore in the relapsed/refractory stage of their disease; and Patients who had not received prior pralatrexate. Patients from PDX-008 were matched with a coordinating patient from one of the external historical databases, with the goal of comparing survival outcomes following currently administered therapies with those of pralatrexate, which, in effect, creates a controlled dataset against which the magnitude of the treatment-effect relating to pralatrexate was measured to assess clinical efficacy. Response rates and PFS data were incomplete, were not collected according to consistent methodology and were not able to be ratified. Therefore, all comparisons were made based on OS data.

A primary analysis on OS and two sensitivity analyses were conducted between PDX-008 and the matched control patients. After the programmatic identification, medical review, and sorting of unique matching patients described for the primary analysis, 66 patients from the PDX-008 study were identified as having 1 appropriate matched control patient. Forty-three PDX-008 patients could not be matched with a historical control patient, largely due to differing histology and number of lines of therapy compared with the historical control patients, as the age and gender were similar between the matched and non-matched PDX-008 patients. Since patients were matched using demographic criteria, it was expected that the PDX-008 patients in this analysis would be demographically similar to the matched-control patients. Table 8 presents the types of therapy that were matched with pralatrexate for the primary analysis. The comparator treatment was multi-agent chemotherapy for the majority of patients within the historical control databases (43 patients, 65%).

Table 8. Types of Comparator Therapies Matched with Pralatrexate

Type of Therapy	Historical Control (N = 66) n (%)
Non-platinum containing multi-agent chemotherapy	25 (38)
Single-agent chemotherapy	21 (32)
Platinum-containing multi-agent chemotherapy	14 (21)
CHOP/CHOP-like	4 (6)
Prednisone	2 (3)

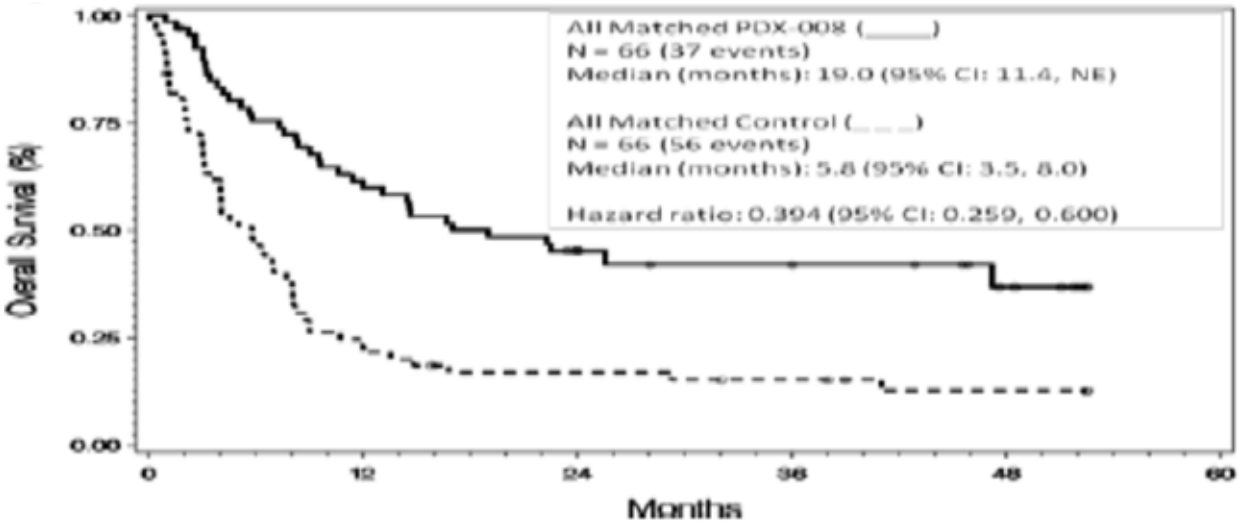
OS was highly significant in favour of the 66 pralatrexate-treated patients compared with the 66 matched-control patients, with an HR of 0.39 (95% CI: 0.26, 0.60). The median OS

[57]Mak V, Shenkier T, Chhanabhai M, Gascoyne RD, Savage KJ, (2011): Survival of Peripheral T-Cell Lymphomas (PTCLs) Patients Following Relapse: Spectrum of Disease and Rare Long-Term Survivors, paper presented at 23rd ASH Annual Meeting and Exposition, 11 December 2011 http://ash.confex.com/ash/2011/webprogram/Paper43645.html[05/12/2011 16:33:30]

of 19.0 months for the 66 pralatrexate-treated patients is more than 3 times longer than the median OS of 5.8 months (95% CI: 3.5, 8.0) observed in matched-control patients.

Pralatrexate provided significantly superior survival outcomes compared with the case-matched historical controls, which represent treatments administered in the real-world clinical setting, including clinical studies, at leading global cancer centres. The median OS observed in the matched-control arm of these analyses is entirely consistent with the poor outcomes reported in the population-based study from the British Columbia Centre for Lymphoma Malignancies, as well as with the median OS observed within each of the four historical databases (range 3.7 to 8.7 months). The median OS for all of these databases was substantially lower than the median OS of pralatrexate from the overall efficacy population (N = 109, 14.7 months) and from the matched-control pralatrexate-treated population (N = 66, 19.0 months), despite a comparison of single-agent pralatrexate with mostly multi-agent regimens. Another important observation from these analyses is that a variety of treatment regimens were used in the matched-control population, which further confirms the absence of a standard of care for relapsed and refractory PTCL patients.

Figure 8. OS for Pralatrexate versus Matched Control Patients



The results of the matched-control analyses are compelling and confirm that pralatrexate mono-therapy provides improved OS outcomes compared with those observed following the unapproved treatment options that are currently used off-label to treat relapsed/refractory PTCL.

7. While not designed to assess response by histopathological sub-group, there was a signal in study PDX-008 that response may be limited in angioimmunoblastic T cell lymphoma

Sponsor response: PTCL is a heterogeneous disease with many distinct subtypes. Study PDX-008 was not designed to show a difference between PTCL patient subtypes, all of whom have a poor prognosis (with the possible exception of ALK+ ALCL) and subgroup analysis is therefore not considered appropriate.

8. In an important comparison (with CHOP), pralatrexate did not have demonstrably better efficacy - although it was used at a more advanced stage of disease.

Sponsor's response: PTCL is a highly aggressive disease which has a poor response to conventional chemotherapy and a 5 year overall survival (OS) of about 25% to 45%. [58]

[58]Rivzi MA, Andrew M. Evens, Martin S. Tallman, Beverly P. Nelson, and Steven T. Rosen (2006): T-cell non-hodgkin lymphoma, Blood 107: 4, 1255-1264. (Submitted as M5.4.230, Volume 58)

Anthracycline-containing chemotherapy, such as CHOP or CHOP-like regimens, is considered to be standard therapy for PTCL, although remission rates are less than satisfactory.[59] More intensive regimens, such as hyper-CVAD and hyper-CHOP, have not shown improved outcomes compared with CHOP regimens.[60] Mak et al., 2011[57] reported that 62% of patients treated were refractory (that is, had a response less than a CR) to their initial chemotherapy. Patients enrolled in PDX-008 had a median number of three prior therapies, and 70% had previously been treated with CHOP. It is not justifiable to compare the response to CHOP initial therapy in *de novo* patients to outcomes in the heavily pre-treated pralatrexate population with relapsed and refractory disease.

Regarding the Delegate considerations of Safety and Exposure

1. ***Experience with pralatrexate in the post-marketing setting is limited (~985-1725 patients).***

Sponsor's response: Since US approval, the cumulative number of Folotyn doses that has been administered is 13,039, which would equate to a total range of approximately 1,863 to 3,260 patients exposed to the drug in the postmarketing setting based on product distribution data. There were 11 initial spontaneous postmarketing adverse event (AE) reports, (as well as 8 initial and 2 follow up AE reports received from the ISS/intent-to-treat (ITT) setting using marketed drug) received during the October 2012 Periodic Safety Report time period. This corresponds to one AE report per 60 doses used. The type and occurrence of AEs received or reported during the reporting period indicate no new safety issues or unusual trends.

2. ***There are distinct safety concerns with pralatrexate, including severe mucositis and myelosuppression, potentially fatal skin reactions and pneumonitis. Rare fatal skin reactions are problematic in that they can occur after first dose.***

Sponsor's response: The safety profile of pralatrexate compares favourably with the therapies currently used off-label to treat relapsed/refractory PTCL, all of which both expose patients to severe toxicity and have not been rigorously tested in this indication. The safety profile of pralatrexate is confirmed by three years of US postmarketing experience and is reflected in the proposed Australian Risk Management Plan (RMP). The overall safety profile for pralatrexate is predictable and manageable. The most frequent Grade 3/4 adverse events are typical of the class and are regularly managed with many of the other agents used by haematologists and oncologists. The dose modification guidelines for mucositis, haematological toxicities, and for all other treatment-related toxicities used in PDX-008 have been incorporated into the dosing recommendations in the labelling. In addition, the draft PI includes precautions for bone marrow suppression, mucosal inflammation, dermatological reactions, tumour lysis syndrome and renal/hepatic impairment.

Dermatological reactions have been reported in a small number of patients, however, this is not a drug- effect limited to pralatrexate, as severe dermatological reactions have also been reported with other products used to treat relapsed/refractory PTCL, for example gemcitabine and lenalidomide including spontaneous reports of severe dermatological reactions, desquamation and bullous skin eruptions, Lyell's syndrome and Stevens-Johnson syndrome in the case of gemcitabine. The following observations can be made regarding the dermatological reactions reported with pralatrexate administration:

[59] Savage KJ et al., 'Peripheral T-cell lymphomas', Blood Reviews (2007) 21, 201–216. (Submitted as M5.4.251, Volume 58)

[60] Escalon MP, 'Prognostic factors and treatment of patients with T-cell non-hodgkin lymphomas, Cancer (2005) 103:10, 2091-2098

- While AEs are common, the majority are non-serious or mild-moderate (rash, erythema, urticaria, pruritus)
- Many SAEs are manifestations of the effectiveness of treatment of the underlying lymphoma involving skin
- Severe dermatological reactions occur early in treatment, generally after the first dose
- Dermatological reactions may increase in severity with continued exposure to pralatrexate
- The majority of the important dermatological reactions resolved with supportive therapy, and some patients were able to continue pralatrexate therapy
- The fatal and/or life-threatening reactions occurred in patients with extensive skin disease and were generally associated with mucositis, neutropenia, and/or infection and included extensive skin involvement.

In accordance with the labelling, patients on pralatrexate are closely monitored for the development of severe dermatological adverse effects, and are instructed to immediately notify their physician if any untoward skin reactions occur. As the most severe reactions have been reported in heavily pretreated patients with extensive skin disease, the population most at risk can be identified and appropriately monitored. This is captured within the proposed Australian RMP.

3. ***Quality of life was not assessed in PDX-008. Many common AEs seen with pralatrexate would impact on quality of life.***

Sponsor's response: It is important to recognise the highly aggressive nature of PTCL disease, and within study PDX-008, the heavily pre-treated nature of the population who had received a median of 3 prior systemic therapies. Responses were seen in patients with varying histologies, with 63% of responses occurring in Cycle 1. The response rate was independent of the number of prior therapies. Adverse events such as mucositis can generally be managed by reduction of dose, proactive labelling, the available Healthcare Professional educational materials and the RMP, thereby limiting the impact on quality of life. Pralatrexate demonstrates a positive benefit/risk ratio in a significantly symptomatic patient population that has been heavily pre-treated with the few available therapeutic options.

4. ***Allowing registration of pralatrexate in the proposed population trades good outcomes in a few subjects (e.g. highly durable response in 5/109) with severe toxicity in many (e.g. grade 3-4 thrombocytopenia, mucositis and neutropenia each in >20%).***

Sponsor's response: Sufficient procedures are in place to ensure patient safety with the precautions in the proposed PI, and with additional RMP monitoring, and as a result, there is no negative impact on the benefit-risk profile of pralatrexate. All available agents used to treat relapsed/refractory PTCL can produce negative effects on the reproductive system, induce myelosuppression, and the majority have been associated with tumour lysis syndrome (TLS). As patients with relapsed/refractory PTCL have limited therapeutic options and will ultimately succumb to their disease without treatment, the efficacy benefit provided by pralatrexate outweighs the potential risks.

Regarding the delegate's conclusion

1. ***It is not clear that pralatrexate does provide a net benefit across this population of cancer patients.***

Sponsor Conclusion: The results of the matched-control analyses are compelling, and confirm that pralatrexate monotherapy provides durable and improved OS outcomes compared with those observed following the unapproved off-label treatment options.

These data more than compensate for the lack of a comparative pivotal Phase II trial in the data set. Pralatrexate demonstrates a positive efficacy benefit and a manageable safety profile within a rare patient population with an acknowledged significant unmet medical need.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), 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 negative benefit – risk profile.

In making this recommendation the ACPM:

- noted there were a range of potential study design issues that could be perceived to impact on the veracity and adequacy of the evidence including;
  - the extent of censoring and the heterogeneity of the peripheral T cell lymphoma (PTCL) patient population
  - the inadequacy of using Overall Response Rate (ORR) as the primary end point,
  - the absence of blinding
  - The absence of an appropriate comparator, specifically the evidence has not demonstrated equivalence or superiority to any currently available agents, (for example methotrexate or pemetrexed if appropriate) that have similar mode of action and are subject to the same potential resistance mechanisms.
- expressed concern over the serious safety signals including fatal toxicities reported, particularly :
  - the fatal skin reaction that can occur on administration of first dose
  - mucositis, thrombocytopenia and neutropenia which were common adverse events

In addition, the ACPM noted that further randomised studies are underway and would welcome any future application that includes this evidence.

Initial outcome

Based on a review of quality, safety and efficacy, TGA decided not to register pralatrexate (Folotyn).

The reason for the Delegate's decision is that efficacy and safety have not been satisfactorily established for the purpose for which pralatrexate (Folotyn) is to be used. The following is an excerpt from the Delegate's Decision Letter:

- The Delegate considered that the indication of a medicine is a reasonable description of the purpose for which a medicine is to be used. Therefore, in relation to s25 of the Act, the Delegate considered that the purpose for which pralatrexate (Folotyn) is to be used is treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy.
- Quality of pralatrexate (Folotyn) was satisfactorily established taking into account the findings of the TGA's quality evaluation and the PSC advice.

- Efficacy and safety have not been satisfactorily established for the purpose for which pralatrexate (Folotyn) is to be used, for the following reasons.
  - There were no data from one or more adequately designed and conducted randomised, controlled studies that supported efficacy and safety of pralatrexate (Folotyn).
  - In relation to whether external (for example historical) controls are an acceptable substitute for a randomised, controlled study, the Delegate considered that the treatment effect of pralatrexate (Folotyn) cannot be considered dramatic when the effect on the entire proposed population is considered. Evidently, there are individual cases where a dramatic effect is achieved. Across the entire proposed population, this is not the case. The Delegate agreed with the authors of the TGA-adopted EU Guideline discussed above, in their discussion about the use of historical controls. The Delegate concluded that the use of historical controls in this case is too prone to uncontrollable and potentially large biases to establish the efficacy and safety of pralatrexate relative to appropriate comparators with acceptable rigour.
  - In relation to whether 'within-patient time-to-progression-like analyses' are an acceptable substitute for a randomised, controlled study, the Delegate noted that despite the sponsor's stated reasons for using a single-arm pivotal trial, the sponsor has plans to conduct a randomised study of pralatrexate against single agent 'physician's choice' (akin to some current treatment regimens) in a similar patient population. Other investigators have also conducted or are conducting randomised, controlled trials in various PTCL populations. The Delegate therefore consider that it is possible to conduct a reasonably powered, randomised study to establish pralatrexate's efficacy and safety relative to a meaningful comparator arm in the proposed population.
  - The Delegate was not satisfied that the results of within-patient time-to-progression -like analyses conducted by the sponsor are supportive of acceptable efficacy, or can act as a substitute for a randomised, controlled study. The Delegate accepted the sponsor's argument that a general decrease in efficacy may be expected with consecutive different therapies. However, ORR after CHOP (given immediately prior to pralatrexate) was 58%, versus an ORR of 35% after pralatrexate in those same patients. CHOP is one of the commoner PTCL therapies. Given the nature of the comparison, the Delegate was not satisfied that the efficacy of pralatrexate has been robustly demonstrated relative to a commonly used therapy.
  - The Delegate did not consider that the results of within-patient time-to-progression -like analyses conducted by the sponsor are supportive of acceptable safety. This is because the analyses did not extend to comparisons of safety outcomes.
  - Everyone exposed to pralatrexate will be at risk of its considerable toxicities, yet pralatrexate offers durable responses and meaningful survival benefit in a relatively small subset of the treated population. It was not clearly established that membership of this subset could be recognised at the outset of treatment, so it is not possible to narrow the indication to allow a positive benefit-risk balance in a narrower group.

Conclusions

The Delegate made a decision under section 25 of the Therapeutic Goods act 1989 ("the Act") not to register pralatrexate (Folotyn). The reason for the decision is that efficacy and safety have not been satisfactorily established for the purpose for which pralatrexate

(Folotyn) is to be used. Consequently, the application made on 6 December 2011 to register pralatrexate (Folotyn) has been rejected.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's report.

The Delegate of the Minister decided to confirm the original decision to reject the application to register pralatrexate (Folotyn) on the ARTG because the Delegate is of the opinion that clinical efficacy and safety of pralatrexate (Folotyn) for the proposed indication has not been satisfactorily established.

The PDX-008 (Propel) study used ORR (Objective Response Rate) as its primary efficiency variable. Patients in the pralatrexate treatment were matched with historical control data in this single-arm study: 65% of the control group were treated with multi-agent chemotherapy. Both the TGA clinical evaluator's report (30 March 2012) and the CHMP reports of the EMA (19 January 2012 and 19 April 2012) noted significant issues with the methodology of the Propel study, including significant censoring and the sensitivity to bias. Taking into consideration censorship of patients, the response rate to pralatrexate with duration >= 14 weeks would only be 16/109 patients (15%), not 29%. The CHMP report further states that " *although the facts regarding the rarity of the disease and the lack of treatment consensus in refractory/relapsing PTCL are acknowledged, the clinical benefit of objective response per se has not been established in this clinical setting and in the absence of dramatic activity, the clinical benefit cannot be considered established. Additionally, a single arm design does not allow estimation of clinical benefit in terms of clinical benefit endpoints such as PFS (Progression Free Survival) or OS (Overall Survival*)." Given these limitations in the design of the PDX-008 study as outlined above, the Delegate could not support the claims that the sponsor make with regard to the efficacy of pralatrexate (Folotyn) for this particular use.

The TGA adopted EU Guideline[61] states "*That without further justification, ORR is not an acceptable primary endpoint for confirmatory trials*". Further, the Guideline states that *"the inability to control bias restricts use of the external control design to situations where the treatment effect is dramatic and the usual course of the disease highly predictable*". The Delegate also noted that the EMA advised the sponsor that they should undertake a controlled study to establish their claims for efficacy. The Delegate concurred with this statement.

At 4.1.2 of the sponsor's appeal document, the sponsor sought to justify the use of historical control data. The Delegate found this problematic. The Delegate agreed with the authors of the TGA-adopted EU Guideline, as referenced above, and concluded that the use of historical controls in this case is prone to significant biases to establish the efficacy of pralatrexate (Folotyn) relative to appropriate comparators with an acceptable degree of rigour.

The sponsor detailed in their Appeal Document the analytical method used including the results of the primary analysis of Overall Survival (OS) and two sensitivity analyses.

[61] EMEA/EWP/205/98 Rev 3 Corr (Guideline on the Evaluation of Anticancer Medicinal Products in Man). http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

The sponsor's appeal states that the comparative efficacy assessment followed the principles set out in the ICH EIO Guideline[62] in order to ensure "*that the analysis would not unfairly favour pralatrexate treatment by minimising dissimilarity in patient characteristics between the treatment group and the external control group*". However, in the Delegate's opinion the sponsor's analyses have involved a very substantial selection of cases. In Sensitivity analysis 1, 75 of 109 PDX-008 patients were matched with 92 of 189 control patients. In Sensitivity analysis 2, 66 of 109 PDX-008 patients were matched one-to-one with 66 of 390 control patients. The matched cohorts were not homogeneous with respect to histology. The historical cohort was not homogeneous with respect to comparator therapies.

In the Delegate's opinion, these factors all potentially pre-dispose to bias and thus unreliable results. The ICH EIO Guideline (2.5.2) states that "*Inability to control bias is the major and well- recognised limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable*".

In the analysis at 4.1.3 of the sponsor's Appeal Document the sponsor refers to patients who had a progression free survival (PFS) ratio (the ratio of a patient's PFS on current treatment relative to the patient's PFS on the last treatment) of >1.3, compared with prior therapy (35 of 109) as an indication of effective therapy. The sponsor also referred to the percentage change in PFS compared with most recent prior therapy (32 patients). Given the fact, as the sponsor pointed out that patients are used as their own controls, the analyses give no support that the results can be attributed to to the whole relapsed/refractory PTCL population for whom the indication is sought. Factors predisposing to favourable results have not been identified. A similar conclusion applies to the analyses of PFS on pralatrexate compared with non-response to most recent prior therapy (17 patients). For this reason, the Delegate further concluded that the sponsor's analysis of the data does not support the indication for pralatrexate (Folotyn).

At 4.3 of the sponsor's Appeal Document, the sponsor refers to "*conflicting opinions on benefit-risk profile of pralatrexate between TGA clinical evaluator and delegate*". The Delegate found the clinical evaluator's comment (Round 1 Clinical Evaluation Report) "*Despite the limitations associated with retrospective analyses and the use of historical controls, the survival data suggest that pralatrexate **may** have the efficacy to provide similar or improved clinical outcomes compared to those seen with available treatment options*" not inconsistent with the decision made by the initial Delegate not to register pralatrexate on the ARTG. As outlined above, the efficacy of pralatrexate has not been established by the study data that the sponsor has provided and further studies are required before a positive benefit-risk profile can be accepted.

With regard to the safety of Pralatrexate, the Delegate further noted the comments made in the nonclinical evaluation regarding the pharmacological characterisation of pralatrexate (Folotyn):

i. A reliable mass-balance study was not included for evaluation.

ii. There was a lack of pharmacokinetic studies in hepatic and in renal impairment.

iii. There was a lack of clinical-drug interaction studies.

These are important considerations for establishing the safety of pralatrexate (Folotyn) in the clinical setting for which it is intended to be used and should be addressed.

In the PDX-008 study, 111 patients were exposed to pralatrexate, 19 of these were treated for at least 6 months. Toxicities included well-known oncological effects such as mucositis,

[62] ICH-EO 10: International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use Guidance: E10: Choice of Control Group and Related Issues in Clinical Trials

myelosuppression and skin reactions. As the initial Delegate pointed out (see the initial Delegate's overview under *Overall Conclusion and Risk/Benefit Assessment* above), there have been a number of fatal skin reactions as well, including following the first dose of pralatrexate. Given the failure to establish efficacy for pralatrexate (Folotyn) in this clinical setting as outlined above, the Delegate was of the opinion that these serious side-effects of treatment are unacceptable.

The Delegate also noted that the FDA has requested further studies be undertaken as part of its priority review of New Drug Application of pralatrexate (Folotyn) (24 September 2009) to prove the efficacy and safety of the medicine.

The Delegate noted the comments of the sponsor's expert statement. This report does not include any evaluable data but rather is in the form of commentary. It was the Delegate's opinion that the expert statement does not add any further weight to the sponsor's claim of efficacy for pralatrexate (Folotyn).

The Delegate acknowledged the concern that the sponsor's raised regarding relying on "Gold Standard" as a reason for rejection of an application for a medicine. The Delegate acknowledged section 25(1) (d) of the Act.

The Delegate confirmed that the decision to reject the sponsor's application for the registration of pralatrexate (Folotyn) on the Australian Register of Therapeutic Products (ARTG) does not rely on applicable "Gold Standard", but rather the overall safety and efficacy of the medicine for the purpose for which it is intended, as referenced to in section 25 (1) (d) of the Act.

Conclusion

For the reasons referred to above, the Delegate decided to confirm the initial decision on the basis that the efficacy and safety of pralatrexate (Folotyn) have not been satisfactorily established for the purpose for which it is to used.

As suggested by the EMA and requested by the FDA, randomised clinical trials utilising a comparator for pralatrexate (Folotyn) would assist the TGA in reconsidering its registration in the future.

Appeal to the administrative appeals tribunal

Subject to the *Administrative Appeals Tribunal Act 1975,* the sponsor made an application to the Administrative Appeals Tribunal (AAT) for a review of this decision.

Outcome of the AAT appealThe TGA and the sponsor reached an agreement about the registration of Pralatrexate (Folotyn) – 20 mg/1 mL and 40 mg/2 mL injection (intravenous infusion vial) (Folotyn) with regard to inclusions in the Risk Management Plan and routine pharmacovigilance and the Administrative Appeals Tribunal made a decision in accordance with this agreement. On 23 December 2014, the Tribunal set aside the decision not to register Folotyn and substituted a decision to approve the registration of Folotyn under subsection 25(3) of the Therapeutic Goods Act 1989 for the following indications:

> *Folotyn is indicated for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extra nodal and Ieukaemic/disseminated) who have progressed after at least one prior therapy*.

The product was entered on the ARTG on the 26 February 2015.

1. The following Specific conditions of registration apply to these products:The Pralatrexate Risk Management Plan (RMP), version 2.2, dated 17 November 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia

Attachment 1. Product Information

The Product Information for Folotyn approved at the time this AusPAR was published is at Attachment 1. For the most recent 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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