Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for pegaspargase

Proprietary Product Name: Oncaspar

Sponsor: Baxalta Australia

September 2018

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 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 < https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ALL	Acute lymphoblastic leukaemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
BFM	Berlin Frankfurt Munster
BSA	Body Surface Area
CALGB ALL	Cancer and Leukaemia Group B ALL
CCG	Children's Cancer Group
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
DFCI	Dana Faber Cancer Institute
DI	Delayed intensification
EFS	Event Free Survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Exposure ratio
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GD	Gestation day

Abbreviation	Meaning
GRAALL	Group for Research on Adult Acute Lymphoblastic Leukaemia
Hyper-CVAD	Hyper Cyclophosphamide Vincristine Adriamycin (doxorubicin) and Dexamethasone
IP	Intraperitoneal
IPC	In-process controls
IU	International units
LOQ	Limit of quantitation
MRD	Minimal residual disease
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NOEL	No observed effect level
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NZW	New Zealand White
OS	Overall survival
PD	Progressive disease
PEGL ASNase	PEGL, Pegaspargase, PEG-L-ASNase, PEGylated asparaginase, Oncaspar
Ph	Philadelphia chromosome
Ph ALL	Philadelphia chromosome positive ALL
PK	Pharmacokinetic
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic Safety Update Report
PTT	Partial thromboplastin time

Abbreviation	Meaning
RPLS	Reversible posterior leukoencephalopathy syndrome
SAS	Special Access Scheme
SEM	Standard error of the mean
SLR	Systematic Literature Review
SOC	System Organ Classification
SR	Standard risk
WBC	White blood cells

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	19 October 2017
Date of entry onto ARTG:	31 October 2017
ARTG number:	279831
Active ingredient:	Pegaspargase
Product name:	Oncaspar
Sponsor's name and address:	Shire Australia Pty Ltd[1] Level 39 Grosvenor Place 225 George Street Sydney NSW 2000
Dose form:	Solution for injection
Strength:	3,750 units / 5 mL
Container:	vial
Pack size:	Single vial
Approved therapeutic use:	*Oncaspar is indicated as a component of antineoplastic combination therapy in patients with Acute Lymphoblastic Leukaemia (ALL)*
Routes of administration:	Intravenous infusion or intramuscular (for small volumes). For further details please see the Product Information
Dosage:	Treatment should be prescribed and administered by physicians and health care personnel experienced in the use of antineoplastic products. For further details please see the Product Information (PI).

[1] The sponsor during the submission process included Baxlata Australia Pty Ltd as well as Shire Australia Pty Ltd.

Product background

This AusPAR describes the application by the sponsor[1] to register Oncaspar pegaspargase 3750 units/5 mL solution vial for intravenous infusion or intramuscular injection the following indication:

> *Oncaspar is indicated as a component of antineoplastic combination therapy in patients with Acute Lymphoblastic Leukaemia (ALL).*

This submission was a hybrid submission which included internal clinical study reports as well as a systematic literature review.

Acute lymphoblastic leukaemia (ALL) cells express very low levels of the enzyme asparagine synthetase; hence they are incapable of synthesising asparagine from aspartate. This characteristic, therefore, is a biologically plausible method of attacking such cells while sparing others. The mechanism of action of asparaginase is the enzymatic cleavage of the amino acid asparagine into aspartic acid and ammonia. Depletion of asparagine in blood serum results in inhibition of protein synthesis, especially in leukaemic blasts which are not able to synthesise asparagine, thus undergoing cell death.

Normal cells, in contrast, are capable of synthesizing asparagine and are less affected by its rapid withdrawal during treatment with the enzyme asparaginase. Pegaspargase is comprised of *Escherichia coli (E.coli*) derived asparaginase conjugated with polyethylene glycol (PEG). The PEGylation does not change the enzymatic properties of asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme. PEGylation of asparaginase has extended the dosing interval to 2 weeks, which provides a major practical advantage over native *E.coli* asparaginase.

There is a long history of use of Oncaspar, mainly overseas but also via the special access scheme (SAS) and clinical trials within Australia. Its integral role in anti-leukaemic efficacy within various ALL protocols is accepted.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 31 October 2017.

At the time the TGA considered this application; a similar application had been approved in the countries as outlined in Table 1.

Table 1: Foreign regulatory status

Country / region	Dates Submission/approval status	Indications
EU – centralised procedure	20 June 2014/ 14 January 2016 Approved	Oncaspar is indicated a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients. Note: Oncaspar was approved in Germany and Poland in 1994 and 2008, respectively, for second-line use in ALL following the development of hypersensitivity to native L-asparaginase

Country / region	Dates Submission/approval status	Indications
USA	24 July 2006 1 February 1994 Approved	Oncaspar is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for treatment of patients with: First line acute lymphoblastic leukaemia Acute lymphoblastic leukaemia and hypersensitivity to asparaginase
Canada	11 March 2016 / 24 February 2017 Approved	Oncaspar is indicated as: A component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients
Brazil	26 Aug 2016 / 12 June2017 Approved	Oncaspar Liquid is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.
Mexico	30 May 2016/ 12 May 2017 Approved	Acute lymphoblastic leukaemia as first therapeutic option and Acute lymphoblastic leukaemia and Asparaginase Hypersensitivity

Submissions were also under review in Colombia, Taiwan, Switzerland and New Zealand.

Orphan drug status

Oncaspar has orphan status in Australia for treatment of patients with ALL. As noted, it has been available via SAS (and clinical trial use) for a considerable period of time.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 2: Registration timeline for Submission PM-2016-02333-1-4

Description	
Submission dossier accepted and first round evaluation commenced	30 September 2016
First round evaluation completed	7 March 2017
Sponsor provides responses on questions raised in first round evaluation	15 May 2017
Second round evaluation completed	20 June 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 July 2017
Sponsor's pre-Advisory Committee response	17 July 2017
Advisory Committee meeting	4 August 2017
Registration decision (Outcome)	19 October 2017
Completion of administrative activities and registration on ARTG	31 October 2017
Number of working days from submission dossier acceptance to registration decision*	226

*Statutory timeframe is 255 working days

III. Quality findings

Introduction

Asparaginases are naturally occurring enzymes which are expressed and produced by microorganisms such as *E.coli.* L-asparaginase has also been found to be present in several animal and plant species, but is not expressed in humans. Oncaspar is a solution for injection containing pegaspargase, a PEGylated derivative of L-asparaginase. It belongs to the pharmacotherapeutic group of antineoplastic agents and immunomodulating agents.

In many patients with acute leukaemia, especially ALL, the malignant cells depend on an exogenous source of L-asparagine to survive. Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid withdrawal during treatment with the enzyme L-asparaginase. This is a unique therapeutic approach on the basis of a metabolic defect in the L-asparagine synthesis of certain malignant cells. Therefore the inclusion of L-asparaginase in the treatment regimen is a cornerstone of treatment protocols for ALL in all paediatric chemotherapeutic regimens and in the majority of adult protocols.

Pegaspargase is a modified (PEGylated) version of the enzyme L-asparaginase obtained from the following components:

- The L-asparaginase intermediate which is a homo-tetramer consisting of four subunits, each with a molecular weight of approximately 35 kDa
- SS-(m)PEG (monomethoxypolyethylene glycol succinimidyl succinate) which is a polymeric N-hydroxysuccinimide (NHS) ester of molecular weight slightly greater than 5,000 Da, and composed of:
  - Monomethoxypolyethylene glycol (abbreviated mPEG or PEG): $CH_3(OCH_2CH_2)_nOH$ where n corresponds to an average of 114.
  - A succinimidyl succinate (SS) linker that reacts with the Ɛ-amino group of exposed lysine residues and the primary amine on the N-terminal leucine on the L-asparaginase enzyme.

The purpose of L-asparaginase PEGylation is to confer superior clinical performance characteristics to the enzyme compared to native L-asparaginase: increased protein half-life (reducing the dosing frequency and hence improving patient comfort) and reduced immunogenicity allowing a fortnightly dosing schedule with comparable efficacy. The activity of PEGylated L-asparaginase is lower than that of native L-asparaginase, which is thought to be due to steric hindrance of the active catalytic site by mPEG.

Oncaspar was developed by Enzon Pharmaceuticals Inc. Development initially focused on ALL patients with known hypersensitivity to native L-asparaginase and Oncaspar was granted marketing approval in the USA and Germany for this indication in 1994. Over time, Oncaspar was increasingly investigated as a first line treatment option in clinical trials (both proprietary and academic) and in the everyday clinical setting. This first line use was approved by the US Food and Drug Administration (FDA) in 2006.

In Australia, due to the frequency of hypersensitivity with Leunase (L-asparaginase ARTG 27513), it has been necessary to include alternative preparations in ALL treatment protocols, even if not TGA approved. In the early 1990s, another, bacteria sourced preparation from *Erwinia caratovora* was made available under the SAS. In the mid-1990s, pegaspargase (Oncaspar) became available, also under the SAS. It is included in a number of treatment protocols for both first and second line use in ALL as well as in a number of clinical trials. A search on the Australia and New Zealand Clinical Trial Registry has revealed 23 clinical trials utilising pegaspargase since 1996 (16 are still ongoing). Therefore, after being available only on the SAS or through clinical trials for approximately 20 years, the sponsor is now submitting an application to register Oncaspar and allow all oncologists access to this important component of ALL treatment.

Structure

L-asparaginase

The amino acid sequence of L-asparaginase was determined by a peptide mapping procedure, providing 100% sequence coverage. The deduced amino acid sequence is corresponds with the sequence predicted on the basis of the DNA coding sequence.

Each L-asparaginase monomer contains two cysteine residues at positions 77 and 105, which are engaged in an intra-molecular disulfide bond.

Quaternary structure; L-asparaginase is a homotetrameric enzyme, comprised of four identical subunits with a mass of 34,592 kDa coupled by weak, non-covalent, largely hydrophobic interactions. The tetrameric structure of the L-asparaginase enzyme is required for enzymatic activity.

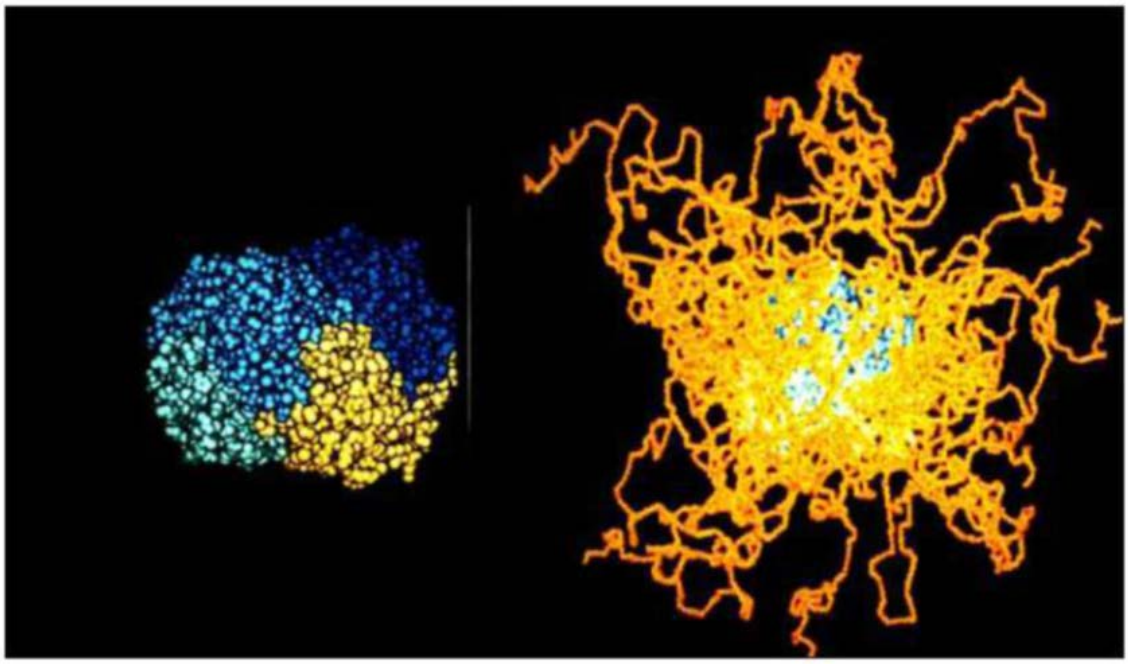
Pegaspargase

Pegaspargase is a modified (PEGylated) version of the enzyme L-asparaginase that is obtained from the following components:

- The L-asparaginase active pharmaceutical ingredient (API) starting material which is a homotetramer consisting of four subunits, each with a molecular weight of approximately 35 kDa
- SS-(m)PEG (monomethoxypolyethylene glycol succinimidyl succinate) which is a polymeric Nhydroxysuccinimide (NHS) ester of molecular weight slightly greater than 5,000 Da, and composed of:
  - Monomethoxypolyethylene glycol (abbreviated mPEG or PEG): CH3(OCH2CH2)nOH where n corresponds to an average of 114;
  - A succinimidyl succinate (SS) linker that reacts with the Ɛ-amino group of exposed lysine residues and the primary amine on the N-terminal leucine on the L-asparaginase enzyme.

The structures of L-asparaginase and pegasparagase are shown side by side in Figure 1. In the pegaspargase illustration (right-hand side), the blue coloured zones represent the L-asparaginase and the orange protrusions the PEG molecules.

Figure 1: Structure of L-Asparaginase (left) and pegasparagase (right)



Physical and chemical properties

The biological activity of pegaspargase (that is catalysis of L-asparagine hydrolysis to form L-aspartate and ammonium) is directly correlated to its clinical effect: certain types of leukemic cells show a low level expression of asparagine synthetase and are therefore highly dependent on exogenous sources of L-asparagine for their survival. A rapid depletion of L-asparagine following treatment with pegaspargase kills the leukemic cells due to deprivation of this amino acid. Normal cells however have the ability to synthesise L-asparagine and are therefore less affected. Pegaspargase is the PEGylated form of L-asparaginase. The addition of PEG to L-asparaginase may result in reduced immunogenicity and should confer a significantly increased half-life to pegaspargase. The increased half-life of pegaspargase compared to native L-asparaginase should allow for

less frequent dosing, thereby further reducing hypersensitivity. The activity of PEGylated L-asparaginase is lower than that of native L-asparaginase, which is thought to be due to steric hindrance of the active catalytic site by PEG.

Drug product

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data the product is photostable.

The proposed shelf life is 8 months when stored at 2 to 8 °C. This is supported by the stability data provided.

In-use stability data have also been submitted. The PI states under instructions for use 'Do not use if the vial has been stored at room temperature (not to exceed 25°C) for more than 48 hours. Please discard after storage at room temperature, do not return to refrigeration.' This is supported pending successful resolution of outstanding issues regarding the allowable shipping excursions.

As part of the response to questions, the sponsor has requested allowable shipping excursions of up to 25 °C for not more than 5 days (or 120 hours). The study in support of the temperature excursion encompassed 5 days only. The sponsor also has an in-use allowable storage condition of 48 hours at ≤ 25 °C listed in the PI. Therefore for an allowable shipping excursion of 5 days at ≤ 25 °C along with an allowable in use condition of 48 hours ≤ 25 °C, the sponsor would be required to submit real time data supporting a cumulative period of 7 days at ≤ 25 °C followed by return to shelf life.

Regional information

Comparability studies

Pegaspargase, the drug substance in Oncaspar, was originally manufactured using L-asparaginase produced by Merck as the starting material. All the original nonclinical and clinical development studies were performed with this material, which formed the basis for regulatory approval in the European Union (Germany) and the United States of America (USA) in 1994 and are also submitted in support of this application. L-asparaginase Lonza is proposed as the starting material for the purpose of this application. To support the use of the Lonza enzyme, the product was analytically compared with Merck/Ovation L-asparaginase. Furthermore, comparability studies between PEGylated Lonza versus PEGylated Merck L-asparaginase were also summarised. The report provided focussed on comparing the structural and physicochemical characteristics of the drug substance (DS)/drug product (DP) from each site.

The evaluator requested further information on analytical comparability be provided with a side by side comparison of batch data generated, including a comparison of all critical in-process control and release specifications at each site. Further comparative data was provided as part of the sponsor's response for L-asparaginase DS:

- Protein Content;
- Potency;
- Specific Activity;

and pegaspargase DS/DP (the only difference between the pegaspargase DS and Oncaspar DP is a sterile filtration step):

- Activity;
- Purity;

- Aggregates;
- Protein concentration;
- Specific Activity;
- 10K Free PEG;
- Total Free PEG;
- Degree of Modification;
- Sub-visible Particulates.

Batch data provided from both sites was within current proposed specifications and all attributes were comparable between sites.

The Merck process is no longer available, therefore additional comparability studies between Merck and Lonza L-asparaginase cannot be performed. Ideally data submitted for a change of manufacturer would include a full comparative assessment of the previous L-asparaginase manufacturer, Merck, (used to generate the original clinical data) with the proposed manufacturer, Lonza, including a direct comparison of all critical in process controls (IPCs), release specifications and stability data. Due to the limited data available for the comparison the full IPC and release specifications a side by side comparison was not available. Notwithstanding this, based on the data provided, it appears that the Merck and Lonza L-asparaginase and subsequent Oncaspar pegaspargase DS/DP are comparable in terms of primary and higher order structure, and analytical behaviour. Furthermore, the purity profile for the proposed Lonza L-asparaginase is markedly improved.

Therefore the comparability data presented, the supplemental comparability data submitted as part of the sponsor's response, along with the clinical history of safe use, provides adequate assurance that the Merck produced L-asparaginase and subsequent pegaspargase DS/DP used for the clinical trials is sufficiently comparable to the proposed Lonza L-asparaginase/pegaspargase. Additionally, the comparability study, along with the product characterisation, batch analysis, IPC, and specification information provided in the dossier provides an appropriate baseline of quality attributes for this product going forward post-approval.

Considerations for the clinical delegate

There are objections on quality grounds to the approval of Oncaspar (pegaspargase) injection, solution 3,750 units/5 mL.

Summary of issues

From microbiology secondary assessment

In the evaluation of sterility aspects, issues were raised with regard to manufacturing control. The evaluator stated:

> *Without confirmation that the acceptance criteria and action taken to contaminated unit action limits will be updated to be in accordance with ISO 13408-1:2008 Amendment 1:2010(E) and ISO 13408-2008 Clause 10, it is not possible to recommend approval of the registration of Oncaspar injection, solution 3750 units/5mL.*

Manufacturers

The sponsor was asked to address the outstanding issues with the following manufacturers: [information redacted].

Control of excipients

It is stated in the dossier that although the components of the PBS solution are part of the DP composition, they are not added during DP manufacture and are therefore not considered as excipients. This statement is incorrect as an excipient is defined as any component of a drug product other than an active ingredient. Furthermore these ingredients are listed as excipients on the product labels, PI, CMI and in the application form. The sponsor was asked to update the dossier listing the specifications, analytical procedures, validation of analytical procedures and justification of specifications for monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride and water for injections. A specified concentration range should be provided for each excipient and included in the DP specifications, or if this concentration will not change from DS to DP, in the DS specifications with a comment to this effect.

Sponsor's response

The sponsor agrees with the proposed changes. The excipients section will be updated to include all excipients used during the DS and DP manufacturing process. Monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride and water for injection are excipients that meet the requirements of USP/Ph. Eur. or equivalent compendium.

The materials are tested upon receipt per the compendial requirements. All analytical procedures are compendial and thus do not warrant validation. The methods have been verified to demonstrate that they are adequate for intended purpose. The specifications are set by the USP and Ph. Eur. Monographs. Concentrations of excipients are controlled by established buffer preparation procedures during the drug substance manufacturing process. Specified concentration for each excipient is described.

Evaluator comments

The quality dossier still contains statements that are incorrect. These statements the sponsor should amend/remove as agreed.

As excipient concentrations may affect Drug Product attributes (for example stability), acceptable limits for excipients around the stated label concentrations must be defined and controlled. The sponsor should be asked to provide the target limits (that is acceptable range) for monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride concentrations in the DP.

In the absence of in process or release testing for the excipients, the sponsor should also:

- Provide validation information that demonstrates the established buffer preparation procedures result in consistent excipient concentrations in the DP within limits defined above.
- Clarify how an out of range concentration would be detected should a failure in the buffer preparation process occur.

Stability

No allowable temperature excursions during shipping were applied for, nor were there any temperature cycling data provided. Therefore the sponsor was informed that, post-approval, DP batches exposed to any temperature excursions outside the ARTG listed storage conditions should be not be supplied, and should be quarantined until a subsequent application to vary has been determined. For more information see TGA Guidance.[2]

[2] TGA Guidance - Temperature excursions of biological medicines (https://www.tga.gov.au/temperature-excursions-biological-medicines) and Part 14.4 of TGA Guidance 14 - Stability testing for prescription medicines, Biological medicines.

Sponsor's response

Study SPAX-07.01 (provided in the response) was executed to investigate the effects of brief temperature excursions on the physical and chemical stability of Oncaspar and to demonstrate whether excursions for up to 5 days (or 120 hours) can be tolerated. Under this study, vials of finished product were immediately exposed to 25 °C for short periods (24 hours, 3 days and 5 days), after manufacturing and then moved to 2 to 8 °C for long term study to mimic worse case conditions. The stability results for this study demonstrated that Oncaspar remained at an acceptable level throughout its shelf life period following temperature excursions up to 25 °C for not more than 5 days (or 120 hours). As such, a total allowable time for intermittent temperature excursion of ≤ 120 hours is applied to account for all temperature exposures throughout the shelf life period.

Evaluator comments

The study presented encompassed 5 days only. The sponsor also has an in-use allowable storage condition of 48 hours at ≤ 25 °C listed in the PI. Therefore for an allowable shipping excursion of 5 days at ≤ 25 °C along with an allowable in use condition of 48 hours ≤ 25 °C, the sponsor would be required to submit real-time data supporting a cumulative period of 7 days at ≤ 25 °C followed by return to shelf life.

Therefore the evaluator cannot recommend approval for both the shipping excursion (5 days ≤ 25 °C) and the in-use storage condition (2 days at ≤ 25 °C). The sponsor has the following options:

Reduce the allowable shipping excursion duration from 5 days (120 hours) to 3 days (72 hours) ≤ 25 °C and keep the in-use storage condition (48 Hours ≤ 25 °C).

- Choose either shipping excursion of 5 days ≤ 25 °C or in-use storage condition (48 hours ≤ 25 °C) but not a combination of both
- Provide real time stability data supporting 7 days ≤ 25 °C followed by return to 2 to 8 °C for the remainder of shelf life

Note regarding comparability study

Pegaspargase, the drug substance in Oncaspar, was originally manufactured using L-asparaginase produced by Merck as the starting material. All the original nonclinical and clinical development studies were performed with this material, which formed the basis for regulatory approval in the European Union (Germany) and the United States of America (USA) in 1994 and are also submitted in support of this application. L-asparaginase Lonza is proposed as the starting material for the purpose of this application. To support the use of the Lonza enzyme, the product was analytically compared with Merck/Ovation L-asparaginase. Furthermore, comparability studies between PEGylated Lonza versus PEGylated Merck L-asparaginase were also summarised. The report provided focussed on comparing the structural and physicochemical characteristics of the DS/DP from each site. Further comparability data was provided as part of the response which encompassed some of the critical release assays for the DS/DP.

The Merck process is no longer available, therefore additional comparability studies between Merck and Lonza L-asparaginase cannot be performed. Ideally data submitted for a change of manufacturer would include a full comparative assessment of the previous L-asparaginase manufacturer, Merck, (used to generate the original clinical data) with the proposed manufacturer, Lonza, including a direct comparison of all critical IPCs, release specifications and stability data. Due to the limited data available for the comparison the full IPC and release specifications a side by side comparison was not available. Notwithstanding this, based on the data provided, it appears that the Merck and Lonza L-asparaginase and subsequent Oncaspar pegaspargase DS/DP are comparable in terms of

primary and higher order structure, and analytical behaviour. Furthermore, the purity profile for the proposed Lonza L-asparaginase is markedly improved.

Therefore the comparability data presented, the supplemental comparability data submitted as part of the sponsor's response, along with the clinical history of safe use, provides adequate assurance that the Merck produced L-asparaginase and subsequent pegaspargase DS/DP used for the clinical trials is sufficiently comparable to the proposed Lonza L-asparaginase/pegaspargase.

Additionally, the comparability study, along with the product characterisation, batch analysis, IPC and specification information provided in the dossier provides an appropriate baseline of quality attributes for this product going forward post-approval.

Proposed conditions of registration

Batch Release Testing & Compliance with Certified Product Details (CPD)

> It is a condition of registration that all batches of Oncaspar (pegaspargase) injection, solution 3,750 units/5 mL imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

IV. Nonclinical findings

Introduction

Pegaspargase is comprised of *E.coli* derived asparaginase conjugated with PEG. The proposed dose varies with age and/or body surface area in paediatric patients, with doses administered every 14 days (IM or IV). The proposed doses are 82.5 U/kg every 14 days for paediatric patients with a body surface area (BSA) < 0.6 m^2, 2,500 U/m^2 every 14 days for patients ≤ 21 years of age and paediatric patients with a BSA ≤ 0.6m^2, and 2,000 U/m^2 every 14 days of adult patients > 21 years of age. The maximum proposed dose in children and adults is 2,500 U/m^2.

Pegaspargase has the same pharmacological activity as colaspase (Leunase injection) which was first included on the TGA ARTG in October 1991 for the treatment of acute lymphoblastic leukaemia, myeloid leukaemia or malignant lymphoma.

General comments on the nonclinical dossier

The submitted nonclinical data (including the majority of the toxicity and toxicokinetic studies establishing the toxicological profile of pegaspargase) comprised mostly published literature reports generated more than 30 years ago. Therefore, these studies were not consistent with current nonclinical ICH guidelines and not conducted to current standards. As a result, the overall quality of the dossier was low. For example, there was no adequate repeated dose toxicity study in a non-rodent species. Two submitted dog studies used only 1 animal/sex/dosing route, the low dose animals were given the high dose after resting for 6 weeks and no histopathological assessment was performed. While these early studies are not of the current standard, it is understood that pegaspargase has been widely used in clinical practice overseas for decades and significant safety information has been acquired since its approval for use in 1994 in the USA and Germany.

All submitted nonclinical studies were carried out with pegaspargase manufactured with native asparaginase enzyme produced by Merck (USA), except for a pharmacokinetic

study in rhesus monkeys (Berg, 1993/NIH Study);[3] where asparaginase was produced by Kyowa-Hakko. None of the nonclinical studies were carried out with the product proposed for marketing, which will be manufactured using native asparaginase produced by the Lonza company. The sponsor stated that the enzyme manufacturer was switched from Merck to Lonza in 2010 for Oncaspar in the US market, while the enzyme for pegaspargase in the Germany and Poland markets had always been from Kyowa-Hakko. Pegylated asparaginase, that is pegaspargase batches used in nonclinical studies were made in Rutgers University (batches 28, 29 and 30) or by Enzon.

There were no nonclinical pharmacology, pharmacokinetics or toxicology studies to demonstrate comparability between the product to be marketed in Australia with the nonclinical materials. The sponsor stated that the enzyme from Lonza was produced by the descendant of the Master Cell Bank used by Merck, and that quality comparability data demonstrated comparability of the enzyme sourced from Merck and Lonza and of the finished products manufactured from these sources. The TGA quality evaluator advised that quality data indicated that the Merck and Lonza L-asparaginase and subsequent Oncaspar pegaspargase drug substance/product are comparable in terms of primary and higher order structure and analytical behaviour. Furthermore, the purity profile for the proposed Lonza L-asparaginase is improved. Whilst the absence of nonclinical comparability data is a major deficiency of the nonclinical data package, this deficiency may be overcome by quality comparability data, clinical comparability and/or adequate clinical efficacy and safety data with the earlier batches and the product for approval.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Pegaspargase was developed to extend the half-life of enzyme activity and reduce immunogenicity of the enzyme asparaginase by pegylation.

Asparaginase hydrolyses asparagine to aspartic acid and ammonia. Asparagine is a non-essential amino acid and is synthesised from aspartic acid and glutamine by the enzyme asparagine synthetase (ASY) in mammalian cells. Childhood ALL has low expression of ASY probably due to the methylation of the ASY gene.[4,5] Consequently, depletion of asparagine in blood by asparaginase results in inhibition of protein synthesis, DNA synthesis and RNA synthesis of ALL cells, and thus apoptosis of the cancer cells.

In vitro studies

No supporting proof of concept studies, or enzyme activity assays were submitted in the nonclinical dossier. However, the enzyme activity (potency) is specified for both the intermediate, asparaginase and pegaspargase and tested for each batch. The data are included in the quality dossier and are evaluated by the quality evaluator.

Pharmacokinetic studies in the rat, dog, rabbit and monkey and toxicity studies showed a direct correlation between the rise in plasma asparaginase enzyme activity and the decline in plasma asparagine amino acid levels to below the limit of quantification. Levels of the asparagine amino acid always remained depleted whilst significant asparaginase enzyme

[3] Berg SL et al. 1993 Pharmacokinetics of PEG-L-asparaginase and plasma and cerebrospinal fluid L-asparagine concentrations in the rhesus monkey. *Cancer Chemother Pharmacol* 1993; 32: 310-314
[4] Richards, NGJ and Kilberg MS (2006) Asparagine synthetase chemotherapy. *Annu Rev Biochem*. 2006; 75: 629-654.
[5] Akagi T et al. (2006) Methylation analysis of asparagine synthetase gene in acute lymphoblastic leukemia cells. *Leukemia.* 2006; 20: 1303-1306.

activity was present in plasma. Further, there was no glutamine (asparagine precursor) depletion, suggesting asparaginase does not affect glutamine degradation.

In vivo studies

Pharmacology studies submitted in the nonclinical dossier included only published literature reports of studies assessing pegaspargase efficacy in mice inoculated intraperitoneal (IP) with murine lymphoma cells or studies in domestic companion dogs with spontaneous lymphosarcoma (that is animals with malignant spontaneous occurring tumours). These mostly non-standard studies were comprised of old published articles and not conducted to modern standards (conducted more than 25 to 30 years ago) and their overall reliability is somewhat limited.

The anti-tumour efficacy of pegaspargase was compared to native asparaginase at IP doses of 250 to 1,000 U/kg to tumour bearing BDF1 mice following IP inoculation of L5178Y lymphosarcoma cells. The PEGylated enzyme showed greater anti-tumour activity than the native enzyme (based on overall survival during 2 months). Similar findings were observed when 6C3HED lymphoma cells were inoculated into mice subsequently treated with 25 to 250 U/kg pegaspargase (all mice at the highest dose survived).

In dogs with spontaneous malignant lymphoma, pegaspargase given by the IP route showed anti-tumour activity at low doses (10 to 30 U/kg);[6] based on remission response rates of 70% (14 out of 20 dogs). The addition of other chemotherapy agents (vincristine, cyclophosphamide, methotrexate and prednisolone) slightly increased the response rate to 88% (15 out of 17 dogs). The addition of a short course of combination chemotherapy also prolonged the duration of response (from 14 to 102 to 7 to 441 days). Higher IP doses (15 to 200 U/kg IP);[7] did not increase rates of remission/survival. Pegaspargase was also effective in some animals which were previously resistant to other chemotherapy treatments. When administered by the IM route, the PEGylated and native enzymes (30 and 400 U/kg, respectively) showed similar anti-tumour activities following the induction period of 2 weeks based on response rates of remission and had similar overall responses based on remission and survival after administration with combination chemotherapy (vincristine, cyclophosphamide, doxorubicin and prednisone).[8]

In another study in dogs with non-Hodgkin's lymphoma weekly doses of pegaspargase (10 or 30 U/kg IM) or native asparaginase (400 U/kg IP) for two weeks followed by a period of induction with combination chemotherapy and subsequent dosing again with pegaspargase or asparaginase as maintenance therapy, pegaspargase was reported as effective as the native asparaginase for remission and survival.[9]

Overall, the pharmacology studies support the proposed use of pegaspargase for the treatment of ALL. The improvement in survival with antineoplastic combination therapy in the dog model suggests additional agents could be provided in combination chemotherapy with pegaspargase to patients.

Secondary pharmacodynamics and safety pharmacology

No in vitro studies screening for off-target activity were submitted. In vitro and in vivo studies in mice showed anti-tumour activity against some human pancreatic cancer cell

[6] MacEwen E G et al 1987 A Preliminary Study on the Evaluation of Asparaginase Polyethylene Glycol Conjugate Against Canine Malignant Lymphoma. *Cancer* 1987; 59: 2011-2015
[7] MacGrath Study 1982. Submission document.
[8] MacEwen EG et al. 1992 Evaluation of L-asparaginase: Polyethylene Glycol Conjugate versus Native L-asparaginase Combined with Chemotherapy. A randomized Double-blind study in Canine Lymphoma. *Journal of Veterinary Internal Medicine* 1992; 6: 220-234.
[9] Teske, E et al. 1990 Polyethylene Glycol-L-asparaginase versus Native L-asparaginase in Canine Non-Hodgkin's Lymphoma. *Eur J Cancer* 1990; 26: 891-895.

lines. Pegaspargase in combination with gemcitabine was more effective than either agent alone.

No specific safety pharmacology studies were submitted, which assessed effects on the cardiovascular, respiratory, central nervous, renal or gastrointestinal systems. Pegaspargase had no overt adverse effect on vital functions in the submitted toxicity studies although central nervous system (CNS) effects and cardiovascular and respiratory functions were not specifically evaluated in the toxicity studies. The sponsor noted the absence of effects on cardiac, respiratory or renal functions in an efficacy study in dogs with non-Hodgkin's lymphoma treated with pegaspargase by IM injection;[9] however, the study did not specifically assess functions of these organ systems. Considering the already established clinical use of pegaspargase overseas, the absence of specific safety pharmacology studies should not preclude the approval of pegaspargase for the proposed indication.

Pharmacokinetics

The pharmacokinetics of pegaspargase was assessed by determining plasma asparaginase activity. The rate of absorption after IM administration of pegaspargase was moderate to slow in animal species (rats and dogs; T_{max} 0.27 to 1.5 days, and slow in humans T_{max} about 3 days). Bioavailability by the IM route was moderate in rats (43 to 61%) and high in mice (76.2%) and dogs (96 to 114%). Exposure was generally dose proportional following IV and IM single doses in rats and dogs, with no consistent sex differences.

Plasma clearance was slow in all test animal species (0.12 to 0.86 mL/hour/kg in rats, rabbits, dogs, monkeys) and humans (0.14 mL/hour/kg). The volume of distribution (Vz or Vss) was small in animal species (39 to 98 mL/kg in rats and 40 to 57 mL/kg in dogs) and humans (57 mL/kg) similar to the blood/plasma volume indicating that pegaspargase does not distribute beyond the systemic circulation. Nonclinical studies also demonstrated that plasma levels of asparagine rapidly dropped below the limit of quantitation (LOQ) immediately following pegaspargase dosing in the rat, dog, rabbit and monkey and that plasma levels of asparagine inversely correlated with plasma asparaginase activity. In monkeys, pegaspargase (IM) did not cross the blood cerebrospinal fluid (CSF) barrier.

Pegaspargase showed a long elimination half-life ($T_{½}$) following administration by various routes of administration in rodents (2 to 4 days), rabbits (6 days), dogs (5 to 12) and monkeys (6.5 days), similar to that in humans (approximately 5 days in non-sensitised patients and 2.5 days in sensitised patients). As expected, pegaspargase showed a plasma asparaginase activity $t_{½}$ much longer than that seen for the non-PEGylated form in animal species (mice: 3.75 days compared with 5 hours and rabbits: 6 days compared with 20 hours). Additionally, immunisation of mice with pegaspargase had no effect on the clearance of pegaspargase (half-life of 3.5 days in pre-immunised animals), whilst asparaginase was cleared immediately in mice pre-immunised with asparaginase, suggesting pegaspargase is less immunogenic than non-PEGylated asparaginase.

There were no studies investigating the distribution, metabolism or excretion of pegaspargase. Clearance of pegaspargase probably involves proteolysis and clearance by the reticulo-endothelial system.[10] PEG (polyethylene glycol) released by degradation of the protein-PEG conjugate is expected to be eliminated primarily as unchanged material through the urine.[11]

[10] Asselin BL et al. (1993). Comparative pharmacokinetic studies of three asparaginase preparations. *J Clin Oncol*; 1993; 11: 1780-1786.
[11] Webster R et al. (2007) PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. *Drug Metab Disp* 2007; 35: 9–16.

Overall, the pharmacokinetic profile of pegaspargase in mice, rats and dogs were sufficiently similar to that in humans to allow them to serve as appropriate models for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

No pharmacokinetic drug interactions studies were submitted. Pharmacokinetic drug-drug interactions are not expected for pegaspargase.

Toxicology

Acute toxicity

Single dose toxicity was investigated in GLP studies carried out recently (in 2007) in rats and dogs by the IV route and one GLP study conducted in 1983 in mice by IP injection.

Very high doses of pegaspargase given by the IP route resulted in the death of mice at 25,000 and 100,000 U/kg, and decreased activity, hunched posture and piloerection. The maximum non-lethal dose in mice was 10,000 U/kg (30,000 U/m^2), 12 times the maximum recommended human dose (MRHD) of 2,500 U/m^2. Mortality was not seen in rats and dogs at all doses tested in the two single dose studies. The highest dose was 500 U/kg IV in both species (equivalent to 3,000 and 10,000 U/m^2, respectively). Toxicokinetic data in rat and dog studies provided direct evidence of systemic exposure. Also there were no deaths in an old study with two dogs receiving two weekly doses of up to 1,200 U/kg IV or IM. Reduced bodyweight was common in rodents. Lacrimation, injected sclera and soft faeces were seen in dogs.

Repeat dose toxicity

Repeated dose Good Laboratory Practice (GLP) compliant toxicity studies were conducted with pegaspargase in mice (13 to 17 weeks; IP and IM; weekly dosing), rats (4 to 5 weeks; IP and IM; dosing 5 times a week) and dogs (2 weeks; IV and IM; weekly dosing). These animal species are considered appropriate species based on pharmacological effects (decreased plasma asparagine levels after pegaspargase dosing) and pharmacokinetics. The studies were conducted more than 30 to 40 years ago (in the 1970s and 1980s) and not carried out to modern guideline requirements or standards. The repeat dose toxicity data are deficient for the registration of a new drug:

- There was no adequate study in a non-rodent species. In the two dog studies (Studies #4A and #4B) only 1 animal/sex/dosing route was used, the low dose animals were given the high dose after resting for 6 weeks, and no histopathological assessment was performed.
- The study duration in rats was short (up to 5 weeks).
- Only a limited number of tissues were processed for histological examination (for example lymph node and bone marrow were not examined).
- Clinical pathology assessment was not performed in the mouse study.
- Cases of pneumonia occurred in all rodent studies in the control and treated groups, which confounded the study findings.
- There was no adequate study by the IV route.

However, pegaspargase has been widely used in clinical practice for decades, and significant information regarding its toxicity profile is expected to have been acquired since its registration in the USA and Germany in 1994. Furthermore, the non-PEGylated

enzyme, asparaginase (Leunase) has been approved for use in Australia for nearly two decades, which provide additional information on potential adverse events of pegaspargase.

Relative exposure

Very sparse blood samples were collected for toxicokinetic analysis in the toxicity studies, and AUC values were not calculated. Exposures in the toxicity studies are compared with the exposure in humans based on dose per body surface area and C_{max} (IM studies only). The highest proposed clinical dose (2,500 U/m^2) regardless of patient age was used for exposure comparison (Table 3).

Following IM dosing at the highest doses in the repeat dose studies, moderate exposures were achieved in rats and dogs based on plasma C_{max} (exposure ratio (ER) 17). Exposure in the mouse study was low (ER approximately1 based on dose per body surface area). The highest doses resulted in body weight loss or reduced weight gain, suggesting the maximum tolerated dose was achieved.

Table 3: Relative exposure in repeat-dose toxicity studies

Species (*n*)	Study	Dose		C ^	Exposure ratio	
		(U/kg)	(U/m^2)		Dose*	C_{max}ǂ
Mouse (Swiss-Webster) *n* = 5/sex	13 weeks (IP weekly) 17 weeks (IM weekly) (Study #5)	50	150	-	0.12	-
		200	600	-	0.48	-
		500	1,500	-	1.2	-
Rat (Wistar) *n* = 6-8/sex	4-5 weeks (IM daily, 5 days/week) (Study #3)	100	600	5.15	2.4	4.3
		200	1,200	7.46	4.8	6.2
		400	2,400	20.51	9.6	17
	4 weeks (IP daily, 5 days/week) (Study #2)	10	60	-	0.24	-
		30	180	-	0.72	-
		60	360	-	1.4	-
Rat (SD) *n* = 6/sex	4 weeks (IP daily, 5 days/week) (Study #8)	400	2,400	-	9.6	-
Dog (Beagle) *n* = 1/sex	2 weeks (IM weekly) (Study #4A, 4B)	200	4,000	4.26	3.2	3.55
		1,200	24,000	19.79	19	17
Human (patients)	Studies ASP-302, ASP-304 (IM, fortnightly)	-	2,500	1.2	-	-

* Animal:human exposure ratios based on total doses over two weeks expressed on a body surface area basis (that is U/m^2) ǂ animal : human C_{max} ^ Data are for female rats (24 h after dosing on Day 11) and male and female dogs (24 hours after the 1st dose at 200 IU/kg and 24 hours after the 2nd dose at 1,200 U/kg)

Toxicities

The major target organ for toxicity (mostly minimal to mild in severity) was spleen. Reduced spleen weight was observed in all mouse and rat studies by IM or IP dosing at all dose levels, although there were no histopathological changes. Despite of the absence of histological lesions in spleen, reduced spleen weight may be associated with compromised

immune response. Lymph node was not histologically examined in the toxicity studies. Thymus atrophy and broadening thymic cortex were observed in dogs and rats, respectively, which were treated with the non-PEGylated asparaginase (Crasnitin).[12] Lymphocytopaenia and atrophy of lymph nodes, thymus and spleen were reported in mice treated with asparaginase (sourced from Merck, Sharp and Dohme Research Laboratories).[13] That study also showed that lymphocytes in asparaginase treated mice did not migrate normally from lymph nodes to lymphoid organs, and splenic lymphocytes from asparaginase treated mice induced significantly less graft-versus-host reaction and incorporated significantly less thymidine into DNA. The immunosuppressive effect was shown to be due to asparagine depletion. Asparaginase treatment also suppressed T cell dependent antibody response (to sheep erythrocytes) and skin graft rejection. A more recent publication[14] also showed that depletion of asparagine by asparaginase causes inhibition and suppression of T cell responses. Asparagine depletion resulted in suppression of cellular processes and pathways involved in immune responses (for example suppression of mammalian target of rapamycin (mTOR) signalling, autophagy, Myc expression and L-lactate secretion). Asparagine depletion was clearly demonstrated in animal species treated with pegaspargase. Pegaspargase treatment may suppress patient immune responses.

Cases of pneumonia, which resulted in deaths, occurred in control and treated groups of all rodent studies conducted in the same laboratory. The incidence was slightly higher in treated than control groups, but the incidence was not correlated with the dose level. Since both control and treated groups were affected, the study authors did not consider the mortalities and pneumonia were due to pegaspargase treatment. Pulmonary findings were also observed in the acute toxicity studies in mice by IP injection of pegaspargase, consisting of peribronchial and/or perivascular lymphoid hyperplasia and interstitial pneumonitis. In two recent single dose, GLP studies in rats and dogs by IV injection, alveolar histiocytosis was detected in rats at 500 U/kg (3,000 U/m^2), but there were no findings of respiratory effects in dogs at up to 500 U/kg IV (10,000 U/m^2). Spleen weights were unaffected in the acute dose studies in rats and dogs, which were necropsied 14 days after dosing. Given the absence of clearly treatment related pulmonary effects in the repeat dose studies, the pulmonary findings in the acute mouse and rat studies are of low clinical relevance.

Minor hepatic effects were evident in rodents following IP or IM dosing. Histological findings in mice following IP dosing at 500 U/kg weekly (but not after IM dosing) included minimal to mild feathery hydropic cytoplasmic vacuolation in both sexes and periportal hepatocellular atrophy in male mice. Clinical chemistry analyses were not conducted in mice. Periportal lipoid degeneration was seen in mice after a single, high IP dose (100,000 U/kg = 300,000 U/m^2). In rats following daily IM dosing (5 days/week), there were minimal to mild increases in plasma alkaline phosphatase (ALP) in females at ≥ 10 U/kg, aspartate transaminase (AST) in females at ≥ 400 U/kg, and cholesterol in males at ≥ 200 U/kg, and decreases in total protein in both sexes at 400 U/kg. Slight decreases in plasma globulin and total protein and a decrease in cholesterol were also detected in rats after a single IV dose of pegaspargase at 100 or 500 U/kg. Liver weights were decreased in high dose females (400 U/kg/day IM 5 days/week for 5 weeks), without microscopic abnormality. There was no evidence of liver toxicity in rats dosed with pegaspargase by IP injection at up to 60 U/kg/day (5 days/week) or 400 U/kg weekly. In dogs (preliminary study with only 1/sex/dosing route), there were elevations in plasma alanine

[12] Lorke D and Tetternborn D (1970) Experimental studies on the toxicity of Crasnitin in animals. *Recent Results Cancer Res. (Fortschritte der Krebsforschung)* 1970; 33: 174-180.
[13] Weksler ME et al (1971) Studies on the immunosuppressive properties of asparaginase. *Immunology*: 1971; 21**:** 137.
[14] Torres A et al (2016) Asparagine deprivation mediated by *Salmonella* asparaginase causes suppression of activation-induced T cell metabolic reprogramming. *J. Leukoc. Biol.*2016; 99: 387-398

aminotransferase (ALT) (2 to 7 x) in males after 2 weekly doses at ≥ 200 U/kg IM. Plasma AST and ALP were unaffected and as mentioned above, gross or microscopic examination was not conducted in the short term repeat dose study. Transient increases in plasma AST and ALT were reported in one dog, a slight decrease in liver function in another dog and slight fatty infiltration of the liver in one dog receiving non-PEGylated asparaginase.[12] In the same study, mild hepatocyte swelling and slight periportal fatty infiltration were reported in rats treated with asparaginase. The animal studies suggest a low to moderate risk of liver toxicity in patients receiving pegaspargase treatment.

Decreased body weight gain was consistently observed in mice, rats and dogs treated with pegaspargase. The decrease in body weight gain was associated with decreased food intake in rats at 400 U/kg IP (weekly dosing) and in dogs at 1,200 U/kg (weekly dosing).

Other findings that were possibly related to treatment were mild anaemia in rats and leucopaenia in dogs following IM dosing. Slight decreases in haemoglobin (approximately 10%) and mean corpuscular volume (5 to 10%) at all doses (100 to 400 U/kg/day, 5 days/week), and haematocrit (approximately 5%) at ≥ 200 U/kg were detected in rats. In dogs there were slight to moderate reductions in white blood cell count in both IV and IM dose groups in the 2 week repeat dose studies (weekly dosing; n = 1 dog/sex). No haematology alterations were observed in other studies. Bone marrow was not examined in the repeat dose studies. No haematological alterations were reported for non-PEGylated asparaginase. Pegaspargase is expected to have a low risk of haematopoietic suppression in humans.

In dogs with non-Hodgkin's lymphoma treated with pegaspargase by IM injection (10, 30 U/kg IM) or asparaginase (400 U/kg IP)[15] adverse clinical signs were only reported following IP asparaginase treatment (anaphylactic shock, anorexia, vomiting, hypersensitivity related oedema, seizure and acute pancreatitis).

Urinalysis showed haematuria in rats of control and treated groups in the IP and IM studies, and the finding was thought to be attributed to underlying respiratory infections. The finding was probably not related to pegaspargase treatment.

Overall, the toxicity profile of pegaspargase is sufficiently similar to that of the non-PEGylated asparaginase. Potential adverse effects in patients include immunosuppression and liver toxicity.

Safety of PEG molecule

Pegaspargase is a covalent conjugate of asparaginase from *E.coli* and monomethoxypolyethylene glycol (PEG; molecular weight approximately 5,000). The PEG molecule is expected to be released from the conjugate and then eliminated by urinary excretion.[16] The safety of PEG has been previously assessed in submissions of other conjugated drug products. There is no safety concern for the PEG in pegaspargase.

Genotoxicity

The genotoxicity of pegaspargase was assessed in a single genetic toxicology test. Pegaspargase was not mutagenic in a non-standard Ames test performed using 4 *Salmonella typhimurium* strains (TA 97a, T98, TA100 and TA102) only at a single concentration of 75 U/plate (with and without metabolic activation), with no positive controls.

[15] Teske E et al. Polyethylene glycol-L-asparaginase versus native L-asparaginase in canine non-Hodgkin's lymphoma. *Eur J Cancer* 1990; 26: 891-895.
[16] Webster R et al. (2007) PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. *Drug Metabolism and Disposition* 2007; 35: 9-16.

In a published literature report;[17] assessing asparaginase treatment in pregnant New Zealand White (NZW) rabbits, chromosomal analyses of asparaginase treated dams and fetuses showed normal karyotypes. Similarly no alteration of karyotype was observed in rabbit white blood cell (WBC) cultures by asparaginase.

As a PEGylated protein, pegaspargase is not expected to be genotoxic.

Carcinogenicity

No carcinogenicity studies were submitted, which is acceptable for a pharmaceutical for the treatment of advanced cancer[18] and given the nature of the drug as a protein.[19]

Reproductive toxicity

There are no fertility, embryofetal development and pre/post-natal development studies with pegaspargase. The repeat dose toxicity studies in rodents (mice and rats) showed no effects on male or female reproductive organs. The long established use in the clinical setting overseas, and some information available for asparaginase (see below) somewhat mitigates the cause for concern for the lack of nonclinical data on the reproductive toxicity of pegaspargase.

Embryofetal toxicity studies with asparaginase showed embryo loss and teratogenicity in rats and rabbits. Published embryofetal toxicity studies reported that asparaginase was teratogenic in rats at ≥ 1000 U/kg IV (6,000 U/m^2; malformations: microphthalmia, malformed vertebral column, sternal cleft and exenteria) with treatment from gestation day (GD) 6 to 15 (no observed effect level (NOEL) of 300 U/kg IV). There were no malformations in another rat study when 100 and 1,000 U/kg asparaginase were administered IV on GD 7 and GD 8. In rats, embryotoxicity (resorption) was evident at lower doses (≥ 300 U/kg; 1,800 U/m^2). In rabbits malformations of the bladder, intestines, liver, tail, limbs, brain, kidney and lung and resorptions were observed at all doses tested (≥ 50 U/kg (600 U/m^2) IV on GD 8 and GD 9).

The teratogenic potential of asparaginase was also shown in rat embryos cultured in vitro. Embryos incubated with ≥ 0.25 U/mL of asparaginase showed growth and development retardation together with malformations of the brain, eyes, face, and trunk and failure of neural tube closure. Asparaginase crossed the placenta in rabbits.[20]

Based on data on asparaginase, pegaspargase is expected to be teratogenic.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[21] This is appropriate, and consistent with the pregnancy classification for non-PEGylated asparaginase.

Local tolerance

Evaluation of injection site reactions after 17 weekly IM injections in mice showed pegaspargase (in phosphate buffered saline, pH 7.3) did not result in any adverse local

[17] Adamson et al. (1970) Evaluation of the embryotoxic activity of L-asparaginase. *Arch Int PharmadynTher* 186(2):310-320

[18] ICH guideline S9: Nonclinical evaluation for anticancer pharmaceuticals.

[19] ICH guideline S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals.

[20] Adamson et al. 1970 Evaluation of the embryotoxic activity of L-asparaginase. *Arch Int PharmadynTher* 1970; 186: 310-320

[21] Pregnancy Category D is classified as Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

reactions. The pegaspargase formulation tested in the mouse study was not the final product proposed for marketing as recommended in testing guidelines,[22] that is the pegaspargase tested was not manufactured using asparaginase produced by the Lonza company and the vehicle used was different from the final clinical formulation. Local tolerance by IV and IM injection will need to be addressed by clinical data.

Antigenicity

Asparaginase is a protein of bacterial origin and generation of anti-pegaspargase drug antibodies (ADA) may be expected. In a mouse study, pegaspargase administration by either the IP or IM route resulted in antibody titres of less than 1:50 for the duration of a 12 week mouse study following weekly pegaspargase dosing. In contrast, following weekly administration of non-PEGylated asparaginase dosing by the IP route, antibodies to asparaginase were detected by Week 3 (titres 1:87,500). In accord with this finding, pre-immunisation of mice with pegaspargase had no effect on pegaspargase clearance, whereas asparaginase was cleared immediately in mice pre-immunised with asparaginase (see discussion under Pharmacokinetics above). Based on animal studies, pegaspargase is expected to be less immunogenic than non-PEGylated asparaginase in patients.

Phototoxicity

Phototoxicity studies were not conducted using pegaspargase, which is acceptable. As noted in the ICH S10 guideline on 'Photosafety evaluation of pharmaceuticals', the cause for concern for phototoxicity does not generally apply to peptides and proteins.

Paediatric use

No specific studies in juvenile animals were submitted.

Comments on the nonclinical safety specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for pegaspargase detailed in the sponsor's draft Risk Management Plan (RMP)(Section II) are in general concordance with those of the nonclinical evaluator except for the following to be included in SII.1 Conclusion of nonclinical data:

- Immune response suppression is considered an important potential risk.

Nonclinical summary and conclusions

- Most submitted studies were conducted in the 1970s and 1980s. Therefore, the nonclinical dossier was not consistent with current nonclinical ICH guidelines and the overall quality was poor. Pivotal safety studies albeit limited in number and scope (for example, only n = 1/sex in the repeat dose studies in dogs) were GLP compliant.
- Materials used in nonclinical studies were early development batches manufactured with asparaginase from Merck, while asparaginase from Lonza is used for the manufacture of the drug substance for marketing in Australia. The sponsor stated that the enzyme from Lonza was produced by the descendant of the Master Cell Bank used by Merck, and that quality comparability data demonstrated comparability of the

[22] Guideline on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)

enzyme sourced from Merck and Lonza and of the finished products manufactured from these sources.

- Advice on comparability from the TGA quality evaluator indicated that the Merck and Lonza L-asparaginase and subsequent Oncaspar pegaspargase drug substance/product are comparable in terms of primary and higher order structure and analytical behaviour. Furthermore, the purity profile for the proposed Lonza L-asparaginase is markedly improved.
- In vivo primary pharmacology studies showed anti-tumour activity of pegaspargase in murine models of lymphoma and in dogs with spontaneous lymphosarcoma. In mice, the anti-tumour activity of pegaspargase (based on increased survival) was greater for the PEGylated enzyme than the native enzyme. In dogs, pegaspargase was effective at relatively low doses (10 to 30 U/kg, equivalent to 200 to 600 U/m^2), and combination chemotherapy increased the response rate and prolonged the duration of response.
- No specific safety pharmacology studies were submitted. No general signs indicative of effects on CNS, cardiovascular and respiratory system functions were reported in single dose and repeat dose toxicity studies, although these functions were not specifically monitored in the studies. In vitro and in vivo secondary pharmacology studies in mice showed anti-tumour activity against some human pancreatic cancer cell lines.
- The pharmacokinetics of pegaspargase in animals was similar to that in humans. Following IM administration, the rate of absorption was moderate to slow in rats and dogs (T_{max} 0.27 to 1.5 days), compared with T_{max} 3 days in humans. Bioavailability by the IM route was moderate in rats (43 to 61%), high in mice (76 %) and dogs (96 to 114%). As expected, pegaspargase has an elimination half-life much longer than for the non-PEGylated form in animal species. The elimination half-lives by various routes of administration (IV, IM, and IP) were long in all the test species (2 to 12 days), similar to that observed in humans. The volume of distribution is small and close to the blood volume.
- There were no studies on pegaspargase tissue distribution, metabolism or excretion. Clearance of pegaspargase probably involves proteolysis and clearance by the reticulo-endothelial system. PEG (polyethylene glycol) released by degradation of the protein-PEG conjugate is expected to be eliminated primarily unchanged in the urine.
- Pegaspargase had a low order of acute toxicity in mice following dosing by the IP route and in rats and dogs by the IV route.
- Repeat-dose toxicity studies by the IP, IM or IV route for up to 13 Weeks were conducted in mice rats and dogs. Low to moderate exposures were achieved in the repeat dose studies, with animal/human exposure ratios up to 1.2 in mice, 10 in rats and 19 in dogs based on dose per body surface area (BSA).
- The major toxicity finding was decreased spleen weight (without histological lesions). Plasma asparagine was depleted after pegaspargase dosing, an expected pharmacological effect. Decreased spleen weight and depletion of asparagine suggest that immune responses might be suppressed in patients treated with pegaspargase. Other findings included mild hepatic effects (minimal to mild feathery hydropic cytoplasmic changes and periportal hepatocellular atrophy in liver of mice, decreased liver weights and slight increases in plasma ALP, AST, cholesterol and decrease in total protein in rats, and elevations in plasma ALT in dogs), mild anaemia in rats, mild leucopaenia in dogs, and reductions in body weight gain in all species.
- Pegaspargase is not expected to be genotoxic. It was not mutagenic in a poorly conducted Ames assay. No carcinogenicity studies were conducted, which is considered acceptable.

- Published studies showed non-PEGylated asparaginase was embryotoxic and teratogenic in rats at ≥ 1,000 U/kg IV (NOEL of 300 U/kg, equivalent to 1,800 U/m^2) and in rabbits at ≥ 50 U/kg IV (equivalent to 600 U/m^2), which is in the therapeutic range of pegaspargase in ALL patients.
- Pegaspargase did not cause injection site reactions in mice following 17 weekly IM injections. The material was well tolerated locally at the injection site in single dose and repeat dose toxicity studies. However, the pegaspargase tested was not manufactured using asparaginase from the manufacturer which will produce the asparaginase proposed for registration (the Lonza company), and the vehicle used was different from the final clinical formulation.
- In a dedicated 12 week antigenicity study in mice, pegaspargase (IP or IM dosing) showed reduced immunogenicity compared to asparaginase (IP). In a pharmacokinetic study, pre-immunisation of mice with pegaspargase had no effect on the clearance of pegaspargase, whereas native asparaginase was cleared immediately in mice immunised with asparaginase.

Conclusions and recommendation

- The primary pharmacology studies are supportive of the proposed indication for the treatment of patients with ALL.
- No specific safety pharmacology studies were submitted, but there were no signs indicative of effects on CNS, cardiovascular and respiratory systems in single dose and repeat dose toxicity studies.
- Pharmacokinetic studies demonstrated prolonged elimination of pegaspargase compared with the non-PEGylated enzyme.
- The major finding in toxicity studies was decreases in spleen weight. Asparaginase was shown to inhibit immune responses as a result of asparagine depletion. These findings suggest that immune responses might be suppressed in patients treated with pegaspargase. Pegaspargase was less immunogenic than non-PEGylated asparaginase in mice.
- Published studies showed native asparaginase was embryotoxic and teratogenic in rats and rabbits and crosses placenta in rabbits. Pregnancy category D is considered appropriate.
- The nonclinical studies were short of nonclinical data requirements for the registration of a new drug. Nearly all nonclinical studies were conducted with pegaspargase manufactured from asparaginase sourced from a manufacturer (Merck) different from the material (Lonza) to be registered in Australia. No pharmacology or toxicology comparability studies were conducted. However, these deficiencies are overcome by quality comparability data and clinical trials using the Merck material.
- Based on adequate quality comparability data, the submitted nonclinical studies are therefore considered adequate and valid.
- There are no nonclinical objections to the registration of Oncaspar for the proposed indication provided safety was adequately demonstrated by the long history of clinical use overseas and clinical trial data with the new source of drug material.

The nonclinical evaluator made recommendations with regard to the PI but these are beyond the scope of the AusPAR.

V. 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

ALL cells express very low levels of the enzyme asparagine synthetase; hence they are incapable of synthesizing asparagine from aspartate. This characteristic, therefore, is a biologically plausible method of attacking such cells while sparing others.

In general, ALL treatment has a remission/induction phase of treatment, an 'intensification' (or consolidation) phase and then continuation and maintenance therapy. Treatment is also directed to the CNS to prevent relapse attributable to leukaemic cells sequestered in this site. All phases of treatment involve combination chemotherapy.

Multiple induction regimens have been developed and most are based on those for children. There are little or no data on comparison between regimens, but most contain vincristine, a corticosteroid, and an anthracycline. Typically, some sort of CNS prophylaxis is also incorporated. Drugs would typically include vincristine, prednisolone, cyclophosphamide, doxorubicin and l-asparaginase. Cytarabine and methotrexate are often added during consolidation treatment, and maintenance therapy often includes 6-mercaptopurine, methotrexate, steroids and vincristine.[23]

There is little to be gained by discussing here the multitude of treatment regimens based upon prognostic factors. Perhaps of key importance to the submission is this excerpt with respect to asparaginase, shown below.

Asparaginase

Asparaginase is a key component of the ALL regimens for children leading to superior complete response (CR) and disease free survival rates. For adults, it is a component of the CALGB ALL regimen;[24] the Berlin Frankfurt Munster (BFM) regimen, the GRAALL 2003 regimen;[25] and the modified Hyper-CVAD regimen;[26] but not the standard Hyper-CVAD regimen.

The importance of asparagine depletion in adults was illustrated in a prospective study of pegylated asparaginase that demonstrated a significant improvement in median overall survival (31 versus 13 months) in those patients who achieved plasma asparagine depletion. Further support comes from paediatric trials that suggest that clinical outcomes improve as the period of complete asparagine depletion in the plasma increases. Protocols for adults must balance the desire to achieve maximum asparagine depletion with the understanding that prolonged depletion is difficult for most adults to tolerate.

Asparaginase can be associated with allergic reactions, coagulopathies, acute pancreatitis, and increased liver transaminases. Asparaginase induces a hypercoagulable state that can result in catastrophic thrombosis of the inferior vena cava or the superior sagittal sinus in addition to deep vein thromboses of the legs or arms. In addition, adults receiving asparaginase commonly develop fatigue, anorexia, confusion, and listlessness.

[23] Up to Date 14.09.16; Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukaemia in adults
[24] CALGB ALL; Cancer and Leukaemia Group B ALL
[25] GRAALL; Group for Research on Adult Acute Lymphoblastic Leukaemia
[26] Hyper-CVAD; Hyper Cyclophosphamide Vincristine Adriamycin (doxorubicin) and Dexamethasone

There are three formulations of asparaginase available, each with different half-lives:

- Native *E.coli* Asparaginase (not available in the US); Half-life approximately one day
- *Erwinia* Asparaginase; Half-life approximately 14 hours
- Pegylated *E.coli* Asparaginase (pegaspargase, Oncaspar); Half-life approximately six days.

The dose and schedule of asparaginase administration varies depending upon the formulation chosen and whether given to children or adults. Investigations are ongoing to determine the ideal dose and schedule. Pegylated asparaginase has become the preferred preparation for most circumstances because it appears to be less immunogenic while providing equal or greater efficacy when compared with the other formulations. In addition, patients who receive pegylated asparaginase appear to be less likely to develop antibodies that result in increased clearance of asparaginase from the circulation and possibly reduced efficacy. These two points are key advantages presented in this dossier as well.

- Pegylated asparaginase; A reasonable schedule for pegylated asparaginase would be either 2,000 units/m^2 given every two weeks or 1,000 units/m^2 given weekly. These doses should result in asparagine depletion in the vast majority of adults for a two week period. Generally, this has been intercalated between courses of more cytotoxic therapy or the combination of vincristine plus corticosteroids.
- Non-pegylated preparations; Non-pegylated asparaginase preparations have a shorter half-life and require daily or every other day administration. They are also more immunogenic. The dose of L-asparaginase used varies from 6000 units/m^2 (in the CALGB regimen) to a fixed dose of 20,000 units (in the modified Hyper-CVAD regimen).

This evaluator notes at present there appears to be one asparaginase product on the ARTG; that of Leunase 10,000 KU injection vial. This is a non-pegylated preparation of asparaginase.

Clinical rationale

The rationale for this submission is to register Oncaspar in Australia with a broad indication that allows use both in first and second line therapy in ALL patients that are either children or adults. This is a consolidation, as it were, of the avenue of approvals that have occurred in other regulatory jurisdictions over a longer time period to result in effectively the same broad approved indication in both the USA and Europe.

The drug has been used in major regulatory jurisdictions for many years, most particularly for second line treatment. Post-market experience is therefore extensive and this evaluator considers the utility of the product in treatment regimens for ALL is largely considered accepted in the public domain literature. The pegylation of the asparaginase in the case of Oncaspar prolongs half-life as well as allegedly reducing potential immunogenicity of the drug compared to, for example, native *E.coli* asparaginase. This application seeks a broad indication that incorporates both first and second line use of the drug in both children and adults. In essence, it consolidates the approvals gained in the EU and USA over time into one submission.

Contents of the clinical dossier

There are formal trials which supported second line use of the drug in the past, and more recent formal trials supporting first line use, largely in children. Published literature has been gathered via extensive database searching that is intended to support both paediatric and adult use in first line treatment of ALL, as well as supplement the second line use

indication in some instances. The dossier is highly complex given the overview documents do not encompass all data in the dossier in an easily referred to manner, and their dates of creation or edit are not readily apparent as document control pages are not present in most if not all of these documents. It is difficult to identify the totality of data for each component of the submission; that is first line use in children; first line use in adults; second line use in children and second line use in adults. This evaluator has gone to great lengths to try to identify all submitted data intended to support each part of the indication and the safety profile of the drug. The focus has deliberately been on publications that make use of pegylated asparaginase rather than solely asparaginase.

Paediatric data

The submission intends to support use in ALL in children as both first and second line treatment; thus paediatric data are a plentiful component of this submission and indeed by far more extensive than that for adults.

Good clinical practice

The formal studies are stated to have met good clinical practice (GCP) standards. Some of the published data state this in their content; most do not. It is anticipated that such publications meet GCP standards as acceptance for publication has required this as mandatory in recent years. Therefore this evaluator is confident that publications up to 10 years old would almost certainly be studies conducted to international standards of GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission cites the following publications as providing pharmacokinetic (PK) information:

- ASP-301:Asselin et al. 1993;[27]
- Angiolillo 2014;[28]
- Avramis 2002;[29]
- Panosyan 2004;[30]
- Pieters 2008;[31]
- Rosen 2003;[32]

[27] Asselin BL et al. 1993 Comparative Pharmacokinetic Studies of Three Asparaginase Preparations. *Journal of Clinical Oncology* 1993; 11: 1780-1786

[28] Angiolillo A L et al 2014 Pharmacokinetic and Pharmacodynamic Properties of Calaspargase Pegol *Escherichia coli* L-Asparaginase in the Treatment of Patients With Acute Lymphoblastic Leukemia: Results From Children's Oncology Group Study AALL07P4 *Journal of Clinical Oncology* 2014; 32: 3874-3882.

[29] Avramis VI et al 2002 A randomized comparison of native *Escherichia coli* asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*. 2002; 99: 1986-1994

[30] Panosyan E H et al 2004. Asparaginase Antibody and Asparaginase Activity in Children with Higher-Risk Acute Lymphoblastic Leukemia Children's Cancer Group Study CCG-1961 *J Pediatr Hematol Oncol* 2004; 26: 217–226

[31] Pieters R et al 2008. Pharmacokinetics, pharmacodynamics, efficacy, and safety of a new recombinant asparaginase preparation in children with previously untreated acute lymphoblastic leukemia: a randomized phase 2 clinical trial. *Blood* 2008; 112: 4832-4838.

In addition, the European Medicines Agency (EMA) European Public Assessment Report (EPAR) (p37) cites the clinical studies:

- ASP-001
- ASP-302
- ASP-304
- CCG-1962 (Avramis 2002 above)
- DFCI-87-001/ (Asselin 1999a);[33]
- AALL07P4 (Angiolillo 2014);[28]

The summary document of Biopharmaceutical Studies lists some of the formal trials above as well as the following:

- DFCI-05-001 (Place et al. 2015);[34]
- CCG-1961 (Published as Panosyan 2004 above)

Therefore, to the best of this evaluator's review, these are the totality of data in support of PK profile. There are formal studies:

- ASP-001
- ASP-302
- ASP-304
- CCG-1962

And publications:

- Asselin et al. 1993;[35],1999;[33]
- Angiolillo 2014;[28]
- Panosyan 2004;[36]
- Pieters 2008;[37]
- Place et al. 2015;[34]
- Rosen 2003;[32]

Some of the immediately above publications are the literature publications of formal studies. In any case, the following represent in this evaluator's view the entirety of the PK data submitted for review.

[32] Rosen O et al. 2003 Pegylated asparaginase in combination with high dose methotrexate for consolidation in adult acute lymphoblastic leukaemia in first remission: a pilot study. *British Journal of Haematology* 2003; 123: 836–841

[33] Asselin B L 1999a. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. In Drug Resistance in Leukemia and Lymphoma III, edited by Kaspers et al Kluwer Academic/ Plenum Publishers New York 1999

[34] Place AE et al. 2015. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open label phase 3 trial. *Lancet Oncol* 2015; 16: 1677-1690

[35] Asselin BL et al. 1993 Comparative Pharmacokinetic Studies of Three Asparaginase Preparations. *Journal of Clinical Oncology* 1993; 11: 1780-1786

[36] Panosyan E H et al 2004. Asparaginase Antibody and Asparaginase Activity in Children with Higher-Risk Acute Lymphoblastic Leukemia Children's Cancer Group Study CCG-1961 *J Pediatr Hematol Oncol* 2004; 26: 217–226

[37] Pieters R et al 2008. Pharmacokinetics, pharmacodynamics, efficacy, and safety of a new recombinant asparaginase preparation in children with previously untreated acute lymphoblastic leukemia: a randomized phase 2 clinical trial. *Blood* 2008; 112: 4832-4838.

Evaluator's conclusions on pharmacokinetics

If one accepts the threshold level for therapeutic activity as 0.1 International Units (IU)/mL, which is strongly supported by two of the publications presented, then data in these studies show that asparaginase activity levels and subsequent decreases in levels of asparagine are achieved at ASNase concentrations at or above this threshold level. The doses of pegylated ASNase of 2,000 IU/m^2 in adults and 2,500 IU/m^2 in children appear more than sufficient to keep subjects over this threshold concentration for the dosing interval timeframe, antibody formation notwithstanding. Toxicity at these dosing levels is not a particular concern based solely upon these data, although immunogenicity is still an issue for some patients, despite the pegylated form of the drug, leading to increased clearance. Thus, such patients need identification as they may need to switch treatment to an alternative preparation of asparaginase, as the draft PI document suggests. What one derives from the PK data is that the doses and dose interval are probably satisfactory, and based upon biological plausibility, but must be monitored for events that skew the drug's activity level, such as hypersensitisation and antibody formation. Also, this evaluator is of the view that, based solely upon the PK data presented here, it may even be the case that a slightly lower dose would achieve optimum therapeutic outcome in the non-hypersensitised patient. Data simply do not exist to circumscribe this with any certainty.

Pharmacodynamics

Studies providing pharmacodynamic data

Similarly with the studies put forward in the dossier for PK information, there is a disparity in the totality of data listed in different locations. The submission cites the following documents as pharmacodynamic data:

- CSR ASP-001
- CSR ASP-102
- Place 2015;[34]
- Avramis 2002 (CCG-1962);[29]
- Pieters 2008;[31]
- Rosen 2003;[32]
- Silverman 2011;[38] 2013;[39]. (These publications seem to relate the Study DFCI-ALL-05-001 data, also contained in Place 2015;[34])
- Van der Sluis 2013;[40].

The clinical overview cites the following additional references:

- ASP-304 (post-dose activity)
- DFCI-87-001(Asselin 1999;[33]) (immunogenicity, post-dose activity)
- CCG-1961 (immunogenicity)

[38] Silverman LB et al 2011. Randomized Comparison of IV PEG and IM E.Coli Asparaginase in Children and Adolescents with Acute Lymphoblastic Leukemia: Results of the DFCI ALL Consortium Protocol 05-01 Poster 874
[39] Silverman LB et al 2013. Results Of The DFCI ALL Consortium Protocol 05-001 For Children and Adolescents With Newly Diagnosed ALL *Blood:* 2013; 122: 838
[40] Van der Sluis I et al 2013 Efficacy and safety of recombinant E.coli-asparaginase in infants (less than one year of age) with acute lymphoblastic leukemia. *Haematologica* 2013; 98; 1697-1701

- AALL07P4 (Angiolillo 2014;[28]) (immunogenicity)
- ASP-301 (early leukaemic cell kill)
- (Multiple review articles summarised in the clinical overview).

In addition, literature references are added in the clinical overview, that are stated to pertain to 'clinical pharmacology':

- Liu et al 2012;[41]
- Schrey et al 2011;[42]
- Schrey et al 2010;[43]
- Zalewska-Szewczyk et al 2009;[44]
- Muller et al 2000;[45]
- Viera Pinheiro et al 2001;[46]
- Jurgens et al 1988;[47]
- Van den Berg 2011;[48]
- Zeidan et al 2009;[49]
- Avramis and Panosyan 2005;[50]
- Avramis and Tiwari 2006.[51]

This evaluator can only be guided principally by the summary of clinical pharmacology document after summarising the above citations.

Evaluator's conclusions on pharmacodynamics

Asparaginase hydrolyses asparagine to aspartic acid and ammonia. Asparagine is a non-essential amino acid synthesised by the body from aspartic acid and glutamine by asparagine synthetase. In ALL, tumour cells can't make asparagine because they lack asparagine synthetase and thus can only obtain it by diffusion from the outside environment. Most other cells are spared, but ASNase can affect high-turnover healthy cells or those that are also reliant upon asparagine diffusing into the cell from its external environment.

[41] Liu C et al 2012 Clinical utility and implications of asparaginase antibodies in acute lymphoblastic leukemia *Leukemia* 2012; 26: 2303-2309
[42] Schrey D et al 2011 Five-Year Single-Center Study of Asparaginase Therapy Within the ALL-BFM 2000 Trial *Pediatr Blood Cancer* 2011; 57: 378-384
[43] Schrey D et al 2010 Therapeutic Drug Monitoring of Asparaginase in the ALL-BFM 2000 Protocol Between 2000 and 2007 *Pediatr Blood Cancer* 2010; 54: 952-958
[44] Zalewska-Szewczyk B et al 2009 The cross-reactivity of anti-asparaginase antibodies against different L-asparaginase preparations *Clin Exp Med* 2009; 9:113-116
[45] Muller H-J et al 2000 Pegylated asparaginase (Oncaspar) in children with ALL: drug monitoring in reinduction according to the ALL/NHL-BFM 95 protocols. *British Journal of Haematology,* 2000, 110, 379-384
[46] Viera Pinheiro JP et al 2001 (84)Drug monitoring in low-dose PEG-asparaginase (Oncaspar) in children with relapsed acute lymphoblastic leukaemia. *British Journal of Haematology* 2001: 113: 115-119
[47] Jurgens H et al 1988 Klinische Erfahrungen mit polyathylenglykol-gekoppelter E.coli L asparaginase bei Patienten mit ALL Mehrfachrezidiv. *Klin Padiatr* 1988; 200: 184-189
[48] Van Den Berg H 2011 Asparaginase revisited. *Leukemia & Lymphoma*, 2011; 52: 168-178
[49] Zeidan A et al 2009 Pegasparaginase: where do we stand*? Expert Opin. Biol. Ther*. 2009; 9: 111-119
[50] Avramis V I and Panosyan E H 2005 Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations The Past, the Present and Recommendations for the Future *Clin Pharmacokinet* 2005; 44: 367-393
[51] Avramis V I and Tiwari P N 2006 Asparaginase (native ASNase or pegylated ASNase) in the treatment of acute lymphoblastic leukemia. *International Journal of Nanomedicine* 2006: 1; 241-254

The clinical author of the overview in this submission presents some of the Oncaspar activity presented in this report, specifically from ASP-304 and DFCI-87-001. This provides data from adults and children and also demonstrates the differences in clearance when subjects have become hypersensitive to the drug. The duration of adequate asparaginase concentration (that is if one considers the threshold to be 0.1 IU/mL) is satisfactory for the non-hypersensitive and those with a low antibody titre who are hypersensitive. But for others with high antibody titres, half-life is much reduced, and the clinical overview author recommends changing to *Erwinia* L-asparaginase, hence monitoring for hypersensitivity is required in the view of this evaluator. This evaluator agrees with the facts that 0.1 IU/mL is a reasonable threshold above which asparaginase activity can be considered satisfactory for clinical effect, and that, in those without hypersensitivity or low antibody titres, half-life is more than satisfactory to support the dosing interval proposed in the PI.

The drug doses and dosing interval proposed will, in the view of this evaluator, result in sufficient serum ASNase concentrations to deplete asparagine to negligible levels and thus have the desired therapeutic effect. The small amount of leukaemic cell kill data suggests that asparagine depletion does indeed translate to the direct clinical outcome of plasma lymphoblast cell death. Hence, as given by the multitude of literature publications to be presented in the efficacy section of this report, the drug appears successful in use both in first and second line treatment of ALL in adults or children, although there is of course a significant safety profile to also be examined as well as the complication of hypersensitisation.

Dosage selection for the pivotal studies

No studies are formally presented as dose finding studies. Dosage was overwhelmingly that proposed in the draft PI document for the various age groups for the submitted studies. Studies that varied dosage or dose interval are briefly cited for convenience below, but are presented elsewhere in this report, primarily in the PK and PD sections. Dosage is not always cited in some of the data presented.

Table 4: Submitted Studies with dose or regimen varying from that in the proposed draft PI

Study	Dosage Regimen
PK/PD	
ASP-001	Cohorts at starting dose of 500 IU/m^2 escalating in increments of 500 IU until toxicity was observed. Range of dose 500 to 8000 IU/m^2 for Oncaspar.
AALL07P4	Either, 2100 IU/m^2 or 2,500 IU/m^2 per fortnight.
Rosen 2003[32]	500 IU/m^2 or 1,000 IU/m^2 per fortnight.
ASP-102	2,000 IU/m^2 reducible to 1,000 IU/m^2
Scherey et al. 2011;[42] 2010[43]	1,000 IU/m^2
Muller et al. 2000[45]	1,000 IU/m^2

Study	Dosage Regimen
Viera Pinheiro et al. 2001[46]	500 IU/m^2
Phase II/III	
NOPHO[52] ALL2008	1,000 IU/m^2
ASP-201A	2,000 IU/m^2
ASP400	2,000 IU/m^2
ALL0331	3 week intervals, PI proposed dose.

The discussion of dosage, in the view of this evaluator, is one of balance between toxicity and ensuring adequate serum levels of ASnase sufficient to deplete asparagine in the body. It would appear from the PD studies presented that such a serum level is 0.1 IU/mL; potentially even 0.05 IU/mL. This is definitively achieved by the dosages proposed in the draft PI document, when one examines the PD data. The dosages in many cases provide adequate serum ASNase levels far longer than the 14 day dosage interval timeframe required, and some study data have shown it might be possible to achieve efficacy outcome on lower doses of drug. However, as this has not been formally studied, the dosages proposed and dose interval proposed are a result of empirical evidence in the many thousands of patients treated as part of ALL drug regimens.

Given the proposed dosages are those doses and dose intervals that have been studied the most in the data submitted, particularly in one or two studies of many thousands of patients eclipsing the patient numbers in other trials, this evaluator is satisfied that the proposed doses are satisfactory for infants, children and adults. What is clear from the PD data is that any antibody formation to the drug results in more rapid clearance and would require dose adjustment or transfer to another type of asparaginase. Such methods have been shown in the study data in terms of switching from native *E.coli* ASNase to Oncaspar, for example.

Efficacy

Studies providing efficacy data

The submission includes

1. a clinical overview that was presented in the European submission
2. an 'addendum' document based upon a literature review conducted for the TGA, and
3. a further literature review conducted as part of the Day 180 questions from the EMA.

The EMA systematic literature review (SLR) focussed on first line treatment in children, which the TGA SLR expanded to include first line treatment in adults. Data on second line treatment does not appear to have been part of the search strategy objectives in either case and might stem from the fact that in other regulatory jurisdictions use in second line treatment has been approved for very many years. What has been confirmed by the sponsor is that the TGA SLR encompasses everything from the EMA SLR, thus the lists of

[52] NOPHO; Nordic Society of Paediatric Haematology and Oncology

literature for review have been verified. The SLR inclusion and exclusion criteria have been examined for both SLRs and although differing slightly in the type of publications included, this evaluator is quite satisfied that the searches were extensive and have revealed worthwhile information while not excluding data that might be detrimental to the use of the drug.

This submission seeks use of the drug in both first line and second line therapy, in both children and adults.

The primary trials for this drug were carried out in the late 1980s. Development was for ALL patients with known hypersensitivity to native L-asparaginase.

First line (formal trials) treatment data (children and adults)

Six studies in 3,643 patients (1,186 treated with Oncaspar) with newly diagnosed ALL provide the initial data supporting first line use of the drug. These studies are given as follows in Table 5.

Table 5: Summary of first line therapy clinical data package for Oncaspar

Study reference and primary record	Study phase	Patient population	Route of administration for Oncaspar arm	Objectives
CCG-1962 (Clinical Study Report)	II	Patients aged 1 to 9 years with newly-diagnosed standard risk ALL.	i.m.	Comparison of Oncaspar and native E coli L-asparaginase in Induction and Delayed Intensification.
DFCI 05-001 [55]	III	Patients aged 1 to 18 years with newly diagnosed standard risk ALL	i.v.	Comparison of toxicity, serum asparaginase activity, and efficacy of i.v. Oncaspar vs i.m. native *E. coli* asparaginase
AALL07P4 (Progress Report; Pop PK Report; [5])	I/II (pilot)	Patients aged 1 to 30 years	i.v.	Comparison of pharmacokinetics of i.v. Oncaspar vs another i.v. pegylated asparaginase
DFCI-91-01 ([75]	III	Children aged ≤18 years with newly-diagnosed ALL (excluding mature B-cell ALL)	i.m.	Improve outcome for children with B-lineage ALL while minimizing toxicity.
CCG-1961 [50];[29];[73];[46]	III	Patients aged 1 to 21 years with newly-diagnosed high risk ALL.	i.m.	Investigate relationships between anti-asparaginase antibodies, asparaginase activity and clinical outcome.
DFCI-87-001 [8] and [9]	III	Children aged 1 to <18 years with newly- diagnosed ALL.	i.m.	Efficacy of a single dose of asparaginase and correlation with anti-leukaemic response and long-term outcome.
ASP-301 (Sub-Study of DFCI-87-001) [7]	I/III	Paediatric patients with newly diagnosed ALL (Comparative Trial of Oncaspar vs. Elspar vs Erwinase)	i.m.	Pharmacokinetics L-Asparaginase depletion Cell kill (*in vivo*) Safety and tolerance
CCG-1991 (Clinical Study Report)	III	Children aged 1 to 9 years with newly-diagnosed standard risk ALL.	i.m.	Investigation of safety of different approaches to the use of methotrexate during Interim Maintenance therapy. Effect of 1 vs 2 Delayed Intensification phases.

As one can see, these data, while supporting first line ALL use, encompass children only apart from Study AALL07P4, which extends to those aged to 30 years.

The Addendum to the clinical overview in light of the TGA SLR cites the following additional trials:

- AALL0232

- AALL0331
- UKALL2003
- NOPHO ALL2008

Second line treatment data (formal trials) in children and adults

Eight trials with n = 218 in total are cited in the clinical overview as supporting Oncaspar use in second line treatment. It is uncertain whether this was a specific development programme or evolved over time. The clinical overview author states many of the studies were conducted in an academic environment and the publication is the main reference, which explains the doubling-up and some confusion determining how many actual discrete bodies of data have been submitted. One can note that, in this data set, all ages are encompassed by the data (see Table 6).

Table 6: Summary of second line clinical data package for Oncaspar

Study reference and primary record	Study Phase	Patient population	Route of administration	Objectives
ASP-001 (Clinical Study Report)	I/II	Patients aged 15 to 73 years with refractory haematological malignancies	i.v.	1. Pharmacokinetics 2. Safety and tolerance 3. Clinical efficacy
ASP-001C / ASP-003C (Clinical Study Report)	II/III	Patients aged 1 to 66 years with relapsed ALL, related leukaemias, testicular lymphoma, mycosis fungoides Compassionate use Multi-regimens for induction / maintenance a. Hypersensitive b. Non-hypersensitive	i.m.	1. Clinical efficacy 2. Safety and tolerance
ASP-102 (Clinical Study Report)	I	Patients aged 18 to 74 years with histological diagnosis of a solid tumour or lymphoma refractory to standard therapies or for which no standard therapies have been described.	i.m.	1. Maximum tolerated dose of methotrexate when followed by Oncaspar 2. Select dose of Oncaspar for Phase II studies 3. Response rate to treatment with Oncaspar
ASP-201A (Clinical Study Report)	II/III	Patients aged 1 to 43 years with relapsed ALL, T-cell lymphoma, acute non lymphoblastic leukaemia (ANLL), acute myelogenous leukaemia c. Hypersensitive d. Non-hypersensitive	i.m. / i.v.	1. Clinical efficacy 2. Safety and tolerance
ASP-203 (Clinical Study Report)	I	Patients aged 30 to 81 years with histological proof of non-Hodgkin's lymphoma requiring chemotherapy and at least one relapse.	i.m.	1. Clinical efficacy 2. Safety and tolerance
ASP-302 (Clinical Study Report)	II/III	Patients aged 1 to 35 with relapsed ALL e. Hypersensitive f. Non-hypersensitive	i.m.	1. Pharmacokinetics 2. Safety and tolerance
ASP-304 (Clinical Study Report)	III	Patients aged 1 to 18 years with relapsed ALL g. Hypersensitive h. Non-hypersensitive (Comparative trial of Oncaspar versus native *E. coli* asparaginase)	i.m	1. Clinical efficacy 2. Safety and tolerance 3. Antibody titres 4. Pharmacokinetics
ASP-400 (Clinical Study Report)	III	Patients aged ≤ 21 years with relapsed ALL, AUL or NHL.	i.v.	Efficacy and safety

Presentation of published data sources

In addition to these data, the clinical overview cites 'important publications' in the published literature. It is not made clear how these were arrived at or what makes their status 'important' per se. The clinical overview refers to first line use of Oncaspar in ALL as being extensive and the subject of a literature review. This literature review upon investigation and confirmation by the sponsor is that conducted as part of 180 day questions from the EMA.

Published literature considered key to the second line use of the drug are contained in Table 8 of the clinical overview and are 11 in number. It is again not clear how the decision about their relevance was made, or how they were located.

The clinical overview then states that first line use (children and adults) is extensively discussed in the systematic literature review of first line use of Oncaspar. One assumes this is referring to the review conducted for the EMA as part of the Day 180 questions, as this was specifically targeted at use of Oncaspar in first line treatment of ALL in paediatric patients. The cut-off date of 15 October 2015 referred to in the clinical overview confirms it. Apparently 13 unique studies of 40 articles gathered used Oncaspar as first line therapy. One (Study CCG-1962) had head-to-head comparison data of Oncaspar and native *E.coli* ASNase used at induction for ALL.

Few studies, in comparison to first line use, studied Oncaspar use in second line treatment, with subjects already hypersensitive to native *E.coli* ASNase. Publications relevant to this are given in a table of the clinical overview. Again, how these studies were determined is not made clear.

In summary, the original clinical overview cites the trial data and EMA SLR pivotal literature that is intended to support the product in the proposed indication. The addendum documents discuss additional data retrieved via the SLR done for the TGA. Given the nature of the searches, this is primarily data that supports the use of the drug as first line in adults.

For the full details of the studies and publications reviewed please see Attachment 2.

Evaluator's conclusions on efficacy

In the view of this evaluator, key data for the support of the use of PEGL ASNase in treating ALL is as follows. Obviously other data support these, but the following are considered particularly useful either for reasons of design, subject numbers, outcome measures or simply the level of detail provided in the dossier. They are described in detail in Attachment 2.

Table 7: Key data for the support of the use of PEGL ASNase in treating ALL

Trial/Publication	Design/subjects	Outcome(s) of interest in this context	Results
First line ALL formal trials			
CCG-1962	Randomised comparison of native *E.coli* ASNase and PEGL ASNase, n = 59 in each treatment groups	Induction response, high titre antibody development, event free survival (EFS).	Mean ± Standard Error of the Mean (SEM) antibody ratio in DI #1 was 1.9 ± 0.8 (n = 47) for children treated with PEGL ASNase and 3.0 ± 0.7 (n = 43) for those treated with native ASNase (p = 0.001, Wilcoxon

Trial/Publication	Design/subjects	Outcome(s) of interest in this context	Results
			test). High titre antibodies were associated with low ASNase activity (≤ 0.1 IU/mL) in the native arm, but not in the PEGL ASNase arm. The 3-year EFS rates for PEGL ASNase and native ASNase were 85% and 78%, respectively (p = 0.773).
DFCI-05-001	Randomised open label head to head comparison of PEGL ASNase and native *E.coli* ASNase. (n = 463)	EFS/OS	The 5 year disease free survival was 90% (95% CI 86–94) for patients randomly assigned to intravenous PEG-asparaginase, 89% (85 to 93) for those randomly assigned to intramuscular native *E coli* l-asparaginase, and 88% (74 to 95) for those who declined to undergo randomisation and were directly assigned to intramuscular *E coli* l-asparaginase. The 5 year overall survival was 96% (93–98), 94% (89–96), and 95% (82–99) for these three patient groups, Respectively.
AALL0232	Phase II cohort of B cell precursor ALL with PEGL ASNase in treatment regimens. Age to 30 years. N = 1035.	EFS	The 5 year event free survival (EFS) for patients 1 to 9 years of age randomized to receive DH, DC, PH, or PC was 93.7 + 5.4%, 84.1 + 8.4%, 81.2 + 7.7%, and 84.0 + 6.9%, respectively, p = 0.03.
UKALL2003	A huge trial of n = 3207 patients, where a subset of 521 minimal residual disease (MRD) low risk patients randomised to one or two DI courses with PEGL ASNase (n = 260, 261)	EFS	There was no significant difference in EFS between the group given one delayed intensification (94·4% at 5 years, 95% CI 91·1–97·7) and that given two delayed intensifications (95·5%, 92·8–98·2; unadjusted odds ratio 1·00, 95% CI 0·43–2·31; two-sided p = 0·99).
First Line ALL publications in Children			
ALL0331	N = 5377 paediatric	EFC, CR, OS	5 year continuous complete

Trial/Publication	Design/subjects	Outcome(s) of interest in this context	Results
	patients with standard risk b cell ALL. PEGL ASnase used in induction regimen for all. 'Standard risk-low' patients randomised to intensive or standard consolidation.		remission rates were, for Standard versus Intensive consolidation, 88% (1.6%) versus. 89.3% (1.5%) (p = 0.13) and 5-year OS rates for SC versus. IC of 95.8% (1.0%) versus. IC 95.7% (1.0%) (p = 0.93). For all trial patients, 5 year EFS was (EFS(SE)) 89% (0.6%) and 5 year overall survival 96% (0.4%).
First Line ALL publications in Adults			
Goekbuget 2013[53]	N = 1529, n = 642 for Study 05/93 and 887 for Study 07/03. Study 07/03 was an intensified regimen.	CR, OS	The CR rate increased in studies 05 to 07 from 88% to 91% (p = .001), most prominently within the age range of 26-35 years (86% to 90%;p = .001). The OS increased from 46% to 65% (p < .0001) (significant in all age groups). Remission duration (RD) at 5 years increased from 49% to 61% (p = .0001), most prominently within the age range of 26-35 years (46% versus 59%; p = .005). OS improved from Study 05 to Study 07 in B-Lin (45% versus 66%; p < .0001) and T-ALL (47% versus 63%; p = .0007) overall.
Rytting 2016[54]	106 adolescent and young adult patients (median age 22 years) with Philadelphia chromosome- (Ph) negative ALL received ABFM from 10/2006 through 3/2014. Their outcome was compared to 102	CR, OS, CRD	The complete remission (CR) rate was 93% with ABFM and 98% with hyper-CVAD. The 5 year complete remission duration (CRD) were 53% and 55% respectively (p = 0.98). The 5 year overall survival (OS) rates were 60% and 60%, respectively.

[53] Gokbuget N et al. Significant improvement of outcome in adolescents and young adults (AYAs) aged 15-5 years with acute lymphoblastic leukemia (ALL) with a pediatric derived adult ALL protocol; results of 1529 AYAs in 2 consecutive trials of the German Multicenter Study Group For Adult ALL (GMALL). 2013. 55th ASH meeting. Oral Session: 614 GMALL 05/93 and 07/03

[54] Rytting M E et al. 2016 Final Results of a Single Institution Experience with a Pediatric-based Regimen, the Augmented Berlin-Frankfurt-Münster (ABFM), in Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia (ALL), and Comparison to the Hyper-CVAD Regimen *American Journal of Hematology* 2016

Trial/Publication	Design/subjects	Outcome(s) of interest in this context	Results
	such patients (median age 27 years), treated with hyper-CVAD.		
Stock 2014[55]	N = 296 patients given the standard regimen from Study AALL0232 in adolescents and young adults with ALL.	EFS, OS	Two-year EFS was 66% (95% CI 60, 72%) and 2 year OS 78% (95% CI 72-83%) in 296 patients.
De Angelo 2015a[56]	N = 110 patients aged 18-50 treated with a regimen including PEGL ASNase.	CR	CR at one month was 89%.
Second Line ALL Formal Trials			
ASP-304	Randomised comparison of second line treatment (second bone marrow relapse) of ALL using native *E.coli* ASNase versus PEGL ASNase in individuals under 21 years. Previously hypersensitive patients were assigned to PEGL ASNase. N = 76; 59 PEGL ASNase, 17 native *E.coli* ASNase.	CR, efficacy in light of previous hypersensitisation.	Response rate overall was 56% for PEGL ASNase and 47% for native *E.coli* ASNase (chi square 0.615). If one considers complete remissions alone, it is 39% for PEGL ASNase and 47% for native *E.coli* ASNase (chi square 0.625). Also 54% of those directly assigned to Oncaspar that had previous hypersensitivity reactions to native *E.coli* ASNase achieved a response.
Second Line ALL Publications in Adults or Children			
Kurtzberg 2011[57]	Compared PEGL ASNase and native ASNase in combination with standard agents	CRR	The overall complete response rate (≤ 5% marrow blasts) was 41%, with no statistically significant difference between PEGL ASNase (47%) and native

[55] Stock W et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): Early results of US Intergroup trial C10403. *Proc ASH* 2014;Abstract 796.
[56] DeAngelo DJ et al. 2015 a A Multicenter Phase II Study Using a Dose Intensified Pegylated-Asparaginase Pediatric Regimen in Adults with Untreated Acute Lymphoblastic Leukemia: A DFCI ALL Consortium Trial. American Society for Hematology 57th annual meeting and exposition.
[57] Kurtzberg J et al 2011. Polyethylene Glycol-conjugated L-asparaginase Versus Native L-asparaginase in Combination With Standard Agents for Children With Acute Lymphoblastic Leukemia in Second Bone Marrow Relapse: A Children's Oncology Group Study (POG 8866) *J Pediatr Hematol Oncol* 2011;33:610-616

Trial/Publication	Design/subjects	Outcome(s) of interest in this context	Results
	for the treatment of second bone marrow relapse in ALL in children. Non-hypersensitive patients were randomised to either PEGL ASNase 2,500 IU/m^2 on Days 1 and 15 or 10,000 IU/m^2 of native *E.coli* ASNase on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24 and 26. Patients with any history of allergy to standard ASNase were immediately assigned to PEGL ASNase. Hence n = 76 with n = 59 given PEGL ASNase and 17 given native *E.coli* ASNase.		*E.coli* ASNase (41%).

This evaluator is of the opinion that first line treatment in children of ALL with PEGL ASNase as part of the treatment regimen has been demonstrated in significant patient numbers in a variety of different study designs and treatment scenarios, which similar outcome data across studies as the forest plots in the clinical overview addendum attest. It also has been shown to be comparable to current standard treatment with native *E.coli* ASNase in terms of efficacy outcomes, whether comparing similar regimens but for asparaginases, or different regimens entirely. Similarly there are a number of sizeable trials showing efficacy comparable or trending better than standard treatments for children or adults given PEGL ASNase as part of second line treatment. Second line treatment has a smaller data set for both children and adults and this is quite small in adults one must concede, however data still support the use of asparaginase and PEGL ASNase in particular in the trials presented, and second line treatment has been approved in two major regulatory jurisdictions for over 20 years. It would seem counter intuitive to require additional data for second line use when clearly the biological plausibility of utility for the drug is reflected in its ability to deplete asparagine. This in turn is only really different in the setting of high titre antibodies, where, first or second line, typically the type of asparaginase is switched. Hence this evaluator is of the view that the data for first and second line use both lend weight to each other in terms of outcome data in most respects.

Safety

The safety profile of the drug is well circumscribed given the decades of real-world use after initial registration.

Patient exposure

Overall approximately 100,200 + patients have received Oncaspar over 20 years, although most patients would not have done so in clinical studies.

Studies providing safety data

First line studies

Formal studies supporting first line use of Oncaspar in children or adults were Studies:

- CCG-1962
- DFCI-05-001
- AALL07P4
- DFCI-91-01
- CCG-1961
- DFCI-87-001/ASP-301
- CCG-1991

The seven studies above comprise approximately 4,140 patient exposures, including 51 patients in Study AALL07P4 where the drug was an active comparator, and principally 2,957 patients in Study CCG-1991 where the drug formed part of background treatment. Exact numbers of patients is difficult as not all publications detailed this satisfactorily. However, in the EMA EPAR, figures for these as well as the second line 'ASP' studies are given exactly (Table 8).

Table 8: from EMA EPAR

Data sources	Hypersensitive patients	Non-Hypersensitive patients	PEG-ASNase dose & schedule
Clinical trials			
Second line original data package (1994)*	78	172	500,1000,2000,2500,4000,8000 IU/m^2 IV 2000, 2500 IU/m^2 IM
Study CCG-1961	142	138	2500 IU/m^2 IM
Study CCG-1962	0	57	2500 IU/m^2 IM
Study DFCI-87-001	0	84	2500 IU/m^2 IM
Study DFCI-91-01	0	377	2500 IU/m^2 IM
Study CCG-1991•	0	2957	2500 IU/m^2 IM
Study AALL07P4◇	0	51	2500 IU/m^2 IM

* including studies ASP-001, ASP-001C, ASP-102, ASP-201A, ASP-203, ASP-302, ASP-304 and ASP-400
°every 2 weeks during induction and every 2 to 16 weeks during continuation therapy
• enrolled newly diagnosed and previously untreated patients with ALL between ages 1 through 9 years
◇ pilot study of intravenous EZN-2285 (SC-PEG *E. coli* L-asparaginase) or intravenous pegasparagase® in the treatment of newly diagnosed patients with high-risk ALL

Second line studies

Formal studies supporting second line use of Oncaspar in children or adults included:

- ASP-001
- ASP-001C-003C
- ASP-102
- ASP-201A

- ASP-203
- ASP-302
- ASP-304
- ASP-400

These studies were smaller and their data are presented in a combined fashion. Three hundred and eighty four doses of Oncaspar were administered to 78 hypersensitive patients (326 IM and 58 IV) and 650 doses were given to the 172 non-hypersensitive patients (432 IM and 218 IV). For safety analysis, any patient who received more than 2 doses of Oncaspar was included and thus data in this second line group of studies were available for 121 patients. Data for doses received less than this numbered 250 patients.

The median number of days on study was 43 (range 1 to 640 days) for all patients, 43 days (range 1 to 559 days) for the hypersensitive patients and 43 days (range 1 to 640 days) for the non-hypersensitive patients. The median number of doses of Oncaspar administered was 2 (range 1 to 37 doses) for all patients, 2 (range 1 to 29 doses) for the hypersensitive patients, and 3 (range 1 to 37 doses) for the non-hypersensitive patients.

Common adverse reactions from the drug's safety profile are cited by the SmPC document with conventional frequency categories as shown in Table 9.

Table 9: Common adverse reactions to Oncaspar

MedDRA Standard System Organ Class	Adverse Reaction
Infections and infestations	*Common:* Infections, Sepsis
Blood and lymphatic system disorders	*Common:* Febrile neutropenia, Anaemia, Thrombosis
Immune system disorders	*Very common:* Hypersensitivity, Urticaria, Rash, Anaphylactic reactions
Endocrine disorders	*Very Common:* Hyperglycaemia
Metabolism and nutrition disorders	*Common:* Hypertriglyceridaemia, Hyperlipidaemia
Nervous system disorders	*Common:* Convulsion, Peripheral Motor Neuropathy, Syncope
Vascular disorders	*Common:* Thrombosis
Respiratory, thoracic and mediastinal disorders	*Common:* Hypoxia
Gastrointestinal disorders	*Very common:* Pancreatitis, Diarrhoea, Abdominal pain *Common:* Vomiting, stomatitis
Musculoskeletal and connective tissue disorders	*Common:* Pain in extremities
Investigations	*Common:* Amylase increased, Alanine aminotransferase increase, Blood bilirubin increase, Neutrophil count decreased, Platelet count decreased, Activated partial thromboplastin time prolonged

One can see this encompasses thrombosis, infection, hypersensitivity/anaphylaxis and blood dyscrasia. Of interest specific thrombosis or haemorrhage in the CNS is not

mentioned although this is not surprising as although it occurs it does not occur at a 'common' or greater frequency. Of note to say at this point also is that the studies did not suggest upon evaluation that the majority of adverse events associated with Oncaspar occurred at different frequencies than those with other ASNase preparations. The types of AEs also appear broadly similar which is hardly surprising given the mechanism of action is similar for all. Although hypersensitivity and immune-based reactions did differ in frequency in some studies, giving the suggestion that Oncaspar could be used when hypersensitivity to native *E.coli* ASNase existed. Furthermore there was an impression given by some study data that hypersensitivity was reduced when using the IM route rather than IV. However other studies found no difference in these rates.

Safety issues with the potential for major regulatory impact

For the full evaluation of the safety issues please see Attachment 2.

Post marketing data

PSURs

EU authorisation was transferred from Medac to Sigma-Tau in 2012. A periodic safety update report (PSUR) for August 2009 to July 2012 was presented. Approximately 207 million units of product were sold during this period for an estimated 13,824 treated patients. Ninety three case reports were received over the same period, with 128 listed reactions and 9 unlisted reactions. Twenty seven were spontaneous reports, 55 from studies and 11 identified in the literature.

The PSUR concluded that the risk benefit profile was unchanged and no action to change SmPC or implement other safety related changes was deemed necessary.

Data from US launch date

Dates from September 1994 to March 2012 identified an exposure of approximately 57,000. A collection of 843 post-authorisation safety reports showed 2,657 preferred terms. Of those reported 20 or more times, the following were encompassed as described in Table 10.

Table 10: Preferred Terms reported ≥ 20 times in US spontaneous reporting (September 1994 to March 2012)

Preferred term	Number of reports	Percentage of all preferred terms reported (n=2,657)
Urticaria	157	5.9%
Hypersensitivity	153	5.8%
Anaphylactic reaction	99	3.7%
Rash	78	2.9%
Vomiting	71	2.7%
Dyspnoea	70	2.6%
Pancreatitis	61	2.3%
Pruritus	58	2.2%
Hyperbilirubinaemia	49	1.8%
Hyperglycaemia	48	1.8%
Lip swelling	44	1.7%
Abdominal pain	41	1.5%
Nausea	39	1.5%
Pyrexia	39	1.5%
Hypotension	35	1.3%
Cough	34	1.3%
Swelling face	32	1.2%
Erythema	26	1.0%
Total	1,134	42.7%

The three most common terms accounted for 15.4% of the total and are immunological in basis. The data reflect both first and second line use as first line was authorised in 2006 in the USA.

Evaluator's conclusions on safety

There were seven formal trials supporting fist-line use of Oncaspar in children or adults. The bulk of subject numbers were children or quite young adults. These data comprised approximately 4,140 patient exposures/treatments. The majority of exposures were in Study CCG-1991 where the drug formed part of background treatment in a multi-drug regimen. Only Trial AALL07P4 used the drug in a head to head comparison in n = 51 patients.

Adverse events were broadly similar in frequency across Oncaspar and native *E.coli* ASNase, and Trial CCG-1962 bears this out. CNS complications, infection, pancreatitis, hyperglycaemia, liver dysfunction and bacteraemia in general featured as adverse events. What is also clear is that Oncaspar appears to have been associated in several instances with a lower rate of hypersensitivity.

Second line formal studies comprised the much smaller-numbered 'ASP' trials, as collectively called by this evaluator. Three hundred and eighty four doses were given to 78 hypersensitive patients and 650 doses to 172 non-hypersensitive patients. Obviously second line use is a reduced totality of experience in terms of formal trials, yet it is important in terms of pre-sensitisation to try and understand adverse events as a result of

hypersensitivity. The Median number of doses of Oncaspar administered was two, with a range of 1 to 37 doses.

Common adverse events are detailed in the EU SmPC as well as the draft Australia PI document. They encompass the most important adverse events noticed in the totality of submission data.

The IM route of administration seems to reduce the likelihood of a hypersensitivity reaction. In the second line trials, 72% did not experience a hypersensitivity reaction via the IM route while only 56% patients didn't using the IV route of administration, in those who were previously hypersensitive. However, these results were not statistically significant between groups (p = 0.1101 and 0.1113, respectively, for number of doses and days on study. What was statistically significant was that within the non-hypersensitive group of patients, 87% receiving drug IV and 94% receiving IM did not experience a hypersensitivity reaction. This was statistically significant, both for number of doses (p = 0.0306) and days on study, (p = 0.0437, respectively). So it would appear that non-hypersensitive patients are more likely to experience a reaction if the IV route is used, giving a reasonable argument for using the IM route in such persons where possible.

Fourteen and 8 published studies were but forward as a result of the TGA SLR in paediatric and adult patients, respectively. In brief, the following conclusions are made:

- The array of adverse events in these trials is similar to that for the formal studies.
- Trends in higher hypersensitivity reactions via dosing the IV route were noted.
- Non-immunological adverse events seem to occur at similar frequencies for Oncaspar and native *E.coli* ASNase.
- Rates of pancreatitis in treated patients vary from 0.8% to 11.0%.
- Various liver markers are changed during treatment. These include Grade 4 lipase increase (0.3% to 0.6%); Grade 4 + hyperbilirubinaemia (< 1%); Grade 1-2 hypertriglyceridaemia 22% and Grade 3 or 4, 47%; Grade 1 or 2 hypercholestrolaemia 9% and Grade 3-4 25%.
- Hyperglycaemia varies in frequency but a range of 1.1% to a maximum of 23% depending upon age and stage of treatment experienced transient hyperglycaemia. These events are considered associated with the use of steroids rather than Oncaspar use in the multi-drug regimens.
- CNS thrombosis has been reported in various publications from 1.6% to 7.4%.
- Thrombosis or bleeding (Grade 2 or higher) has varied from 7% to 19%. In one publication, Tuckuviene et al[58], cumulative rate of thromboembolism in adolescents 15 to 17 years was 20.5% (95% CI (12.6, 29.7)).
- PSUR data (August 2009 to July 2012) represents an estimated 13,824 patient treatment experience. The data do not alter the conclusions reached on the safety profile of the drug from clinical studies.
- Data on approximately 57000 exposures since the USA launch date to March 2012 do not suggest (1) previously unknown adverse events, nor (2) and significant disparity in their frequency. If anything, the AEs occur at lower rates, but given the nature of spontaneous reporting, this is hardly surprising that formal or published trials suggest higher rates with the closer level of safety scrutiny and reporting in that paradigm.

[58] Tuckuviene R et al 2016 Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study. *Journal of Thrombosis and Haemostasis* 2016; 14: 485-494

- Many of these adverse events appear to have higher rates in adults; the adult data often provide the upper range in the information cited directly above.
- Apart from hypersensitivity profiles for each ASNase preparation, available data do not make it possible to deduce whether particular adverse events occur at differing frequencies depending upon the ASNase product used. Broadly, the safety profile is similar to that for native *E.coli* ASNase.

Given that hypersensitivity and anti-drug antibodies can develop in a sizable fraction of the treated population, and that this has significant impact upon clinical effectiveness, as well as possibly occurring without any outward sign, this evaluator is of the view that serum asparaginase and anti-asparaginase antibodies should be monitored when treating patients. More detailed comments are contained in the comment upon the draft PI document for this submission.

This evaluator has formed the impression that Oncaspar has a similar constellation of adverse events to that of native *E.coli* ASNase, with potential advantages in terms of hypersensitivity or cross-reactivity of sensitisation from native *E.coli* ASNase. As a result, with similar or better efficacy outcomes, the risk benefit profile of the drug for the indications presented is, in the view of this evaluator, not precisely circumscribed but nonetheless favourable.

First round benefit-risk assessment

First round assessment of benefits

The specifics of efficacy and safety are presented in summaries in the respective parts of this report. To summarise:

- The drug has objective benefit when compared head-to-head in a small number of patients using both Oncaspar and native *E.coli* ASNase. Hence it would appear to be at least as efficacious as native *E.coli* ASNase when interpreting the data collectively.
- The drug demonstrates in non-comparative trials event free survival (EFS) and overall survival (OS) data that are comparable or better to that achieved with native *E.coli* ASNase, for children and adults, albeit with fewer data in adults. The collective forest plots in this report best demonstrate this.
- If one compares EFS or OS data up to 5 years of follow up, EFS and OS are comparable or better than using native *E.coli* ASNase when Oncaspar is used in a multi-drug regimen treating ALL in adults or children.
- Outcomes in children up to 10 years are superior to those after, however this is in keeping with the use of native *E.coli* ASNase as well. Younger patients fare better as a general observation, and age is a prognostic factor.
- While outcome data in adults, particularly in second line treatment, are few compared to the wealth of data for first line treatment, nonetheless sizable subject outcomes are still available upon which to base a judgement of efficacy. If one accepts that efficacy pivots on the ability of asparaginases to deplete asparagine, then the true issue becomes one of (1) antibody monitoring and drug switching where necessary, and (2) the tolerability of dosing, where children clearly tolerate a larger dose.
- Oncaspar demonstrates what appears to be an objectively defined serum level (≥ 0.1 IU/mL) between doses using a 14 day dosing interval that satisfactorily depletes serum asparagine where high titres of anti-drug antibody are not present. Hence the dose and dosing interval have some biologically plausible support as well as pharmacodynamics evidence based upon the mechanism of action.

- While formal dose ranging studies are absent, the trials present that have varied doses do give some objective support to the doses chosen for the draft PI. The question of whether a serum level of ASNase lower than 0.1 IU/mL effectively depletes serum asparagine, in the view of this evaluator, is uncertain. Hence it is also uncertain whether a slightly lower dose might still suffice to deplete serum asparagine (a different dose being likely for adults or children, due to differing ability to tolerate the drug, as is the case now). This evaluator certainly thinks than a serum asparaginase level of 0.1 IU/mL has been shown to adequately deplete asparagine for at least the 14 day dose interval period unless hypersensitisation and antibody formation results in increased clearance of drug. Hence the drug doses chosen do, in the view of this evaluator, achieve their objective from a mechanism of action perspective.
- Oncaspar has the advantage of a prolonged dosing interval in comparison to native *E.coli* ASNase. It also has a theoretical advantage of a reduced size of dose at each dosing time, due to the prolonged half-life of the preparation. This may theoretically benefit users in terms of adverse events that may have threshold ASNase levels, although the dossier does not explore this; this is an opinion of this evaluator.
- Oncaspar has been shown to be of utility where hypersensitisation to native *E.coli* ASNase has occurred in patients. It can potentially confer better efficacy than continuing to give native *E.coli* ASNase, and furthermore elicit lower anti-drug antibody formation in such patients than that for native *E.coli* ASNase. Data in adults are few but this evaluator sees little reason to consider that a significant issue. The issue is one of sensitization and the need to switch to Oncaspar or Erwinase, not one of age.
- Oncaspar is a useful potential choice to switch a patient to where any issue with native *E.coli* ASNase arises, in particular allergy, hypersensitisation, or anaphylaxis.
- Oncaspar appears to have a similar safety profile to native *E.coli* ASNase in terms of the nature and frequency of adverse events. The only situation where there is evidence this is disparate appears to be immunologically-based adverse events, where the drug may offer an advantage in specific clinical settings.

First round assessment of risks

- Oncaspar has a repertoire of significant and serious possible adverse events, in particular CNS thrombosis/haemorrhage, thrombosis in general, and pancreatitis. Other serious events include infection, liver chemistry derangement and lipid abnormalities. The suite of adverse events appear similar to that for native *E.coli* ASNase, however, in terms of immune-based AEs, Oncaspar may perform better than native *E.coli* ASNase.
- As for other ASNase preparations, there is a risk of antibody formation against the drug which, if present in high titre, can result in substantially increased clearance of drug and reduced half-life.

First round assessment of benefit-risk balance

The drug is proposed for first line or second line treatment of ALL in adults and children, as part of various accepted treatment protocols with multiple medications. Outcome data for ALL has been discussed at the commencement of this report, and it is the judgement of this evaluator that the use of asparaginases in the treatment of ALL results in comparable or improved EFS and/or OS at multiple time points when compared with other treatment regimens. While this is true for native *E.coli* ASNase, it is also true for Oncaspar and indeed some advantages as described above are presented with the use of Oncaspar. Indeed, the place of this drug in the published literature appears to be a matter of 'utility understood'

rather than subject to judgement. To clarify, many of the publications examine other lesser matters associated with the treatment of ALL with Oncaspar, not the question of whether it had acceptable risk/balance in the first instance.

The collective data demonstrate a clear positive outcome in terms of objective measures of EFS and OS for ALL patients. While the safety profile contains substantial potential adverse events, this is clearly offset in the view of this evaluator by EFS data. What would have been additionally helpful in assessing this point would have been more patient-centric outcome points for quality of life. Nonetheless, the drug has been approved in the USA and EU for the same breadth of indications at this point, and indeed the data set is more extensive than that provided and later expanded to the EU via an SLR. The Australian SLR addressed the important question of additional recent outcome data in adults; however the SLR revealed scant publications and these tended to confirm the known efficacy and safety profile rather than raise issues with new or unforeseen risks or ADRs that had not been observed previously.

In light of the above facts, the efficacy outcome data, the safety profile in comparison to other asparaginases and the apparent trend for improved outcomes with respect to immune based adverse events, this evaluator is of the view that Oncaspar, with decades long use in the real world and trial experience in many thousands of patients, has a relatively well circumscribed efficacy/safety profile and thus the overall risk benefit can be regarded as positive. While data in adults are scant in comparison to those in children, there are still significant data showing acceptable risk/benefit in adults. This evaluator is of the view that the utility of the drug is via a known mechanism and so long as treatment includes monitoring for hypersensitisation and antibody formation, the drug's efficacy will be as demonstrated. The paucity of data in adults or indeed adults who have been previously hypersensitised with native *E.coli* ASNase is not considered a key issue.

First round recommendation regarding authorisation

Oncaspar is recommended for approval with the breadth of indication proposed in the draft PI.

There was no second round clinical evaluation.

VI. Pharmacovigilance findings

- The sponsor has applied to register a new biological entity, pegaspargase (Oncaspar). It is a PEGylated version of L-asparaginase. Oncaspar is proposed to be used for the treatment of acute lymphoblastic leukaemia (ALL) as a component of antineoplastic combination therapy. The proposed dosing regimen is based on the age of the patient and their body surface area, administered every two weeks.
- Oncaspar was granted orphan drug status by the TGA in April 2016 for the treatment of patients with ALL. It has been available on the Special Access Scheme (SAS) in Australia since the mid 1990's for treatment of patients with hypersensitivity reactions to L-asparaginase (Leunase).
- The sponsor has submitted EU-RMP version 1.0 (dated 17 November 2015; data lock point (DLP) 31 December 2013) and Australian Specific Annex (ASA) version 1.0 (dated 25 August 2016) in support of this application. In its post first round response, the sponsor has submitted an updated ASA (version 1.1 dated 28 April 2017) in support of this application.

- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below. The highlighted safety concerns was included in the ASA following a recommendation in the round 1 RMP evaluation:

Table 11: Summary of Safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity (Including Severe hypersensitivity and Anaphylactic shock)	✓	–	✓	–
	Pancreatitis	✓	–	✓	–
	Hyperlipidaemia	✓	–	✓	–
	Haemorrhage	✓	–	✓	–
	Thromboembolic events	✓	–	✓	–
	Hyperglycaemia	✓	–	✓	–
	Hepatotoxicity	✓	–	✓	–
	Infection	✓	–	✓	–
	Neurotoxicity	✓	–	✓	–
	Hyperammonaemia*	✓	–	✓	–
	Embryotoxicity and teratogenicity	✓	–	✓	
	Interactions with anticoagulants, corticosteroids, methotrexate and cytarabine, vincristine and live vaccines, and medicines with increased toxicity due to pegaspargase induced impaired liver metabolism	✓	–	✓	–
Important potential risks	Immunogenicity	✓	–	✓	–
	Reversible posterior leukoencephalopathy syndrome (RPLS)	✓	–	✓	–
Missing information	Effects on fertility	✓	–	✓	–
	Safety following IV route of administration	✓	–	✓	–
	Adverse events with a long latency	✓	–	✓	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Safety of patients with severe liver impairment	✓	–	✓	–
	Safety in patients with renal impairment	✓	–	✓	–
	Use in elderly patients	✓	–	✓	–

*Recommended by the RMP Evaluator and accepted by the sponsor in its response.

- No additional pharmacovigilance are proposed. There are two post-authorisation efficacy studies being conducted in the EU.
- No additional risk minimisation activities have been proposed. This is considered acceptable based on the known safety profile, history of clinical use through the SAS and the familiarity of prescribers with this product.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is: Implement EU-RMP (version 1.0; dated 17 November 2015; DLP. 31 December 2013) with Australian Specific Annex (version 1.1, dated 28 April 2017) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Summary of international regulatory status

USA – FDA (checked 28 June 2017)

Oncaspar is approved in the US with the following indication:

> *Oncaspar is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for treatment of patients with:*
>
> *First line acute lymphoblastic leukemia (1.1)*
>
> *Acute lymphoblastic leukemia and hypersensitivity to asparaginase (1.2)*

The recommended dose in the USPI is 2,500 IU/m^2 IM or IV no more frequently than every 14 days, regardless of age. This wording does not 'specify' fortnightly dosing.

Contraindications include history of serious allergic reactions to Oncaspar, serious thrombosis with prior L-asparaginase therapy, pancreatitis with prior L-asparaginase therapy, and serious haemorrhagic events with prior L-asparaginase therapy.

There are warning and precautions related to: anaphylaxis or serious allergic reactions; thrombosis (for example CNS thrombosis); pancreatitis; glucose intolerance; coagulopathy; and hepatotoxicity. The latter warning is a recent (2014) addition to labelling, at which time 'hyperlipidaemia' was included in the Adverse Reactions section.

The US PI cites as evidence the following trials:

First-line ALL:

Study 1: randomised, active controlled study of 118 patients with a median age of 4.7 years (range 1.1 to 9.9); 59 patients were randomised to Oncaspar, and 48/59 received all 3 planned doses; 59 patients were randomised to native *E.coli* L-asparaginase. Study 1 also contributed PK and PD data to the USPI. This study equates to CCG-1962.

Study 2: ongoing, multi-factorial design study with interim safety data for 2,770 patients; median age 4 years (range 1 to 10); schedule of Oncaspar depended on arm, with intermittent doses for up to 10 months. This study appears to equate to CCG-1991.

In considering the evidence base, it is relevant that first line use was approved by the FDA in 2006.

Previously treated ALL:

Safety data were obtained from 5 clinical trials that enrolled a total of 174 patients with relapsed ALL who received Oncaspar as a single agent or in combination with multi-agent chemotherapy. This included 62 patients with prior hypersensitivity reactions to asparaginase (native *E.coli* L-asparaginase or native *Erwinia* L-asaparaginase).

In considering the presented evidence base, it is relevant that this use was approved by the FDA in 1994. It is probably also fair to say that the US PI is a product of an earlier period of PI development (for example in terms of level of detail for certain Precautions), despite the updates made since 1994 (as recently as 2014).

There is also reference in the USPI to 3 PK studies in 37 patients with relapsed ALL.

In the US, according to NCCN[59] Guidelines Version 1.2017 (ALL), ALL-C 3-4 of 4, only two forms of asparaginase are in clinical use: pegaspargase and native *Erwinia* asparaginase.

EU; EMA (checked 28 June 2017)

Oncaspar was approved in the EMA in 2016 with the following indication:

Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.

Dosing in the SmPC matches that proposed for the Australian PI.

The efficacy and safety evidence base presented in the SmPC is as follows:

First-line (non-hypersensitive) ALL:

'Study 1' as per USPI's 'Study 1' (standard risk ALL patients). This study equates to CCG-1962.

A pilot study for newly diagnosed patients 1 to 30 years of age with high risk B-precursor ALL ('Study 2' in the SmPC); n = 166 (54 randomised to Oncaspar, and 111 to another PEGylated asparaginase product). This study equates to AALL07P4.

ALL patients hypersensitive to native *E.coli* L-asparaginase:

[59] NCCN; National Comprehensive Cancer Network

6 open label studies in relapsed / refractory haematological disease, involving a total of 94 patients with ALL and a history of prior clinical allergic reaction to native *E.coli* L-asparaginase, all but one given either 2,000 or 2,500 U/m^2 IM or IV Oncaspar.

These studies were: ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400 and ASP-001C/003C.

Other studies contributed to understanding of the pharmacological profile.

Background

Acute lymphoblastic leukaemia (ALL)

Much evidence presented about the efficacy and safety of pegaspargase is stratified by patient age, because of striking variation in ALL prognosis with age. This is described by Stock et al (2011) in a review of pegaspargase toxicity in adults[60]:

> The survival of patients with acute lymphoblastic leukaemia (ALL) has a striking dependence on the age of the patient at diagnosis, with a dramatic decline as a function of age beginning in late childhood, plummeting during adolescence, and declining steadily thereafter (Figure 2).

Figure 2: Five year observed survival rate of patients with ALL

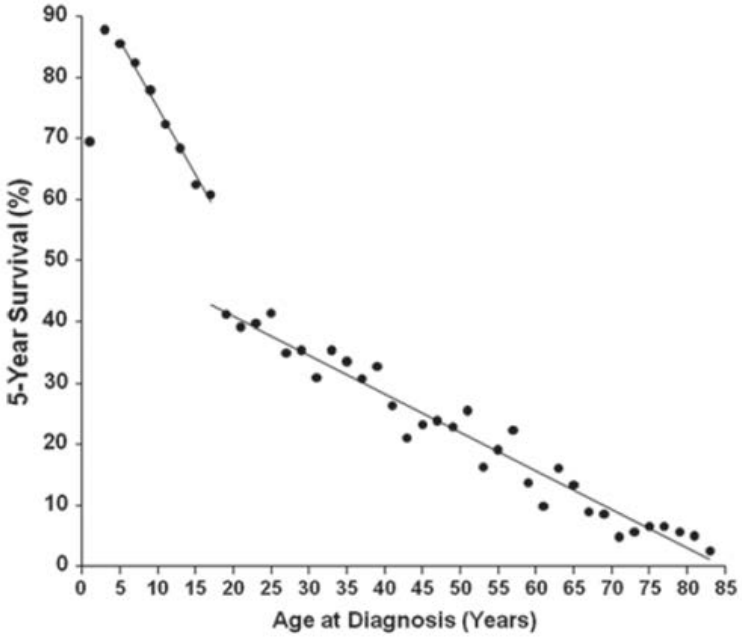


Figure 2: Five year observed survival rate of patients with ALL diagnosed in the USA between 2000 and 2007, by age at diagnose of 2 year intervals. Slopes are linear regressions for ages 4 to 1 7 and 18 to 83 years. Data from surveillance, epidemiology and end results (SEER) 17, accessed 2 May 2010. Relative survival has an essentially identical pattern.

Paediatric ALL

Five year OS is > 85%, with 5 year event-free survival (EFS) > 93% in low risk groups.[61] This good result is considered to be due in part to availability of asparaginase (but also due to re-induction, delayed intensification, prophylaxis against CNS relapse, etcetera).

[60] Stock, Douer, DeAngelo et al (2011). Prevention and management of asparaginase / pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel, *Leukemia & Lymphoma* 2011; 52: 2237-2253

Death resulting from treatment toxicity remains a challenge: 'in a review of over 1,000 children with ALL treated at St. Jude Children's Research Hospital, the estimated 10 year cumulative incidence of treatment related death was 2.9%'. Infants and children 10 + years of age were at higher risk of treatment related mortality. Such mortality is due to infection in the majority of cases.

10 to 15% of children fail initial treatment (the rate is higher, for example 30%, in certain high risk sub-groups); outcome in these patients is worse. Patients with relapsed ALL require aggressive re-induction therapy and intensification, 'often using agents not administered in the original treatment protocol'.

Adult ALL

Kantarjian et al. (2017);[62] note that with use of intensive chemotherapy regimens, CR rates are 85 to 90% and long-term survival rates are 30 to 50%. Upon relapse, remission rates are 18 to 44% with standard salvage chemotherapy; duration of remission is often short and median OS with relapsed / refractory ALL is less than 6 months.

Asparaginase and pegaspargase

Pegaspargase has been available in Australia via the SAS and also via clinical trials for about 20 years. (Baxalta Australia Pty Ltd is the first sponsor to apply for registration of the product in Australia).

Patil, Coutsouvelis and Spencer (2011);[63] wrote a review of asparaginase in management of adult ALL which also provides ALL background information, including some insights into how this therapy was pioneered; for example the attributes and role of guinea pig serum. Kawedia and Rytting (2014) also usefully review asparaginase in ALL.[64]

L-asparaginase is considered part of the standard of care for many ALL patients. The EviQ supporting document 'Asparaginase' was copied and provided with this overview [not included here].[65] Information about the following asparaginase preparations is from EviQ and the CER (see Table 12 below).

Table 12: Information about some asparaginase preparations (from EviQ)

Formulation	L-asparaginase (colaspase)	*Erwinia* asparaginase (crisantaspase)	Pegasparaginase
Bacterial source	*E.coli*	*Erwinia* chrysanthemi[66]	*E.coli* and attached to polyethylene glycol
Brand name	Leunase	Erwinase	Oncaspar
Presentation	10,000 Kyowa units / vial	10,000 IU / 3 mL vial	3,750 IU / 5 mL

[61] Horton and Steuber, 2017 Overview of the treatment of acute lymphoblastic leukaemia in children and adolescents. Up-to-date Topic 6245; Version 43.0; Last updated Jun 22 201
[62] Kantarjian et al (2017) Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *NEJM* 2017 376: 836 - 847
[63] Patil, Coutsouvelis and Spencer (2011) Asparaginase in the management of adult acute lymphoblastic leukaemia: is it used appropriately? *Cancer Treat Rev* 2011; 37: 202-207
[64] Kawedia and Rytting (2014) Asparaginase in acute lymphoblastic leukaemia. *Clinical Lymphoma, Myeloma and Leukaemia*, 2014;14: S14-7
[65] This document, found at https://www.eviq.org.au/Protocol/tabid/66/id/918/Default.aspx (ID 000918 V.1; last modified 14 Oct 2015), makes use of the review paper by Stock et al (2011).
[66] Apparently renamed *D.dadantii* (https://en.wikipedia.org/wiki/Dickeya_dadantii)

Formulation	L-asparaginase (colaspase)	*Erwinia* asparaginase (crisantaspase)	Pegasparaginase
TGA status	ARTG (1991)	SAS A	SAS A
Half-life	1 day	14 hrs	6 days

Asparaginase is used in paediatric ALL in induction therapy, and potentially in augmented post-remission therapy for those at higher risk (as per UKALL 2003), as well as in delayed intensification (DI) regimes (post-remission and post-consolidation).[61] It has been employed in maintenance, but this appears to be a less common approach.[57]

EviQ (which focuses on adult ALL) recommends several ALL protocols, including Berlin Frankfurt Munster (BFM) 2,000, where L-asparaginase (colaspase) is used IV in induction (8 doses) and also in re-induction (4 doses), with further doses for high risk and very high risk patients. BFM 2,000 is recommended by EviQ for adolescent and young adults with ALL. The other EviQ protocol for Ph ALL;[67] in adults, HyperCVAD;[68] Parts A + B + POMP, does not include asparaginase. This aligns with advice in National Comprehensive Cancer Network (NCCN) ALL guidelines that pegaspargase is a common component of therapy for children, adolescents and young adults with ALL. In NCCN guidance, some adult regimens involve pegaspargase, others do not.

The dosing regimen recommended by EviQ for pegasparagase (Oncaspar) conforms to the USPI, rather than the SmPC or proposed Australian PI.

Specifically regarding Oncaspar, the evaluator notes:

> The drug was developed by Enzon Pharmaceuticals Inc. in the late 1980's. Oncaspar sold in the USA, once approved, used enzyme manufactured by Merck. That in Germany and Poland after initial EU approval used enzyme manufactured by Kyowa-Hakko. For both, pegylation and subsequent manufacturing steps are carried out by Sigma-Tau Pharmaceuticals Inc in Indianapolis. In 2010, the enzyme manufacture was switched from Merck to Lonza and this was supported by a quality-based comparability data package. No new clinical data were generated.

More information is available from the quality product summary.

Oncaspar is not the only PEGylated asparaginase that has been developed, so reference to 'PEGL ASNase' in the CER should be treated somewhat cautiously. However, it is the only PEGylated asparaginase that is widely available.

Mechanism of action

The clinical evaluator notes:

> ALL cells express very low levels of the enzyme asparagine synthetase; hence they are incapable of synthesizing asparagine from aspartate. This characteristic, therefore, is a biologically plausible method of attacking such cells while sparing others.

The proposed PI states regarding mechanism of action:

> The mechanism of action of asparaginase is the enzymatic cleavage of the amino acid asparagine into aspartic acid and ammonia. Depletion of asparagine in blood

[67] Ph ALL; Philadelphia chromosome positive ALL
[68] HyperCVAD; Hyper Cyclophosphamide Vincristine Adriamycin (doxorubicin) and Dexamethasone

> serum results in inhibition of protein synthesis, especially in leukaemic blasts which are not able to synthesise asparagine, thus undergoing cell death.
>
> Normal cells, in contrast, are capable of synthesizing asparagine and are less affected by its rapid withdrawal during treatment with the enzyme asparaginase. The PEGylation does not change the enzymatic properties of asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme.

The nonclinical evaluation report (NCER) casts light on why ALL cells have low levels of asparagine synthetase:

> Asparaginase hydrolyses asparagine to aspartic acid and ammonia. Asparagine is a non-essential amino acid and is synthesised from aspartic acid and glutamine by the enzyme asparagine synthetase (ASY) in mammalian cells. Childhood ALL has low expression of ASY probably due to the methylation of the ASY gene. Consequently, depletion of asparagine in blood by asparaginase results in inhibition of protein synthesis, DNA synthesis and RNA synthesis of ALL cells, and thus apoptosis of the cancer cells.

Quality

The quality product summary was considered.

In the product summary document is an evaluation summary with useful information about the structure of Oncaspar, amongst other things.

There were objections on multiple quality grounds to approval, as follows:

1. Assessment of microbiological risk

From microbiology secondary assessment: the microbiology evaluator at the time the summary was written had sterility issues that were unresolved and stated:

> Without confirmation that the acceptance criteria and action taken to contaminated unit action limits will be updated to be in accordance with ISO 13408-1:2008 Amendment 1:2010(E) and ISO 13408-2008 Clause 10, it is not possible to recommend approval of the registration of Oncaspar Injection, solution 3750 units/5mL.

2. Good manufacturing practice

GMP clearance has not been given for multiple sites.

3. Control of excipients

In summary, the evaluator recommended that acceptable limits for excipients around the stated label concentrations must be defined and controlled. Further:

The sponsor should be asked to provide:

a. The target limits (that is acceptable range) for monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride concentrations in the DP.

b. In the absence of in process or release testing for the excipients, the sponsor should also:

   i. Provide validation information that demonstrates the established buffer preparation procedures result in consistent excipient concentrations in the DP within limits defined above.

   ii. Clarify how an out of range concentration would be detected should a failure in the buffer preparation process occur.

Comment: Question for sponsor Please summarise your broad approach to the issues raised in the quality evaluation, for the ACM's understanding (but do not use the Pre-ACM Response as a vehicle for your complete response to these issues).

There was also advice given to the sponsor concerning drug product batches exposed to temperature excursions outside the ARTG listed storage conditions. The sponsor was presented with options to address this issue.

Comment: Question for sponsor: Please comment on how you propose to address the issue of temperature excursion.

Recommended conditions of registration for quality issues were provided from the quality product summary.

Nonclinical

There were no objections to registration. The following observation was made:

> The nonclinical studies were short of nonclinical data requirements for the registration of a new drug. Nearly all nonclinical studies were conducted with pegaspargase manufactured from asparaginase sourced from a manufacturer (Merck) different from the material (Lonza) to be registered in Australia. No pharmacology or toxicology comparability studies were conducted. However, these deficiencies are overcome by quality comparability data and clinical trials using the Merck material.

Nonclinical evidence of a direct immunosuppressive effect of asparaginase is useful, since clinical studies are uniformly confounded by the disease process / concomitant therapy.

Pregnancy Category D was proposed by the sponsor and agreed by the evaluator.

Clinical

Clinical Evaluator's view

The clinical evaluator supported approval. Attachment 2, Section 9 sets out the basis for this position. It is suggested this part of the CER be read early, to orient the reader to key clinical issues in the dossier and its evaluation.

Overview of data

Many studies were submitted to support registration; some were classified as 'formal clinical studies' and others as 'published papers', sourced from several systemic reviews of the literature. The evaluator noted the complexity of the dossier.

Pharmacology

Pharmacokinetic data are described from CER (please see Attachment 2, Section 4). Pharmacodynamic data are described from CER (Please see Attachment 2 Section 5).

PD and PK information proposed for inclusion in the Australian PI resembles that in the SmPC. The USPI is similar to the SmPC in presentation of PK and PD data, though extra information is included about Study CCG-1962 ('Study 1' in USPI and SmPC parlance):

Concentrations greater than 0.1 IU/mL were observed in over 90% of the samples from patients treated with Oncaspar during induction, Delayed Intensification 1, and Delayed Intensification 2 for approximately 20 days.

Study CCG-1962

Study CCG-1962 (children 1 to 9 years) is pivotal to understanding of Oncaspar's PK profile, and is evaluated in Section 4.1.4 of Attachment 2. The evaluator notes that based on this study, 'a lower dose might suffice but this dose (2,500 IU/m^2 IM) seems to ensure an appropriate asparaginase activity level for all patients regardless of any individual variation in clearance etcetera'. The recommended dose for children (with BSA ≥ 0.6 m^2) is 2,500 U/m^2, in the Australian PI and SmPC (and 2,500 IU/m^2 for all patients in the USPI).

There is some variation in details of PK for relapsed patients across the USPI and SmPC (the latter equating to proposed Australian text) as shown in Table 13.

Table 13: Comparison of USPI and SmPC (and proposed Australian PI)

USPI	SmPC and proposed Australian PI
In 3 pharmacokinetic studies, 37 patients with relapsed ALL received Oncaspar at 2,500 International Units/m^2 intramuscularly every 2 weeks. The plasma half-life of Oncaspar was 3.2 ± 1.8 days in 9 patients who were previously hypersensitive to native E. coli L-asparaginase and 5.7 ± 3.2 days in 28 non-hypersensitive patients. The area under the plasma concentration-time curve (AUC) was 9.5 ± 4.0 International Units/mL/day in the previously hypersensitive patients and 9.8 ± 6.0 International Units/mL/day in the non-hypersensitive patients.	Patients with ALL with several relapses were treated either with Oncaspar or with native E. coli asparaginase as part of an induction therapy. Oncaspar was given in a dose of 2,500 U/m^2 body surface IM on days 1 and 15 of induction. The mean plasma half-life of Oncaspar was 8 days in non- hypersensitive patients (AUC 10.35 U/mL/day), and 2.7 days in hypersensitive patients with ALL (AUC 3.52 U/mL/day).

The main difference is in description of half-life for relapsed ALL patients who were not hypersensitive (USPI: 5.7 days; SmPC: 8 days) but in both datasets, half-life is noticeably shorter in those with hypersensitivity.

In Section 4.1.2 of Attachment 2, the evaluator describes Study ASP-302 in relapsed ALL patients. Of note is Table 14 below which shoe the PK by patient population.

Table 14: Study ASP-302, Pharmacokinetics summary by patient population

PHARMACOKINETICS SUMMARY BY PATIENT POPULATION

	HYPERSENSITIVE PATIENTS (n=2)	NON-HYPERSENSITIVE PATIENTS (n=9)	TOTAL PATIENTS (n=11)
HALF-LIFE (days) Mean ± S.D.	2.69 ± 1.97	4.83 ± 2.62	4.44 ± 2.58
AUC [(IU/mL).day] Mean ± S.D.	3.52 ± 4.23	10.35 ± 5.63	9.11 ± 5.90

It is interesting that half-life and AUC match SmPC (and proposed Australian PI) values for hypersensitive patients, and AUC matches for non-hypersensitive patients; but half-life for non-hypersensitive patients does not match.

Comment: Question for sponsor: Please explain the derivation of PI half-life and AUC values for relapsed hypersensitive and non-hypersensitive ALL patients with reference to Study ASP-302 and other sources.

In several other studies (for example ASP-304 (see Sections 4.1.3 and 5.1.8 from Attachment 2) and Asselin et al. 1993;[69] see Section 4.1.5 Attachment 2)) there was some evidence of shorter half-life and / or lower exposure (AUC) in those with high antibody levels, previous hypersensitivity, or both.

Many studies assumed asparagine depletion requires asparaginase activity of 100 IU/L (equivalent to 0.1 IU/mL). From several studies, the evaluator questioned whether asparaginase activity higher than 50 IU/L (0.05 IU/mL) might also be sufficient. The evaluator noted a dose regimen to achieve this lower threshold has not been established, and that data to support regimens other than that proposed are inadequate.

It is difficult to see evidence in the CER supporting the dosing regimen in paediatric patients with BSA < 0.6 m^2; and younger patients (since BSA correlates with age, crudely speaking these will be infants) will receive less Oncaspar than if following the USPI.

- A 2 year male old might typically have a BSA of 0.5 m^2 and weigh 15 kg. That toddler is to receive 1,237.5 IU every 14 days, similar to the 1,250 IU calculated from BSA (as per USPI).
- A 6 month old male might have a BSA of 0.4 m^2 and weigh 8 kg. That infant is to receive 660 IU every 14 days, about two-thirds the amount calculated from BSA.
- A newborn male might have a BSA of 0.22 m^2 and weigh 3.5 kg. That newborn is to receive 289 IU every 14 days, about half the amount calculated from BSA.

Comment: Question for sponsor: Please explain the derivation of dosing in children with a body surface area < 0.6 m^2.

Asparaginase is a foreign protein and is evidently highly immunogenic, with antibodies commonly contributing to major allergic responses and / or to dramatically increased clearance. Study CCG-1962 (Attachment 2 Section 7.2.1.1) compares immunogenicity of Oncaspar and native *E.coli* asparaginase in first line ALL. Study CCG-1961 (Attachment 2, Section 7.2.1.5) is also informative in this regard, but patients in this study received native *E.coli* asparaginase prior to PEGylated asparaginase. While immunogenicity can be signalled by allergic AEs, 'silent inactivation' of activity may occur with development of neutralising antibodies in the absence of clinical allergy, and such patients will not be switched to a different drug (for example *Erwinia* asparaginase) and will thus be denied effective therapy.

Oncaspar may be less immunogenic than native *E.coli* asparaginase (indeed the US PI states there is insufficient information to determine whether development of antibodies is associated with greater risk of allergic reactions, altered PK or loss of anti-leukaemic efficacy).

Efficacy

The evaluator integrates efficacy data in Section 7.5 of Attachment 2, and this section of is perhaps the best place to start examining the dossier's evidence of efficacy. In the more

[69] Asselin BL et al. 1993 Comparative Pharmacokinetic Studies of Three Asparaginase Preparations. *Journal of Clinical Oncology* 1993; 11: 1780-1786

detailed earlier parts of Section 7, the evaluator distinguishes between 'formal clinical trials' (Section 7.2, stratified by line of therapy) and published studies (Section 7.3, stratified by line of therapy and, within first line, also by age group; child versus adult). The evaluator's 'table of key efficacy data is above in Table 7.

First-line use

The evaluator tabulates supportive 'formal' trials in Section 7.2 of Attachment 2. Of note:

- Study CCG-1962 is included (this is 'Study 1' in the USPI and in the SmPC), and evaluated in Sections 7.2.1.1 and 7.3.1.24.
- AALL07P4 (progress report) is included (this is 'Study 2' in the SmPC), and evaluated in Section 7.2.1.3 of Attachment 2.

Other 'formal' studies identified as highly relevant by the clinical evaluator include:

- Place et al. 2015;[70] (DFCI-05-001);[71] (Attachment 2 Sections 7.2.1.2, 7.2.1.13 and 7.3.1.23). This was described as the most important trial in the Dossier, by the evaluator. It supports equivalence of efficacy outcomes for Oncaspar and native *E.coli* ASNase.
- Asselin et al. 1999;[72,73] (DFCI-87-001) (Attachment 2 Section 7.2.1.6), where a subset of patients with greater clearance had a relatively low response rate. From this the evaluator recommends that monitoring for hypersensitivity and antibody formation should be an integral part of patient management.
- Three other studies (DFCI-91-01;[74,75] (Attachment 2, Section 7.2.1.4); AALL0232;[76,77] (Attachment 2 Section 7.2.1.9) and UKALL2003;[78,79] (Attachment 2 Sections 7.2.1.11and 7.3.1.23) were singled out as providing satisfactory 5 year event free survival data in children and younger adults treated with protocols including PEGylated asparaginase.

In Section 7.3.1.23, Attachment 2, the evaluator synthesises published evidence of efficacy in first line use in children. Study ALL0331 is described as a huge, contemporary study in

[70] Place AE et al. 2015. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open label phase 3 trial. *Lancet Oncol* 2015; 16: 1677-1690
[71] DFCI = Dana-Farber Cancer Institute
[72] Asselin B L 1999a. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. In Drug Resistance in Leukemia and Lymphoma III, edited by Kaspers et al Kluwer Academic/ Plenum Publishers New York 1999.
[73] Asselin B L et al 1999b. Prognostic significance of early response to a single dose of asparaginase in childhood acute lymphoblastic leukemia*. J Pediatr Hematol Oncol.* 1999b; 21: 6-12
[74] Silverman LB et al 2001 Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood* 2001;97: 1211-1218
[75] Silverman LB et al 2010 Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). *Leukemia* 2010; 24: 320-334
[76] Larsen EC et al. 2011 Comparison of high dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high risk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Oncology Group Study AALL0232*. J Clin Oncol* (Meeting Abstracts) 2011; 29:Suppl 3
[77] Winick N J et al 2011 Dexamethasone (DEX) versus prednisone (PRED) during induction for children with Highrisk acute lymphoblastic leukemia (HRALL): A report from the Children's Oncology Group Study AALL0232*. J Clin Oncol*: 2011; 29: (suppl; abstr 9504)
[78] Vora A et al 2013 Treatment reduction for children and young adults with low risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial*. Lancet Oncol.* 2013; 14:199-209
[79] Vora A et al 2014Augmented post-remission therapy for a minimal residual disease-defi ned high risk subgroup of children and young people with clinical standard risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet Oncol* 2014; 15: 809-818

thousands of patients that supports use of first line Oncaspar for B cell ALL in children. In conclusion, the evaluator writes:

- Use of asparaginase per se is an accepted part of current first line treatment in children with ALL.
- Oncaspar appears to have similar efficacy outcomes in terms of EFS and OS compared with native *E.coli* asparaginase.
- Oncaspar has a treatment advantage of wider dose intervals.
- Oncaspar appears to elicit fewer allergic reactions when given IM, although data are weak.
- Oncaspar appears to elicit lower rates of antibody formation than native *E.coli* asparaginase, although one cannot claim this definitively.
- The dose of Oncaspar proposed in the draft PI matches virtually all of the trial doses used.
- Monitoring asparaginase serum levels and / or serum levels of asparagine appears a useful activity given the uncertainty of hypersensitivity / antibody development and the resulting effects this can have on drug clearance and thus asparagine presence in the body.
- The use of Oncaspar in the first line treatment of children with ALL has been satisfactorily established in the opinion of this evaluator.

In Section 7.3.2.11, Attachment 2, the evaluator synthesises published evidence of efficacy in first line use in adults. Of note, the evaluator draws attention to the De Angelo 2015a;[80] study as providing evidence supporting the 2,000 IU/m^2 dose in adults (although in fact this study set out to examine 2,500 IU/m^2 every two weeks, and scaled back to 2,000 IU/m^2 every three weeks because of toxicities). Several other publications are also considered relevant. In conclusion, the evaluator writes:

- The body of evidence for first line treatment in adults is smaller than that for children.
- The degree of detail provided in some of the citations was poor.
- The data collectively represent many hundreds of patients treated first line for ALL with PEGL ASNase as a component of that treatment.
- The proposed dose of 2,000 IU/m^2 was used in several instances, supporting this choice of dose as balancing against known toxicities.
- Often the use of PEGL ASNase in a given trial is compared to a regimen without PEGL ASNase, but one which also differs from that of the PEGL ASNase containing regimen, making it difficult to ascribe a quantified benefit from the PEGL ASNase itself.
- Adults from 18 to 72 (years) are shown to derive benefit from ALL treatment regimens containing PEGL ASNase. These regimens have, on balance, produced similar outcomes as other treatment regimens for ALL where comparisons have been present.
- While not an ideal data set, this evaluator considers the role of PEGL ASNase in the treatment of adults with ALL has been satisfactorily demonstrated. The reduction of dose from paediatric levels appears directly as a result of greater toxicity in adults at paediatric doses.

[80] DeAngelo DJ et al. 2015 a A Multicenter Phase II Study Using a Dose Intensified Pegylated-Asparaginase Pediatric Regimen in Adults with Untreated Acute Lymphoblastic Leukemia: A DFCI ALL Consortium Trial. *American Society for Hematology* 57th annual meeting and exposition.

Regarding the last dot-point, discussion by Patil et al. (2011);[81] is interesting.

Given the view that evidence for first line treatment in adults is not overwhelming, it is relevant that the sponsor commits to submit the results of a study in adults where PEG-ASP is used in a first line setting, by 31 December 2018.

Second line use

The evaluator tabulates supportive 'formal' studies in Table 42 Attachment 2. Study ASP-304 (Attachment 2, Section 7.2.2.7)) was influential. The evaluator summarises findings from Section 7.2.2.10. The evaluator also draws attention to the study by Abshire et al. (2000);[82] (Section 7.3.3.2)in relapsed ALL in children, where weekly dosing appeared better than fortnightly dosing, and to a study by Kurtzberg et al (2011);[83] (Attachment 2, Section 7.3.3.1 and Table 95).

The evaluator notes that for second-line use, data are adequate for paediatric ALL but are sparse for adult ALL (particularly for older adults).

Pooled efficacy outcomes

The evaluator presented pooled outcomes Attachment 2, Section 7.4. In aggregate, there is strong support for the efficacy of Oncaspar, based on EFS and also OS outcomes, mostly in paediatric patients but also adults. The pooled estimates may not be weighted by sample size (for example Figure 29 Attachment 2, PEG outcomes: Stock et al.;[84] reported a 66% 2 year EFS with n = 296; Fathi et al.;[85] 28% 2 year EFS with n = 18, but a pooled estimate of 48%).

Comment: Question for sponsor: Are pooled estimates presented (in CER pages 151 to 158) weighted by sample size?

Safety

Safety is evaluated in Attachment 2, Section 8. As with efficacy, the evaluator distinguished 'formal clinical studies' (evaluated for safety outcomes mainly within Attachment 2 Section 8.1) and 'published studies' (evaluated for safety outcomes mainly within Attachment 2 Section 8.4).

Section 8.7 of Attachment 2, provides the evaluator's conclusions about safety and provides a good orientation to the safety evidence base provided in the dossier.

Hepatotoxicity / abnormal LFTs

The evaluator draws together key studies informing about risk of abnormal LFTs and / or hepatotoxicity in Attachment 2, Section 8.2.3 (paediatric use) and Section 8.2.8 (adult use). Abnormal LFTs (including elevated bilirubin) were commonly reported, but reports of hepatitis or hepatotoxicity per se were not particularly prominent. On the other hand, elevations in bilirubin can cause dose delays for drugs such as vinca alkaloids and anthracyclines.

[81] Patil, Coutsouvelis and Spencer (2011). Asparaginase in the management of adult acute lymphoblastic leukaemia: is it used appropriately? *Cancer Treat Rev* 2011; 37: 202-207
[82] Abshire T C et al. Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a pediatric oncology group study *Blood.* 2000;96:1709-1715
[83] Kurtzberg J et al. 2011Polyethylene Glycol-conjugated L-asparaginase Versus Native L-asparaginase in Combination With Standard Agents for Children With Acute Lymphoblastic Leukemia in Second Bone Marrow Relapse: A Children's Oncology Group Study (POG 8866) *J Pediatr Hematol Oncol* 2011; 33: 610-616
[84] Stock W et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): Early results of US Intergroup trial C10403. *Proc ASH* 2014;Abstract 796.
[85] Fathi AT et al. Phase 2 study of intensified chemotherapy and allogeneic hematopoietic stem cell transplantation for older patients with acute lymphoblastic leukemia. *Cancer*. 2016 May 12. doi: 10.1002/cncr.30037. (Epub ahead of print)

Pancreatitis

The evaluator draws together key studies informing about pancreatitis risk Attachment 2, Section 8.2.2 (paediatric use) and Section 8.2.7 (adult use). Pancreatitis is considered a frequent and serious toxicity associated with pegaspargase (and native asparaginases).

The experience in DFCI-87-001 is instructive (see Attachment 2, Section 8.1.1.6); initial high amylase was followed by clinical pancreatitis in a subset, which became severe in a further subset of patients receiving asparaginase in the intensification phase.

The report by Raja et al (2014);[86] (see Table 95, Attachment 2) is helpful in clarifying that if pancreatitis develops (as it did in 45/786 studied children), severe manifestations (for example necrosis) are not uncommon. One patient died from pancreatitis. The study did conclude that in mild cases, re-exposure to Oncaspar is safe. The sponsor did not request any change to the current contraindication ('history of pancreatitis') based on this study, but it is noted that Knoderer et al (2007);[87] (see Table 95, Attachment 2) drew similar conclusions.

Comment: Question to sponsor: Is the mechanism of pancreatitis known? Is it always related to hypertriglyceridaemia, which is a recognised cause of pancreatitis? Does this link suggest the need for regular serum lipid monitoring to mitigate risk of hypertriglyceride-induced pancreatitis? Does this suggest the need to treat high triglycerides to allow safer ongoing use of Oncaspar?

Hypertriglyceridaemia

The US PI notes hypertriglyceridaemia and hypercholesterolemia have been reported in patients given Oncaspar. Hypertriglyceridaemia might be due to hepatotoxicity.

In some patients (for example in Study DFCI-05-001; see Attachment 2 Section 8.1.1.2) hypertriglyceridaemia is pronounced. In that study, 8% of patients reported Grade 4/5 hypertriglyceridaemia, versus 4% receiving native *E.coli* asparaginase. This is relevant given the potential link with pancreatitis.

Hypersensitivity / allergy / anaphylaxis

The evaluator draws together key studies informing about allergic risk in Attachment 2 Section 8.2.1 (paediatric use) and Section 8.2.6 (adult use).

Of interest, Horton and Steuber (2017);[88] state:

> Anaphylactic reactions to PEG-asparaginase can be delayed by several hours. Because of this delay, a period of observation following administration of PEG-asparaginase has become common practice at many institutions. (See 'Infusion reactions to systemic chemotherapy', section on 'L-asparaginase'.)

The CCG-1962 trial (Attachment 2 Section 7.2.1.13) suggested pegaspargase is less immunogenic than native *E.coli* ASNase, but Place et al (2015);[89] found no difference (Attachment 2 Table 96).

The NOPHO ALL2008 study as reported by Henriksen et al (2015);[90] (Attachment 2 Section 7.2.1.12) describes the extent of allergic reactions to PEGL ASNase; but the dose

[86] Raja R A et al 2014 Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol. *British Journal of Haematology* 2014; doi:10.1111/bjh.12733
[87] Knoderer H M et al 2007 Predicting Asparaginase-Associated Pancreatitis. *Pediatr Blood Cancer* 2007;49:634–639
[88] Horton and Steuber (2017). Overview of the treatment of acute lymphoblastic leukaemia in children and adolescents. Up-to-date Topic 6245; Version 43.0; Last updated Jun 22 2017
[89] Place AE et al. 2015. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open label phase 3 trial. *Lancet Oncol* 2015; 16: 1677-1690

used was lower than proposed. 82 out of 615 children had an allergy to PEGylated asparaginase.

An issue repeatedly studied in this field is whether route of administration (IV versus IM) influences risk of allergic AEs. The evaluator concludes that IM use is associated with a lower risk of hypersensitivity. For example:

- In Study AALL0331;[91] (Attachment 2 Section 7.2.1.10), there was a higher rate of anaphylaxis / allergic reaction with IV administration (1.8%) than with IM (0.5%).
- See also Attachment 2 Sections 8.2.1 to Section 8.2.4, where the conclusions of a detailed analysis about this issue are reported:
- Patients with a prior history of hypersensitivity who received Oncaspar IV were the most likely to experience a hypersensitivity reaction and patients with no prior history of hypersensitivity that received Oncaspar IM were the least likely to experience a hypersensitivity. It was also observed across all strata that the survival curves flattened after the initial 3 doses indicating that the probability of a patient developing a hypersensitivity reaction is greatest in response to the initial 3 doses of Oncaspar regardless of the route of administration or hypersensitivity history.
- Abbott et al.; [92],and Alrazzak et al.;[93] (Table 96 Attachment 2), MacDonald et al.;[94] (Attachment 2 Section 7.3.1 10 and Table 96) and Maloney et al.;[95] (Table 96) have the same conclusion.

Of note, NCCN guidelines (ALL-C 3 of 4) state the IV route is increasingly being used.

A paper by Chang et al.;[96] concluded that premedication did not reduce the rate of allergic AEs. However, contrary views have also been put (for example Stock et al, 2011).[97] One concern with the use of steroid pre-medication is that suppression of allergic AEs will remove that clinical indication of the development of neutralising antibodies. (This issue might be addressed by asparaginase monitoring.)

EviQ concludes that for pegasparaginase, as per Stock et al (2011);[97] 'If not on concurrent corticosteroids, premedication with hydrocortisone 100 mg IV is recommended'.

Comment: Question for ACM: Should the PI recommend use of pre-medication to mitigate risk of allergy? Should the PI recommend IM over IV administration, or a

[90] Henriksen L T et al 2015 PEG-Asparaginase Allergy in Children With Acute Lymphoblastic Leukemia in the NOPHO ALL2008 Protocol. *Pediatr Blood Cancer* 2015; 62: 427-433

[91] Maloney KW et al. Association of intravenous (IV) and intramuscular (IM) pegaspargase (PEG) administration with rate of adverse events (AE) in standard risk (SR) acute lymphoblastic leukemia (ALL) Children's Oncology Group (COG) trials. *Journal of Clinical Oncology*; 2015; 33(15 (supplement)): 10035

[92] Abbott LS et al. Allergic Reactions Associated with Intravenous versus Intramuscular Pegaspargase: A Retrospective Chart Review. *Paediatr Drugs*. 2015; 17:315-321.

[93] Alrazzak M et al. The Incidence of Hypersensitivity Reactions to Pegylated Asparaginase in Children With Acute Lymphoblastic Leukemia: A City-wide Experience. *J Pediatr Hematol Oncol*. 2016 Jan;38(1):e16-20. doi:10.1097/MPH.0000000000000465

[94] MacDonald T et al. Allergic Reactions With Intravenous Compared With Intramuscular Pegaspargase in Children With High risk Acute Lymphoblastic Leukemia: A Population-based Study From the Maritimes; Canada. *J Pediatr Hematol Oncol*. 2016 Feb 26. (Epub ahead of print)

[95] Maloney KW et al. 2013 Excellent event free (EFS) and overall survival (OS) for children with standard risk acute lymphoblastic leukemia (SR ALL) despite the absence of a significant impact on outcome with the addition of an intensified consolidation: Results of Children's Oncology Group (COG) AALL0331. *Blood* 2013; 122: 837

[96] Chang A et al. Allergic reactions associated with pegaspargase in adults. *Leuk Lymphoma*. 2016 Mar 14:1-4. (Epub ahead of print)

[97]Stock W et al 2011 Prevention and management of asparaginase/pegasparaginaseassociated toxicities in adults and older adolescents: recommendations of an expert panel *Leukemia and Lymphoma* 2011; 52: 2237–2253

slower infusion, or any other strategies to minimise the risk of hypersensitivity?

Thrombosis and coagulopathy / bleeding

The evaluator draws together key studies informing about risk of thrombosis in Attachment 2 Section 8.2.5 (paediatric use) and Section 8.2.10 (adult use). The evaluator notes:

> Asparaginase induces a hypercoagulable state that can result in catastrophic thrombosis of the inferior vena cava or the superior sagittal sinus in addition to deep vein thromboses of the legs or arms.

Horton and Steuber (2017)[88] explain the hypercoagulable state:

> Thrombosis is a major complication that may be life-threatening and impact future therapy. In contemporary treatment protocols, the incidence of thrombotic complications among children with ALL receiving asparaginase has varied among studies from as low as 1.8 percent to as high as 15 percent in children with prothrombotic risk factors.[98]
>
> Asparaginase depletes plasma asparagine, thereby inhibiting protein synthesis in leukemic cells and the synthesis of several plasma proteins. The latter effect causes deficiencies of albumin, thyroxine-binding globulin, and various coagulation proteins, including prothrombin, factors V, VII, VIII, IX, X, XI, fibrinogen, antithrombin, protein C, protein S, and plasminogen. These deficiencies result in prolongation of the prothrombin time, activated partial thromboplastin time (aPTT), thrombin time, and hypofibrinogenaemia, with fibrinogen levels often less than 100 mg/dL. *E. coli* asparaginase and *Erwinia* asparaginase appear to have equivalent risk of severe thrombosis, including central nervous system haemorrhage.

It is further noted that risk factors for thrombosis in paediatric ALL treatment include: asparaginase; concomitant steroids; thrombophilic genetic abnormalities; and presence of central lines.

The NOPHO ALL (2008) study as reported by Tuckuviene et al (2016);[99] (Attachment 2 Section 7.1 2 12 and Table 96) describes the extent of thromboembolism encountered with Oncaspar.

Various studies reported changes in coagulation profile.

There is some reference to use of prophylactic anti-thrombin in reduction of thrombotic AEs. Fresh frozen plasma may replete asparagine.[97] The use of fresh / frozen plasma is recommended in the proposed PI in some circumstances.

Comment: Question for sponsor: What is the justification for recommending use of fresh or frozen plasma ahead of AT and in the absence of thrombosis?

The EviQ guidance refers to 'replacement therapy' and states regarding prevention:

> It is not possible to provide firm recommendations regarding thromboprophylaxis and factor replacement for patients on asparaginase, owing to the lack of high quality trial data addressing this specific question. It is recommended that individual units develop a strategy of blood factor monitoring (AT, fibrinogen, INR) and a thromboprophylaxis / factor replacement regimen for patients on

[98] Ref 45 = Payne JH, Vora AJ. Thrombosis and acute lymphoblastic leukaemia. Br J Haematol 2007; 138:430.
[99] Tuckuviene R et al 2016 Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study. *Journal of Thrombosis and Haemostasis* 2016; 14: 485-494

asparaginase. The exact strategy for each unit will be influenced by the available laboratory resources.

Hyperglycaemia

The evaluator draws together key studies informing about risk of hyperglycaemia in Attachment 2 Section 8.2.4 (paediatric use) and Section 8.2.9 (adult use). Some investigators have linked the observed AEs to steroid use.

The US PI warns about glucose intolerance, which is sometimes irreversible (although it is noted in a 2009 paper by Lowas et al.;[100] (Table 95 Attachment 2) that asparaginase is associated with *transient* hyperglycaemia in about 20% of paediatric ALL patient). There is advice to monitor serum glucose.

CNS effects

CNS thrombosis has been identified as a rare but serious AE associated with Oncaspar use. Other less specific neurological AEs have also been reported. Hyperammonaemia has been implicated in such CNS-related AEs. The proposed PI's Precaution concerning CNS effects makes no reference to monitoring of serum ammonia levels in patients with relevant symptoms, although there is a later comment under 'Other Precautions'.

Interestingly, the PI for Leunase was recently updated to discuss PRES:

> Posterior Reversible Encephalopathy Syndrome: Posterior Reversible Encephalopathy Syndrome (PRES), a neurological disorder, may occur rarely during treatment with colaspase. This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Clinical symptoms of PRES include headache, seizures, altered mental status, hypertension and visual disturbances (primarily cortical blindness or homonymous hemianopsia). It is unclear whether the PRES is caused by colaspase, concomitant treatment or the underlying diseases.
>
> Leunase should be ceased if PRES is suspected or diagnosed. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary.

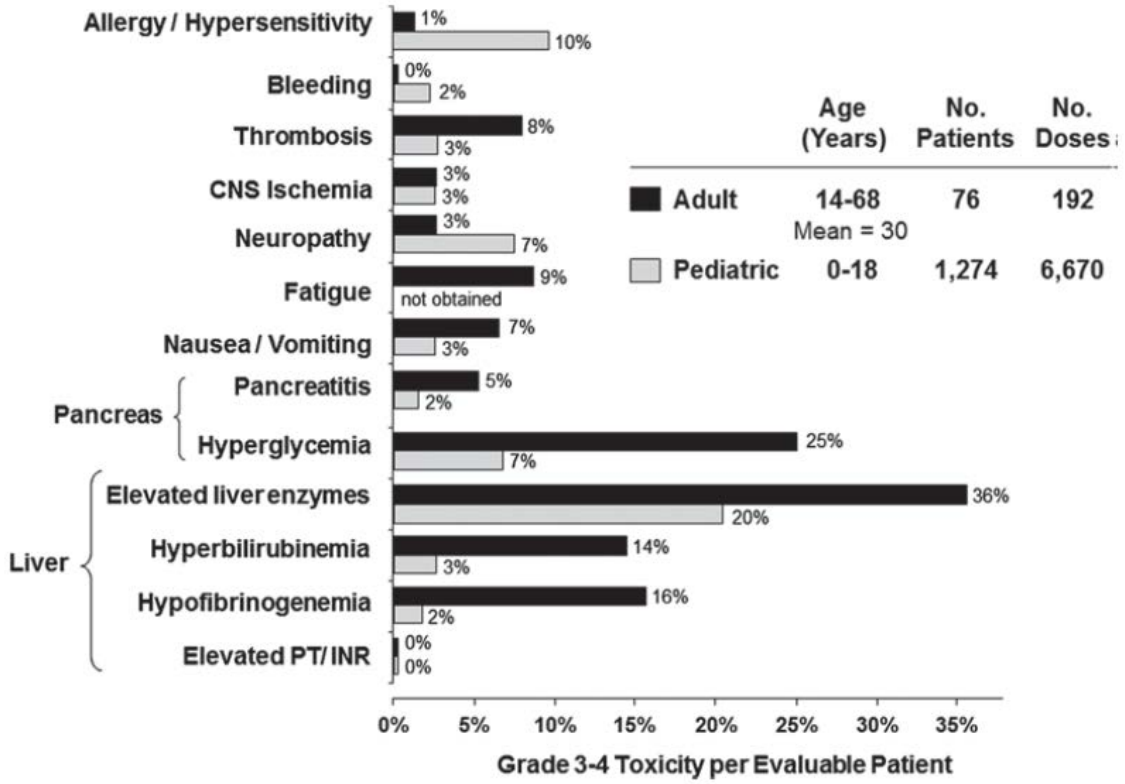
The proposed Oncaspar PI references reversible posterior leukoencephalopathy syndrome (RPLS) in the Adverse Effects section.

Toxicity by age

This topic is addressed by Stock et al (2011);[97] with reference to a figure from a paper by Advani et al. (Figure 3).

[100] Lowas S R et al 2009 Prevalence of Transient Hyperglycemia During Induction Chemotherapy for Pediatric Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 2009; 52: 814-818

Figure 3: Proportion of adult and paediatric patients with ALL with apparent* Grade 3 or 4 pegASNase related toxicities



Proportion of adult and paediatric patients with ALL with apparent* Grade 3 to 4 pegASNase related toxicities. Data from poster presentation by Advani and associates.[101] *Apparent refers to the difficulty in determining whether the observed toxicity was due to pegASNase or to another agent in the multidrug regimen of ALL therapy, or to a combination of drugs that would not have occurred with pegASNase alone.

Risk management plan

The 'Summary of Safety Concerns' appears comprehensive. Only routine pharmacovigilance and risk minimisation measures are proposed. There are no outstanding RMP recommendations.

Recommended condition of registration

Implement EU-RMP (version 1.0; dated 17 November 2015; DLP. 31 December 2013) with Australian Specific Annex (version 1.1, dated 28 April 2017) and any future updates as a condition of registration.

[101] Advani AS et al Frontline-Treatment Of Acute Lymphoblastic Leukemia (ALL) In Older Adolescents and Young Adults (AYA) Using a Pediatric Regimen Is Feasible: Toxicity Results of the Prospective US Intergroup Trial C10403 (Alliance) Session: 614. Acute Lymphoblastic Leukemia: Therapy, excluding Transplantation: Poster III

Risk-benefit analysis

Delegate's considerations

General comments

There is a long history of use of Oncaspar, mainly overseas but also via SAS and clinical trials within Australia. Its integral role in anti-leukaemic efficacy within various ALL protocols is accepted. While it is accompanied by substantial toxicity, the benefit / risk balance for Oncaspar is accepted as positive (with the caveat that quality issues impact on assessment of benefit / risk; see below).

Pegylation of asparaginase has extended the dosing interval to 2 weeks, which provides a major practical advantage over Leunase.

Quality issues

There are multiple quality issues that until resolved preclude registration of Oncaspar.

Use with multi-agent regimens

The proposed PI assumes that pegaspargase will be used in the context of a multi-agent regimen, and does not specify (for example in the Dosage and Administration section) what such regimen/s are appropriate.

To illustrate an alternative approach, the PI for arsenic trioxide (Phenasen; for APL):

1. in the Indications section, specifies use in combination with all-trans retinoic acid and / or chemotherapy, in previously untreated APL patients (but the initial indication, use in rrAPL, does not specify use of any other agent);
2. in the Dosage and Administration section, specifies a particular arsenic trioxide dose regimen corresponding to the regimen used in the pivotal study/s per patient group (that is high risk patients versus low-intermediate risk patients), and also mentions dose regimens for combination agents; and
3. in the Clinical Trials section, exclusively describes trials conforming to the specified overall treatment regimen (at least in the more recently approved first line setting).

It is reasonable to assume, however, that patients being treated with pegaspargase will be treated by suitably qualified specialists, in accordance with established protocols. In this setting, less detail in the PI may be considered acceptable. Furthermore, protocols for ALL are complicated, vary depending on risk stratification, and may not be used uniformly across Australian ALL treatment centres. Detailed specification in the PI may be challenging without clear advice from the ACM that one or a few protocols involving pegaspargase are predominant in Australia.

Comment: Question for the ACM: Is the proposed Oncaspar PI acceptable in its broad approach of providing little detail about pegaspargase-containing regimens considered acceptable or supported by specific pivotal studies?

For context, the Leunase PI states in this regard:

> Dosage should be individualised based on the clinical response and tolerance of the patient. Specialist texts should be consulted for recommended dosing schedules (including sequence of administration), when used alone or in combination.

Dose interval

The proposed dose regimen in the Oncaspar draft PI recommends use 'every 14 days' but does not attempt to match recommended use to particular protocols. For example, a naïve reading of the PI might assume use is ongoing every 14 days. It is considered that this

product will only be prescribed by suitably qualified specialists, who will use the product by and large in keeping with established protocols (see issue raised above). Despite this, it is noted by Patil et al (2011)[81] that:

> …as in the paediatric literature, it appears that prolonged suppression of asparagine early on in the treatment is important for long term disease control in adults with ALL. However, compared to the paediatric protocols, lower cumulative doses of asparaginase are used in the majority of the adult protocols and the treatment is generally not given throughout the induction and intensification phases as is practiced in paediatrics.

In children as in adults, the dose interval is recommended within the draft PI as 14 days; however, Patil et al (2011) note:

> A prospective randomised study;[102] involving children with relapsed ALL demonstrated a 7-fold reduction in the risk of induction failure using weekly peg-asparaginase compared to twice weekly dosing schedule and noted that the complete remission rates were significantly higher in those with higher asparaginase levels.

On the other hand, the US PI recommends use 'no more frequently than every 14 days; leaving longer dosing intervals open for consideration. Toxicity outcomes reported by De Angelo (2015a);[103] are notable in this regard.

One approach to address this issue is to recommend more strongly the monitoring of asparaginase activity on therapy, for example by monitoring asparagine levels.

Another broad approach is to be more prescriptive in the PI about use of pegaspargase with particular regimens, where the pegaspargase regimen will be more constrained.

Comment: Question for the ACM: Is the level of detail in the PI about the pegaspargase dose interval acceptable? Should there be more detail, for example reference to particular multi-agent regimens? Should there be less detail, that is flexibility to account for drug / activity monitoring, or to account for data from studies such as that reported by Abshire et al (2000)?[82]

Use in adults

Common practice appears to involve use of pegaspargase in children, adolescents and young adults, but not necessarily in older adults. The evaluator has noted that data in adults (particularly data in second-line use) are relatively sparse. However, while there has been half a century of use of asparaginase in children, there is also now increasing use of pegaspargase in adults; linked to a suspicion that worse survival in adults with ALL is related to a treatment effect.[84] In this regard, NCCN Guidelines note greater cumulative doses of drugs (corticosteroids, vincristine and asparaginase) and earlier, more frequent and / or more intensive CNS directed therapy may be key.

Dose modification recommendations

The proposed PI does not include integrated dose modification recommendations in the Dosage and Administration section.

Comment: Question for sponsor: Why are no dose modification recommendations included in the PI? It is acknowledged that where possible, treatment should

[102] Abshire T, et al 2000 Weekly polyethylene glycol conjugated L-asparaginase compared to biweekly dosing production superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a pediatric oncology group study. *Blood* 2000; 96: 1709-1715.
[103] DeAngelo DJ et al. 2015 a A Multicenter Phase II Study Using a Dose Intensified Pegylated-Asparaginase Pediatric Regimen in Adults with Untreated Acute Lymphoblastic Leukemia: A DFCI ALL Consortium Trial. American Society for Hematology 57th annual meeting and exposition.

be continued to allow anti-leukaemic efficacy, but there is still a role for instructions about dose reduction or delay, and, where necessary, discontinuation

Comment: Question for the ACM: Would the PI be improved by inclusion of dose modification guidelines as per the EviQ 'Supporting Document' (where relevant for Oncaspar) and / or the review by Stock et al (2011)?

Asparaginase antibodies and monitoring

The proposed PI states:

> *Treating physicians may elect to monitor the trough serum asparaginase activity two weeks after administration of Oncaspar. If activity falls below 0.1 IU/mL, it may be necessary to switch to another asparaginase preparation (see Precautions: Asparaginase antibodies).*

The USPI makes no such comment, although it does reference asparagine monitoring in its 'Study 1' in the Clinical Trials section of the PI.

The SmPC makes the following comment:

> *Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of Oncaspar. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered.*

Further information is supplies under 'Special warnings and precautions for use', which equates with the text proposed in the Australian PI under 'asparaginase antibodies'; though the latter refers to alignment with local practice.

The clinical evaluator recommends more prescriptive instructions about monitoring of serum asparaginase activity.

Horton and Steuber (2017);[88] state:

> Asparaginase inactivation and therapeutic drug monitoring.
>
> Between 2 to 8 percent of patients receiving *E. coli* asparaginase develop silent inactivation due to the production of neutralizing anti-asparaginase antibodies.[104,105].
>
> Therapeutic drug monitoring of asparaginase activity can accurately determine if a patient has neutralizing antibodies that are inactivating the target enzymatic activity of asparaginase.[105] Those with neutralizing antibodies have asparaginase activity well below the therapeutic threshold and can often be treated with *Erwinia* asparaginase as an effective alternative since there is only approximately 10 percent antibody cross-reactivity between *E.coli* and *Erwinia* asparaginase preparations.[106] (See 'Infusion reactions to systemic chemotherapy', section on 'Formulations'.)
>
> A retrospective study of 763 paediatric patients with ALL examined therapeutic drug monitoring and suggested that lower doses of PEG-asparaginase can be used to maintain asparagine depletion[107]; these results will need to be confirmed in

[104] Ref 36 = Strullu M, et al. Silent hypersensitivity to Escherichia coli asparaginase in children with acute lymphoblastic leukemia. *Leuk Lymphoma* 2010; 51:1464
[105] Ref 37 = Tong WH, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood* 2014; 123:2026
[106] Ref 38 = Salzer WL, et al. Development of asparaginase Erwinia chrysanthemi for the treatment of acute lymphoblastic leukemia. *Ann N Y Acad Sci* 2014; 1329:81.
[107]Ref 39 = Schrey D, et al. Therapeutic drug monitoring of asparaginase in the ALL-BFM 2000 protocol between 2000 and 2007. *Pediatr Blood Cancer* 2010; 54:952.

prospective clinical trials. It is currently unknown if decreasing the asparaginase dose will result in fewer thrombotic or haemorrhagic complications. (See 'Thrombosis' below.)

There is an informative discussion about monitoring by Patil et al (2011).[81] Monitoring could be of asparaginase (enzyme) levels, anti-asparaginase titres, or asparagine levels. Patil et al consider asparagine monitoring preferable on theoretical grounds. Likewise, Kawedia and Rytting (2014) examine this issue carefully.[64]

Comment: Question for sponsor: Is an assay available to measure *asparaginase*, or *asparagine* levels, in Australia? It is noted that the sponsor indicates there are no universally validated an*ti-asparaginase antibody* assays, but are any available in Australia?

Comment: Question for ACM: Is local practice regarding asparaginase monitoring consistent across Australia? What is it? Should there be a more inflexible recommendation about asparaginase monitoring in the PI?

Product information (PI)

Comment: Question for ACM: The PI is modelled on the SmPC which appears to be older in style, for example quite brief. Is it sufficient?

Questions to sponsor

1. Please summarise your broad approach to the issues raised in the quality evaluation, for the ACM's understanding (but do not use the Pre-ACM Response as a vehicle for your complete response to these issues).
2. Please comment on how you propose to address the issue of temperature excursion.
3. Please explain the derivation of PI half-life and AUC values for relapsed hypersensitive and non-hypersensitive ALL patients with reference to ASP-302 and other sources.
4. Please explain the derivation of dosing in children with a body surface area < 0.6 m^2.
5. Are pooled estimates presented in CER pages 151-158 weighted by sample size?
6. Is the mechanism of pancreatitis known? Is it always related to hypertriglyceritidaemia, which is a recognised cause of pancreatitis? Does this link suggest the need for regular serum lipid monitoring to mitigate risk of hypertriglyceride induced pancreatitis? Does this suggest the need to treat high triglycerides to allow safer ongoing use of Oncaspar?
7. Should the PI recommend use of pre-medication to mitigate risk of allergy? Should the PI recommend IM over IV administration, or a slower infusion, or any other strategies to minimise the risk of hypersensitivity?
8. What is the justification for recommending use of fresh or frozen plasma ahead of AT and in the absence of thrombosis?
9. Why are no dose modification recommendations included in the PI? It is acknowledged that where possible, treatment should be continued to allow anti-leukaemic efficacy, but there is still a role for instructions about dose reduction or delay, and, where necessary, discontinuation.
10. Is an assay available to measure asparaginase, or asparagine levels, in Australia? It is noted that the sponsor indicates there are no universally validated anti-asparaginase antibody assays, but are any available in Australia?
11. Please justify each proposed PI contraindication against current thresholds used to decide whether Oncaspar can be used.

Proposed action

The application cannot be approved until quality issues are resolved.

Setting quality issues aside, there is sufficient evidence of positive benefit / risk balance in the proposed population, and unresolved issues pertain to recommendations (or lack thereof) and the level of detail in the PI.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Is the proposed Oncaspar PI acceptable in its broad approach of providing little detail about pegaspargase-containing regimens considered acceptable or supported by specific pivotal studies?
2. Is the level of detail in the PI about the pegaspargase dose interval acceptable? Should there be more detail, for example reference to particular multi-agent regimens? Should there be less detail, that is flexibility to account for drug / activity monitoring, or to account for data from studies such as that reported by Abshire et al (2000)?
3. Would the PI be improved by inclusion of dose modification guidelines as per the EviQ 'Supporting Document' (where relevant for Oncaspar) and / or the review by Stock et al (2011)?
4. Is local practice regarding asparaginase monitoring consistent across Australia? What is it? Should there be a more inflexible recommendation about asparaginase monitoring in the PI?
5. The PI is modelled on the SmPC which appears to be older in style, for example quite brief. Is it sufficient?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Please note that the sponsor has been asked additional questions and responses should be included in the sponsor's Pre-ACM Response for the ACM's review.

Response from sponsor

Questions to sponsor

1. *Please summarise your broad approach to the issues raised in the Module 3 evaluation, for the ACM's understanding.*

Sponsor's response:

Concerns regarding media fill acceptance criteria, GMP clearances, as well as excipient control during the manufacture of Oncaspar will be addressed in a separate response that will be provided to the quality evaluator directly.

2. *Please comment on how you propose to address the issue of temperature excursion.*

Sponsor's response:

Concerns regarding temperature excursions during the shipping of Oncaspar will be addressed in a separate response that will be provided to the quality evaluator.

3. *Please explain the derivation of PI half-life and AUC values for relapsed hypersensitive and non-hypersensitive ALL patients with reference to ASP-302 and other sources.*

Sponsor's response:

We acknowledge the observations provided by the Delegate. The sponsor is currently assessing the derivations of the half-life and AUC values seen within the other sources. In reference to the proposed Australian PI draft, the sponsor proposes the half-life and AUC values for relapsed hypersensitive and non-hypersensitive ALL patients to align with the complete data referenced from ASP-302, as follows:

> Patients with ALL with several relapses were treated either with Oncaspar or with native E. coli asparaginase as part of an induction therapy. Oncaspar was given in a dose of 2,500 U/m^2 body surface IM on days 1 and 15 of induction. The mean plasma half-life of Oncaspar was 4.8 days in non- hypersensitive patients (AUC 10.35 U/mL/day), and 2.7 days in hypersensitive patients with ALL (AUC 3.52 U/mL/day).

4. *Please explain the derivation of dosing in children with a body surface area < 0.6 m^2.*

Sponsor's response:

The recommended posology is 82.5 U/kg body weight for children with a body surface area < 0.6 m^2 every 14 days. A cautious approach to drug dosing in infants is designed to avoid excessive drug toxicities, therefore the majority of paediatric protocols apply a cut-off for surface area based on dosing at 10kg, which roughly corresponds to BSA of 0.6m^2 (Sharkey et al, 2001)[108]. This dose was calculated based on the following equation which has been used historically for elucidation of dose for chemotherapeutic agents in very small children:

Dose administered = (Foreseen dose for BSA (m^2) x body weight (kg)) / 30.

When applied to Oncaspar and a patient weighing 9.9 kg, this results in the following:

> Dose administered = (2,500 x 9.9) / 30 = 825 U.
>
> Approximating the weight of the infant to 10 kg, this becomes 82.5 U/kg.

Based on calculations done for patients enrolled on CCG-1962 with a BSA of < 0.6m^2 (which corresponds to an infant's weight) the dose of 82.5 U/kg offered an intermediate dose between administration of 2,500 U/m^2 and 1000 U/m^2. This therefore minimises the risk of either over- or under-dosing. As such, this dose has been recommended (authorized) since the 1994 approval of Oncaspar in Germany and has been the accepted dose in the paediatric oncology community for very small children.

5. *Are pooled estimates presented in CER pages 151-158 weighted by sample size?*

Sponsor's response:

Pooled efficacy outcomes:

The evaluator presented pooled outcomes. In aggregate, there is strong support for the efficacy of Oncaspar, based on EFS and also OS outcomes, mostly in paediatric patients but also adults. The pooled estimates may not be weighted by sample size (for example Figure 29 Attachment 2, PEG outcomes: Stock et al[84] 66% 2 year EFS with n = 296, Fathi et al[85]28% 2 year EFS with n = 18, but a pooled estimate of 48%).

The pooled estimates presented in clinical evaluation report were weighted by sample size. The impact of a study's sample size was captured by its effect on the study standard

[108] Sharkey I et al, 2001 Body surface area estimation in children using weight alone: application in paediatric oncology. *British Journal of Cancer* 2001; 85: 23-28

error, which was used in the random effect analysis. The pooled estimate was obtained, assuming normality, using the software Comprehensive Meta-Analysis (CMA), version 2.

6. *Is the mechanism of pancreatitis known? Is it always related to hypertriglyceridaemia, which is a recognised cause of pancreatitis? Does this link suggest the need for regular serum lipid monitoring to mitigate risk of hypertriglyceratide-induced pancreatitis? Does this suggest the need to treat high triglycerides to allow safer ongoing use of Oncaspar?*

Sponsor's response:

Although it is clear that in a non-malignant adult population, the risk of acute pancreatitis increases with severe hypertriglyceridemia, perhaps due to an accumulation of triglycerides within the pancreas that are hydrolysed by pancreatic lipase, this association does not necessarily hold true for the asparaginase associated pancreatitis (AAP; Raja et al, 2016[109])

The pathogenesis of asparaginase-induced pancreatitis is not clearly understood, although there are several published hypotheses. The most extensively studied risk factors include intensive asparaginase administration, older age, Native American ancestry and genetic variants involving genes critical to purine metabolism and cytoskeleton function: CPA2, HOPGA1, GWAS, GHIT, DOCK5, ACTN2 and MICAL2 (Liu et al, 2016).[110] Recently Shuang Peng and his colleagues implemented asparaginase induced calcium fluctuations as the cause of AAP. He demonstrated that asparaginase acts on protease activated receptor 2 (PAR2) to evoke sustained elevations of calcium leading to reduced intracellular ATP formation and ultimately necrosis of the acinar cells (Peng et al, 2016)[111].

It has been demonstrated by Raheel Altaf Raja and his colleagues that AAP does not seem to be associated with hypertriglyceridaemia. Although preventive measures to prevent the occurrence of hypertriglyceridaemia exist (for example dietary restrictions, fibrates, insulin infusions, heparin infusions and plasmapheresis) it is not clear if these interventions reduce the risk of AAP. The investigators did not find that patients with AAP had significantly higher triglycerides than those patients who did not experience pancreatitis. Furthermore, this study concluded that monitoring of pancreatic enzymes does not predict the development of AAP and that triglyceride levels do not appear to be associated with the development of AAP, therefore regular serum lipid monitoring is not currently recommended (Raja et al, 2016)[109]. There is no data to support (or refute) the treatment of hypertriglyceridemia for the purposes of preventing or treating AAP. Elevated triglyceride levels should be treated according to local guidelines.

7. *Should the PI recommend use of pre-medication to mitigate risk of allergy? Should the PI recommend IM over IV administration, or a slower infusion, or any other strategies to minimise the risk of hypersensitivity?*

Sponsor's response:

In the event of a serious hypersensitivity reaction to Oncaspar, such as anaphylaxis, discontinuation is recommended; this should be conveyed in the PI. However, there have been numerous reports of alternative strategies taken in order to allow for continued use of this cornerstone therapy for the treatment of ALL, even in the face of serious hypersensitivity. Dr. Ozge Soyer and her colleagues suggest that Oncaspar may be

[109] Raja R A et al 2016. Asparaginase-associated pancreatitis is not predicted by hypertriglyceridemia or pancreatic enzyme levels in children with acute lymphoblastic leukemia. Pediatric Blood & Cancer 2016; DOI: 10.1002/pbc.26183

[110] Liu C et al, 2016 Clinical and Genetic Risk Factors for Acute Pancreatitis in Patients With Acute Lymphoblastic Leukemia *J Clin Oncol* 2016; 34:2133-2140.

[111] Peng S et al 2016. Calcium and adenosine triphosphate control of cellular pathology: asparaginase-induced pancreatitis elicited via protease-activated receptor 2 *Phil. Trans. R. Soc. B* 2016; 371: 20150423.

cautiously re-administered with pre-medications (for example – antihistamines, corticosteroids, etcetera.).[112] This was supported by Dr. Jin-Tack Kim and his colleagues in which they successfully treated 33 patients with premedication prior to L-asparaginase therapy with only mild hypersensitivity in 11 cases, no serious reactions.[113] Desensitization techniques were also successfully reported in both articles by Soyer and Kim.

Although slowing down the infusion may theoretically decrease the risk of an infusion related reaction, which is often misdiagnosed as hypersensitivity, this technique is unlikely to prevent a true hypersensitivity reaction. There is no evidence to support these hypotheses as they relate to Oncaspar and the sponsor therefore defers from adding this to the PI.

A number of previously published studies have reported an incidence of hypersensitivity with IV infusion as opposed to IM administration);[114,115] however, other reports have shown comparable rates with either mode of administration, such as a single centre study conducted from 2006 to 2008 (August et al, 2013)[116]. Additionally Soyer and her colleagues reported that the only anaphylactic reactions experienced with the modified St. Jude Total XIII protocol between 2004 to 2008 were those following IM administration as opposed to IV.[112] When Oncaspar is administered IM, local and delayed reactions can manifest irrespective of whether they are local or systemic, which may occur after the patient has left the oncology clinic, leading to underreporting of IM associated hypersensitivy reactions compared with IV administration where reactions tend to occur much earlier and almost always before the patient leaves the clinic.[117] Additionally, IV infusion of Oncaspar has been more often associated with a greater rise and peak of serum ammonia levels compared to IM injection which can result in a variety of symptoms mistaken as hypersensitivity including nausea, vomiting, headache and rash.[118] Additionally, the pharmacokinetics of asparaginase activity differ greatly between routes of administration with IV showing a more rapid time to peak activity compared with IM, which may have implications for hypersensitivity events.[118] Given the mixed experiences reported with the different routes of asparaginase administration, the sponsor defers from recommending one method over another in the PI as it relates to hypersensitivity reactions.

8. *What is the justification for recommending use of fresh or frozen plasma ahead of AT and in the absence of thrombosis?*

Sponsor's response:

The sponsor does not recommend administering fresh frozen plasma (FFP) and/or antithrombin (AT) supplementation regardless of thrombosis status. Wendy Stock and her colleagues published on management strategies in the event of intracranial thrombohaemorrhagic complications in the older adolescent and adult populations. Here, they suggest that the use of ATIII concentrates and/or cyropreciptate may replace AT and

[112] Soyer O U et al 2009. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. *J Allergy Clin Immunol* 2009; 123: 895-899.
[113] Kim J-T et al 2016. Effectiveness of Premedication and Rapid Desensitization in Hypersensitivity to L-Asparaginase. *J Allergy Clin Immunol* 2016; 137, A 130
[114] Nesbit M et al, 1979. Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. *The American Journal of Pediatric Hematology/Oncology.* 1979; 1: 9-13
[115] Pidaparti M and Bostrom 2012 comprison of allergic reactions to pegasparaginase given intravenously versus intramuscularly. *Pediatric Blood and Cancer* 2012; 59: 436-439
[116] August KJ et al, 2013. Comparison of hypersensitivity reactions to PEGasparaginase in children after intravenous and intramuscular administration. *J Pediatr Hematol Oncol*. 2013; 35: e283–e286
[117] Peterson W C et al., 2014 Comparison of Allergic Reactions to Intravenous and Intramuscular Pegaspargase in Children with Acute Lymphoblastic *Leukemia Pediatric Hematology and Oncology* 2014; 31: 311-317
[118] Burke M J 2014. How to manage asparaginase hypersensitivity in acute lymphoblastic leukemia. *Future Oncol.* 2014; 10: 2615-2627

fibrinogen, respectively; alternatively, FFP may be used in the event that ATIII is not available.[97] As stated in the article, the infusions of these anti-coagulant supplements may replete asparagine and counteract the anti-leukemic effect of asparaginase. Although these are reasonable management strategies, the sponsor believes that both thrombosis prophylaxis and management strategies should be per local guidelines, which may vary.

9. *Why are no dose modification recommendations included in the PI? It is acknowledged that where possible, treatment should be continued to allow anti-leukaemic efficacy, but there is still a role for instructions about dose reduction or delay, and, where necessary, discontinuation.*

Sponsor's response:

The goal of asparaginase therapy is to deplete serum asparagine. Although several studies have suggested that this is accomplished at an asparaginase activity level of 0.1 IU/mL, it has been thought that there could be inter-patient pharmacokinetic variability that may allow for dose adjustment. This theory was examined in the DFCI 00-01 study with the native Lasparaginase formulation in which it was found that individualised dosing proved to be an independent predictor of favorable EFS.[119] This type of dose adjustment as based on PK was not previously studied, however, will be looked at in the recently opened DFCI 16-001 trial. No other dose modifications have been examined clinically for Oncaspar.

10. *Is an assay available to measure asparaginase, or asparagine levels, in Australia? It is noted that the sponsor indicates there are no universally validated anti-asparaginase antibody assays, but are any available in Australia?*

Sponsor's response:

It should be noted that measurement of asparagine levels are very difficult as asparaginase continues its deamination of asparagine ex vivo (in the test tube), therefore, asparaginase activity levels have become the most reliable surrogate marker of asparagine depletion.

Currently, a validated assay method to measure asparaginase levels is not available in Australia; however, work is currently underway, by more than one laboratory to prepare and validate such a method and make it available in future.

There are multiple difficulties regarding testing for the antibodies (for example which type: IgG or IgM; and asparaginase being a large molecule, the antibodies can form against many different antigenic sites). Therefore, the sponsor does not believe there are any validated anti-asparaginase antibody assays available in Australia

11. *Please justify each proposed PI contraindication against current thresholds used to decide whether Oncaspar can be used.*

Sponsor's response:

Please refer to sponsor's comments on PI response document for the detailed response.

[119] Douer D et al, 2014 Pharmacokinetics-Based Integration of Multiple Doses of Intravenous Pegaspargase in a Pediatric Regimen for Adults With Newly Diagnosed Acute Lymphoblastic Leukemia. *J Clin Oncol* 2014; 32: 905-911

Advisory committee considerations[120]

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

The ACM advised the following in response to the Delegate's specific questions on the submission:

The committee is requested to provide advice on the following specific issues:

1. ***Is the proposed Oncaspar PI acceptable in its broad approach of providing little detail about pegaspargase-containing regimens considered acceptable or supported by specific pivotal studies?***

The ACM agreed that the indication as stated in the PI was acceptable:

> *'Oncaspar is indicated as a component of antineoplastic combination therapy in patients with Acute Lymphoblastic Leukaemia (ALL)'.*

The ACM noted that pegaspargase is used in induction and other phases of all treatment protocols, almost always in combination with other drugs. The ACM were of the view that there are a number of co-operative group protocols, both published and in ongoing trials at hand at the one time and that it is not possible for the PI to be prescriptive in these circumstances.

2. ***Is the level of detail in the PI about the pegaspargase dose interval acceptable? Should there be more detail, for example reference to particular multi-agent regimens? Should there be less detail, that is flexibility to account for drug / activity monitoring, or to account for data from studies such as that reported by Abshire et al (2000)?***

The ACM agreed that the detail for dose interval in the PI is acceptable. ACM noted that recommendation to multiagent regimens is quickly out-dated. The ACM also noted that the PI states 'recommended dose', which allows for more flexibility in dosing, for example, the Abshire Study.

3. ***Would the PI be improved by inclusion of dose modification guidelines as per the EviQ 'Supporting Document' (where relevant for Oncaspar) and / or the review by Stock et al (2011)?***

The ACM agreed that the PI would be beneficial by inclusion of dose modification if detailed as guidelines not prescriptive. The ACM noted that using EviQ rather than Stock would be preferred especially with respect to liver toxicity and pancreatitis. However, Stock could be cited as an option for more information.

4. ***Is local practice regarding asparaginase monitoring consistent across Australia? What is it? Should there be a more inflexible recommendation about asparaginase monitoring in the PI?***

The ACM agreed that asparaginase monitoring is not consistent across Australia and that the antibody would be difficult to monitor in 'real time' in Australia. ACM noted that there

[120] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

are no freely available methods of routinely monitoring patients on asparaginase. The monitoring is generally used only on clinical trials and not applicable to patients that are not on a trial. The ACM agreed that for these reasons, it is necessary to have more flexible recommendations about asparaginase monitoring in the PI.

5. The PI is modelled on the SmPC which appears to be older in style, for example quite brief. Is it sufficient?

The ACM agreed that the PI modelling on the summary of product characteristics (SmPC) is generally sufficient, and recommends that the sponsor consider more detailed side-effect management guidelines.

Other comments:

The ACM noted the proposed very young paediatric dosing regimen and noted the difference in the dosing approach proposed in the submission compared to the EviQ approach taken in the US. EviQ recommends dosing regardless of age and models. The ACM recommended that the reasons for different dosing approaches be further assessed.

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

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Oncaspar pegaspargase 3750 units/5 mL solution vial for injection, indicated for:

> *Oncaspar is indicated as a component of antineoplastic combination therapy in patients with Acute Lymphoblastic Leukaemia (ALL).*

Specific conditions of registration applying to these goods

- The pegaspargase EU Risk Management Plan (RMP), version 1.0, dated 17 November 2015; DLP 31 December 2013, with Australian Specific Annex (version 1.1, dated 28 April 2017), and any subsequent revisions, as agreed with the TGA will be implemented in Australia as a condition of registration.
- Batch Release Testing and Compliance with Certified Product Details (CPD):
  - It is a condition of registration that all batches of Oncaspar (pegaspargase) injection, solution 3,750 units/5 mL imported into Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that each batch of Oncaspar (pegaspargase) injection, solution 3,750 units/5 mL imported into Australia is not released for sale until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.
  - The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for Oncaspar approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi>

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au