Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Bendamustine hydrochloride

Proprietary Product Name: Ribomustin

Sponsor: Janssen-Cilag Pty Ltd

January 2015

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

About AusPARs

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

Contents

List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse Events
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ASCT	Autologous Stem Cell Transplant
ASH	American Society of Hematology
AUC	Area under the plasma concentration versus time curve
B	Bendamustine
B-CLL	B-cell chronic lymphocytic leukaemia
BEN	Bendamustine
BMF	Bendamustine, Methotrexate, 5-Fluorouracil
BOP	Bendamustine, Vincristine, Prednisone
BP	Bendamustine, Prednisolone
BR	Bendamustine, Rituximab
BSA	Body surface area
C	Chlorambucil
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone
CI	Confidence Interval
CLB	Chlorambucil
CLL	Chronic Lymphocytic Leukaemia
C_{max}	Peak Concentration
CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil

Abbreviation	Meaning
COP or CVP	Cyclophosphamide, Vincristine, Prednisone
CR	Complete Response, Complete Remission
Creat	Creatinine
CRP	C-reactive Protein
CRu	Complete Response Unconfirmed
CT	Computed tomography
CTC	Common Toxicity Criteria
CTD	Common Technical Document
CTX	Cyclophosphamide
CYP	Cytochrome P450
DEX	Dexamethasone
DNA	Deoxyribonucleic Acid
EFS	Event Free Survival
EMA	European medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
HD	Hodgkin's Disease
HIV	Human Immunodeficiency Virus
HP1	Monohydroxy-bendamustine
HP2	Dihydroxy-bendamustine
Hyper-CVAD	Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
ICH	International Conference on Harmonisation

Abbreviation	Meaning
ICRA	Independent Committee for Response Assessment
IDA	Idarubicin
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Independent review board
ITP	Immune Thrombocytopenia
ITT	Intention to treat
IV	Intravenous
LDH	Lactate Dehydrogenase
LP	Lymphoplasmocytoid
M3	Bendamustine oxidised metabolite
M4	N-desmethyl-bendamustine
MCL	Mantle Cell Lymphoma
MM	Multiple Myeloma
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NCI	National Cancer Institute
NCI-WG	National Cancer Institute Working Group
NHL	Non-Hodgkin's Lymphomas
nPR	Nodular Partial Remission
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PO	Per Os; by mouth, oral
PR	Partial Response, Partial Remission

Abbreviation	Meaning
PP	Per-protocol
PT	Preferred term
QoL	Quality of life
R	Rituximab
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone
R-FCM	Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone
SAE	Serious Adverse Event
SD	Stable Disease
SLL	Small Lymphocytic Leukaemia
SmPC	Summary of Product Characteristics
StiL	Study Group Indolent Lymphoma
SUSAR	Suspected Unexpected Serious Adverse Reactions
T_{max}	Time of Maximal Plasma Concentration
TTNT	Time to Next Treatment
TTF	Time to Treatment Failure
UK	United Kingdom
WBC	White Blood Cell Count
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of TGA decision:	26 June 2014
Active ingredient:	Bendamustine hydrochloride
Product name:	Ribomustin
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
Dose form:	Powder for concentrated injection
Strengths:	25 mg and 100 mg
Container:	Amber glass vials
Pack size:	Carton with 1 vial
Approved therapeutic use:	· *First-line treatment of chronic lymphocytic Ieukaemia (Binet stage B or C). Efficacy relative to first-line therapies other than chlorambucil has not been established.* · *Previously untreated indolent CD20-positive, stage 111-IV Non-Hodgkin's lymphoma, in combination with rituximab.* · *Previously untreated CD20-positive, stage 1/1-IV Mantle Cell Lymphoma in combination with rituximab, in patients in eligible for autologous stem cell transplantation.* · *Relapsed/Refractory indolent Non-Hodgkin's lymphoma*.
Route of administration:	Intravenous (IV) (after reconstitution and dilution)
Dosage:	For intravenous infusion over 30 - 60 minutes (see Special Precautions for Disposal and Handling in Product Information for further details). Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.
ARTG numbers:	211684 and 211685

Product background

This AusPAR describes the application by Janssen-Cilag to register bendamustine hydrochloride, a new chemical entity, for use in the treatment of chronic lymphocytic leukaemia and lymphoma under the tradename Ribomustin.

Ribomustin is an alkylating anti-neoplastic agent proposed as treatment for:

- First line treatment of Chronic Lymphocytic Leukaemia (CLL; Binet stage B or C)
- Previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. (in combination with rituximab in CD20 positive patients)
- Relapsed/Refractory indolent Non-Hodgkin's lymphoma

Bendamustine hydrochloride is primarily an alkylating agent. Other nitrogen mustards include cyclophosphamide, melphalan and ifosfamide.

Chronic Lymphocytic Leukaemia (CLL)

Binet or Rai stage guides treatment approach[1] and the sponsor proposes to incorporate Binet stage into the indication. Binet stages are as follows:

- Stage A: Hb ≥10 g/dL; platelets ≥100,000/mm^3; and <3 enlarged areas
- Stage B: Hb ≥10 g/dL; platelets ≥100,000/mm^3; and ≥3 enlarged areas
- Stage C: Hb <10 g/dL; platelets <100,000/mm^3; any number of enlarged areas

The treatment landscape for CLL is changing, with studies of experimental agents being published recently including obinutuzumab, ibrutinib, idelalisib and ABT-199[2,3]. Table 1 lists the more established treatments. Choice of treatment may be guided by patient frailty and comorbidity.

Table 1: Selected currently registered agents / regimens in CLL (unordered)

Agent or regimen	Source	Comment	Indication in PI (relevant text only)
chlorambucil	eviQ		Treatment of …certain forms of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, Waldenstrom's macroglobulinaemia …
fludarabine	Reference 1		Treatment of B-cell CLL
FCR = fludarabine, cyclophosphamide, rituximab	eviQ		Rituximab component: Mabthera is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

[1] Treatment recommendations for CLL are summarised by EviQ at <https://www.eviq.org.au/LinkClick.aspx?fileticket=O3CABT-1999wOsf986I%3d&tabid=60>
[2] ABT-199 is an inhibitor of B-cell lymphoma 2(BCL-2).
[3] Rai and Barrientos. Movement towards optimization of CLL therapy. NEJM 2014; 370: 1160-1162

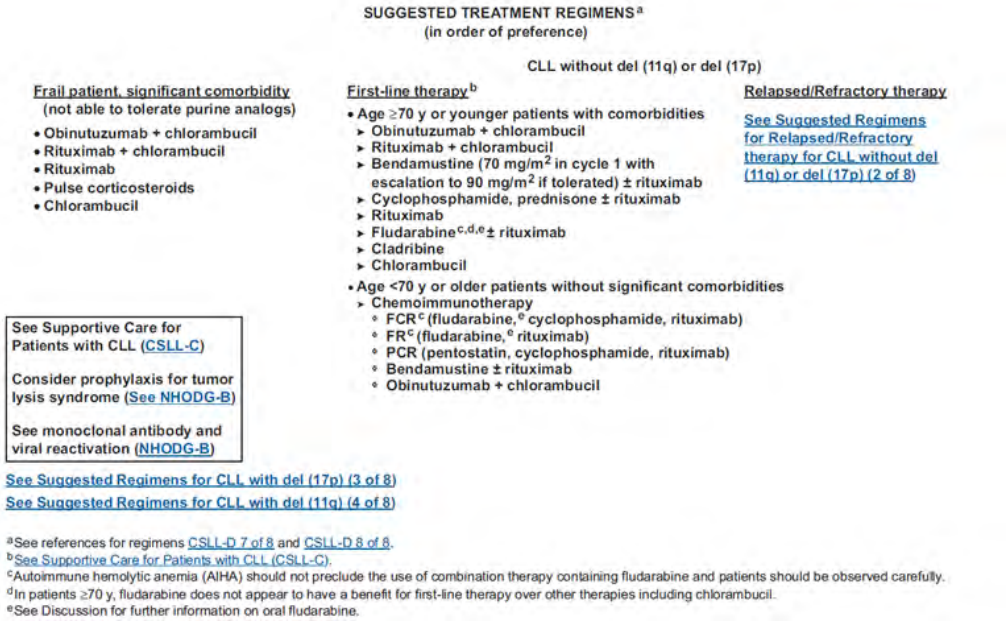
Agent or regimen	Source	Comment	Indication in PI (relevant text only)
Cladribine	eviQ	Considered second-line in CLL	Leustatin is indicated for the treatment of patients with Hairy Cell Leukaemia. It is also indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia in whom treatment with alkylating agents has failed.
Alemtuzumab	PI	Considered second-line	MabCampath is indicated for the treatment of patients with B - cell chronic lymphocytic leukaemia (B - CLL).
ofatumumab	eviQ	Third-line	Arzerra, as a single agent, is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.
1 = <http://www.australianprescriber.com/magazine/29/3/76/9>			

Table 2, from National Comprehensive Cancer Network (NCCN) guidelines, suggests that both rituximab + chlorambucil and rituximab alone are preferred over chlorambucil in both the frail and in first-line therapy of the non-frail elderly (over 70 years of age). This is not the case in EviQ[4], where the indication for chlorambucil is stated to be:

> *Patients with CLL where treatment is indicated but where therapy with purine analogues [e.g. fludarabine] is deemed inappropriate, often because of the age of the patient and associated co-morbidities*

[4] EviQ Cancer Treatments Online is a point of care clinical information resource that provides health professionals with current evidence based, peer reviewed, best practice cancer treatment protocols and information. eviQ is relevant to the Australian clinical environment and can be accessed free 24 hours a day. <https://www.eviq.org.au/>

Table 2: NCCN guidelines (CLL/SLL version 2.2014)



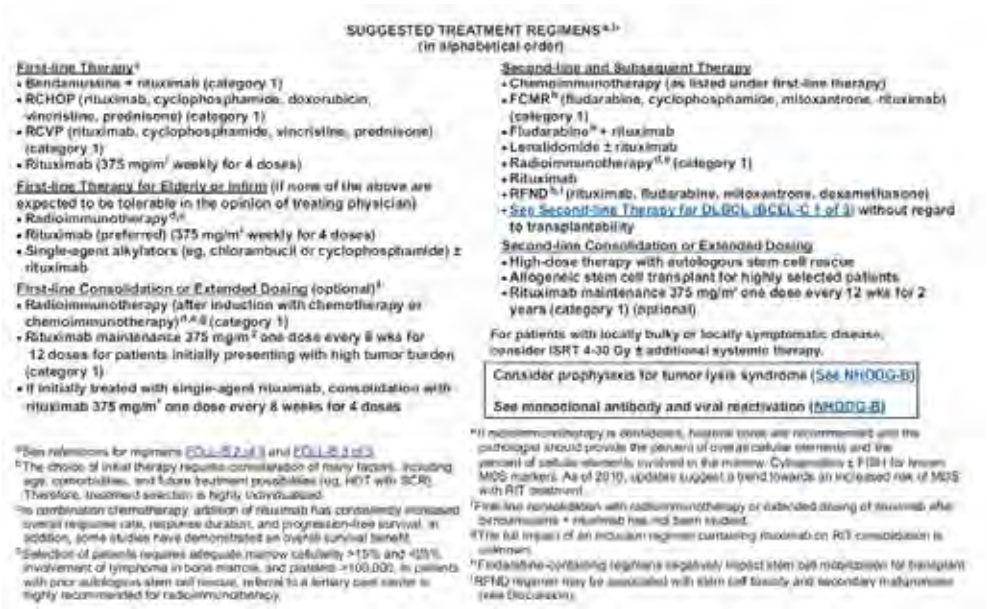
NCCN recommends fludarabine-containing regimens for first-line use in non-frail younger patients. EviQ recommends fludarabine + cyclophosphamide + rituximab (for 'CD20 positive B-cell CLL').

In patients with del(17p), more potent regimens are recommended. In patients with del(11q), outcomes are better in patients who receive an alkylator.

Non-Hodgkin's Lymphoma (NHL)

NHL can be classified as indolent or aggressive. Indolent subtypes include follicular lymphoma (see Table 3 for NCCN-recommended treatment regimens), marginal zone lymphoma, splenic marginal zone lymphoma, Waldenstrom's macroglobulinaemia and primary cutaneous anaplastic large cell lymphoma. Treatment of non-follicular types varies from that of follicular lymphoma, for example, there may be a role for splenectomy in initial treatment of splenic marginal zone lymphoma (MZL).

Table 3: NCCN guidelines (Follicular lymphoma Grade 1-2, version 2.2014)



SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

First-line Therapy[a]
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)
- Rituximab (375 mg/m^2 weekly for 4 doses)

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- Radioimmunotherapy[d,e]
- Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)
- Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab

First-line Consolidation or Extended Dosing (optional)[f]
- Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,g] (category 1)
- Rituximab maintenance 375 mg/m^2 one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)
- If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m^2 one dose every 8 weeks for 4 doses

Second-line and Subsequent Therapy
- Chemoimmunotherapy (as listed under first-line therapy)
- FCMR[h] (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- Fludarabine[e] + rituximab
- Lenalidomide ± rituximab
- Radioimmunotherapy[d,e] (category 1)
- Rituximab
- RFND[h,i] (rituximab, fludarabine, mitoxantrone, dexamethasone)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3) without regard to transplantability

Second-line Consolidation or Extended Dosing
- High-dose therapy with autologous stem cell rescue
- Allogeneic stem cell transplant for highly selected patients
- Rituximab maintenance 375 mg/m^2 one dose every 12 wks for 2 years (category 1) (optional)

For patients with locally bulky or locally symptomatic disease, consider ISRT 4-30 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens FOLL-R 2 of 3 and FOLL-R 3 of 3.
[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c]In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition, some studies have demonstrated an overall survival benefit.
[d]Selection of patients requires adequate marrow cellularity >15% and <50% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.
[e]If radioimmunotherapy is considered, historic tools are recommended until the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT treatment.
[f]First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.
[g]The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.
[h]Fludarabine-containing regimens negatively impact stem cell mobilization for transplant.
[i]RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

Mantle cell lymphoma is categorised as aggressive NHL (rather than indolent). NCCN-recommended treatments are included as Table 4. There are recommendations in EviQ about treatment of MCL.

Table 4: NCCN guidelines (Mantle cell lymphoma, version 2.2014)

SUGGESTED TREATMENT REGIMENS[a]
(in alphabetical order)

Induction Therapy
- Aggressive therapy
  - CALGB regimen[b] (Treatment 1, 2, 2.5: rituximab + methotrexate with augmented CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]; Treatment 3: etoposide, cytarabine, rituximab; Treatment 4: carmustine, etoposide, cyclophosphamide/autologous stem cell rescue; Treatment 5: rituximab maintenance) (Treatment 2.5 is given if the pre-Treatment 3 bone marrow biopsy contains >15% MCL.)
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
  - NORDIC regimen[b] (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)
  - Alternating RCHOP/RDHAP[b] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)
  - Sequential RCHOP/RICE[b] (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, ifosfamide, carboplatin, etoposide)
- Less aggressive therapy
  - Bendamustine + rituximab
  - CHOP + rituximab[c] followed by consolidation with rituximab maintenance (375 mg/m^2 every 8 wks until progression) (category 1 for maintenance)
  - Cladribine + rituximab
  - Modified rituximab-HyperCVAD with rituximab maintenance in patients older than 65 y

First-line Consolidation[d]
- Clinical trial
- High-dose therapy with autologous stem cell rescue[e]

Second-line Therapy
- Bendamustine ± rituximab
- Bortezomib ± rituximab
- Cladribine + rituximab
- FC (fludarabine, cyclophosphamide) ± rituximab
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab)
- FMR (fludarabine, mitoxantrone, rituximab)
- Ibrutinib
- Lenalidomide ± rituximab
- PCR (pentostatin, cyclophosphamide, rituximab)
- PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3) without regard to transplantability

Second-line Consolidation
- Allogeneic stem cell transplant (nonmyeloablative or myeloablative)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MANT-A 2 of 3 and MANT-A 3 of 3.
[b]These regimens include first-line consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR).
[c]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.
[d]Typically patients will receive an aggressive induction regimen prior to consolidation; however, less aggressive regimens followed by consolidation with high-dose therapy may also result in a good long-term outcome.
[e]Randomized data with anthracycline-containing regimens suggest an improvement in progression-free survival with the addition of first-line high-dose therapy with autologous stem cell consolidation.

Regulatory status

The product is a new chemical entity for Australian regulatory purposes.

Ribomustin is approved in Switzerland for first line treatment of CLL (2009) and follicular non-Hodgkin's lymphoma in first line therapy in combination with rituximab (2012), in Canada for NHL and CLL (2012), in the United Kingdom for CLL, Multiple Myeloma (MM) and NHL (2010) and in the USA for first line treatment of CLL (2007).

Product Information

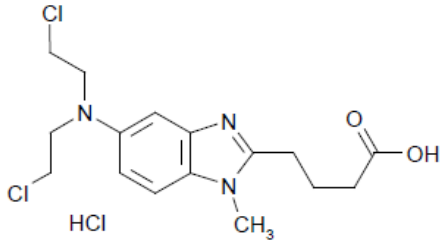
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance

Bendamustine is a synthetic drug It has a di(chloroethyl)amine group which can potentially give crosslinking alkylation of deoxyribonucleic acid (DNA) strands(Figure 1). Janssen-Cilag also notes the 'antimetabolite activity of the purine analogue structure'.

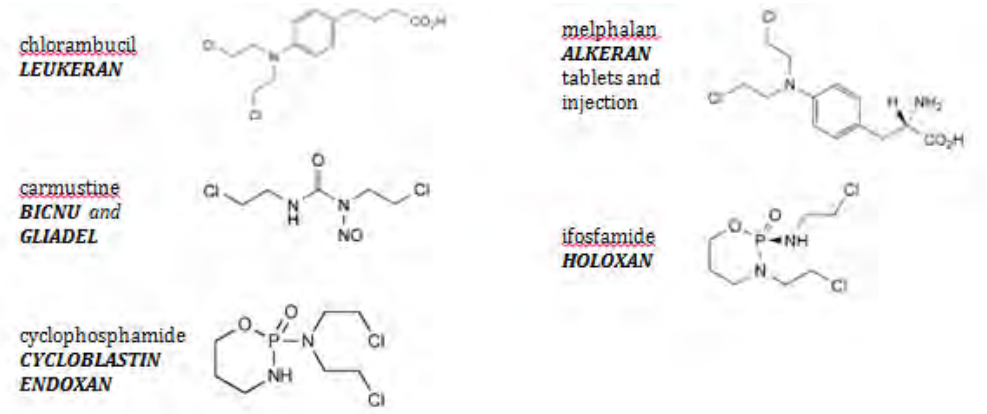
Figure 1. Chemical structure of bendamustine hydrochloride



$C_{16}H_{21}N_3Cl_2O_2.HCl$ MW 394.7 (free base 358.3)

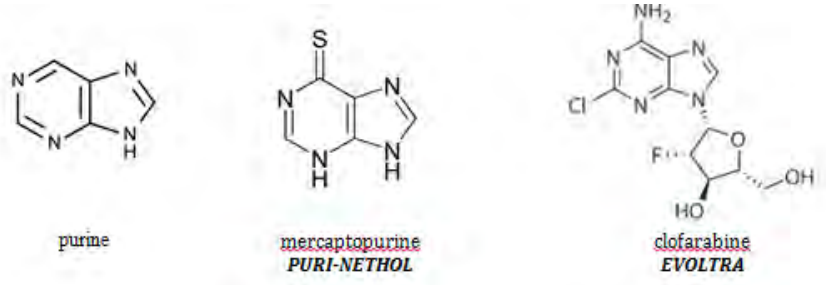
The di(chloroethyl)amine moiety is fairly common in alkylating drugs (see below).

Figure 2. Other alkylating drugs



The benzimidazole in bendamustine bears some resemblance to a purine base (that is, adenine and guanine), but little relationship to purine analogues used as drugs (compared to mercaptopurine, clofarabine and so on) (Figure 3).

Figure 3. Purine and purine analogues



The aqueous solubility of bendamustine hydrochloride is 14 mg/mL but it reacts with water, hydrolysing the chloroethyl groups which abolishes the alkylating activity. Thus the injection product is a lyophilised powder for stability reasons.

There are no European Pharmacopoeia or United States Pharmacopeia monographs.

More details of the synthetic starting material are needed. Although chemically sensitive to hydrolysis, the drug substance generally has low levels of the hydrolysis products Monohydroxy-bendamustine (HP1) and Dihydroxy-bendamustine (HP2) (which are also known metabolites). The impurities with proposed limits above the standard qualification threshold are the initial hydrolysis product HP1, the synthetic intermediate ethyl ester ('BM1EE'and a dimerised degradation product ('BM1 dimer')). All recent batches have had low levels of these impurities. Control of some residues (thionyl chloride and ethylene oxide) is poor. Controls on impurities could reasonably be tightened.

The solid drug substance is stable on storage.

Drug product

Janssen-Cilag proposes registration of a single vial packs containing either 25 mg or 100 mg of bendamustine hydrochloride (equivalent to 22.7 or 90.8 mg bendamustine). The only excipient in the powders for injection is mannitol (30 or 120 mg). The recommended dose regimens use between 90 mg/m^2 and 120 mg/m^2 per dose but with provision for 50% dose reductions if toxicity is seen.

New drugs are now developed to be labelled in terms of the amount of free base and so on. However, bendamustine was developed some years ago and the products are labelled overseas in Europe in terms of the amount of bendamustine hydrochloride (that is, 25 or 100 mg). The evaluator thinks that it would be confusing to attempt to apply the new labelling approach now but the labelling approach should be explained in the Product Information.

Also unconventionally, the powder for injection is not formulated with an 'overfill', so that the labelled 25 mg or 100 mg is not actually accessible after reconstitution (although the extractable amount will be close). This should also be made clear in the Product Information.

Bendamustine is administered by slow intravenous infusion after reconstitution with water for injections and dilution with sodium chloride 9 mg/mL injection. The 25 mg vials are reconstituted with 10 mL water for injections, the 100 mg with 40 mL, giving, on shaking, a clear colourless 2.5 mg /mL solution. This concentrate is then diluted with saline to 'about 500 mL.' Bendamustine in the infusion solution hydrolyses at a rate dependent on temperature. At 25ºC there is about 5% conversion to HP1 in 3.5 hours.

The powder for injection is made by lyophilisation of a filtered solution of drug and mannitol in aqueous ethanol under nitrogen. Unusually, two finished product manufacturing sites are proposed, using essentially the same manufacturing process. Sterility and endotoxin aspects are acceptable if the labelling is suitably finalised.

The dissolution of bendamustine during manufacture results in some hydrolysis, so that levels of HP1 are higher in the powder for injection. The impurities with proposed limits above the qualification threshold are the initial hydrolysis product 'HP1', the ethyl ester, a putative degradant 'HP3' and a dimerised degradation product ('BM1 dimer'). The only impurity which shows clear increases on storage is the dimer, albeit with somewhat surprising differences in the rate of formation between batches. The proposed expiry limits for impurities are not warranted by the batch data and could be tightened.

Curiously the powder for injection (bendamustine hydrochloride plus mannitol) is dramatically more sensitive to light than the pure drug. It is thus presented in amber vials

although even these allow some degradation under strong light and there are therefore warnings to keep the vials in the carton until use.

Clinical trial formulations

Bendamustine hydrochloride was developed in the 1960's by Jenapharm (former East Germany). Jenapharm registered a powder for injection formulation (25 mg) in the former East Germany as Cytostasan in 1971. After German reunification, the product has been marketed in its current formulation since 1991, mostly under the new trade name Ribomustin. The 100 mg strength was introduced in 1999. Ribomustin is thus registered in Europe.

Bendamustine hydrochloride powder for injection has been available in the USA since 2008 under the tradename Treanda, registered by Cephalon. Curiously, this has a different formulation from that proposed for registration in Australia (bendamustine HCl : mannitol 100:170 mg versus 100:120 proposed). The FDA reviews refer to the same clinical studies as were submitted in Australia, while noting some formulation modifications.

Formulation development was not usefully discussed in the submission. The sponsor's Clinical Overview states:

> *The formulation used in the pharmacokinetic studies is identical to that of the product marketed in Germany. The identical product launched and marketed in Germany has been used in all clinical safety and efficacy studies supporting this marketing authorisation application.*

Published information indicates that a dramatically different, 'fast and convenient' formulation was developed in 2013 by Teva. The new Treanda formulation is now available in the USA as 45 mg/0.5 mL or 180 mg/2 mL non-aqueous solutions (formulated with propylene glycol and N,N-dimethylacetamide; these do not make micelles.)

It is unlikely that the different drug : mannitol ratios will be clinically significant (the injection tonicity is dominated by the saline infusion used in dilution). The new non-aqueous injection solutions might, however, show somewhat different local effects amongst other things.

Biopharmaceutics

While literature data reports quite high oral bioavailability, only intravenous administration is proposed. No bioequivalence studies were submitted given the route of administration.

Pharmaceutical Subcommittee (PSC) advice

It is not planned to refer the submission to the Pharmaceutical Subcommittee as there are no unusual pharmaceutical issues.

Recommendation

There are some labelling and Product Information issues to be resolved. Impurity limits could be tightened. This has been proposed to the sponsor and updated information may be available to the Advisory Committee on Prescription Medicines (ACPM), or the Ddelegate might choose to make limits a condition of registration.

III. Nonclinical findings

Introduction

The submitted nonclinical data were in general accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on the nonclinical evaluation of anticancer pharmaceuticals.[5] Bendamustine has been marketed in the former East German Democratic Republic since 1971 for similar indications to that sought here but has only recently been approved for use in other countries (since 2008). As such, the dossier was a hybrid dossier consisting of conventional data and literature based data. A number of the published papers and study reports submitted are dated (>15 years old), and as a consequence, lacked some information that would normally be expected and the study designs did not always conform to current regulatory requirements. Nonetheless, the submitted nonclinical data package is considered adequate, given the years of clinical experience with this drug.

Pharmacology

Primary pharmacology

Bendamustine was developed to have a dual action combining the alkylating activity of the nitrogen mustards with the antimetabolite properties of purine analogues.[6] Even so, bendamustine appears to act primarily as an alkylating agent which causes the formation of intra-strand and inter-strand cross-links between DNA bases.[7] *In vitro*, bendamustine inhibited the growth of several leukaemia cell lines, including acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and non-Hodgkin's lymphoma cells. The 50% inhibitory concentration (IC_{50}) values ranged from 10 to 200 µM, similar to the clinical peak plasma concentration (C_{max}) of 28.2 µM. Inhibitory activity was also seen on cells from other cancers. Cell cycle arrest in leukaemia cells was indicated, with an increase in the number of cells in the early S phase of the cell cycle.

The anti-tumour efficacy of bendamustine was assessed in mouse xenograft and allograft tumour models. Only studies with leukaemia/lymphoma models are discussed here. There was a dose-related reduction in the growth of human lymphoma tumours, which was significant at ≥10 mg/kg/day (30 mg/m^2/day) intraperitoneal (IP) for 5 consecutive days. The maximum increase in survival time was approximately40% in mice bearing leukaemia/lymphoma grafts. However, there was a significant difference in efficacy depending on the route of administration and whether transplantation was via IP, intravenous (IV) or subcutaneous (SC) methods.

The hydroxylated metabolites of bendamustine, HP1 and HP2, had little to no inhibitory activity (IC_{50} ≥550 µM) against a number of human tumour cell lines. Therefore, these metabolites are not expected to contribute to the efficacy during clinical use. The demethylated metabolite (M4), inhibited the growth of stimulated and non-stimulated primary human lymphocytes, and human lymphoblastoid cells. However, the potency of this compound was 2 to 6 times less than that of bendamustine (based on IC_{50}). Given the

[5]ICH Guidance for Industry. S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
[6] Leoni, L.M. (2011) Bendamustine: Rescue of an Effective Antineoplastic Agent From the Mid-Twentieth Century. *Semin Hematol* 48: S4 –S11.
[7] Reviewed in Gandhi, V. (2002) Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. *Semin. Oncol.* 29 (Suppl 13): 4–11.

low circulating level of this metabolite (0.69% of the parent), M4 is not expected to contribute to the clinical efficacy.

The efficacy of bendamustine was reduced 7 to 8 fold in cells that overexpressed P-glycoprotein or Breast Cancer Resistance Protein (BCRP) and 4 fold reduced in cells overexpressing MRP. Overexpression of DHFR (dihydrofolate reductase) had no significant effect on efficacy. Cells that had acquired resistance to bendamustine did not necessarily acquire resistance to other nitrogen mustards (Leoni *et al.*, 2003).[8]

Pharmacodynamic drug interactions

The anti-tumour efficacy of the combination of rituximab and bendamustine was assessed in mice bearing human Burkitt's lymphoma (expresses CD20) xenografts. While growth delay was seen with either rituximab (75 mg/kg IV, dosing every other day (Q2D) ×3) or bendamustine (10–15 mg/kg IP, QD×5) alone (tumour volume 34 to 40% and 11 to 24%, respectively, of untreated control), the combination of these two agents had a more profound effect on tumour growth than either agent alone (tumour volume 4.9 to 10% of control). Therefore, the data support the combined use of rituximab and bendamustine for the treatment of CD20-positive B cell lymphomas.

Secondary pharmacodynamics and safety pharmacology

Bendamustine inhibited the growth of bone marrow stem cells (mouse and human) and human peripheral lymphocytes (B cells were more sensitive than T cells) at similar concentrations required to inhibit cancer cells. Less inhibitory activity was seen on human bone marrow stromal cells (IC_{50} 500–200 μM). Bendamustine was not cytotoxic to human hepatocytes; however the maximum tested concentration was low (100 μM; 3.5 times the clinical C_{max}), and no great weight can be placed on the negative findings. Given the mechanism of action of bendamustine as an alkylating agent, off-target effects are expected with this type of drug.

Specialised safety pharmacology studies assessed effects on the cardiovascular and renal systems. These studies were Good Laboratory Practice (GLP) compliant. Effects on the respiratory and gastrointestinal systems were assessed in a published paper (Härtl *et al.*, 1971) and gross effects on the central nervous system (CNS) were determined in submitted toxicity studies. Unfortunately, the reporting in the published paper was limited (no information on time of assessment, formulation details, and on occasions, drug concentration) and therefore the power of the study is considered limited.

There was no effect on action potential duration in canine Purkinje fibres at ≤7.5 μg/mL (17 times the free clinical C_{max}). *In vitro*, bendamustine inhibited the potassium (hERG-1) tail current (20 to 65%) at ≥20 μM (17 times the free clinical C_{max}). The No Observable Effect level (NOEL) of 2 μM is only marginally greater than the maximum clinical free plasma fraction (1.21 μM). No effect on QT interval[9] was seen in dogs that received ≤6.6 mg/kg/day IV bendamustine. However, the peak plasma levels (9.13 μg/mL) were subclinical (compared to clinical C_{max} of 10.1 μg/mL) and, therefore, little weight can be placed on the negative findings. Based on the in vitro data, bendamustine has the potential to prolong the QT interval during clinical use.

[8] Leoni, L.M., B. Bailey, J. Reifert, C. Niemeyer, H. Bendall, L. Dauffenbach and C. Kerfoot. (2003) SDX-105 (Bendamustine), a Clinically Active Antineoplastic Agent Possesses a Unique Mechanism of Action [Abstract].
[9] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

There were no clinical signs of CNS toxicity in any of the repeat-dose toxicity studies but the achieved C_{max} values were generally subclinical, making the negative findings difficult to interpret. There were several signs that bendamustine has an effect on the parasympathetic nervous system; hypotension was seen in cats at ≥10 mg/kg (150 mg/m^2) IV, stimulation of intestinal movement was seen in the ilea of cats and guinea pigs (at ≤5 µg/mL; less than the clinical C_{max}) and vomiting and salivation were observed in the toxicity studies. Härtl (1971) provided some evidence that bendamustine may inhibit acetylcholinesterase activity. The effects on the gastrointestinal and cardiovascular systems are consistent with an anticholinesterase activity.

In rats that received ≥20 mg/kg IV bendamustine (estimated exposures similar to the clinical area under the plasma concentration versus time curve (AUC)), there was evidence of dysfunction of glomerular filtration, consisting of a kaliuretic and natriuretic effect. The kidney was a primary organ for toxicity in the animal studies.

Pharmacokinetics

Following IV administration, the plasma elimination half-life was short in rats and dogs (9 min) and slightly longer in human subjects (27 min). As such, there was no evidence of accumulation with repeat-dosing. There were no sex differences in any of the pharmacokinetic parameters in rats or dogs. The systemic exposure increased approximately dose-proportionally in rats and higher than dose-proportionally in dogs. Exposures to metabolites M3 (γ-hydroxy bendamustine) and M4 (N-desmethyl bendamustine) relative to the parent were generally similar in rats and human subjects, and are considered to be only minor human metabolites (<4% of the parent).

Plasma protein binding was high and independent of concentration in human plasma (94.7 to 96.2%) but lower in dog plasma (72.6 to 78.4%). No studies assessed the extent of protein binding in the plasma of rats, the other species used in toxicity studies. The absence of this information is not expected to affect the ability to compare exposures in rats with those in human subjects, given the high protein binding in the latter species. Binding of radioactively labelled (^{14}C) bendamustine to human serum albumin was significant with 14 to 26% of the radioactivity covalently bound to this protein. There was no notable binding to α_1-acid glycoprotein. There was no specific partitioning into blood cells. The volume of distribution in human subjects (no animal data available) was less than total body water, suggesting limited extravascular distribution. Consistent with this, following IV administration of ^{14}C-bendamustine to mice, rats and dogs, tissue:plasma C_{max} ratios were generally <1, except for organs involved in excretion (kidneys, bladder, liver). High levels of radioactivity in the gastrointestinal (GI) tract of all three species indicate significant biliary excretion. There was limited penetration of the blood-brain barrier with peak brain levels ≤6% of peak plasma levels in mice, rats and dogs. There was no specific affinity for or retention in melanin-containing tissues in pigmented rats. In dogs, however, retention of radioactivity was evident in the skin (pigmented and non-pigmented), skeletal muscle and white fat. Such retention was not seen in mice or rats and the significance of this finding in a single species is not known.

The metabolism of bendamustine appeared to be generally similar across species (mice, rats, dogs and humans) and unchanged drug appeared to be the main circulating drug-related component. The major pathways of metabolism of bendamustine involved hydrolytic dehalogenation (to mono- and dihydroxy bendamustine; HP1 and HP2, respectively), oxidation (to γ-hydroxy bendamustine [M3]) and N-alkylation (to N-desmethyl bendamustine [M4]). HP1 and HP2, the latter of which is the main human metabolite (plasma levels approximately20% of the parent [based on AUC]), appear to be formed by chemical hydrolysis, rather than an enzymatic process. In vitro studies indicated that cytochrome P450 (CYP) isozyme 1A2 plays a major role and CYP2A6 a possible minor role, in the formation of M3 and M4. Other minor pathways of metabolism

included carboxylic acid formation and sulfate, glutathione and cysteine conjugation. All major relevant human metabolites were detected in rats and/or dogs, the two species used in the toxicity studies.

Biliary excretion was indicated in mice, rats and dogs. The extent of biliary excretion was reported to be approximately45% in rats.[10] As such, significant amounts of drug-related material were excreted in the faeces with only 20 to 37% of the administered dose excreted in the urine of rats, dogs and human subjects.

Overall, the pharmacokinetic profile of bendamustine was qualitatively similar in rats, dogs and humans, thus supporting the use of the chosen species in the toxicity studies.

Pharmacokinetic drug interactions

Bendamustine had no effect on the human plasma protein binding of warfarin. Prednisone, doxorubicin, vincristine and mitoxantrone had no effect on the binding of bendamustine to human plasma proteins. Therefore, pharmacokinetic drug interactions involving protein binding are unlikely. While bendamustine is metabolised by CYP1A2 (to form M3 and M4), this is only a minor metabolic pathway (altogether <5%) and therefore, inhibitors/inducers of CYP450 enzymes are not expected to significantly alter the safety/efficacy profile of bendamustine. Bendamustine did not significantly induce CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1 or 3A4/5 activity in human hepatocytes nor inhibit CYP1A2, 2C9/10, 2D6, 2E1 or 3A4 activity in human liver microsomes at ≤200 μM (165 times the clinical C_{max}). Therefore, pharmacokinetic drug interactions involving CYP450 enzymes are not expected with bendamustine. No specialised studies assessed the effect of bendamustine on transporters. In vitro pharmacology studies indicated bendamustine was a substrate for P-glycoprotein, Breast Cancer Resistance Protein (BCRP) and Multidrug Resistance Proteins (MRP). Therefore, oral inhibitors of P-glycoprotein or BCRP could potentially increase the systemic exposure to bendamustine (due to enterohepatic recirculation - decreased biliary excretion and increased intestinal reabsorption) and may increase drug exposure in the CNS.

Toxicity

Acute toxicity

One study assessed the toxicity of a single IV dose of bendamustine in mice and rats. The study was primarily designed to determine the 50% lethal dose (LD_{50}) and was not GLP-compliant, only one sex (males) was examined in each species, group sizes were not reported and relevant summary and individual animal data were missing from the report. Nonetheless, the observation period was adequate (21 days), a maximum non-lethal dose was determined, gross necropsies were performed and target organs for toxicity were identified. The maximum non-lethal IV dose in mice and rats was 50 mg/kg and 30 mg/kg, respectively. One hundred percent lethality was observed at 100 mg/kg IV in mice and 80 mg/kg IV in rats, clearly indicating a narrow margin between a dose for which there are no deaths and a dose for which there is 100% lethality (though this should be considered carefully in the absence of data indicating animal numbers). Depending on dose, deaths occurred 1 to 10 days after administration. Clinical signs beginning 1 to 2 h post-dose, included sedation, tremor, ataxia, reduction of reflexes, convulsions and respiratory distress. After 1 to 2 days, diarrhoea and weight loss were evident. The thymus and spleen were identified as target organs for toxicity with atrophy of these organs observed during postmortem analyses.

[10] Bezek, S, V. Scasnar, T. Trnovec and R. Grupe. (1991) Hepatobiliary elimination of bendamustin (Cytostasan®) in rats. *Pharmazie* 46: 810–811.

Repeat-dose toxicity

Pivotal repeat-dose toxicity studies were of 15 weeks duration in rats and dogs with bendamustine provided by IV infusion once daily for 3 to 4 days every 3 (rats) or 5 (dogs) weeks. Two studies assessed the oral toxicity of bendamustine to rats. The pivotal IV studies were GLP compliant and were generally adequately conducted. The duration of the studies and the choice of species (based on pharmacokinetic considerations) are acceptable. The chosen dosing regimen is considered sufficiently similar to the proposed clinical dosing regimen (2 days every 3 to 4 weeks). The dose levels chosen in dogs were acceptable, limited by excessive toxicity. Higher IV doses may have been achievable in rats, as there was no clear dose-limiting toxicity and significant bodyweight suppression was only seen in males. Nonetheless, the oral toxicity studies used high daily oral doses of bendamustine and provide additional information on the toxicity profile of bendamustine. Given the differences in route and dosing regimen, a comparison of exposure in the oral studies with clinical exposure (by the IV route) is difficult, but estimated maximum exposures are expected to be higher than those achieved in the IV studies.

Relative exposure

Exposure ratios have been calculated based on a 24 h exposure only or a 15 week exposure, to account for the slightly different dosing regimens in the rat, dog and clinical studies. Either way, maximum exposures in the dog study were subclinical, while maximum exposures in the rat study were similar to the clinical exposure (Table 5). Therefore, all toxicity findings should be considered as potentially clinically relevant.

Table 5: Relative exposure in pivotal repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	C_{max} (µg/mL)	AUC (µg·h/mL)		Exposure ratio based on:		
				24 h	15 weeks	C_{max}	$AUC_{24\,h}$	$AUC_{15\ weeks}$
Rat[a] (SD)	15 weeks	5	2.88	1.48	22.2	0.3	0.2	0.2
		10	6.83	3.62	54.2	0.7	0.4	0.6
		15	12.99	6.76	101.4	1.3	0.7	1.1
Dog[b] (Beagle)	15 weeks	1.65	1.56	0.64	7.7	0.2	0.1	0.1
		3.3	3.75	1.45	17.4	0.4	0.2	0.2
		6.6	9.13	3.66	43.9	0.9	0.4	0.5
Human (tumour patients)[c]		[120 mg/m^2]	10.1	9.52	95.2	–	–	–

[a]AUC_{24h}: combined male and female AUC_{0-t} data from Day 87; $AUC_{15\ weeks}$: AUC_{24h} × 3 (days) × 5 (cycles); [b]AUC_{24h}: combined male and female AUC_{24h} data from Day 1 (Cycle 1); $AUC_{15\ weeks}$: AUC_{24h} × 4 (days) × 3 (cycles); [c]$AUC_{15\ weeks}$: AUC_{24h} × 2 (days) × 5 (cycles)

Major toxicities

Toxicity findings with bendamustine included those typical of this class of drug (effects on the bone marrow, lymphoid tissue, gastrointestinal tract and male reproductive organs), as well as unique toxicities (on the heart and kidney).

Toxicological effects typical of the alkylating agent class

Reduced white blood cells (in particular lymphocytes) were seen in rats at 15 mg/kg IV and dogs at ≥1.65 mg/kg IV. At higher doses in dogs (≥3.3 mg/kg), these changes were accompanied by evidence of reduced cellularity in the lymph nodes and splenic white pulp and an increased severity of thymic involution/atrophy. Similar effects on the lymph node, spleen and thymus were only seen in rats given high daily oral doses (≥40 mg/kg/day PO for 3 months; approximately 10 mg/kg/day IV, assuming 25% oral bioavailability [from submitted absorption study]). Bone marrow suppression was also seen in rats at these doses. All of the haematological and lymphoid effects are expected for this type of drug, and were reversible, but indicate a risk of infection during clinical use.

Clinical signs of gastrointestinal distress (brown/white frothy vomitus, red coloured faeces) were seen in dogs that received 6.6 mg/kg IV bendamustine, with congestion and haemorrhage in the GI tract evident at necropsy. After bendamustine is excreted into the gut, it may inhibit the replacement of the lining of the gut, thereby leading to haemorrhage. Necrosis and inflammation in the jejunum and prominent mitotic figures in the crypt epithelium of the duodenum were also seen during post-mortem examinations. These gastrointestinal effects were a dose-limiting toxicity in dogs, leading to the premature termination of the high dose (6.6 mg/kg IV) group. While there were no GI tract changes in the pivotal rat IV study, epithelial necrosis was seen in rats that received high daily oral doses (≥40 mg/kg/day) for 1 month. Gastrointestinal disturbances may be expected during clinical use.

The male reproductive organs were target organs for toxicity in dogs that received IV doses and rats that received oral doses of bendamustine. Testicular atrophy was seen in dogs that received ≥1.65 mg/kg IV bendamustine, while at higher doses (6.6 mg/kg IV to dogs; ≥40 mg/kg/day PO to rats), abnormal or a reduced level of spermatogenic cells were evident in the epididymal duct. Effects on the male reproductive organs are expected for this type of product.

Toxicological findings distinct from most of the other alkylating agents

Cardiomyopathy was seen in male rats that received 15 mg/kg IV bendamustine. In dogs, cardiac lesions, all of minimal severity, consisted of myocardial interstitial inflammation (females at ≥3.3 mg/kg IV), focal haemorrhage of the left atrioventricular valve (females at 6.6 mg/kg IV) and leukocytosis (males at 6.6 mg/kg IV).

Presumably as the kidneys have a significant role in the excretion of bendamustine, kidney damage was evident in both rats and dogs. Renal effects consisted of tubular epithelial karyomegaly (at ≥5 mg/kg IV in male rats and 15 mg/kg IV in female rats), tubular epithelial degeneration/regeneration (at ≥10 mg/kg IV in male rats and 15 mg/kg IV in female rats), glomerulitis and enlarged nuclei (at ≥3.3 mg/kg IV in dogs). Impairment of glomerular filtration was evident in safety pharmacology studies conducted in rats. Given the renal effects occurred at low relative exposures, these are likely to be clinically-relevant. This may need to be considered if bendamustine were to be administered to patients with some degree of renal impairment.

Other effects

Other effects seen in rats that received 15 mg/kg IV bendamustine included vacuolation of the adrenal cortex (males only) and hepatocytic vacuolation (females only). There was no other evidence of liver damage (such as elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or other hepatic lesions), and there were no hepatic findings in the oral toxicity studies, where presumably higher exposures were achieved. Likewise, adrenal gland cortical vacuolation was not consistently seen across the rat toxicity studies. Given the nature of the findings (predominantly adaptive rather than a

toxic effect) and the lack of a consistent effect across studies, the hepatic and adrenal gland findings are unlikely to be a significant concern during clinical use.

Genotoxicity

The potential genotoxicity of bendamustine was investigated in the standard battery of tests, conducted in accordance with ICH guidelines. All assays were appropriately validated and conducted under GLP conditions. Bendamustine was shown to be mutagenic in the bacterial mutation assay and clastogenic in in vitro (human lymphocytes) and in vivo (rat micronucleus test) studies. These positive genotoxicity findings are not surprising, given the intended pharmacological action of this drug (as an alkylating agent).

Carcinogenicity

According to ICH S9[5], carcinogenicity studies are generally not required to support the registration of an anticancer agent. Based on the positive genotoxicity findings, bendamustine can be assumed to be carcinogenic. One submitted published paper[11] confirmed the carcinogenic potential of bendamustine. After 4 daily IP or PO doses to female mice, drug-related tumours appeared during the life-time follow-up period: peritoneal sarcoma in mice that received IP doses (≥50 mg/kg/day or 150 mg/m^2) and pulmonary adenomas and mammary carcinomas in mice that received oral doses (250 mg/kg/day).

Reproductive toxicity

Reproductive toxicity studies were restricted to embryofetal effects in mice and rats. The absence of fertility and postnatal development studies is considered acceptable given the intended patient group.[5] The male reproductive organs were target organs for toxicity in the repeat-dose studies. As with other alkylating agents, effects on male fertility may be expected with bendamustine.

Single IP doses of bendamustine to pregnant mice and rats during the period of organogenesis, resulted in embryofetal lethality (characterised by an increase in resorption rate and a reduced number of live fetuses), reduced (live) fetal body weight (more evident in mice than rats) and an increased number of fetuses with external (dwarfism, short or bent tail, hepatic or intestinal ectopia, turricephaly and cleft palate) and internal (rib malformations and spinal deformities in mice, hydrocephalus, hydronephrosis and hydroureter in rats) abnormalities. There was also a significant increase in the number of mouse fetuses bearing accessory ribs. The doses at which embryofetal deaths and teratogenic effects occurred were less than twice the clinical dose in mice (70 mg/kg or 210 mg/m^2) and subclinical in rats (20 mg/kg or 60 mg/m^2). Therefore, as with other alkylating agents, adverse embryofetal effects are probable if bendamustine is administered to pregnant women.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[12] This category is generally for drugs which, owing to their pharmacological action, may cause fetal damage but without causing malformations. In light of the teratogenicity seen with bendamustine in animal studies,

[11] Güttner, V.J., G. Bruns and W. Jungstand. (1974) Onkogene Wirkung von γ -[1-Methyl-5-bis-(β-chloräthyl)-aminobenzimidazolyl-(2)]buttersäurehydrochlorid (Cytostasan®) bei der Maus [*Oncogenicity of γ-[1-methyl-5-bis-(β-chloroethyl)-aminobenzimidazolyl-(2)]-butyric acid hydrochloride (Cytostasan®) in mice*] *Arch. Geschwulstforsch* 43: 16–21.

[12] Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Category D[13] is considered more appropriate and the category is consistent with that for other alkylating agents. This is a category for drugs which may be expected to cause an increased incidence of fetal malformations or irreversible damage, possibly as a result of pharmacological action.

Local tolerance

Perivenous injection of ≥0.6 mg/mL or intra-arterial injection of ≥0.2 mg/mL to rabbits produced local reactions such as slight to moderate bruising which also affected the adjacent SC tissue following perivenous injection. As these effects occurred at clinically relevant concentrations (approximately0.2 mg/mL), the data indicate a risk of local tissue damage in the event of extravasation.

Phototoxicity

Bendamustine was not phototoxic to Balb/c 3T3 cells.[14]

Impurities

The proposed expiry limits for 4 degradants are above the ICH qualification threshold. Three of these have been adequately qualified. The proposed limit for one degradant is not supported by submitted data.

Paediatric use

No specific studies in juvenile animals were submitted.

Nonclinical summary

- The nonclinical submission a hybrid dossier consisting of published papers and sponsor commissioned studies. Overall, given the years of clinical experience with the drug, the submitted nonclinical data package was considered adequate.
- In vitro, bendamustine inhibited the growth of several leukaemia cell lines. Reduced tumour growth was seen in mouse xenograft and allograft leukaemia/lymphoma models. In general, the submitted pharmacology studies support the proposed indications. Some resistance was seen in cells that overexpress the transporters, P-glycoprotein, BCRP and MRP.
- In mice bearing a human CD20 positive lymphoma, more significant tumour growth delays were seen with the combination of rituximab and bendamustine, than with either agent alone.
- Safety pharmacology studies or submitted papers assessed effects on the cardiovascular, respiratory, gastrointestinal and renal systems. In vitro, bendamustine inhibited the potassium (hERG-1) tail current at clinically relevant concentrations. In vivo data for cardiovascular effects in dogs are inconclusive. Based on the in vitro data, bendamustine has the potential to prolong the QT interval during clinical use. Effects on the parasympathetic nervous system were evident in animals (or animal

[13] Category D: 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.
[14] BALB/c 3T3 cells originated from BALB/c mouse whole embryo cultures. They possess the ability to divide indefinitely but are highly sensitive to the post-confluence inhibition of cell division. This clone is sensitive to chemical transformation.

biomaterials) at clinically relevant doses/concentrations; hypotension, stimulation of intestinal movement, vomiting and salivation. Dysfunction of glomerular filtration and kidney damage were seen at clinical exposures in rats and/or dogs.

- Following IV administration, the plasma elimination half-life was relatively short in rats and dogs and slightly longer in human subjects. In human plasma, a significant level of drug related material was covalently bound to human serum albumin. The volume of distribution in human subjects was less than total body water and limited extravascular distribution of drug related material was seen in rats. The metabolism of bendamustine appeared to be generally similar across species with unchanged drug as the main circulating drug-related component. Transformation of bendamustine involved chemical hydrolysis and oxidative reactions involving CYP1A2 and to a lesser extent, CYP2A6. Biliary excretion was significant in animals, though 20 to 37% of the administered dose was excreted in the urine.
- Based on in vitro studies, pharmacokinetic drug interactions involving protein binding or CYP450 enzymes are unlikely with bendamustine. As bendamustine was a substrate for P-glycoprotein, BCRP and MRP, inhibitors of these transporters may increase the systemic or CNS exposure to bendamustine.
- A single-dose toxicity study with mice and rats, indicated a narrow margin between an IV dose for which there are no deaths and an IV dose for which there is 100% lethality.
- Repeat-dose toxicity studies by the IV route were of up to 15 weeks duration in rats and dogs. Two studies assessed the oral toxicity of bendamustine to rats. Maximum exposures in the IV studies were similar to or less than the clinical exposure. Toxicity findings of clinical relevance include bone marrow suppression and lymphoid depletion (with corresponding reductions in, predominantly, lymphocytes), gastrointestinal disturbances (such as vomiting) and testicular atrophy, all of which are expected for this type of drug. Atypical findings were also seen in the heart (cardiomyopathy and inflammation) and kidneys (tubular epithelial karyomegaly, tubular epithelial degeneration/regeneration and glomerulitis).
- Bendamustine, as expected for an alkylating agent, was mutagenic in the bacterial mutation assay and clastogenic in in vitro (human lymphocytes) and in vivo (rat micronucleus test) studies. The carcinogenic potential of bendamustine was confirmed in mice.
- Reproductive toxicity studies were restricted to embryofetal effects in mice and rats (given a single IP dose of bendamustine during the period of organogenesis. Embryofetal toxicity (including embryofetal deaths and teratogenicity) was seen in both species at clinically-relevant doses.
- A risk of local tissue damage exists in the event of extravasation.
- Bendamustine was not phototoxic.
- The proposed expiry limit for one degradant is not supported by submitted data.

Nonclinical conclusions and recommendation

- The in vitro pharmacology studies generally support the proposed clinical use of bendamustine, either as monotherapy or in combination with rituximab.
- The safety profile of bendamustine indicated the following findings of potential clinical relevance:
  - QT prolongation in electrocardiograms (ECGs)
  - Hypotension

- § Gastrointestinal disturbances
- § Lymphoid depletion
- § Effects on the male reproductive organs

– Kidney damage

– Cardiomyopathy

· Bone marrow suppression and a reduction in lymphocytes, indicates a higher risk of infections in patients.

· As the safety profile of bendamustine is largely similar to other alkylating agents (with the exception of kidney damage and cardiomyopathy) and there has been significant clinical use of the drug over the past 30 years, there are no objections on nonclinical grounds to the proposed registration of Ribomustin for the proposed indications.

Amendments to the draft Product Information were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

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

Introduction

Clinical rationale

The sponsor's application letter states that bendamustine was first synthesized in the former German Democratic Republic (GDR) in the early 1960s. It goes on to state that 'in vitro studies have demonstrated that bendamustine's anti-tumour activity and mode of action is different to other structurally related compounds, which may contribute to the distinct profile observed in the clinical studies described in [the submitted] dossier'. The application letter included an attachment from an Australian haematologist supporting the use of bendamustine in combination with rituximab for the treatment of previously untreated indolent NHL and MCL in CD20 positive patients, and as monotherapy for the treatment of relapsed/refractory NHL.

Comment: The clinical rationale for the submission is acceptable.

Guidance

The submission included minutes of a pre-submission meeting between officers of the Therapeutic Goods Administration (TGA) and representatives of the sponsor held on 27 May 2011 to discuss the proposed hybrid package for registration of bendamustine for CLL and indolent NHL and MCL. The minutes indicate that the sponsor's proposal to submit a hybrid submission was acceptable to the TGA. The minutes also indicate that there was discussion on the standard treatment for MCL, and the TGA indicated that Torisel (temsirolimus) was available for treatment of this condition. The minutes note that the independent Australian haematologist accompanying the sponsor's representatives stated that Torisel is not usually used in his hospital and that there really was no standard therapy for MCL.

The relevant TGA adopted European Union (EU) guidelines for this submission include the *Guideline on the Evaluation of Anticancer Medicinal Products in Man* (CPMP/EWP/205/95/Rev/3/Corr), Appendix 1 to the guideline (*Methodological Considerations for Using*

Progression Free Survival (PFS) as Primary Endpoint in Confirmatory Trials for Registration (EMEA/CHMP/ EWP/ 27994/2008) and Appendix 2 to the guideline (*Confirmatory Studies in Haematological Malignancies* (EMA/CHMP/520088/2008).

> Comment: The sponsor's application letter states that conventional data has been submitted supporting the first-line CLL and the relapsed/refractory indolent NHL indications, while literature based data has been submitted supporting the first-line indolent NHL and MCL indication. The sponsor's application letter nominates only one pivotal, very recent publication as support for the first-line indolent NHL and MCL indication.[15] It should be noted that at the time of the submission bendamustine appeared not to have been approved in any overseas countries for the first-line treatment of indolent NHL and MCL. Therefore, it is considered unusual that recent literature based data have been submitted to support registration of an indication not approved in any overseas countries. It is considered that, in general, indications not approved in any overseas countries and based on recently completed studies should be supported by conventional study reports rather than literature based data. The amount of efficacy and safety data that can be provided in a published paper is very limited compared with a comprehensive study report specifically compiled by the sponsor. This is particular relevant to the evaluation of the safety of a new chemical entity for a new indication. There are significant clinical concerns about the provision of a submission based on the results of a recently published study to support the approval of bendamustine for first-line treatment of indolent NHL and MCL.

Contents of the clinical dossier

The submission was a hybrid containing both literature-based and conventional study reports. The study was provided in Common Technical Document (CTD) format. The submitted data package was large and included clinical pharmacology studies and reports, clinical efficacy and safety studies supporting the three proposed indications, post-marketing data reports, and a number of written summaries of the data. The clinical evaluation of the submission is based on the electronic data (CD) provided by the sponsor. The CD was well structured and easy to navigate.

The relevant clinical data provided in the submission are summarized below:

- 13 clinical PK reports
- 5 reports relating to 1 controlled clinical study pertinent to the CLL indication including initial study report, 1 follow-up study report with Appendix 14 (listing of tables), Appendix 14 (actual tables) and Appendix 16.1.9 (Biometric report)
- 2 uncontrolled clinical study reports pertinent to the CLL indication
- 2 other clinical study reports pertinent to the CLL indication
- 18 reports relating to 1 controlled clinical study pertinent to the indication for first-line treatment of NHL and MCL with bendamustine in combination with rituximab
- 7 uncontrolled study reports pertinent to the indication for relapsed/refractory NHL in patients refractory to rituximab
- 1 controlled clinical study report pertinent to the treatment of MM
- 5 reports relating to post-marketing experience

[15] Rummel MJ et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle cell lymphomas: and open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet; published on-line February, 2013. <http://dx.doi.org/10.1016/> S0140-6736(12)61763-2.

- Literature references
- 6 in vitro method validation reports relating to bioanalytical and analytical methods for human studies
- 1 in vitro report relating to in vitro production of metabolites M3 and M4

Paediatric data

The sponsor submitted a statement relating to the paediatric development program. This statement indicated that no paediatric data supporting the use of bendamustine in a paediatric population has been submitted to the TGA. However, paediatric data in children aged 2 to 11 years have been submitted to the European Union (EU), while paediatric data in children from the age of 28 days up to adolescents aged 17 years have been submitted to the FDA (USA).

> Comment: It is unclear from the submitted document which indications being sought in Australia are being sought in the EU and/or the USA for a paediatric population. No reasons were provided in the document for not submitting paediatric data to the TGA. This will be followed-up in a first-round question to the sponsor.

Good clinical practice

All pivotal and supportive clinical efficacy and safety studies have been under in accordance with the principles of Good Clinical Practice (GCP). All studies undertaken by the sponsor or sponsors of bendamustine have been undertaken in accordance with GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Phase I studies

The submission included 12 clinical study reports identified as 'Patient PK and Initial Tolerability Study Reports' and 1 clinical study report listed under 'Intrinsic Factor PK Study Reports. In addition, the submission included 1 in vitro report listed under 'Reports of Hepatic Metabolism and Drug Interaction Studies' and 6 in vitro method validation reports listed under 'Reports of Bioanalytical and Analytical Methods for Human Studies'. The 13 clinical PK reports are summarised below in Table 6.

Table 6: Clinical PK reports.

Study ID	Subject Matter
BioProof R1-01-02	Detection of bendamustine and related compounds in human plasma using HPLC/FL.
BioProof R1-01-02 Addendum 1	Detection of bendamustine and related compounds in human plasma using HPLC/FL.
BioProof R1-02-Juni-2002	PKs of bendamustine and related compounds in patients of Phase I study 20BEND 1.
Humb-Uni-Berlin 1987	Expert report on studies on kinetics of bendamustine.

Study ID	Subject Matter
Klinge 6000683-01	Analytics of bendamustine in 3 selected patients from Phase I studies.
Klinge 6000683-02	PKs of bendamustine in 3 selected patients of Phase 1 study 98B02.
riboseph 20BEND 1	CSR bendamustine days 1 and 2 every 3 weeks, open-label, non-randomized, Phase 1 study.
riboseph 20BEN03	CSR bendamustine days 1 and 2 every 3 weeks, open-label, non-randomized, Phase 1 study.
riboseph 98B02	MTD, DLT, PK, safety and tolerability after repeated IV bendamustine administration.
riboseph 98B02W	MTD, DLT, PK, safety and tolerability after weekly IV bendamustine administration.
Uni Leipz 2002	Determination of bendamustine and related compounds in human urine using HPLC/FL.
Uni Leipz 2004	Biliary elimination, efficacy and toxicity of bendamustine and metabolites, cholangiocarcinoma
riboseph 98B03	Phase 1 study, PK, clearance, toxicity of bendamustine, hepatic and renal impairment.

Note: MTD = maximum tolerated dose; DLT = dose limiting toxicity; HPLC/FL = high performance liquid chromatography/fluorescent detection.

The evaluation of pharmacokinetics in this clinical evaluation report (CER) focuses on the pharmacokinetic (PK) data from the clinical study reports in patients with cancer. The PK data were based on a number of relatively small Phase I studies undertaken between about 1985 and 2005. There were no clinical PK studies in healthy volunteers, which is not unexpected for a cytotoxic drug.

Phase III studies

In addition to the Phase I PK studies, the Phase III efficacy and safety study (SDX-105-03) included PK data on 12 patients with indolent NHL who are refractory to rituximab. This Phase III study is considered to be the pivotal efficacy and safety study supporting bendamustine for the treatment of 'relapsed/refractory indolent NHL'. The PK data for Study SDX-105-03 was provided as a separate report identified as Report Number DP-2007-043 in Appendix 16.1.3 to SDX-105-03, and these data have been evaluated. The SDX-105-03 study report also stated that a population PK analysis (CP-07-002) and a pharmacokinetic/pharmacodynamic analysis (CP-07-003) had been undertaken and were to be reported separately. However, these two analyses could not be identified in the submitted data. There were no PK data for bendamustine from the pivotal Phase III studies supporting the indications for 'first-line treatment of CLL' or for 'first-line treatment of NHL and MCL'.

Evaluator's conclusions on pharmacokinetics

The submitted PK data included information on 78 patients with cancer of various types from five Phase I studies and 11 patients with indolent NHL refractory to rituximab from the pivotal Phase III efficacy and safety study (SDX-1050-03). The sponsor's Clinical Overview identifies the most important PK studies as 20BEND1 (n=13), 98B03 (n=36), and BE04 (n=6). However, the sponsor's Clinical Overview did not discuss the PK results from the Phase III Study SDX-1050-03 and the PK report from this study was not identified or cross-referenced in the relevant PK Table of Contents (TOC) section of the submission. Nevertheless, the PK data from Study SDX-105-03 are considered to be clinically relevant and have been reviewed in this CER. There were no PK data from the pivotal Phase III studies in patients with CLL or in patients with previously untreated indolent NHL and MCL. There were some deficiencies in the submitted PK data but in view of the extensive clinical efficacy and safety data submitted by sponsor it is considered that these deficiencies should not preclude approval of bendamustine.

In Study 98B03, bendamustine 120 mg/m^2 administered IV over 30 minutes to 12 cancer patients with normal renal and hepatic function resulted in a mean± standard deviation (SD) C_{max} of 10.8±7.0 µg/mL and a mean±SD AUC_{all} of 11.7±10.6 µg•hr/mL. The intersubject variability in the C_{max} and AUC_{all} values was high with the coefficients of variation (CVs) being 65% and 91%, respectively. In this study, bendamustine peak plasma concentration was achieved at the end of the 30 minute infusion and the drug was rapidly cleared from the plasma with mean±SD elimination half-life of 28.2±15.9 minutes and mean±SD total plasma clearance of 639.4±601.6 mL/min.

In Study SDX-105-03, bendamustine 120 mg/m^2 administered IV over 60 minutes to patients with indolent NHL refractory to rituximab resulted in a mean±SD C_{max} of 5.6±2.4 µg/mL (n=10) and a mean±SD AUC_{inf} of 7.2±3.8 µgxhr/mL (n=9). The intersubject variability in the C_{max} and AUC_{inf} values was moderate with the coefficients of variation (CVs) being 43% and 53%, respectively. In this study, median bendamustine peak plasma concentration was achieved at the end of the 60 minute infusion and the drug was relatively rapidly cleared from the plasma with mean±SD elimination half-life of 4.9±4.5 hours and mean±SD total plasma clearance of 716.6±682.8 mL/min.

The mean half-life in Study SDX-105-3 following a 60 minute infusion of 120 mg/m^2 of 4.9 hours was notably longer than the mean half-life in Study 98B03 of 28.2 minutes following a 30 minute infusion of 120 mg/m^2. Nevertheless, the mean half-life data from both studies suggests that there will be no significant accumulation of bendamustine on Day 2 of the proposed regimens or across cycles (that is, bendamustine administered on Days 1 and 2, every 21 or 28 days for at least 6 cycles).

There were no formal dose proportionality studies. However, cross-study comparative data showed that the plasma PK parameters for bendamustine appeared to be dose-independent and non-capacity limited over the dose range 100 to 260 mg/m^2 following IV infusion over 30 minutes (98B02, 98B03, 20BEN03, 20BEND1).

The mean ± SD steady state volume of distribution in Study SDX-105-03 was 25.3 ± 28.6 L. The result indicates that inter-subject variability in this parameter is very high (that is, CV > 100%). Bendamustine was highly protein bound (94% to 96%), and binding was independent of concentration over the range 1 to 50 µg/mL. Binding of bendamustine was predominantly to serum albumin (80% to 92%), and with minor binding to α-1-acid glycoprotein (2% to 6%). The drug was evenly distributed between plasma and red blood cells and distribution was concentration independent.

In vitro data indicate that bendamustine is metabolized via CYP 1A2 to gamma-hydroxy-bendamustine (M3) and desmethyl-bendamustine (M4) (BioD-99-37-KLG-01). In vivo data indicate that the concentrations of the M3 and M4 metabolites were notably lower than the parent compound. In Study 98B03, M3 and M4 accounted for about 3% and 0.6%,

respectively, of the AUC_{all} of bendamustine in patients (n=12) with cancer and normal renal and hepatic function. In Study SDX-105-03, based on AUC_{inf} values, M4 accounted for about 1% of the parent compound in 11 patients and M3 accounted for about 10% of the parent compound in 1 patient. These results suggest that the cytotoxic activity of bendamustine is derived primarily from the parent compound rather than its M3 and M4 metabolites. In addition to Phase I metabolites formed from CYP 1A2 activity, Phase II metabolites have been identified following conjugation with glutathione.[16]

In addition to Phase I and II metabolism, bendamustine also undergoes chemical hydrolysis to monohydroxy-bendamustine (HP1) and dihydroxy-bendamustine (HP2). In Study 98B03, plasma HP1 concentration was about 1.6% of the parent compound and HP2 was undetectable. The anti-tumour activity of HP1 and HP2 is more than 10 times lower than the anti-tumour activity of bendamustine. Consequently, it can be estimated HP1 and HP2 account for a clinically insignificant amount of anti-tumour activity.

In Study 98B03, in 12 cancer patients with normal renal and hepatic function the total plasma clearance of bendamustine was 639.4±601.6 mL/min, and about 20% of the administered dose of the drug was excreted in the urine as bendamustine and metabolites (HP1 > bendamustine > HP2 > M3 > M4). Approximately 5.5% of the dose was eliminated in the urine as unchanged bendamustine. The results suggest that bendamustine is primarily cleared from the plasma by non-renal mechanisms and that the renal clearance is approximately 35 mL/min. As the renal clearance of bendamustine is less than the fraction of the drug unbound times glomerular filtration rate (GFR), bendamustine must be reabsorbed from the renal tubules and may or may not be secreted.

Biliary excretion of bendamustine and its metabolites account for about 9% of the administered dose of the drug. Only small amounts of bendamustine, HP1, HP2, M3 and M4 were detected in bile, and an additional 10 mainly polar metabolites were identified. More than 80% of the metabolites appearing in the bile were accounted for by HP1, HP2, M3 and M4.

The effects on hepatic and renal impairment on the PKs of bendamustine were investigated in Study 98B03. There was no data on patients with severe hepatic impairment and limited data on patients with moderate hepatic impairment. The PK results suggest that no dosage adjustment is required in patients with mild hepatic impairment but administration of bendamustine to patients with moderate or severe hepatic impairment should be avoided due to the absence of adequate data in these patient groups. The PK data on patients with severe renal impairment are limited but suggest that while no dosage adjustments are required caution is required when the drug is used in this patient population. The total renal elimination of bendamustine and metabolites HP1, HP2, M3 and M4 was reduced by 75% (versus normal renal function) in patients (n=12) with end-stage renal disease (ESRD), and by 80% (versus normal renal function) in patients (n=3) with dialysis-dependent ESRD.

There are no in vivo drug-drug PK interactions studies. The in vitro data suggest that CYP 1A2 inhibitors have the potential to increase the plasma bendamustine concentration, while CYP 1A2 inducers have the potential to decrease the plasma bendamustine concentration. In vitro data showed that bendamustine does not inhibit CYP 1A2, 2C9/10, 2D6, 2E1 or 3A4 (BioD-99-37-KLG-01) and is not an inducer or inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, or CYP3A4/5 (XenoTech DM-2005-004). *In vitro* data showed that bendamustine did not displace protein-bound warfarin when co-incubated with human serum albumin, while co-incubation of bendamustine with prednisone, doxorubicin, vincristine, or mitoxantrone individually suggests that these drugs do not

[16] Teichert J et al. Synthesis and characterization of some new phase II metabolites of the alkylator bendamustine and their identification in human bile, urine, and plasma from patients with cholangiocarcinoma. Drug Metabolism and Disposition 2005; 33:984-992.

displace protein-bound bendamustine. There were no PK studies assessing the role of active transporters in bendamustine distribution.

The main deficiencies in the submitted PK data (human) are listed below:

- No in vivo drug-drug PK studies were submitted assessing the potential interaction between bendamustine and drugs which inhibit or induce CYP 1A2. The in vitro data indicate that bendamustine is metabolized via CYP 1A2 to the active metabolites gamma-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4). Consequently, CYP 1A2 inhibitor and inducers have the potential to increase or decrease plasma bendamustine concentration, respectively, when administered concomitantly.
- No in vitro studies with active transporters.
- No mass-balance studies in humans.
- No PK studies in patients with severe hepatic impairment and limited data on patients with moderate hepatic impairment. The provided study is considered not to reflect current best practice for PK studies in patients with renal or hepatic impairment.
- No PK studies in special groups including only elderly patients, only males or females, and different racial groups.

Pharmacodynamics

The clinical pharmacodynamic studies related primarily to the determination of maximum tolerated dose (MTD) and dose limiting toxicity (DLT) in Phase I studies in patients with specific cancers. These studies were aimed at defining the most appropriate bendamustine dosage regimens for assessment in subsequent Phase III studies. In this CER, the Phase I studies supporting the proposed dose regimens for the proposed indications have been reviewed in the section *Dosage selection for the pivotal study* (below and Attachment 2) No PK/PD data relating specifically to efficacy or safety outcomes could be identified in the submission. However, a PK/PD study based on data from Study SDX-105-03 (report CP-07-003) appears to have been undertaken. The pharmacodynamics of the drug appears to have been extensively investigated in the nonclinical studies.

Dosage selection for the pivotal studies

Chronic lymphocytic leukaemia

The sponsor's proposed regimen for bendamustine for the treatment of CLL is 100 mg/m^2 administered by IV infusion over 30 to 60 minutes on Days 1 and 2, every 4 weeks for up to 6 cycles. This is the dose that was used in the pivotal study submitted in support of the proposed CLL indication (02CLIII). The sponsor states that two dose finding studies were carried out with bendamustine (Lissitchkov et al., 2005[17]/ Ribosepharm GmbH 99CLL2E (BG); Bergmann et al., 2005[18] / Ribosepharm GmbH 99CLL2E [DR]). There were no formal dose ranging studies.

[17] Lissitchkov T, Arnaudov G, Peytchev D, Merkle K. Phase-I/II study to evaluate dose limiting toxicity, maximum tolerated dose, and tolerability of bendamustine HCL in pre-treated patients with B-chronic lymphocytic leukaemia (Binet stages B and C) requiring therapy. J Cancer Res Clin Oncol 2005; 132: 99-104
[18] Bergmann MA, Goebeler ME, Herold M, et al. (2005) Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL study group. The Haematology Journal 2005; 90,10:1357-1364

Ribosepharm GmbH 99CLL2E (BG), was a Phase I/II open-label study sponsored by Astellas Pharma GmbH, Germany, and was conducted in one centre in Bulgaria from March 2001 to September 2002. The primary objectives of the study were to determine the DLT and MTD of second-line bendamustine monotherapy in patients with symptomatic B-cell CLL (Binet stage B or C) requiring therapy after failure of prior chemotherapy, and at least one treatment had to be chlorambucil (with or without prednisone). A total of 15 fludarabine-naive patients were treated with bendamustine at a starting dose of 100 mg/m^2 on Days 1 and 2 every 3 weeks. The MTD was defined as the dose at which ≤ 1 patient experienced DLT after the first course of a dose level (maximum 6 patients). DLT was considered to be any Common Terminology Criteria (CTC)[19] Grade 3/4 non-haematological toxicity, or CTC Grade 4 haematological toxicity. In this study, the MTD was 110 mg/m^2 (1/6 patients with a DLT), and the bendamustine dose recommended for further study in patients with previously untreated CLL was 100 mg/m^2 on Days 1 and 2 every 4 weeks.

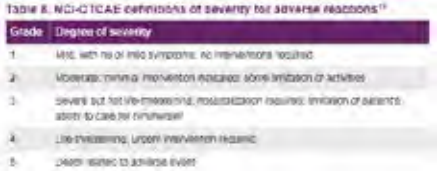
Ribosepharm GmbH 99CLL2E [DR] was sponsored by Astellas Pharma GmbH, Germany, and reported the findings of a Phase I/II, open-label study of the German CLL study group. The study was conducted in multiple centres in Germany from October 200 to March 2002. The primary objectives of the study were the same as those for *Ribosepharm GmbH 99CLL2E (BG),* except that patients were required to have received at least one prior therapy that included chlorambucil or fludarabine. A total of 16 patients (median age 67 years) with relapsed or refractory CLL were enrolled. All patients had been pre-treated with a median of three different regimens. Bendamustine was given at a starting dose of 100 mg/m^2 on Days 1 and 2 every 3 to 4 weeks. If no DLT occurred in the first 3 patients after the first treatment course, a dose escalation of 10 mg/m^2/day was planned for the next dose cohort. In this study, the MTD was 70 mg/m^2. Six (6) patients had DLT resulting in three dose de-escalation steps from 100 mg/m^2 to 70 mg/m^2. In this study, the recommended dose in refractory CLL was 70 mg/m^2 on Days 1 and 2 every 4 weeks.

Scientific Protocol Review Board experts for Study 02CLLIII considered the data from the two dose finding studies and recommended bendamustine 100 mg/m^2 on Days 1 and 2 every 4 weeks for first-line chemotherapy of CLL. The dose of chlorambucil selected for the control arm of study 02CLLIII was 0.8 mg/kg (Broca's weight) on Days 1 and 15 every 4 weeks, which followed the German CLL Study Group's (GCLLSG) recommendation for adequate chlorambucil dosing.

Relapsed/refractory indolent NHL (refractory to rituximab)

The sponsor's proposed regimen for the treatment of relapsed/refractory indolent NHL (refractory to rituximab) is 120 mg/m^2 administered IV over 30 to 60 minutes on Days 1 and 2, every 3 to weeks for at least 6 cycles. The sponsor identified two published studies supporting the dosage used in the pivotal study.[20,21] There were no formal dose ranging studies.

[19] To standardize the reporting of adverse reactions in clinical trials, National Cancer Institute (NCI) has developed Common Terminology Criteria for Adverse Events (NCI-CTCAE). According to the NCI-CTCAE, adverse reactions are reported by grade (level of severity) on a scale of 1 to 5. Generally, the descriptions follow the guidelines below.



Grade	Degree of severity
1	Mild; with no or mild symptoms; no intervention required
2	Moderate; minimal intervention indicated; some limitation of activities
3	Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for himself/herself
4	Life-threatening; urgent intervention required
5	Death related to adverse event

[20] Heider A, Niederle N. Efficacy and toxicity of bendamustine in patients with relapsed low-grade non-Hodgkin's lymphomas. Anti-Cancer Drugs 2001;12:725-9.
[21] Weidmann E, Kim SZ, Rost A, Schuppert H, Seipelt G, Hoelzer D, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Ann Oncol 2002;8:1285-9.

In *Heider and Niederle (2001)*, the efficacy and toxicity of bendamustine 120 mg/m^2 administered IV over 60 minutes on two consecutive days repeated every 3 weeks was assessed in a single-centre (Germany), single-arm, open-label study in 52 evaluable patients with histologically confirmed low grade NHL who had progressed or relapsed after at least one cytostatic pretreatment. Complete remission (CR) was induced in 11% of patients, partial remission (PR) in 62%, and stable disease (SD) in 10%. The median duration of remission was 16 months and the median survival time was 36 months. The most commonly reported toxicities (World Health Organization (WHO) grades) were: nausea/vomiting (37% [Grade 1]; 19% [Grade 2]); leukopenia (56% [Grade 2], 23% [Grade 3], 6% [Grade 3]); red blood cells (RBC) decreased (63% [Grade 1], 17% [Grade 2]); and thrombocytopenia (33% [Grade 1], 10% [Grade 2]). Allergies were reported in 8% of patients (2% Grade 1 and 6% Grade 2). There were no reports of cardiotoxicity, neurotoxicity or alopecia. The authors of this study concluded that 'bendamustine proved to be very effective and was well tolerated in pretreated patients with relapsed or primary resistant low-grade NHL'.

In *Weidmann et al (2002),* the efficacy and toxicity of bendamustine 120 mg/m^2 administered IV over 30 minutes on Days 1 and 2, every 3 weeks for up to 6 cycles was assessed in a two-centre (Germany), single-arm, open-label study in 18 evaluable patients with relapsed or refractory high grade NHL. Response was evaluated after 2, 4 and 6 cycles and every 3 months after completion of treatment. Complete response (CR) was induced in 17% of patients and partial response (PR) in 28% of patients, resulting in a total response rate of 38% (8/18). In 10 (56%) patients, treatment progressed during treatment. In 60 evaluable treatment cycles, WHO Grade 3 or 4 events were reported in 8% to 13% of cycles (anaemia in 8%, thrombocytopenia in 13%, leukopenia in 12%, granulocytopenia 10%). In 2 patients, bendamustine had to be stopped because of prolonged Grade 4 thrombocytopenia and leukopenia. Overall, haematological toxicities resulted in dose delays or dose reduction in 22% of the scheduled treatment cycles. None of the patients received myeloid growth factors. In 60 evaluable treatment cycles, non-haematological WHO Grade 3 or 4 events of nausea/vomiting occurred in 2% of cycles, fever in 2% of cycles, infections in 3% of cycles, alopecia in 7% of cycles, and diarrhoea in 0% of cycles. No treatment related deaths occurred. The authors of this study concluded that 'bendamustine is effective in aggressive lymphoma and can be recommended for [palliative treatment]'.

First-line treatment of NHL and MCL

The sponsor's proposed combination regimen for the first-line treatment of NHL and MCL is bendamustine 90 mg/m^2 administered over 30 to 60 minutes on Days 1 and 2, every 4 weeks for up to 6 cycles, with rituximab being administered on the first day or each cycle. There were no formal dose ranging studies with the proposed combination therapy.

Efficacy

First line treatment of chronic lymphocytic leukaemia (Binet stage B or C)

Studies providing efficacy data

The sponsor's covering letter identifies one pivotal Phase III study (02CLLIII) supporting the submission to register bendamustine for the first line treatment of CLL (Binet stage B of C). No other studies were identified in the covering letter as being pivotal or supportive for the registration of bendamustine for this indication. Examination of the clinical data (Reports of Efficacy and Safety Studies - Indication CLL) identifies Study 02CLLLIII, Riboseph 99CLL.2E-BG; Riboseph 99CLL.2E-DE and Friedr-Schiller-Uni-Jena as well as rRiboseph 96BMF02-01. In addition to the five studies, the submitted literature references

included a number of studies providing background information on bendamustine for the treatment of CLL.

None of the four additional studies submitted are considered to provide pivotal or supportive data for the proposed indication. Two studies (*Riboseph 99CLL.2E-BG* and *Riboseph 99CLL.2E-DE*) were Phase I/II, open-label, dose-finding studies designed to determine MTD and DLT of bendamustine in second-line treatment of patients with relapsed or refractory CLL. These two studies have been described above in this CER. Two studies (*Friedr-Schiller-Uni-Jena; Riboseph 96BMF02-01*) were Phase III, open-label studies comparing bendamustine in combination with methotrexate and 5-fluorouracil with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil for the treatment of metastatic breast cancer.

Evaluators summary of efficacy

Chronic lymphocytic leukaemia

The submission included one pivotal, multinational, multicentre, open-label, Phase III study (02CLLIII) supporting the application to register bendamustine for the first-line treatment of CLL (Binet stage B or C). The study included 319 treatment-naive patients with B-CLL (Binet Stage B or C) randomized sequentially to bendamustine 100 mg/m^2 administered by IV infusion over 30 minutes on Days 1 and 2 every 4 weeks (n=162), or chlorambucil 0.8 mg/kg (Broca's normal weight) administered Po on Days 1 and 15 or, if necessary given as divided doses on Days 1/2 and Days 15/16, every 4 weeks (n=157). All patients who received the study drug started at least 1 cycle and received up to 6 cycles. The proportion of patients in the safety population receiving treatment for 6 cycles was 64.0% (104/161) in the bendamustine arm and 62.9% (95/151) in the chlorambucil arm. The mean (SD) number of treatment cycles in both treatment arms was 4.9 (1.7).

The first primary efficacy endpoint was the overall response rate (ORR), and response included patients with CR plus PR plus Nodular Partial Remission (nPR). The response criteria were required to be met for at least 8 weeks. The ORR (ICRA assessment) was statistically significantly greater in the bendamustine arm than in the chlorambucil arm (67.9%, 110/162 versus 30.6%, 48/157, respectively; p<0.0001). The CR was notably greater in the bendamustine arm compared with the chlorambucil arm (30.9%, 50/162 versus 1.9%, 3/157, respectively), while the PR was similar in the two treatment arms (26.5%, 43/162 versus 26.1%, 41/157, respectively). The treatment effect (difference between the two treatment arms in the proportion of patients with overall response) was 37.3% (95% Confidence Interval (CI): 21.7%, 47.4%) in favour of the bendamustine arm, after adjusting for Binet stage. The ORR based on the investigator assessment (sensitivity analysis) was consistent with results of the ORR based on the primary ICRA analysis. The ORR was significantly greater in the bendamustine arm compared with the chlorambucil arm irrespective of whether patients were categorized as Binet stage B or C. Similarly, the benefit of bendamustine compared with chlorambucil as regards the ORR was observed in both male and female patients, and in patients aged < 65 years and ≥ 65 years.

The second primary efficacy endpoint was progression free survival (PFS), defined as the time from the date of randomization to the date of first PD, or relapse after intercurrent remission, or death from any cause. Median PFS (ICRA assessment) was 13.3 months longer in the bendamustine arm than in the chlorambucil arm (21.6 months [95% CI: 18.6, 31.0 months] versus 8.3 months [95% CI: 5.9, 11.3 months]; p<0.0001). According to Kaplan Meier (KM) estimates, the proportion of patients free of progression 12 months after randomization was notably greater in the bendamustine arm than in the chlorambucil arm (78.6% versus 34.9%, respectively). The Hazard ratio (HR) Chlorambucil (CLB)/BEN was 4.37 (95% CI: 3.14, 4.37), indicating that there was a

significant approximately 4.4 fold increased risk of experiencing an event in the chlorambucil arm compared with the bendamustine arm. PFS based on investigator assessment (sensitivity analysis) was consistent with PFS based on the primary ICRA analysis. Median PFS was longer in the bendamustine arm than in the chlorambucil arm irrespective of whether patients were categorized as Binet stage B or C, and there was no statistically significant difference between Binet B and C categories as regards the proportion of patients experiencing an event. Similarly, the PFS benefit of bendamustine compared with chlorambucil was observed in both male and female patients, and in patients aged < 65 years and aged ≥ 65 years.

The first primary efficacy endpoint (ORR) was tested first (two-sided p<0.0001<0.016 Pocock critical bound for a 5 stage sequential design). The first primary endpoint was analysed by the Cochran–Mantel–Haenszel (CMH) test stratified by Binet group for each individual sequence and combined using the inverse-phi method). As the p-value for the first primary efficacy was < 0.016, testing of the second primary efficacy (PFS) could proceed (two sided p< 0.0001< 0.016 Pocock critical bound for a 5 stage sequential design). The second primary endpoint was analysed by the log-rank test stratified by Binet stage for each individual sequence and combined using the inverse phi method. Based on the observed results for both primary efficacy endpoints, the null hypothesis was rejected as the final p values for both endpoints remained under the critical value of $\alpha_1 = 0.016$.

The secondary efficacy endpoints of time to progression and duration of remission both significantly favoured the bendamustine arm compared with the chlorambucil arm, and supported the results of two primary efficacy endpoint analyses. However, no significant difference in the secondary efficacy endpoint of overall survival (OS) between the bendamustine and the chlorambucil arms was observed, based on the data available at the cut-off date. The OS data showed no statistically significant difference between the bendamustine and chlorambucil arms (Hazard Ratio (HR) CLB/BEN = 1.45 (95% CI: 0.91, 2,31); p=0.1623). However, due to the immaturity of the OS data, the KM estimate of median duration of survival was available only for patients in the chlorambucil arm (65.4 months [95%: 55.1, NA months). A total of 72 patients died during the observational period, 31 (19.3%) in the bendamustine arm and 41 (26.1%) in the chlorambucil arm. As regards the secondary efficacy endpoint of quality of life, bendamustine did not provide a quality of life benefit compared with chlorambucil.

The limitations of the submitted efficacy data provided to support the registration of bendamustine for the first-line treatment of CLL (Binet stage B or C) are:

- The submission included only one pivotal Phase III study supporting registration of bendamustine for the proposed indication (02CLLIII). However, the results of this study were robust, with both primary efficacy endpoints (overall response and PFS) statistically significantly favouring bendamustine compared with chlorambucil. Support for the primary efficacy endpoints were provided by the secondary efficacy outcomes of time to progression and duration of remission but there was no evidence from the pivotal study that bendamustine provides an overall survival benefit or improves quality of life compared with chlorambucil. There is a TGA adopted EU guideline for submissions that include only one pivotal Phase III study supporting approval.[22] This guideline states that where confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling' and lists a number of criteria which 'the regulatory evaluation will need to consider'. In general, it is considered that the submitted pivotal Phase III study meet the criteria listed in the guideline. It is considered that the application to register bendamustine for CLL should not be precluded simply on the basis that only one pivotal study was submitted supporting the application,

[22] CPMP/EWP/2330/99 Points to consider on application with 1. Meta-analyses and 2. One pivotal study.

- The pivotal study (02CLLIII) was open-label in design and, consequently, is subject to the well-known biases associated with studies of this design. However, the two primary efficacy endpoints were assessed by independent evaluators (ICRA) blinded to treatment allocation. The results of the study were robust and the sensitivity analyses of the two primary efficacy endpoints supported the ICRA primary analyses of these endpoints. The subgroup analyses of the two primary efficacy endpoints supported the primary analyses of both endpoints. It is considered that the data should not be rejected due to the open-label design of the study.
- The patient population in the pivotal study (02CLLIII) was relative young and the majority of patients were categorised as WHO Performance Status (PS) 0. In Australia, it is likely that this patient population might have been offered combination treatment with fludarabine/cyclophosphamide/rituximab as first-line treatment for CLL rather than chlorambucil. The sponsor states that fludarabine was not approved as first-line treatment for CLL when the study was planned and that chlorambucil is still likely to be a first-line treatment option for elderly patients. In the EU, bendamustine is approved as first-line treatment for CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Overall, it is considered that registration of bendamustine as first-line treatment for CLL (Binet stage B or C) should not be precluded on the basis that a more appropriate control treatment arm might have been fludarabine combination chemotherapy. In addition, it is considered that the indication should not limit bendamustine to those patients for whom fludarabine combination chemotherapy is not appropriate.
- The pivotal study (02CLLIII) excluded patients older than 75 years, and the mean age (range) of patients in the Intention-to-Treat (ITT) population for bendamustine and chlorambucil was 63.0 years (47, 77 years) and 63.6 (35, 78 years). Consequently, the study population is younger than Australian patients with CLL for whom bendamustine might be a treatment option. Reassurance concerning the efficacy of bendamustine in older patients comes from the subgroup analyses of the two primary efficacy endpoints (ORR and PFS) showing that treatment with bendamustine was significantly superior compared with treatment with chlorambucil independent of age (< 65 years, ≥ 65 years). However, there were no efficacy data on patients aged ≥ 75 years and the availability of such data from the pivotal study are likely to be negligible, given that patients > 75 years were excluded and the upper age range for the total population was 77 years. It is considered that the lack of efficacy data in patients aged ≥ 75 years is a deficiency in the submission but should not preclude registration of bendamustine for the CLL indication.
- In the pivotal study (02CLLIII), no significant difference in OS between the bendamustine and the chlorambucil arm was observed. While a significant difference between the two treatment arms might emerge following a longer period of follow-up, future assessment of OS will be confounded by the high proportion of patients receiving other antineoplastic therapy after the last dose of the study drug. In the follow-up analysis (safety population), 79 (49%) patients in the bendamustine arm received antineoplastic therapy after the last dose of the study drug compared with 99 (63%) patients in the chlorambucil arm. Of particular note, 41 (27.2%) patients in the chlorambucil arm received bendamustine as a single agent, and 5 (3.1%) patients received bendamustine in combination with other agents. It is considered that the absence of data demonstrating an OS benefit for patients treated with bendamustine should not preclude registration of the drug for the CLL indication.
- In the pivotal study (02CLLIII), the second primary efficacy endpoint of PFS was defined as the time from randomization to progression, relapse, or death. In the submitted data, while the total number of patients with PFS events could be identified, the number of patients with each of the three events contributing to the total number

could not be clearly identified. While this deficiency should not preclude registration, the sponsor should provide this data for evaluation as part of the second round assessment procedure.

Relapsed/refractory indolent NHL

The submission is considered to include one, pivotal Phase III study (SDX-105-03). In this study, 100 patients in the primary analysis set aged at least 18 years with indolent B-cell NHL refractory to rituximab were evaluable for efficacy. Patients were considered to be refractory to rituximab if the disease had progressed during treatment (that is, no response) or within 6 months of treatment (that is, time to progression < 6 months) with rituximab or a rituximab-containing regimen. Patients were treated with bendamustine 120 mg/m^2 via IV infusion over 30 to 60 minutes on days 1 and 2 every 3 weeks for at 6 least cycles (that is, consistent with the proposed regimen), and could receive a further 2 cycles up to a maximum of 8 cycles based on continued clinical benefit. Follow-up of each patient was to progression of disease, death, start of a new anti-cancer therapy, or up to 2 years from the last dose of bendamustine.

The pivotal study was single-arm and open-label. Consequently, it is subject to the well-known biases associated with studies of this design. However, all patients in the treated population (n=100) had disease that was refractory to rituximab and nearly all (99%) of the treated population had been previously treated with chemotherapy (92% ≤ 3 prior courses, 8% > 3 prior courses). In addition, 25% of patients had received previous radio-immunotherapy, 20% had received previous radiation therapy and 8% had undergone cancer surgery. Therefore, in this heavily pre-treated patient population with indolent NHL refractory to rituximab it can be reasonably inferred that significant benefits following treatment with single arm bendamustine are likely to be due to the drug rather than to chance alone. Furthermore, there appears to be no 'gold-standard' active control treatment that could have reasonably been used as a comparator for monotherapy bendamustine in this patient population.

The sponsor claims that tumour regression following bendamustine monotherapy in the pivotal study in patients with refractory NHL can be attributed to active treatment with the drug. Consequently, ORR (CR, Complete Response Unconfirmed (Cru) or PR) can be considered to be a satisfactory outcome measure of efficacy in the context of this single-agent therapy study in this patient population. The sponsor considered that it was not scientifically necessary for the pivotal study to include a comparison group in order to determine the anti-tumour effect and clinical benefit of bendamustine monotherapy, as the occurrence of a high response rate with a durable response would reflect patient benefit due to bendamustine treatment regimen. The sponsor stated that its view relating to a single-arm study is consistent with the FDA guidance for industry document concerning clinical trial endpoints for the approval of cancer drugs and biologicals published in 2007, and with agreements between the FDA and sponsor regarding the pivotal study. The sponsor stated that the FDA advised that a single-arm study in the absence of a randomized trial against approved therapy in a rituximab-refractory patient population might be sufficient for approval if the clinical results were convincing. It is noted that the FDA has approved an indication for indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen based on the single pivotal study (SDX-105-01) (CDER, application number 22-203, Summary Review).

The results for the primary efficacy endpoints of ORR (IRC assessment) of 75% (95% CI: 65%, 83%; p<0.0001) and median DR (IRC assessment) of 40 weeks (95% CI: 31, 47 weeks) are statistically significantly greater than the protocol defined measures of minimal meaningful clinical efficacy (that is, null hypothesis of less than 40% for ORR and less than 4 months [17 weeks] for DR). The median DR for patients with CR, CRu, and PR

was 45, 59, and 36 weeks, respectively, showing that response was durable for patients with each of the response outcomes contributing to the overall response. The results for the ORR and DR observed in the primary analysis (IRC assessment) were consistent with the results in the subgroup analyses (IRC assessment) for these two endpoints based on baseline disease characteristics. In addition, the results for the primary analyses of the ORR and DR based on IRC assessments and investigator assessments were consistent.

Treatment with bendamustine in patients refractory to prior alkylator and prior chemotherapy therapy resulted in meaningful improvements in ORR and DR. In patients with disease refractory to prior alkylator therapy the ORR was 60% (18/30 patients) (95% CI: 41%, 77%) and in patients with disease refractory to the last prior chemotherapy regimen the ORR was 64% (23/36 patients) (95% CI: 46%, 79%). In patients with disease refractory to prior alkylator therapy the median DR was 33.3 weeks (95% CI: 21.4, NA weeks), and in patients with disease refractory to the last prior chemotherapy regimen the median DR was 27.3 weeks (95% CI: 214, NA weeks).

In the pivotal study, the median PFS (secondary efficacy endpoint) based on IRC assessment was 40.3 weeks (95% CI: 35.0, 41.9 weeks), and was primarily driven by disease progression (47 patients) followed by death (5 patients) and change of therapy (5 patients). PFS was 51, 65, and 42 weeks for patients with CR, CRu, and PR, respectively. Meaningful improvement in PFS was seen in all subgroups based on baseline disease characteristics.

Support for the pivotal study was provided by the results from an exploratory Phase II, multicentre, open-label, single-arm study in patients with indolent or transformed B-cell NHL refractory to rituximab (SDX-105-01). This study was of similar design to the pivotal study and was undertaken prior to that study. The bendamustine treatment regimen in this study was identical to the pivotal study (SDX-105-03). Of the 76 patients included in this study, 61 (80%) had indolent NHL (predominantly follicular lymphoma, 46 patients) and 15 (20%) patients had transformed NHL (predominantly follicular lymphoma, 11 patients).

In Study SDX-105-01, all 76 patients in the primary analysis set had received previous rituximab containing regimens and their lymphoma was deemed refractory to rituximab treatment. The median and mean number of previous rituximab-containing courses was 2, ranging from 1 to 4. In this study, a patient could have been refractory to rituximab treatment in a previous single agent or combination regimen but have responded to a subsequent rituximab-containing regimen and have been included in the study. Consequently, 23 (30%) of the patients included in the study had responded to their most recent rituximab regimen. When the worst response to any rituximab containing regimen was assessed, 53 (70%) patients treated with a rituximab containing regimen showed stable disease or disease progression. Of the 23 patients with a CR, PR or unknown as their worst response, 10 patients had an interval of less than 180 days between the last dose of rituximab and disease progression or recurrence. Six (6) patients had an interval of less than 180 days between the last dose of rituximab and the first dose of a subsequent regimen or bendamustine, consistent with an early relapse, and for 7 patients the rituximab-refractory status of their lymphoma was unclear.

In the primary analysis set of Study SDX-105-01 (n=76), the ORR was 76.3% (95% CI: 65.2%, 85.3%). Of the 76 patients in the primary analysis set, 58 (76%) achieved a response (11, 14%, CR; 14, 18%, CRu; 33, 43%, PR), while SD was reported in 3 (4%) and PD in 13 (17%) with missing/unknown results for 2 (3%). The lower bound 95% CI of the ORR was > 35%, and in this study bendamustine was considered to be a promising treatment for the proposed indication if the pre-specified true overall response rate was ≥ 35%.

The median DR for patients with a response (CR, CRu or PR) in Study SDX-105-01 was 29.0 weeks (95% CI: 22.1, 43.1 weeks), based on 38 patients with a response and 20 censored patients out of the 58 patients in the analysis. The median PFS for all patients in the primary analysis was 31.0 weeks (95% CI: 26.1, 38.7 weeks), based on 55 patients with an event and 21 censored patients out of the 76 patients in the analysis. The KM estimate of the proportion of patients in the primary analysis set remaining progression-free after 48 weeks was 21%.

In Study SDX-105-01, the ORR was 66.67% (95% CI: 38.3%, 88.18%) in patients with transformed disease (that is, 10 patients out of 15, including Cr = 0, Cru = 2, and PR = 8), and 78.69% (95% CI: 66.32%, 88.1%) in patients without transformed disease (that is, 48 patients out of 61, including Cr = 11, CRu = 12, PR =25).

There were no survival data from Study SDX-105-03 (pivotal) or Study SDX-105-01 (exploratory/supportive) for patients with indolent NHL refractory to rituximab. However, survival benefit in this patient population is likely to be particularly difficult to show. Consequently, the results for the ORR based on CR, CRu, or PR and the durability of response (DR) in this patient population demonstrated in both the pivotal and exploratory/supportive studies are considered to be clinically meaningful.

Studies SDX-105-02 and 93BOP01 were both nominated by the sponsor as being pivotal for the proposed indication. However, both studies are considered to be neither pivotal nor supportive for the proposed indication of relapsed/refractory indolent NHL. Both studies included bendamustine in combination with other agents rather than as monotherapy and in both studies patients were not required to be refractory to treatment with rituximab. Furthermore, in Study 93BOP01 patients were included only if they had received no prior chemotherapy or radiotherapy.

First-line treatment of indolent NHL and mantle-cell lymphoma

The submission included the results from one pivotal Phase III study supporting the application to register bendamustine in combination with rituximab for the first-line treatment of indolent NHL and MCL in patients with stage III/IV CD20 positive disease.[15] The pivotal study was undertaken in multiple centres in Germany (81 centres) and 274 patients were randomized to open-label treatment with bendamustine-rituximab (B-R) (261 analysed) and 275 patients randomized to open-label treatment with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone (R-CHOP) (275 analysed). The two treatments were administered for up to a maximum of 6 cycles. Neither treatment arm was followed by maintenance or consolidation therapy.

The study was designed to show that B-R was non-inferior to R-CHOP, based on PFS (investigator assessment). The median time to follow-up was 45 months (interquartile range (IQR): 25, 75). PFS (primary efficacy endpoint) was significantly longer in the B-R arm than in the R-CHOP arm (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001), with the median PFS being approximately 38 months longer in the B-R arm than in the R-CHOP arm (69.5 months [IQR: 26.1, NR] versus 31.2 months [IQR: 15.2, 65.7], respectively). The results indicate that B-R is non-inferior to R-CHOP, based on PFS, as the HR for this endpoint was ≤ 1.32.

In a pre-planned analysis, PFS was significantly improved in patients treated with B-R compared with R-CHOP for histological subtypes of follicular lymphoma (p=0.0072), MCL (p=0.0044) and Waldenstrom's macroglobulinaemia (p=0.0033), but not for marginal-zone lymphoma (p=0.3249). In exploratory subgroup analyses, clinically significant improvement in PFS in the B-R arm compared with the R-CHOP arm was found to be independent of age (≤ 60 and > 60 years) and FLIPI subgroup (favourable and unfavourable risk. In a multivariate analysis with backward selection, mantle-cell histology and LDH concentrations greater than 240 IU/L were independent predictors of

poor PFS outcome. However, in this adjusted analysis treatment B-R still showed a significant PFS benefit compared with R-CHOP (HR = 0.56 [95% CI: 0.43, 0.72]; p<0.0001) and the results were similar to the unadjusted analysis (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001).

The secondary efficacy endpoints of ORR (CR + PR) were similar for the two treatment arms, while the CR rate significantly favoured B-R compared with R-CHOP. The secondary efficacy endpoint of Time to Next Treatment (TTNT) significantly favoured the B-R arm compared with the R-CHOP arm but the median TTNT had not been reached in the B-R arm at the date of the data cut-off. No differences were observed in OS between the B-R arm and the R-CHOP arm (43 versus 45 deaths) and median OS had not been reached at the date of the data cut-off for the analysis.

Overall, *Rummel et al 2013*[15] is considered to show that first-line induction treatment with B-R is non-inferior to R-CHOP as regards PFS in patients with CD20 positive Stage III or IV indolent NHL and MCL. However, no follow-up maintenance therapy was administered to patients responding to induction treatment with B-R. It is noted (Rummel et al., 2013) that there is an ongoing study comparing the effects of rituximab maintenance therapy (every 2 months for 2 or 4 years) in patients who initially respond (CR or PR) to B-R induction (StiL study MAINTAIN). However, this study includes only rituximab treatment arms (2 and 4 years) and no 'observation only' comparator treatment arm. Rituximab maintenance therapy for up to a maximum of 2 years is approved in Australia for patients with follicular NHL lymphoma who have responded to an R-CHOP induction regimen and data show that maintenance treatment for this period significantly improves PFS compared with observation.

The limitations of the submitted data supporting the proposed indication are:

- The absence of efficacy data establishing that rituximab can maintain efficacy in patients achieving a response to induction treatment with B-R is considered to be a significant limitation of the submitted data. It is currently unknown whether the significant PFS benefit seen with B-R induction therapy will be maintained, with or without subsequent maintenance treatment with rituximab.
- No randomized, controlled, double-blind data supporting the proposed indication. However, given the difference between the two treatment regimens it would be difficult to implement a double-blind study comparing the two treatments. Furthermore, the study was well designed and the results showing that B-R was at least non-inferior to R-CHOP were statistically robust.
- Treatment outcomes were determined by investigators using WHO criteria for response. In order to reduce bias associated with subjective differences in investigator assessment it would have been preferable to have used a small number of centralized independent assessors blinded to treatment allocation.
- The data supporting the proposed indication (Rummel et al 2013)[15] included patients from only one country (Germany), although 81 centres were involved. This limits the generalizability of the study results to other patient populations. Furthermore, no data could be identified in the pivotal study describing the racial background of the study population. Despite these limitations, the results in the study population are likely to be generalizable to the Australian population.
- The data supporting the proposed indication included only one pivotal study (Rummel et al 2013). However, there is a TGA adopted EU guideline for submissions that include only one pivotal Phase III study supporting approval.[22] This guideline states that where confirmatory evidence is provided by one pivotal study only, this study will have to be 'exceptionally compelling' and lists a number of criteria to which the 'regulatory evaluation will need to consider'. In general, it is considered that the

efficacy data from the submitted pivotal Phase III study meets the criteria listed in the guideline.

Safety

Studies providing safety data

Studies 02CLIII, SDX-105-103, SDX-105-101 and a published paper Rummel et al 2013[24] provided safety data for this submission.

Patient exposure

See Attachment 2, sections 7.1.1 and 7.2.1.

Provided postmarketing data

The postmarketing data included two periodic safety update reports in ICH format for bendamustine covering the periods 1 April 2007 through to 6 July 2010 (Periodic Update Safety Report (PSUR) 1), and 7 July 2010 to 7 July to 6 January 2011 (PSUR 2). In addition, the postmarketing data included a document written in German dated 11/1998 which appears to be a postmarketing report, a PSUR identified as number 1 (Bulgaria) for the period 1 January 1994 to 30 April 2004 and an Overall Safety Update Report (SUR) for the period 1 January 1994 to 31 March 2007 that appears to have been prepared for the EU decentralized evaluation procedure. The postmarketing data from the two PSURs in ICH format have been reviewed.

PSUR1 and PSUR2 - ICH format

The PSUR/ICH format documents indicate that the international birth date (IBD) of bendamustine HCl is 10 November 1971 in the former German Democratic Republic. In addition, the documents indicate that by European Commission Decision of 7 July 2010, bendamustine as powder for concentrate for solution for infusion was recommended for approval in EU Member States.

PSUR2 states that the formulation for IV administration is currently approved in 17 countries and marketed in 14 countries. The PSUR also indicates that a new oral formulation (liquid filled hard capsules, containing 55.10 mg bendamustine per capsule) is being investigated.

PSUR2 indicates that cumulative market exposure to bendamustine since 1994 has been approximately 104,375 patients (42,974 exposed to 100 mg/m^2/day and 61,401 exposed to 120 mg/m^2/day). No sales data are available for the time period from 1971 to 1994.

In Europe, estimated postmarketing exposure from 2007 through to 2010 was 9,594 CLL patients, 8,934 NHL patients, 5,294 MM patients, and 9,265 other patients. In the USA, estimated postmarketing exposure from 2008 through to 2012 was 14,300 CLL patients and 16,200 NHL patients.

PSUR2 indicates that Astellas has received 1,471 medically confirmed cases describing adverse events since 1 April 2007 through to 6 January 2011 (1,071 in PSUR1 plus 401 in PSUR2).

In PSUR2, the following events of interest requiring monitoring were identified (same as PSUR1):

- Secondary malignancies
- Steven-Johnson syndrome/Toxic epidermal necrolysis

- Opportunistic infections
- Cardiac events
- Hepatic events
- Renal events
- Pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain), which the sponsor considered to be possibly due to silicon oil contamination and required temporarily monitoring until all batches contaminated with silicon oil have expired.

Evaluator's conclusions on safety

Chronic lymphocytic leukaemia

In the pivotal study (02CLLIII), the safety population included 161 patients in the bendamustine arm and 151 patients in the chlorambucil arm. Based on the 'rule of three', the upper limit of the 95% CI for the rate of adverse reactions associated with bendamustine is approximately 2%. Consequently, it is unlikely that adverse reactions associated with bendamustine occurring with an incidence of < 2% have been detected in the pivotal study. The mean (SD) number of treatment cycles in each arm was identical at 4.9 (1.7) cycles, as was the range of treatment cycles (1-6). The mean (SD) relative dose per cycle was 89.4% (21.0%) in the bendamustine arm and 94.7% (20.8%) in the chlorambucil arm. The difference in the planned dose between the two treatment arms reflects the higher percentage of dose reductions due to toxicity in the bendamustine arm than in the chlorambucil arm (33.5% versus 30.5%). The median observation time in patients at the time of the follow-up analysis was 35 months (range: 1, 68).[23]

Overall, the safety profile of bendamustine for the treatment of CLL was notably inferior to that of chlorambucil. In the bendamustine arm, 88.8% (n=143) of patients experienced at least one adverse event (AE) (660 events) compared with 80.8% (n=122) of patients in the chlorambucil arm (385 events) and the majority of AEs in both treatment arms were considered to be treatment-related or to have missing causality information (82.0%, 132 patients, 471 events versus 64.2%, 97 patients, 225 events, respectively).

Severe AEs (Grade 3 or 4 CTC/Cheson) occurred more frequently in patients in the bendamustine arm than in the chlorambucil arm (52.8%, 85 patients, 175 events versus 31.1%, 47 patients, 72 events) and both severe haematological AEs and severe non-haematological AEs occurred notably more commonly in the bendamustine arm than in the chlorambucil arm.

Severe haematological AEs (Grade 3 or 4 CTC/Cheson) were reported in 40.4% (n=65) patients in the bendamustine arm and 19.2% (n=40.4%) of patients in the chlorambucil arm. The most commonly reported severe haematological AE (Grade 3 or 4 CTC/Cheson) in both the bendamustine and chlorambucil treatment arms was neutropenia, including granulocytopenia (23.0%, 37 patients versus 10.6%, 16 patients, respectively). Severe infections (Grade 3 or 4 CTC/Cheson) were reported notably more commonly in the bendamustine arm than in chlorambucil arm (8.7%, 14 patients versus 3.3%, 5 patients), and severe allergic reactions (Grade 3 or 4 CTC/Cheson) occurred more commonly in the bendamustine than in the chlorambucil arm (5.6%, 9 patients versus 5, 3.3%).

Serious adverse events (other than death) occurred more frequently in patients in the bendamustine arm than in the chlorambucil arm (19.3%, 31 patients, 38 events versus

[23] Knauf W et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009; 27:4378-4384.

12.6%, 19 patients, 22 events), and there were 31 (19.3%) deaths in the bendamustine arm and 41 (27.2%) deaths in the chlorambucil arm.

Withdrawals due to unacceptable toxicity or risk/benefit assessment occurred notably more frequently in the bendamustine arm than in the chlorambucil arm (11.2%, 18 patients versus 3.3%, 5 patients), while dose modifications due to AEs occurred in a similar proportion of patients in the two treatment arms (33.5%, 54 patients versus 30.5%, 46 patients, respectively).

The changes in haematology laboratory parameters have been discussed above. There were no marked differences between the two treatment arms in clinical chemistry laboratory changes or urinalysis changes over the course of the study. There were no notable differences between the two treatment arms relating to vital signs of changes from baseline in weight, BSA, blood pressure, pulse rate or temperature. There were not notable changes in WHO PS over the course of the study in the two treatment arms. ECG changes remained largely unchanged over the course of the study in both treatment arms, but no systematic assessment of changes in the QT interval were undertaken.

Refractory/relapsed indolent NHL

The safety of bendamustine for the treatment of indolent NHL refractory to rituximab has been assessed in 176 patients (100 patients in the pivotal Study SDX-105-03 and 76 patients in the supportive Study SDX-105-01). The safety assessment is based on open-label bendamustine data. Consequently, the interpretation of the data is limited due to the absence of a control group. However, selection of an appropriate control treatment would have been problematic in this population of heavily pre-treated patients with indolent relapsed/refractory NHL.

In the pivotal study (n=100), the median number of treatment cycles was 6 and the mean relative dose intensity was 88%, and in the supportive study (n=76) the median number of treatment cycles was 5 and the mean relative dose intensity was 87%. The safety profile of bendamustine was similar in both studies and was consistent with the safety profile of the drug in patients with CLL. In the total population (n=176), all patients experienced at least one AE and nearly all of these events (96%) were considered to be treatment-related.

In the pivotal study (n=100), the median cycle length was 22.4 days and 68% (n=68) of patients had dose reductions or delays or did not receive both doses in the cycle at some point during the course of treatment. In the supportive study (n=76), the median cycle length was 23.1 days and 61% (n=46) of patients had dose reductions or delays or did not receive both doses in the cycle at some during the course of treatment.

The major safety concern with the use of bendamustine in patients with relapsed/refractory indolent NHL relate to haematological toxicity. In the total population, 'blood and lymphatic disorders' (System Organ Class (SOC)) occurred in 62% (109/176) of patients. Haematological AEs reported in ≥ 20 % of patients in the total population were neutropenia (38%), anaemia (35%) and thrombocytopenia (31%). Of note, Grade 3 or 4 haematological AEs occurring in ≥ 10% of patients in the total population were neutropenia (32%), thrombocytopenia (24%) and anaemia (12%). The serious adverse event (SAE) of febrile neutropenia was reported in 5% (n=9) of patients in the total population, while the SAEs of anaemia and neutropenia were reported in 3% (n=5) and 2% (n=3) of patients, respectively.

In both the pivotal and supportive studies, haematological AEs were the most commonly reported events leading to discontinuation of study drug treatment. In the pivotal study, discontinuations of study drug treatment due to thrombocytopenia occurred in 9% (n=9) of patients, followed by neutropenia in 4% (n=4). In the supportive study, discontinuations of study drug treatment due to thrombocytopenia occurred in 17% (n=13) of patients followed by neutropenia and anaemia in 7% (n=5) and 3% (n=2),

respectively. In the pivotal study, dose delays occurred in 30% (n=30) of patients due to neutropenia and 19% (n=19) of patients due to thrombocytopenia.

In the pivotal study, haematology laboratory test results showed that lymphopenia was the most commonly observed abnormality associated with worst case Grade 3 or 4 CTCAEs over all treatment cycles (419 [82%] of 513 patient-cycles), with most patients experiencing worst Grade 3 or 4 lymphopenia following bendamustine (97% [94/97]). Neutropenia worst Grade 3 or 4 CTCAE was observed in 20% (104/513) of patient-cycles, with 63% (61/97) of patients experiencing worst Grade 3 or 4 neutropenia following bendamustine. Overall, thrombocytopenia worst Grade 3 or 4 CTCAE was observed in 8% (41/531) of patient-cycles and 25% (25/100) of patients, while anaemia worst Grade 3 or 4 CTCAE was observed in 4% (19/531) of patient-cycles and 10% (10/100) of patients. The haematology laboratory results for the supportive study were consistent with those for the pivotal study.

Of the non-haematological AEs, those occurring in ≥ 20% of patients in the total population (n=176) were nausea (75%), fatigue (57%), vomiting (40%), diarrhoea (37%), pyrexia (34%), constipation (29%), anorexia (23%), cough (22%), and headache (21%). Non-haematological Grade 3 or 4 AEs occurred in 53% of patients, and Grade 3 or 4 AEs reported in ≥ 2% of patients were fatigue (11%), febrile neutropenia (6%), pneumonia (5%), dehydration (5%), hypokalaemia (5%), nausea (4%), vomiting (3%), diarrhoea (3%), herpes zoster (3%), back pain (3%), pyrexia (2%), asthenia (2%), urinary tract infection (2%), weight decreased (2%), anorexia (2%) and dyspnoea (2%).

In the pivotal study, SAEs occurred in 39 (39%) patients including death in 11 (11%) patients, while in the supportive study SAEs occurred in 26 (34%) of patients including death in 3 (4%) patients. In the pivotal study, the most common SAEs occurring in ≥ 5% of patients were febrile neutropenia (6%, 6 patients), and pneumonia (5%, 5 patients). In the supportive study, SAEs occurring in 4% of patients were anaemia (5%, 4 patients), and febrile neutropenia, pneumonia, and dehydration each occurring in 4% (3 patients) of patients.

In the pivotal study, 31 (31%) patients discontinued study drug treatment due to AEs and 27 (27%) of these patients discontinued treatment due to drug-related AEs. Discontinuations of study drug treatment due to AEs reported in ≥ 2 patients were reported for thrombocytopenia (9 [9%] patients), fatigue (6 [6%] patients) and neutropenia (4 [4%] patients). In the supportive study, 30 (39%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs in ≥ 2 patients were thrombocytopenia (13 [17%] patients), neutropenia (5 [7%] patients) and anaemia (2 [3%] patients).

Clinical chemistry laboratory abnormalities observed during both the supportive and pivotal studies do not give rise to concern. Similarly, changes in the vital signs of pulse rate, blood pressure, temperature and weight gain do not give rise to concern. However, weight loss over the course of treatment was observed in a notable proportion of patients in both the pivotal and supportive studies. There appears to have been only a small number of patients with clinically abnormal ECG recordings the pivotal and supportive studies but there was no systematic assessment of QT interval changes in either study.

First-line indolent NHL and MCL

The safety data for the proposed first-line treatment of indolent NHL and MCL are from one study *Rummel et al.,* 2013. The safety data from this study includes information on 267 patients who received at least one 'dose' of B-R and 252 patients who received at least one 'dose' of R-CHOP. It was not clear whether the one 'dose' referred to one cycle. The

safety data from *Rummel et al (2013)*[24] showed that B-R was generally better tolerated than R-CHOP. However, while the data are promising it is considered that they are not sufficient to make a definitive assessment of the safety of B-R for the proposed indication.

In order for a definitive assessment of the safety of B-R for the proposed indication to be made the sponsor should provide conventional safety data included in a CSR. Evaluation of conventional safety data is considered to be particularly important for the proposed indication, given that B-R has not been approved in any country for first-line treatment of indolent NHL or MCL in treatment-naive patients. Consequently, there are no safety data based on extensive overseas experience with the B-R combination for the proposed indication that would support approval in the absence of conventional safety data.

The limitations of the submitted safety data include:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle. The extent of exposure in the two treatment groups needs to be known in order to meaningfully compare their safety profiles. Significant imbalance in the extent of exposure between two treatment groups might complicate interpretation of the safety data.
- No data on the proportion of patients requiring dose modifications due to AEs, or on the nature of the AEs resulting in dose modifications. Data on dose modifications include patients requiring downward dose adjustments because of toxicity and patients requiring temporary treatment discontinuations due to toxicity. Significant imbalance in dose modification data between the two treatment groups might impact on benefit-risk assessment.
- No data on the total number of AEs experienced by patients in the two treatment groups (overall and individual events). Significant imbalance in the number of clinically significant AEs between the two treatment groups might impact on benefit-risk assessment.
- No data on the incidence of AEs by treatment cycle.
- No data on AEs that were considered to be treatment-related.
- No data on conventional defined serious adverse events (that is, fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalisation, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological) but no case narratives of the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing SAEs were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (that is, causes of death and case narratives). Significant imbalance in the nature of the deaths between the two treatment groups might impact on benefit-risk assessment.
- No data on permanent treatment discontinuation of the study-drugs due to AEs. Significant imbalance in permanent treatment discontinuation between the two treatment groups might impact on benefit-risk assessment.

[24]Rummel MJ et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle cell lymphomas: and open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet published on-line February 2013. <http://dx.doi.org/10.1016/S0140-6736(12)61763-2>.

- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists or transfusions with blood products for anaemia or thrombocytopenia.
- No data on changes in vital signs or the ECG during the course of the study were provided.
- No data safety data based on age differences (e.g., ≥ 65 years versus < 65 years).

First round benefit-risk assessment

First round assessment of benefits

Chronic lymphocytic leukaemia

It is considered that the pivotal study (02CLLIII) has satisfactorily demonstrated that the benefits of bendamustine (n=162) for the treatment of patients with CLL (Binet stage B or C) at the dose proposed for registration were significantly superior to chlorambucil (n=157). The duration of treatment depended on response. Patients with complete or partial remission received two consolidation cycles with a maximum of 6 cycles. Patients with no change in their disease status received at least 3 cycles. Patients in whom the disease progressed discontinued study treatment. The benefits described below relate to the outcome assessments undertaken by the ICRA.

The overall response rate (ORR = CR+PR=nPR) was significantly greater in patients treated with bendamustine compared with chlorambucil (67.9% versus 30.6%, respectively, p<0.0001). The treatment effect (difference in ORR between the two treatment arms) significantly favoured patients treated with bendamustine compared with chlorambucil (37.3% [95% CI: 21.7%, 47.4%]; p<0.001), after adjusting for Binet stage. The treatment effect in favour of bendamustine was also seen in patients with CLL Binet stage B or C, and was similar in the two stages (36.5% and 39.1%, respectively). The CR was notably greater in patients treated with bendamustine compared with chlorambucil (30.9% versus 1.9%, respectively). The benefits of bendamustine were also observed in both male and female patients and patients < 65 years of age and ≥ 65 years of age (with no data on patients > 75 years of age).

The median duration of progression free survival was 13.3 months longer in bendamustine treated patients compared with chlorambucil treated patients (21.6 months [95% CI: 18.6, 31.0 months] versus 8.3 months [95% CI: 5.9, 11.3 months]; p<0.0001). According to KM estimates, the proportion of patients free of progression 12 months after randomization was notably greater in the bendamustine arm than in the chlorambucil arm (78.6% versus 34.9%, respectively). The HR Chlorambucil (CLB)/ Bendamustine (BEN) was 4.37 (95% CI: 3.14, 4.37), indicating that patients treated with chlorambucil had a 4.4 fold significantly increased risk of experiencing an event compared with patients in the bendamustine arm. The benefits of bendamustine compared with chlorambucil relating to PFS were also observed in patients with CLL Binet stage B or C, both male and female patients and patients < 65 years of age and ≥ 65 years of age (with no data on patients > 75 years of age).

The median time to progression from the start of therapy to PD, or relapse after intercurrent remission or CLL related death was 15.6 months greater in bendamustine treated patients compared with chlorambucil treated patients (23.9 months [95% CI: 20.7, 31.5 months] versus 8.3 months [95% CI: 6.0, 11.4 months]; p<0.0001). According to KM estimates, 81.2% of patients in the bendamustine arm and 35.4% of patients in the chlorambucil arm were free of progression 12 months after randomization. The HR CLB/BEN was 4.70 (95% CI: 3.36, 6.58), indicating that patients treated with chlorambucil

had a significantly increased risk (4.7 fold) of experiencing an event compared with patients in the bendamustine arm.

The median duration of overall response from the time of maximum response (CR, nPR, PR) to PD or death was 13.8 months longer in patients treated with bendamustine compared with chlorambucil (21 months [95% CI: 17.4, 27.0 months] versus 8.0 [95% CI: 6.3, 9.3], respectively, p<0.0001). According to KM estimates, 75.6% of patients in the bendamustine arm and 24.1% of patients in the chlorambucil group were still responding 12 months after randomization. The HR CLB/BEN was 4.46 (95% CI: 2.89, 6.88), indicating that patients treated with chlorambucil had a 4.5-fold significantly increased risk of experiencing an event compared with patients in the bendamustine arm.

For patients treated with bendamustine compared with chlorambucil, the median duration of CR was 21.3 months longer (29.3 versus 8.0 months), the median duration of nPR was 7.7 months longer (18.6 versus 10.9 months), and the median PT was 10.9 months longer (17.4 versus 6.5 months).

Patients treated with bendamustine did not demonstrate a significant overall survival benefit compared with patients treated with chlorambucil, with no marked differences between the two treatment arms being observed at the date of data cut-off for the analysis. Patients treated with bendamustine did not demonstrate a significant improvement in quality of life compared with patients treated with chlorambucil, with no marked differences between the two treatment arms being observed in these parameters in the third interim analysis.

Relapsed/refractory indolent NHL

The benefits of bendamustine as monotherapy for the treatment of indolent B-cell NHL refractory to rituximab have been satisfactorily demonstrated in one pivotal Phase III study (SDX-105-03) in 100 patients. Limited supportive efficacy data is provided by the Phase II study (SDX-105-01) in 76 patients. However, it should be noted that the Phase II study included 15 (20%) patients with transformed NHL rather than indolent NHL and 23 (30%) patients had responded to their most recent rituximab-regimen while 8 (11%) patients had an unknown response to this regimen.

The bendamustine regimen used in the both the pivotal and supportive studies was 120 mg/m^2 on days 1 and 2 every 3 weeks for at least 6 cycles and this is the dosage regimen being proposed by the sponsor for the treatment of indolent NHLs refractory to rituximab. In both the pivotal and supportive studies, the benefits of bendamustine were demonstrated in open-label, single-dose studies. However, in heavily pre-treated patients with indolent NHL refractory to rituximab and/or chemotherapy it is reasonable to infer that the benefits seen with bendamustine as monotherapy relate to the effects of the drug on the disease.

In the pivotal study, the ORR and the DR were co-primary efficacy endpoints and the results for both endpoints were required to be statistically significant in order for the study to have established a treatment benefit for bendamustine. PFS in this study was a secondary efficacy endpoint.

In the pivotal study, the ORR (IRC assessment) in the primary analysis set (n=100) was 75% (95% CI: 65%, 83%) and was statistically significant (p<0.0001) as the ORR was ≥ 40%. It had been pre-specified that the null hypothesis was to be rejected if the ORR was ≥ 40%. It is noted that both the point estimate for the ORR and the lower bound 95% CI of the estimate are well above 40%. The ORR was based on the best-response of CR, CRu or PR. Overall response was achieved by 75 out of the 100 patients in the primary analysis set, and included 14 (14%) patients with CR, 3 (3%) patients with CRu and 58 (58%) patients with PR. In the 25 (25%) patients in the primary analysis set not meeting the

response criteria for inclusion in the ORR analysis, 16 (16%) had SD, 7 (7%) had PD and 2 (2%) had an unknown response.

In the pivotal study, the median DR (IRC assessment) in the primary analysis set with a best overall response of CR, CRu, or PR was 40.1 weeks (95% CI: 31.0, 46.9 weeks), based on 39 (52%) patients with PD/death/change of therapy and 36 (48%) censored patients out of a total of 75 patients included in the analysis. The results were significant as it had been pre-specified that the null hypothesis was to be rejected if the median DR was > 6 months (26 weeks) and the lower bound 95% CI was > 4 months (17 weeks). Patients who responded had durable responses (medians of 45, 59, and 36 weeks for patients with CR, CRu, and PR, respectively).

In the pivotal study, the median PFS (IRC assessment) in all patients in the primary analysis set was 40.3 weeks (95% CI: 35.0, 51.9), based on 57 (57%) patients with PD/death/change of therapy and 43 (43%) censored patients out of a total of 100 patients in the analysis. The analysis was primarily driven by disease progression (47 patients) followed by death (5 patients) and change of therapy (5 patients).

In the supportive study (SDX-105-01), the ORR (investigator assessment) in the primary analysis set (n=76) was 76.3% (95% CI: 65.2%, 85.3%). It had been pre-specified that bendamustine was considered to be 'promising' if the ORR was 35% or higher. Of the 76 patients in the primary analysis set, 58 (76%) achieved a response (11, 14%, CR; 14, 18%, CRu; 33, 43%, PR).

The ORR was 67% (95% CI: 38%, 88%) in patients with transformed disease (that is, 10 patients out of 15, including Cr = 0, Cru = 2, and PR = 8), and 79% (95% CI: 66%, 88%) in patients without transformed disease (that is, 48 patients out of 61, including Cr = 11, CRu = 12, PR =25).

In the supportive study, the median DR (investigator assessment) in the primary analysis for patients who had achieved CR, CRu, or PR was 29.0 weeks (95% CI: 22.1, 43.1 weeks), based on 38 patients with progressive disease/death/change of therapy and 20 censored patients out of the total 58 patients in the analysis. The median PFS in the primary analysis for all patients was 31.0 weeks (95% CI: 26.1, 38.7 weeks), based on 55 patients with progressive disease/death/change of therapy and 21 censored patients out of the total 76 patients in the analysis.

Overall, the data from the pivotal and supportive studies are considered to show that bendamustine at the proposed dose for the treatment of patients with indolent NHL refractory to rituximab results in a clinically meaningful benefit in the ORR, DR and PSF. However, there are no data from the pivotal or supportive studies indicating that bendamustine at the proposed dose will provide a survival benefit in this patient population.

First-line treatment of indolent NHL and mantle-cell lymphoma.

The benefits of treatment with bendamustine in combination with rituximab (B-R) for the treatment of first-line treatment of indolent NHL and MCL in patients with CD20 positive Stage III/IV disease have been satisfactorily established in one pivotal study (StiL NHL 1-2003) with published results.[24] In the pivotal study, bendamustine 90 mg/m^2 administered by IV infusion over 30 to 60 minutes on Days 1 and 2 of a 4 week cycle for up to 6 cycles plus rituximab 375 mg/m^2 IV on Day 1 of each Cycle 1 was compared with R-CHOP for up to 6 cycles (an Australian approved regimen for first line treatment of CD20 positive Stage III/IV follicular B-cell lymphoma) The median duration of patient follow-up in the study was 45 months (IQR: 25, 75 months), and 261 patients were assessed in the B-R arm and 275 patients were assessed in the R-CHOP arm.

The pivotal study established that B-R was at least non-inferior to R-CHOP, as assessed by PFS (the primary efficacy endpoint). PFS was significantly longer in patients treated with

B-R compared with R-CHOP (HR = 0.58 [95% CI: 0.44, 0.74]; p< 0.0001). The median duration of PFS for patients treated with B-R was 38.3 months longer than for patients treated with R-CHOP (69.5 months [IQR: 26.1, NR] versus 31.2 months [IQR: 15.2, 65.7], respectively) and this difference is considered to be clinically meaningful. In a pre-planned analysis, PFS was significantly improved in patients treated with B-R compared with R-CHOP for histological subtypes of follicular lymphoma (p=0.0072), mantle-cell lymphoma (p=0.0044) and Waldenstrom's macroglobulinaemia (p=0.0033) but not for marginal-zone lymphoma (p=0.3249).

The secondary efficacy endpoints of ORR (CR + PR) were similar for the two treatment arms, 93% (242/261) in the B-R arm compared with 91% (231/253) in the R-CHOP arm. However, the CR was significantly higher in the B-R arm compared with the R-CHOP arm (40% [104/261] versus 30% [76/253]), respectively, p=0.021).

The secondary efficacy endpoint of TTNT was significantly longer in the B-R arm compared with the R-CHOP arm (HR = 0.52 [95% CI: 0.39, 0.69]; p<0.0001). The median TTNT was not reached for the B-R arm (IQR: 35.1 months, not reached), while in the R-CHOP arm the median TTNT was 42.3 months (IQR: 18.2 months, not reached). At the time of the analysis, 74 salvage treatments had been started by patients in the B-R arm compared with 116 in the R-CHOP arm.

There was no difference between the two treatment arms in OS with 43 deaths being reported in the B-R compared with 45 deaths in the R-CHOP arm. The median duration of OS had not been reached in either treatment arm.

The were no data assessing whether the beneficial effect on PFS of the B-R induction regimen can be maintained with or without follow-up rituximab maintenance/consolidation treatment.

First round assessment of risks

Chronic lymphocytic leukaemia

The data from the pivotal study (02CLLIII) indicates that the risks associated with bendamustine for the treatment of CLL are notably greater than the risks associated with chlorambucil. The risk of experiencing at least one AE occurred more frequently in the bendamustine arm than in the chlorambucil arm (88.8%, 143/161, 660 events versus 80.8%, 385/151, 385 events) and the majority of these events were considered to be treatment-related or to have a missing causality assessment (82.0%, 132/161, 471 events versus 64.2%, 97/151, 225 events, respectively). Unless otherwise stated, the risks reviewed below are based on all causality events in the safety population.

Disorders (SOC) reported in ≥ 10% of patients in either treatment arm in descending of order of frequency in the bendamustine arm (n=161) versus the chlorambucil arm (n=151) were: blood and lymphatic system disorders (57.1% versus 35.8%); general disorders and administrative site conditions (37.3% versus 15.2%); gastrointestinal disorders (30.4% versus 27.2%); infections and infestations (30.4% versus 25.2%); skin and subcutaneous tissue disorders (26.1% versus 12.6%); investigations (16.8% versus 13.2%); metabolism and nutrition disorders (15.5% versus 6.0%); respiratory, thoracic and mediastinal disorders (13.0% versus 9.9%); and nervous system disorders (10.6% versus 10.6%).

AEs reported in ≥ 5% of patients in either treatment arm and in ≥ 2% more patients in the bendamustine arm (n=161) compared with the chlorambucil arm (n=151), in descending order of frequency in the bendamustine arm were: neutropenia (27.3% versus 13.9%); pyrexia (24.8%, versus 5.3%); thrombocytopenia (24.8% versus 20.5%); anaemia (21.7% versus 13.9%); nausea (19.3% versus 13.9%); leukopenia (17.4% versus 3.3%); vomiting (15.5% versus 6.6%); diarrhoea (9.9% versus 4.0%); rash (9.3% versus 4.6%); asthenia

(8.7% versus 4.6%); fatigue (8.7% versus 4.6%); hyperuricaemia (7.5% versus 1.3%); lymphopenia (6.2% versus 0.7%); infection (6.2% versus 1.3%) chills (5.6% versus 1.3%); weight decreased (5.6% versus 3.3%); pruritis (5.0% versus 2.6%); and hypersensitivity (5.0% versus 2.0%). There were no AEs occurring in ≥ 5% of patients in either treatment arm and in ≥ 2% more patients in the chlorambucil arm compared with the bendamustine arm.

The risk of experiencing a severe AE (Grade 3 or 4/CTC or Cheson) was greater in patients in the bendamustine arm than in the chlorambucil arm (52.8%, 85 patients, 175 events versus 31.1%, 47 patients, 72 events), and both severe (Grade 3 or 4 CTC) haematological and non-haematological AEs occurred notably more commonly in the bendamustine arm than in the chlorambucil arm.

Severe haematological AEs (Grade 3 or 4/CTC or Cheson) were reported in 40.4% (n=65) patients in the bendamustine arm and 19.2% (n=29) of patients in the chlorambucil arm. Severe haematological AEs appeared to be manageable by dose modification and/or symptomatic treatment rather than withdrawal from treatment. In the ITT population, granulocyte colony stimulating factors (GSFs) were administered to 10 (6.2%) patients in the bendamustine arm and 1 (0.6%) patient in the chlorambucil arm, while erythropoietic growth factors were administered to 4 (2.5%) patients in the bendamustine arm and 2 (1.3%) patients in the chlorambucil arm. Haematological AEs resulting in treatment withdrawal were reported in 3 (1.9%) patients in the bendamustine arm (1x event each of anaemia, leukopenia, neutropenia and thrombocytopenia) and 1 (0.7%) patient in the chlorambucil arm (1 event of neutropenia).

The most commonly reported severe haematological AE (Grade 3 or 4/CTC or Cheson) in both the bendamustine and chlorambucil arms was neutropenia, including granulocytopenia (23.0%, 37 patients versus 10.6%, 16 patients, respectively). Neutropenia resulted in dose modifications in 10.6% (n=17) of patients in the bendamustine arm and 8.6% (n=13) patients in the chlorambucil arm and permanent withdrawal from treatment in 1 (0.7%) patient in each of the two treatment arms. Other severe haematological AEs (Grade 3 or 4/CTC or Cheson) in the bendamustine versus chlorambucil arms were leukopenia (14.3%, 23 patients versus 1.3%, 2 patients), thrombocytopenia, including platelet count decreased (11.8%, 19 patients versus 8.6%, 13 patients), lymphopenia (6.2%, 10 patients versus 0%), anaemia, including haemoglobin decreased (3.1%, 5 patients versus 0.7%, 1 patient), haemolytic autoimmune anaemia (0.6%, 1 patient versus 0.7%, 1 patient) and autoimmune thrombocytopenia (0.6%, 1 patient versus 0%). The results for severe haematological AEs indicate that the risk of myletoxicity is notably greater in patients treated with bendamustine compared with chlorambucil.

Severe non-haematological AEs (CTC 3 or 4) were reported in 41.0% (n=66) of patients in the bendamustine arm (113 events) and 17.2% (n=26) patients in the chlorambucil arm. The most commonly occurring severe grouped non-haematological events (Grade 3 or 4 CTC) were infections, reported notably more commonly in the bendamustine arm than in chlorambucil arm (8.7%, 14 patients versus 3.3%, 5 patients) and severe allergic reactions, reported more commonly in the bendamustine arm than in the chlorambucil arm (6.5%, 9 patients versus 3.3%, 5 patients).

Severe non-haematological AEs (Grade 3 or 4/CTC or Cheson) occurring in ≥ 2 patients in the combined treatment groups by SOCs were (bendamustine versus chlorambucil): gastrointestinal disorders - diarrhoea (2, 1.2% versus 0%), vomiting (2, 1.2% versus 0%), and nausea (1, 0.6% versus 1, 0.7%); general disorders and administration site conditions - pyrexia (3, 1.9% versus 2, 1.3%) and fatigue (2, 1.2% versus 0%); immune system disorders - hypersensitivity (2, 1.2% versus 0%); infections and infestations - pneumonia (4, 2.5% versus 0%) and infection (3, 1.9% versus 0%); investigations – Lactate dehydrogenase (LDH) increased (2, 1.2% versus 0%); metabolism and nutrition disorders

- hyperuricaemia (3, 1.9% versus 0%) and hyperkalaemia (1, 0.6% versus 1, 0.7%); neoplasms benign, malignant and unspecified - tumour lysis syndrome (2, 1.2% versus 0%); renal and urinary disorders - renal impairment (2, 1.2% versus 0%); respiratory, thoracic and mediastinal disorders - dyspnoea (2, 1.2% versus 2, 1.3%), pleural effusion (2, 1.2% versus 1, 0.7%) and cough (1, 0.6% versus 1, 0.7%); skin and subcutaneous tissue disorders - rash (4, 2.5% versus 3, 2.0%) and rash generalized (1, 0.6% versus 1, 0.7%); and vascular disorders - hypertensive crisis (3, 1.9% versus 0%) and hypertension (2, 1.2% versus 0%).

Serious AEs (other than death), were reported more commonly in patients in the bendamustine arm compared with patients in the chlorambucil arm (19.3%, 31 patients, 38 event versus 12.8%, 19 patients, 22 events). Blood and lymphatic disorder (SOC) SAEs occurred more frequently in patients in the bendamustine arm (3.1%, n=5) than in the chlorambucil arm (0.7%, n=1), and the following SAEs (preferred term (PT)) were reported only in patients in the bendamustine arm anaemia (n=2), anaemia haemolytic anaemia (n=1), autoimmune thrombocytopenia (n=1), haemolysis (n=1), and pancytopaenia (n=1). Gastrointestinal disorder (SOC) SAEs occurred with similar frequency in both the bendamustine and the chlorambucil arms (1.2%, 2 versus 1.3%, respectively). SAEs occurring in ≥ 2 patients in either treatment arm and more commonly in the bendamustine arm compared with the chlorambucil arm were hypersensitivity (3, 1.9% versus 1. 0.7%), pneumonia (3, 1.9%), anaemia (2, 1.2% versus 0%), vomiting (2, 1.2% versus 0%), pyrexia (2, 1.2% versus 1, 0.7%), tumour lysis syndrome (2, 1.2% versus 0%). The only SAE occurring in ≥ 2 patients in the chlorambucil arm and more commonly in this arm than in the bendamustine arm was herpes zoster (2, 1.3% versus 0.6%).

Death occurred in 19.3% (n=31) of patients in the bendamustine arm and 27.7% (n=41) of patients in the chlorambucil arm. Of the 72 deaths, 4 patients died up to 30 days after the last study drug (1, 0.6%, bendamustine; 3, 2.0%, chlorambucil) and 68 patients died after study treatment. Of the 4 patients who died up to 30 days after last study drug, the reasons for the death were CLL (n=1, chlorambucil), haemorrhage (n=1, chlorambucil), chronic obstructive pulmonary disease (COPD)/dyspnoea/acute heart and pulmonary insufficiency (n=1, bendamustine), and heart failure (n=1, chlorambucil). Approximately 50% of the total number of deaths in both treatment arms was considered to be related to CLL.

Treatment withdrawals due unacceptable toxicity of risk/benefit occurred notably more frequently in the bendamustine arm than in the chlorambucil arm (11.2%, 18 patients versus 3.3%, 5 patients). The most frequently reported AEs resulting in withdrawal in ≥ 2 patients due to unacceptable toxicity or risk/benefit were (bendamustine versus chlorambucil), hypersensitivity (1.9%, 3 versus 0.7%, 1), pyrexia (1.2%, 2 versus 0.7%, 1), neutropenia (0.7%, 1 versus 0.7%, 1) and rash (1.2%, 2 versus 0%). All other events each occurred in 1 patient and nearly all patients were in the bendamustine arm.

Other significant AEs of interest (apart from the 2 patients with tumour lysis in the bendamustine arm noted above) were 2 cases of secondary neoplasm in patients in the bendamustine arm (1 bronchial carcinoma; 1 lung cancer).

Relapsed/refractory indolent NHL

The risks of bendamustine for the treatment of relapsed/refractory indolent NHL are based on open-label data on 176 patients exposed to the drug for up to 8 cycles (pivotal study - median of 6 cycles, mean relative dose intensity of 88% in 100; supportive study - median of 5 cycles, mean relative dose intensity of 87% in 76 patients). Of the 176 patients with indolent NHL refractory to rituximab treated with bendamustine at the proposed dose, all patients (100%) experienced at least one AE and in nearly all patients (96%) the AEs were considered to be related to treatment with the study drug.

The risks of greatest clinical concern associated with bendamustine treatment relate to haematological AEs. In the total population (n=176), haematological AEs reported in ≥ 20 % of patients were neutropenia (38%), anaemia (35%), and thrombocytopenia (31%). Of note, severe and life-threatening haematological AEs (Grade 3 or 4) occurring in ≥ 10% of patients were neutropenia (32%), thrombocytopenia (24%) and anaemia (12%). SAEs of febrile neutropenia were reported in 5% (n=9) of patients, while SAEs of anaemia and neutropenia were reported in 3% (n=5) and 2% (n=3) of patients, respectively.

In both the pivotal and supportive studies, haematological AEs were the most commonly reported events leading to discontinuation of study drug treatment. In the pivotal study, discontinuations of study drug treatment due to thrombocytopenia occurred in 9% (n=9) of patients, followed by neutropenia in 4% (n=4) of patients. In the supportive study, discontinuations of study drug treatment due to thrombocytopenia occurred in 17% (n=13) of patients followed by neutropenia and anaemia in 7% (n=5) and 3% (n=2), respectively. In the pivotal study, dose delays occurred in 30% (n=30) of patients due to neutropenia and 19% (n=19) of patients due to thrombocytopenia. The most commonly reported AEs resulting in dose delays were neutropenia in the pivotal study and thrombocytopenia in the supportive study.

GSFs were administered to 38% of patients in the pivotal study and to 36% of patients in the supportive study, while the proportions of patients treated with erythropoietin agonists were 33% and 37%, respectively. Blood product transfusions were administered to 18% of patients in the pivotal study and 30% of patients in the supportive study. Only 1 patient in each of the pivotal and supportive studies required a platelet transfusion, while 18 and 23 patients, respectively, required transfusion with a RBC containing product.

The risks of experiencing a non-haematological AE were high but the majority of these events were mild or moderate in severity (Grade 1 or 2) and appear to have been manageable by symptomatic therapy and/or dose reduction/dose delay. Non-haematological AEs occurring in ≥ 20% of patients in the total population (n=176or reported as Grade 3 or 4 in ≥ 2% of patients are listed in Attachment 2.

In the pivotal study, SAEs occurred in 39 (39%) patients including death in 11 (11%) patients, while in the supportive study SAEs occurred in 26 (34%) of patients including death in 3 (4%) patients. In the pivotal study, the most common SAEs occurring in ≥ 5% of patients were febrile neutropenia (6%) and pneumonia (5%). In the supportive study, the most common SAEs occurring in ≥ 4% of patients were anaemia (5%) and 4% for each of febrile neutropenia, pneumonia, and dehydration.

In the pivotal study, of the 11 deaths reported during the study, 2 were considered to be definitely related to the study drug (1 x Cytomegalovirus (CMV) infection with normal absolute neutrophil count (ANC); 1 x diffuse inter-alveolar haemorrhage), 2 were considered to be probably related to the study drug (1 x respiratory failure/pneumonia; 1 x pneumonia/septic shock/cardiomyopathy), 2 were considered to be possibly related to the study drug (1 x respiratory failure; 1 x worsening of COPD), and 5 were considered to be unrelated to the study drug (disease progression). In the supportive study, the 3 deaths due to AEs were myelodysplastic syndrome considered to be possibly related to the study drug in 1 patient, renal failure considered as unlikely to be related to the study drug in 1 patient and chronic myelomonocytic leukaemia considered to be possibly related to the study drug in 1 patient.

In the pivotal study, 31 (31%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs reported in ≥ 2% of patients were thrombocytopenia (9%), fatigue (6%), and neutropenia (4%). In the supportive study, 30 (39%) patients discontinued study drug treatment due to AEs. Discontinuations of study drug treatment due to AEs in ≥ 2 % patients were thrombocytopenia (17%), neutropenia (7%) and anaemia (3%).

In the pivotal study (n=100), 24 (24%) patients had dose reductions as specified in the protocol and 68 (68%) patients had dose reductions or dose delays or did not received both doses in a cycle at some point during their treatment. The most common reason for dose delay was neutropenia. In the supportive study (n=76), 19 (25%) patients had dose reductions as specified in the protocol, and 46 (61%) patients had dose reductions or dose delays, or did not received both doses in a cycle at some point during their treatment. The most common reason for dose delay was thrombocytopenia.

Infections were reported in 61% (107/176) of patients in the total population. In the pivotal study, 15% of patients had Grade 3 infections, and 6% patients had Grade 4 infections consisting of pneumonia, sepsis, clostridial infection, infection systemic, septic shock, mycobacterial infection, and tuberculosis. One patient had Grade 4 septic shock with a fatal outcome and one patient had Grade 3 lung infection considered definitely related to bendamustine treatment which resolved with no residual effect. Overall, in the pivotal study 20 patients had fever or infection with Grade 3 or 4 neutropenia, and most events resolved and were considered to be not related to study drug treatment. In the supportive study, 20% (n=15) of patients had Grade 3 infections and 1% (n=1) had a Grade 4 infection (sepsis). The only Grade 3 infections occurring in more than 1 patient was pneumonia (4, 5%). Overall, in the supportive study 21% (n=16) of patients had febrile neutropenia/neutropenia with infection and 39% (n=30) of patients had infection without documented neutropenia.

Acute drug reactions/hypersensitivity events within 24 hours of the bendamustine infusion were reported in 20% (35/176) of patients in the total population, and most of the events were mild or moderate in severity (Grade 1 or 2). No cases of anaphylaxis were reported. The nature of the reactions and events were typical of those expected to be seen with drug infusion. Cardiac-related disorders were reported in 18% (31/176) of patients in the total population. There is no conclusive evidence that bendamustine is associated with cardiotoxicity. Secondary neoplasms were reported in 3% (5/176) of patients in the total population (3 myelodysplastic syndrome, 1 chronic myelomonocytic leukaemia and 1 x squamous cell carcinoma).

The haematological laboratory abnormalities observed in the pivotal and supportive studies have been discussed above. The clinical chemistry laboratory abnormalities observed in the pivotal and supportive studies were similar and do not give rise to significant concern. In the pivotal study, Grade 3 clinical chemistry abnormalities over the course of the 8 treatment cycles occurring in ≥ 2 patients were hyperglycaemia (5 [5%] patients), hypokalaemia (5 [5%] patients), hypocalcaemia (3 [3%] patients), hyperkalaemia (2 [2%] patients), increased serum creatinine (2 [2%] patients), and Hypoalbuminaemia (2 [2%] patients), while Grade 4 events were reported for hyponatraemia (1 [1%] patient), hypokalaemia (1 [1%] patient) and increased serum creatinine (1 [1%] patient). In the supportive study, Grade 3 clinical chemistry results over the course of the 8 cycles occurring in ≥ 2 patients were hypokalaemia (3 [4%] patients), hyperkalaemia (2 [3%] patients) and hyperglycaemia (2 [3%] patients), while Grade 4 events were reported for hypercalcaemia in 1 (1%) patient.

In the pivotal study there were no Grade 3 or 4 AST or ALT clinical chemistry laboratory abnormalities over the course of the 8 treatment cycles, but grade 1 or 2 events occurred commonly for both enzymes (32% [AST]; 26% [ALT]). Similarly, in the supportive study there were no Grade 3 or AST or ALT clinical chemistry abnormalities occurring over the course of the 8 treatment cycles but Grade 1 or 2 events occurred commonly for both enzymes (40% [AST]; 16% [ALT]).

The observed changes in vital signs of pulse rate, blood pressure, temperature or weight gain over the course of the pivotal and supportive studies do not give rise to concern. However, weight loss over the course of the study occurred in 56% of patients in the pivotal study and 50% of patients in the supportive study but the majority of events in

both studies were mild (Grade 1) in severity. The number of clinically significant abnormalities in the ECG recordings over the course of the pivotal and supportive studies was small and does not give rise to concern. However, there was no systematic assessment of QT interval change in bendamustine treated patients in either the pivotal or supportive study.

First-line indolent NHL and MCL

The safety data from the single-pivotal study (Rummel et al., 2013)[24] are promising and suggest that the risks of treatment with B-R for the proposed indication are similar to those for R-CHOP. However, in the absence of conventional safety data for the proposed indication a definitive assessment of the risks of treatment with B-R for the proposed indication cannot be made.

First round assessment of benefit-risk balance

Chronic lymphocytic leukaemia

The benefit/risk balance for bendamustine for the treatment of CLL at the proposed dose is considered to be acceptable. However, while the benefits of bendamustine for CLL are greater than those of chlorambucil, the risks of treatment with bendamustine are notably greater than those of chlorambucil. Consequently, although the benefit/risk balance for bendamustine for the treatment of CLL is considered to be acceptable, the benefits are considered to only marginally outweigh the risks. The risks of treatment with bendamustine appear to be manageable by dose reduction and prophylactic and symptomatic treatment of toxicities rather than treatment discontinuation. There appears to be no difference in overall survival between the two treatment regimens.

Refractory/relapsed indolent NHL

The benefit/risk balance for bendamustine for the treatment of patients with indolent relapsed/refractory NHL refractory to rituximab at the proposed dose is considered to be acceptable.

First-line indolent NHL and MCL

The benefit/risk balance is promising for bendamustine in combination with rituximab for first-line treatment of indolent NHL and MCL in patients with CD20 positive Stage III/IV disease, based on published data from Rummel et al 2013.[24] However, in the absence of confirmatory conventional safety data no definitive assessment of the benefit/risk balance of the proposed B-R regimen for the proposed indication can be made.

First round recommendation regarding authorisation

Chronic lymphocytic leukaemia

It is recommended that bendamustine HCl (Ribomustin®) be approved for the

> '*first line treatment of chronic lymphocytic leukaemia (Binet stage B or C)*'.

Relapsed refractory indolent NHL

It is recommended that bendamustine HCl (Ribomustin®) be approved for the treatment of

> '*indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen'*.

The recommended indication differs from that proposed by the sponsor. It is considered that the recommended indication reflects the patient population in the pivotal Phase III study (SDX-105-03), and aligns with the dosage regimen stated in the proposed PI (that is, monotherapy for indolent NHL refractory to rituximab).

First-line indolent NHL and MCL

It is recommended that the proposed regimen of bendamustine HCl (Ribomustin®) in combination with rituximab be rejected for

> '*previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients*'.

The reason for rejection is the absence of conventional safety data confirming that the proposed treatment regimen of bendamustine is safe for the proposed indication. The specific deficiencies in the submitted safety data are:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle.
- No data on the proportion of patients requiring dose modifications (dose reductions or temporary treatment discontinuations) due to AEs, or on the nature of the AEs resulting in dose modifications.
- No data on the total number of AEs experienced by patients in the two treatment groups (overall, and individual events).
- No data on the incidence of AEs by treatment cycle.
- No data on AEs considered as treatment-related.
- No data on conventionally defined serious adverse events (that is, fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalisation, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological) but no case narratives of the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing serious adverse events were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (that is, causes of death and case narratives).
- No data on permanent treatment discontinuation of the study-drugs due to AEs.
- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists, or transfusions with blood products for anaemia or thrombocytopenia.
- No data on changes in vital signs or the ECG during the course of the study.
- No data safety data based on age differences (for example ≥ 65 years versus < 65 years).

Clinical questions

Paediatric development program

1. No paediatric data have been submitted to the TGA. However, the relevant document relating to the Paediatric Development Program indicates that paediatric data have been submitted to the EU and the FDA. Please indicate the specific indications being sought for the paediatric population (and relevant age ranges) in the EU and the FDA. Please justify why paediatric data has not been submitted to the TGA but has been provided to the EU and USA drug regulatory authorities.

Pharmacokinetics

1. The study report for SDX-105-03 indicates that this study included a population pharmacokinetic analysis (CP-07-002) and a pharmacokinetic/pharmacodynamic analysis (CP-07-003). These analyses could not be identified in the submission. Please provide copies of both analyses.
2. In Preiss (Humboldt University Berlin 1987) a tentative bendamustine hydrochloric acid metabolite was identified as β-hydroxy-bendamustine according to the high-performance liquid chromatography (HPLC) analytical method used in this study. This metabolite accounted for about 25% of the IV bendamustine dose. However, this metabolite does not appear to have been identified in subsequent PK studies using validated HPLC/with Fluorescent Detection (FC) methods. Was the metabolite an artefact of the analytical method used in the study? Please clarify this matter.
3. The mean half-life of bendamustine was notably longer following 120 mg/m^2 infused over 60 minutes (SDX-105-03) than 100 mg/m^2 infused over 30 minutes (98B03) (that is, 4.9 hours versus 28.2 minutes, respectively). Please comment on the reasons for this difference.
4. In the study report DP-2007-043 on bendamustine PKs from Study SDX-105-03, the mean (SD) the volume in the terminal state (Vz) (L) is given as 208.2 (167.1) L and the volume in steady state (Vss) is given as 25.3 (28.6) L (see DP-2007-043). Please comment on the apparent inconsistency between the two values.
5. There were no PK studies assessing the role of active transporters in bendamustine distribution. Does the sponsor have results from such studies? If not, does the sponsor plan to undertake such studies? If not, please justify.
6. In vitro data indicate that bendamustine is metabolised by CYP 1A2. Does the sponsor intend to undertake in vivo drug-drug PK interaction studies between bendamustine and CYP 1A2 inducers and inhibitors? If not, please justify?
7. Please comment on the relative contributions of non-renal and renal clearance to the total clearance of bendamustine in patients with normal renal and hepatic function. Please provide estimates of hepatic and renal clearance in patients with normal renal and hepatic function. Does the sponsor propose to undertake a mass balance study of bendamustine in humans? If not please justify.
8. Does the sponsor intend to undertake PK studies in patients with renal and hepatic impairment that meet current standards of best-practice for such studies (see relevant EU guidelines). If not, please justify?

Efficacy

1. CLL: The pivotal study (02CLLIII) excluded patients older than 75 years and the mean age (range) of patients in the ITT population for bendamustine and chlorambucil was

63.0 years (47, 77 years) and 63.6 (35, 78 years). Consequently, the study population appears to be younger than Australian patients with CLL for whom bendamustine might be a treatment option. Subgroup analyses of the two primary efficacy endpoints (overall response and PFS) showed that treatment with bendamustine was significantly superior to treatment with chlorambucil independent of age (< 65 years, ≥ 65 years). However, there were no specific efficacy data on patients aged ≥ 75 years and the availability of such data from the pivotal study are likely to be negligible, given that patients aged > 75 years were excluded from the study and the upper age range for the total population was 77 years. Please comment on the generalisability of the data from the pivotal study population to the Australian population of patients with treatment-naive CLL for whom bendamustine might be a treatment option.

2. CLL: In the Canadian monograph the results for response for study 02CLIII summarized in Table 38 (see Attachment 2) notably differ from the ICRA results provided in the submission in the second CSR (see Table 39; Attachment 2) and from those presented in the proposed Australian PI. The differences are particularly marked for the CR and PR assessments. Please account for these differences.

3. CLL: In the second CSR for study 02CLIII it is stated that one of the methods used to assess the response involved the electronic CRF (eCRF) calculating the overall response according to a programmed algorithm based on the NCI-WG Criteria for response assessment.[25] Please provide the results for this analysis using the data provided in the second CSR.

4. CLL: The break-down of PFS into its components could not be identified for any of the analyses (that is, no separate patient numbers for progression, relapse or death contributing to the total number of events). Please provide the break-down of PFS events for the primary analysis (ICRA), the sensitivity analysis (investigator assessment), Binet B and C assessments, males and females and patients < 65 years of age and ≥ 65 years of age.

5. CLL: No information on the median duration of follow-up could be identified in the submitted data. However, in Knauf et al (2009)[26] it is stated that median observation time in patients in the follow-up analysis was 35 months (range: 1, 68 months). Please confirm the median observation time in patients in the follow-up analysis.

6. Relapsed/refractory indolent NHL: Please provide separate ORRs for the 31 patients from Study SDX-105-01 who were either sensitive to their most recent rituximab-containing treatment regimen (n=23) or had an unknown response (n=8) to their most recent rituximab-containing regimen and the 45 patients who were refractory to their most recent rituximab containing regimen.

7. Relapsed/refractory indolent NHL: Has all long-term follow-up data for Study SDX-105-103 accrued? If so, please provide the results for the efficacy outcomes of ORR, DR and PFS.

8. First-line indolent NHL and MCL: The application for the proposed indication for bendamustine in combination with rituximab for the first line treatment of indolent NHL and MCL is supported by one pivotal study (StiL NHL 1-2003), and published results for this study are provided in Rummel et al (2013).[24] The submission included an English translation from German of the initial protocol for this study identified as StiL NHL 1-2003 (September 2003). However, it is obvious from Rummel et al (2013)[24], and from a document included in the submitted literature references (Chen

[25] Cheson BD et al. National Cancer Institute - Sponsored working group guidelines for chronic lymphocytic leukemia: revises guidelines for diagnosis and treatment. Blood 1996;87:4990-4997.
[26] Knauf W et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009; 27:4378-4384.

and Li, Cephalon Statistical Analysis Plan for StiL NHL 1-2003, 5 May 2011), that the initial protocol underwent a number of amendments. Please provide the final protocol for StiL NHL 1-2003, indicating all amendments and the final statistical analysis plan for this study. In addition, please explain why the Cephalon final statistical analysis plan for StiL NHL 1-2003 was provided in the literature references rather than in the relevant studies for evaluation section.

9. First-line indolent NHL and MCL: Why were the final Complete Study Report (CSR) and the final Biometric Report for study StiL NHL 1-2003 not provided? Presumably the published study Rummel et al (2013)[24] were based on these reports. In the absence of conventional safety data, a comprehensive regulatory assessment of the safety of bendamustine in combination with rituximab for the proposed indication cannot be undertaken.
10. First-line indolent NHL and MCL: Does the sponsor have the results from Rummel et al (2013) of efficacy analyses in the ITT population? If so, please provide these results.

Safety

1. Relapsed/refractory indolent NHL: In Study SDX-105-01, it is stated that thrombocytopenia was the most common AE resulting in dose delay. How many patients (n [%]) experienced a dose delay because of thrombocytopenia?
2. In the postmarketing data (PSUR 2), reference was made to pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain), being possibly due to silicone oil contamination. Consequently, PSUR 2 indicates that these events are being temporarily monitored until all batches bendamustine potentially contaminated with silicon oil have expired. Please provide updated information on cases of pulmonary embolism reported in association with bendamustine and on the sponsor's plans for continuing monitoring of pulmonary embolism (including symptoms of dyspnoea, tachypnoea, and pleuritic pain). Please comment on procedures undertaken to prevent future recurrence of silicon oil contamination.

Second round clinical evaluation

Overview

The sponsor provided a response, dated 26 February 2014, to the clinical questions raised in the first round clinical evaluation report. The sponsor’s response has been evaluated based on the clinical data relating to the questions raised in the first round clinical evaluation. The sponsor's response was provided in electronic NeeS format on DVD (1 disc). The sponsor responded to each of the questions raised in the first round clinical evaluation report. The first round clinical evaluation report, the second round clinical evaluation of the sponsor’s response, and the second round clinical evaluation report have all been prepared by the same clinical evaluator.

For details of the sponsor’s responses and the evaluator’s comments on the sponsor’s responses see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

Chronic lymphocytic leukaemia

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the treatment of CLL (Binet stage B or C) remain unchanged from those identified in the First Round Evaluation.

Relapsed/refractory indolent NHL

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the treatment of indolent B-cell NHL refractory to rituximab remain unchanged from those identified in the First Round Evaluation.

First-line treatment of indolent NHL and mantle-cell lymphoma

After consideration of the responses to the clinical questions, the positive benefits of bendamustine for the first-line treatment of indolent NHL and mantle-cell lymphoma remain unchanged from those identified in the First Round Evaluation.

Second round assessment of risks

Chronic lymphocytic leukaemia

After consideration of the responses to the clinical questions, the risks of bendamustine for the treatment of chronic lymphatic leukaemia remain unchanged from those identified in the First Round Evaluation.

Relapsed/refractory indolent NHL

After consideration of the responses to the clinical questions, the risks of bendamustine for the treatment of relapsed/refractory indolent NHL remain unchanged from those identified in the First Round Evaluation.

First-line indolent NHL and MCL

The safety data from the single-pivotal study (Rummel et al., 2013[24]) are promising and suggest that the risks of treatment with B-R for the proposed indication are similar to those for R-CHOP. However, in the absence of comprehensive safety data from a complete study report a definitive assessment of the risks of treatment with B-R for the proposed indication cannot be made.

The sponsor's response confirms that the data supporting the first line indolent NHL indication are based on a published paper (Rummel et al., 2013[24]) and other publicly available information. The sponsor states that it is not in a position to supply any information not in the public domain, which includes the final protocol and complete study report for the pivotal study. The sponsor acknowledges that the data to support the first line indolent NHL indication are limited. However, the sponsor considers that there is an unmet clinical need for medicines to treat this condition and refers to approaches from clinicians requesting access to bendamustine for treatment of the condition. Nevertheless, for regulatory purposes it is considered that comprehensive safety data from a complete study report are required in order to satisfactorily establish the safety of bendamustine for the proposed indication.

Second round assessment of benefit-risk balance

Chronic lymphatic leukaemia

The benefit-risk balance for the treatment of chronic lymphatic leukaemia is favourable. However, while the benefits of bendamustine for CLL are greater than those of chlorambucil, the risks of treatment with bendamustine are notably greater than those of chlorambucil. Consequently, although the benefit/risk balance for bendamustine for the treatment of CLL is considered to be favourable, the benefits are considered to only marginally outweigh the risks. The risks of treatment with bendamustine appear to be manageable by dose reduction and prophylactic and symptomatic treatment of toxicities rather than treatment discontinuation. There appears to be no difference in overall survival between the bendamustine and chlorambucil treatment regimens for the treatment of CLL.

Refractory/relapsed indolent NHL

The benefit-risk balance for bendamustine for the treatment of patients with indolent relapsed/refractory NHL refractory to rituximab is considered to be favourable.

First-line indolent NHL and MCL

Based on published data from Rummel et al 2013[24], the benefit-risk balance is promising for bendamustine in combination with rituximab (B-R) for first-line treatment of indolent NHL and MCL in patients with CD20 positive stage III/IV disease. However, in the absence of confirmatory safety data from a CSR it is considered that no conclusive assessment of the benefit-risk balance of the proposed B-R treatment regimen for the proposed indication can be made.

Second round recommendation regarding authorisation

Chronic lymphocytic leukaemia

It is recommended that bendamustine HCl (Ribomustin®) be approved for the

> '*first line treatment of chronic lymphocytic leukaemia (Binet stage B or C)*'.

Relapsed refractory indolent NHL

It is recommended that bendamustine HCl (Ribomustin®) be approved for

> *'the treatment of 'indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen'*.

The recommended indication differs from that proposed by the sponsor. It is considered that the recommended indication reflects the patient population in the pivotal Phase III study (SDX-105-03), and aligns with the dosage regimen stated in the proposed PI (that is, monotherapy for indolent NHL refractory to rituximab).

First-line indolent NHL and MCL

It is recommended that the proposed regimen of bendamustine HCl (Ribomustin®) in combination with rituximab be rejected for

> *'previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients'*.

The reason for rejection is the absence of confirmatory safety data from a Complete Study Report (CSR) confirming that the proposed treatment regimen of bendamustine is safe for the proposed indication. The specific deficiencies in the submitted safety data are:

- No data on the extent of exposure relating to number of patients per cycle, mean number of cycles per patient, overall dose per cycle (mean and relative dose), and mean total dose per cycle.
- No data on the proportion of patients requiring dose modifications (dose reductions or temporary treatment discontinuations) due to AEs, or on the nature of the AEs resulting in dose modifications.
- No data on the total number of AEs experienced by patients in the two treatment groups (overall and individual events).
- No data on the incidence of AEs by treatment cycle.
- No data on AEs considered to be treatment related.
- No data on conventionally defined serious adverse events (that is, fatal or life threatening, resulting in persistent disability or incapacity, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in congenital and/or causing secondary malignancies). Limited data on secondary malignancies were provided (total number and haematological) but no case narratives for the two patients with secondary haematological malignancies were provided and no information on the nature of secondary non-haematological malignancies were provided. No case narratives of patients experiencing serious adverse events were provided. No data were provided on suspected unexpected serious adverse reactions (SUSARs).
- No comprehensive data on deaths in the safety analysis population (that is, causes of death and case narratives).
- No data on permanent treatment discontinuation of the study drugs due to AEs.
- No data on the nature of the infections reported in the two treatment groups.
- No data on the proportion of patients requiring treatment with erythropoietin agonists, or transfusions with blood products for anaemia or thrombocytopenia.
- No data on changes in vital signs or the ECG during the course of the study.
- No data safety data based on age differences (e.g., ≥ 65 years versus < 65 years).

V. Pharmacovigilance findings

Risk management plan

The EU-RMP Version 2.0 (dated 4 March 2011) with an Australian Specific Annex (ASA) Version: 1.0 (dated 1 July 2013) was submitted to the TGA for evaluation.

Summary: ongoing safety concerns

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 7.

Table 7: Summary of ongoing safety concerns

Important identified risks	1. Blood and lymphatic system disorders 2. Infections 3. Severe skin reactions 4. Cardiac disorders 5. Tumour lysis syndrome 6. Drug hypersensitivity
Important potential risks	1. Secondary malignancies 2. Renal toxicity
Important missing information	1 Exposure during pregnancy and lactation 2. Patients below age 18 years 3. Effects on different races

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns. Additional pharmacovigilance activities are proposed to further monitor and characterise the important missing information: 'Patients below age 18 years'.

The sponsor proposes to further characterise the important missing information: 'Patients below age 18 years' in the ongoing study Cephalon C18083/2046: An Open Label Study of Bendamustine Hydrochloride for the Treatment of Paediatric Patients With Relapsed or Refractory Acute Leukemia. The EU-RMP states: *'The patients are being recruited in the following countries, USA, Canada, Israel, Australia, South Korea, Brazil, Mexico, Russia, Poland and Belarus. Twenty six patients are planned to be enrolled, and at present 9 patients have entered the trial. It is the first (known) study in children with bendamustine.'* However, the ASA makes no reference to this study. The EU-RMP refers to Annex 5 for details of the final study protocol (Version: 01), but no such detail can be found. The EU-RMP also indicates that the planned date for the submission of final data is second quarter of 2013.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important missing information: 'Effect on different races' for which no routine risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

It is considered that the sponsor's response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Table 8 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states that safety considerations that are raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information and/or the Nonclinical and Clinical Evaluation Report will be considered in light of the implications for the RMP by the company when available.	This is acceptable.
The apparent differences between the proposed indications for Australia and the approved indications in the EU and the USA are drawn to the Delegate's attention.	The sponsor has noted this comment.	
It is recommended that the sponsor consider the following amendments to this list of ongoing safety concerns: The draft product information (PI) document states: 'No data is available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dL) (see CONTRAINDICATIONS)' and 'RIBOMUSTIN is contraindicated in patients with: Severe hepatic impairment (serum bilirubin > 3.0 mg/dL)'. Consequently it is suggested that 'Patients with severe hepatic impairment' be included as important missing information. The draft PI document states: 'Experience in patients with severe renal impairment is	The sponsor has advised that 'Hepatotoxicity' and 'Renal toxicity' have been included as Important Potential Risks. Routine pharmacovigilance and routine risk minimisation have been proposed for these ongoing safety concerns. The sponsor acknowledges that nonclinical data indicates that bendamustine is embryotoxic, teratogenic and carcinogenic and asks the TGA to clarify whether the term 'genotoxicity' is adequate in lieu of the above recommendation, since carcinogenicity is already a subcategory of secondary malignancies (Important	While not entirely satisfactory, the first part of the response is acceptable as these risks in general have been included as ongoing safety concerns and will be monitored by routine pharmacovigilance and have routine risk minimisation applied. The second part of the response is also acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
limited.' Consequently it is suggested that 'Patients with severe renal impairment' be included as important missing information. The draft PI document includes nonclinical data under the subheadings: 'Genotoxicity' and 'Carcinogenicity' indicating that bendamustine is embryotoxic, teratogenic and carcinogenic. Consequently it is suggested that 'Reproductive system and breast disorders' be included as an important potential risk. If the sponsor decides to include these ongoing safety concerns in Australia for RIBOMUSTIN then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the EU-RMP and /or the ASA should be revised accordingly.	Potential Risk).	and it is expected that 'Genotoxicity' will be included as a new ongoing safety concern in a revised ASA, with consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for this important potential risk in Australia.
The sponsor should provide an assurance that all routine pharmacovigilance activities conducted in Australia by Janssen-Cilag Pty Ltd will be in accordance with the current regulatory guideline.	The sponsor has now provided such an assurance.	This is acceptable.
The ongoing Study C18083/2046 is not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocol has not been requested for review. Nevertheless the sponsor should provide an update on the status of this study as the planned date for the submission of final data has already passed. In addition reference should be made to this study in an updated ASA.	The sponsor states: *'The Cephalon study, C18083/2046, which was conducted to address the important missing information of bendamustine exposure in patients below age 18 years was completed in 2012. Since Janssen is not the sponsor of the study, we do not have complete access to the clinical information. However, a summary of the study result has been included in Sections SV.2.2 and SV.3 of EU-RMP v06Sep2013 and is also provided in Appendix 1, Table 1 of this response document. The ASA has been updated to*	This is acceptable. In regard to the outcomes of this study the sponsor also states: *'The RPD* (recommended paediatric dose) *was shown to be tolerated in this population of heavily pretreated patients and the safety profile was broadly similar to that in adults*

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	include a reference to this study (see attached ASA v2.0, Table 2: Summary of the Risk Management Plan in Australia).'	*with indolent NHL treated with at the same dose and schedule.'* There would appear to be no other proposed studies / additional pharmacovigilance activities in the Pharmacovigilance Plan.
The studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	The sponsor states: *'Currently, there are no forthcoming studies for the proposed indications.'*	This is acceptable as there would appear to be no further proposed studies/additional pharmacovigilance activities in the Pharmacovigilance Plan (see above).
The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important missing information: 'Effect on different races' for which no routine risk minimisation activities are proposed. It is agreed that at this time the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.	The sponsor states: *'Janssen acknowledges the RMP evaluator's comment. Further, please note that 'Effect on different races' is no longer considered Important Missing Information requiring routine risk minimisation activities. A rationale for the update is provided in Section SIV.3.9 of EU-RMP v06Sep2013: Patients of Different Racial and/or Ethnic Origin. It states that a review of the available pharmacokinetic (PK) data from both the US and Japanese studies showed no clinically meaningful difference between the PK of bendamustine in Caucasian, Hispanic and Black*	This deletion of the important missing information: 'Effect on different races' as an ongoing safety concerns is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	North American or Japanese subjects. Therefore, it is anticipated that there will be no clinically relevant differences in the PK, clinical or safety profile in these populations.'	
The sponsor's handling of the potential for medication errors using routine pharmacovigilance and routine risk minimisation activities is considered satisfactory.	The sponsor has noted this comment.	
The sponsor should provide a tabular 'Summary of the Risk Management Plan in Australia' in a revised ASA, including reference to specific wording pertaining to the routine risk minimisation activities for the specified ongoing safety concerns in the proposed Australian PI and Consumer Medicine Information (CMI). As previously recommended consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for any new ongoing safety concerns. Such consideration should be reflected in this summary table.	The ASA now includes Table 2: 'Summary of the Risk Management Plan in Australia', which provides an assurance that the specific routine risk minimisation measures in the EU Summary of product Characteristics (SPC) is also included in the Australian PI and CMI for all the specified ongoing safety concerns.	This is acceptable.
In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.	The sponsor has noted this comment.	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as follows: For the important identified risk: 'Tumour lysis syndrome', the approved UK Patient Information Leaflet states: 'Take special care with Levact in case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of Levact. Your doctor will be aware of this and may give you other medicines to help prevent it.' It is suggested that words to this effect should be included in the Australian CMI to enhance safe use of these products.	The sponsor states: *'Appropriate text will be added to the CMI to advise patients of the potential risk with Tumour Lysis Syndrome.'*	This is acceptable.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The 'Summary of Changes to the Risk Management Plan Over Time' of the updated EU-RMP identified as Version number: 2 (dated 6 July 2013) states: *'This section is not applicable in this RMP.'* This appears incongruous with the EU-RMP provided with the initial submission, which was also identified as Version number: 2.0, but dated 4 March 2011. Not only has the version control process appears to have gone awry but this statement appears to be incorrect as 'Hepatotoxicity' and 'Central neurotoxicity' have now been added as new important potential risks while 'Exposure during pregnancy and lactation' and 'Effect on different races' have now been deleted as important missing information. In addition, 'Pharmacological class effects' of the initial EU-RMP refers to 'Reproductive system and breast disorders'. However, 'Pharmacological class effects' of the updated EU-RMP no longer makes reference to this pharmacological class effect. No rational explanation appears to have been provided for its absence. Numerous other discrepancies, such as referring to 'Routine pharmacovigilance' as a routine risk minimisation measure while entries in the EU Summary of Product Characteristics (SPC) are referred to as 'Additional risk minimisation measures' (see 'Summary Table of Risk

Minimisation Measures' and 'Risk Minimisation Measures' table which are inconsistent with the 'Risk Minimisation Measures by Safety Concern' table) have also been observed. The sponsor should correct these discrepancies and internal inconsistencies, including identifying and explaining the material differences between the EU-RMP provided with the initial submission and the corrected version. The ASA will need to be updated to reference this corrected version, including studies referenced in the Pharmacovigilance Plan of the EU-RMP.

'Pharmacological class effects' of the initial EU-RMP refers to 'Reproductive system and breast disorders'. Given that the draft Australian PI document includes nonclinical data indicating that bendamustine is embryotoxic, teratogenic and carcinogenic, the sponsor was asked to consider including the important potential risk: 'Reproductive system and breast disorders' as a new ongoing safety concern. The sponsor acknowledges this issue and asks the TGA to clarify whether the term 'genotoxicity' is adequate in lieu of the above recommendation, since carcinogenicity is already a subcategory of secondary malignancies (Important Potential Risk). This is acceptable and it is expected that 'Genotoxicity' will be included as a new ongoing safety concern in a revised ASA, with consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for this important potential risk in Australia.

Section 3.B of the updated ASA states:

> *Based on compelling nonclinical data regarding the embryo-/feto lethal, teratogenic and genotoxic effects of bendamustine, similar outcomes are expected for clinical subjects. 'Exposure during pregnancy and lactation' was therefore removed from the Important Missing Information section of the EU-RMP. Nonetheless, Janssen proposes to monitor all reports of bendamustine exposure during pregnancy and lactation during postauthorisation usage via the implementation of targeted follow-up questionnaires. For all pregnancy exposure cases, follow-up will continue until pregnancy outcome as per the company standard operating procedure for pregnancy exposure. An analysis of bendamustine exposure in this patient population will be provided in future PSURs.*

The proposal to delete the important missing information: 'Exposure during pregnancy and lactation' as an ongoing safety concern is not acceptable, and must be reinstated as such in a revised ASA. In addition a copy of the related targeted follow-up questionnaire, which is considered to be routine pharmacovigilance, should be provided to the TGA.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

No wording can be suggested until the EU-RMP and an ASA have been adequately and appropriately revised (see above).

Key changes to the updated RMP

In their response to the TGA consolidated requests for further information the sponsor provided an updated EU Risk Management Plan (Version: 2.0, dated 6 September 2013) with an updated ASA (Version: 2.0, dated 21 February 2014). Key changes from the versions evaluated in the first round are summarised below.

Table 9: Key changes to the updated RMP

Format	The EU-RMP has been formatted to accommodate the new EU-RMP template as published on the European Medicines Agency (EMA) website resulting in a general restructuring of the data.
Ongoing safety concerns	The important potential risks: 'Hepatotoxicity' and 'Acute Central Neurotoxicity' have been included as new ongoing safety concerns to be monitored by routine pharmacovigilance activities. The important missing information: 'Exposure during pregnancy and lactation' and 'Effect on different races' have been deleted as ongoing safety concerns.
Pharmacovigilance activities	The Pharmacovigilance Plan has been revised to include or delete the ongoing safety concerns highlighted above. The sponsor has reported that study C18083/2046, which was conducted to address the important missing information of bendamustine exposure in patients below age 18 years, was completed in 2012. The sponsor states: *'The RPD* (recommended paediatric dose) *was shown to be tolerated in this population of heavily pretreated patients and the safety profile was broadly similar to that in adults with indolent NHL treated with at the same dose and schedule.'* There would appear to be no other proposed studies / additional pharmacovigilance activities in the Pharmacovigilance Plan.
Risk minimisation activities	Risk minimisation measures have been revised to include or delete the ongoing safety concerns highlighted above. The ASA now includes Table 2: 'Summary of the Risk Management Plan in Australia', which provides an assurance that the specific routine risk minimisation measures in the EU SPC is also included in the Australian PI and CMI for all the specified ongoing safety concerns.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no quality objections to registration. The quality evaluator notes in the Summary for ACPM:

> *There are some labelling and Product Information issues to be resolved. Impurity limits could be tightened. This has been proposed to the sponsor and updated information may be available to the ACPM, or the delegate might choose to make limits a condition of registration.*

Nonclinical

There were no objections to registration.

The nonclinical evaluator considered bendamustine has the potential to prolong the QT interval (it inhibited the potassium (hERG-1) tail current at 17 times the free clinical C_{max}).

There was nonclinical evidence that bendamustine modulates the parasympathetic nervous system (hypotension, stimulation of intestinal transit, vomiting and salivation were seen in animal toxicity studies; there was some evidence that acetylcholinesterase may be inhibited).

Toxicity in bone marrow, lymphoid tissue, gastrointestinal tract and male reproductive organs were considered class effects of alkylating agents; toxic effects on the heart and kidneys were specific to bendamustine. In rats, cardiomyopathy was found; in dogs, various mild cardiac lesions were found. In both species, kidney damage was found (at relatively low exposures).

Carcinogenicity of bendamustine was confirmed in mice. Also, the nonclinical findings confirmed that adverse embryofoetal effects are probable, if there is exposure in pregnancy. The evaluator recommends pregnancy Category D rather than the C proposed by the sponsor (see Nonclinical Findings above for details of Pregnancy Categories).

The proposed limit for one impurity is both above the ICH qualification threshold and not supported by data.

Clinical

The clinical evaluator discusses the literature-based part of the submission, concluding 'there are significant clinical concerns about the provision of a submission based on the results of a recently published study to support the approval of bendamustine for first-line treatment of indolent NHL and MCL'.

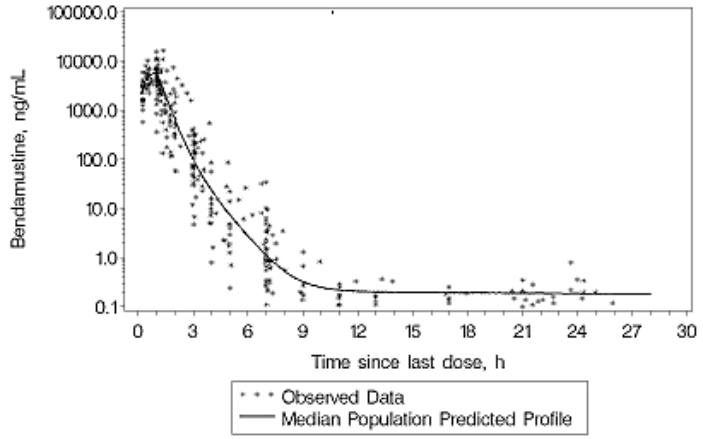
The clinical evaluator finds there is a positive benefit-risk balance for bendamustine in CLL and in refractory/relapsed indolent NHL. The clinical evaluator argues that assessment of risk cannot be made in a first-line indolent NHL and MCL setting, and consequently recommends rejection of the indication in this setting.

Pharmacokinetics (PK)

PK findings are described in the CER; a summary of bendamustine's PK characteristics and the deficiencies in the PK characterisation of bendamustine is part of the clinical evaluator's conclusions on PK.

PK data from Study SDX-105-103 (60 minute infusion) indicated a mean half-life of 4.9 h. This mean value takes into account the terminal disposition phase and most bendamustine is cleared from plasma more quickly, as illustrated below from the population PK analysis CP-07-002 based on data from SDX-105-103 below.

Figure 4: Plasma concentration versus time since last dose (h)



The mean half-life of the intermediate disposition phase was 0.72 h, comparable with the half-life indicated by Phase I studies of 30 minute infusions. The clinical evaluator concludes there is little risk of bendamustine accumulation with multiple doses. The long half-life in the terminal phase is consistent with some of the dose being distributed outside of the vascular space. Limited penetration of the blood-brain barrier was noted.

The clinical evaluator recommends patients with moderate to severe hepatic impairment avoid bendamustine, on the basis that the one study in hepatic impairment (98B03) did not include many patients with moderate or severe impairment. In mild impairment, there was no signal of any effect on C_{max} or AUC; confidence intervals were wide. A basis for any effect of hepatic impairment on bendamustine PK is present, since clearance is primarily non-renal.

CYP1A2 has been identified as an enzyme that metabolises the drug to the metabolites M3 and M4 but this appears to be a minor pathway; bendamustine also 'undergoes rapid chemical hydrolysis in an aqueous environment' and this accounts for significant metabolite formation.

A mass-balance study found 45.5% of the dose administered was recovered in urine and 25.2% was recovered in faeces; only 3.3% of the administered dose was recovered in urine as bendamustine, and <1% as M3 and M4 metabolites, suggesting metabolism via less well-characterised pathways.

Population PK analysis of data from Study SDX-105-103 suggested no impact of mild to moderate renal impairment on bendamustine PK but no patients with severe renal dysfunction were included in the population PK analysis. There was limited evidence that bendamustine can be dialysed to an extent.

There were no in vivo drug interaction studies and the absence of in vivo study of the effects of CYP1A2 inducers/inhibitors was considered a deficiency but the nonclinical evaluator viewed metabolism via CYP1A2 as a minor pathway and thought it unlikely that inhibitors and inducers of CYP450 enzymes would significantly alter the PK profile of bendamustine. The sponsor signalled that in vitro data suggest bendamustine may be a substrate for P-gp; there are no in vivo data. The nonclinical evaluator considered oral P-gp and BCRP inhibitors could increase systemic exposure to bendamustine (NB: enterohepatic recirculation of the drug) and may increase drug exposure in the CNS.

Efficacy

Dosage selection is explained on pages 36-37 of the CER. Dosage for pivotal studies was decided on the basis of results of published studies in CLL and relapsed / refractory indolent NHL.

Efficacy in first-line CLL (Binet stage B or C)

Evidence for efficacy in this setting is described in the CER. Evidence is provided by one pivotal study, 02CLLIII; the clinical evaluator notes two dose ranging studies for bendamustine in CLL (Riboseph 99CLL.2E-BG; Riboseph 99CLL.2E-DE) but does not consider these studies to be influential.

Study 02CLLIII

This was an open-label, randomised study in treatment-naïve patients with B-cell CLL (Binet Stages B-C) requiring therapy. It was conducted from 2002-2008, in 8 European countries (22/45 centres in Germany). The clinical evaluator emphasised the second of two Clinical Study Reports for this study as it included more mature ('follow-up') data.

Inclusion and exclusion criteria are listed in the CER. The study included patients <75 years old. CLL is often a disease of the elderly (median age at diagnosis is 72 years), so this diminishes generalisability of study results to Australian CLL patients.

Patients were randomised 1:1 to receive either:

- Bendamustine (n=162), 100 mg/m2/day (30 minute IV infusion) on Days 1 to 2 every 4 weeks; or
- Chlorambucil (n=157), 0.8 mg/kg per oral on Days 1 and 15, every 4 weeks

The clinical evaluator considered chlorambucil an appropriate comparator but noted that a combination fludarabine regimen may have been preferable (in a relatively young CLL patient, fludarabine/cyclophosphamide/rituximab may be offered in Australia). The sponsor states that chlorambucil is likely to be a first-line agent for elderly patients and the clinical evaluator accepts that the indication need not be narrowed to those patients for whom fludarabine combination therapy is not appropriate. The recommended dose regimen in first-line CLL in the Australian PI for chlorambucil is 0.1-0.15 mg/kg/day.

Follow-up was 1 year from end of treatment. Treatment duration depended on response after 3 cycles. Some 104/161 bendamustine patients received 6 cycles and 95/151 chlorambucil patients received 6 cycles. The mean number of cycles was 4.9 in each arm.

ORR and PFS were co-primary endpoints, assessed in the ITT population as adjudicated by an independent committee for response assessment (ICRA, n=3). ORR was based on best response and this needed to be sustained for at least 8 weeks. As well as complete response and partial response, objective response also incorporated nodular partial response. Patients were excluded from the per-protocol analysis if they failed to fulfil the 'need to treat' criteria of Cheson et al (1996).[27]

Mean age was 63.0 years (range 47-77 years) in the bendamustine arm, versus 63.6 years (35 to 78 years) in the chlorambucil arm. 60% of patients were male; almost all were Caucausian. 71% of patients were Binet stage B, 29% stage C. Time between CLL diagnosis and enrolment was median 7.75 months (bendamustine) versus 8.24 months (chlorambucil) or mean 18.8 versus 24.6 months. Given that the population is relatively young, consideration should be given to extent of co-morbity. This is detailed in the CER and there is no indication of a particularly high burden of significant co-morbidity.

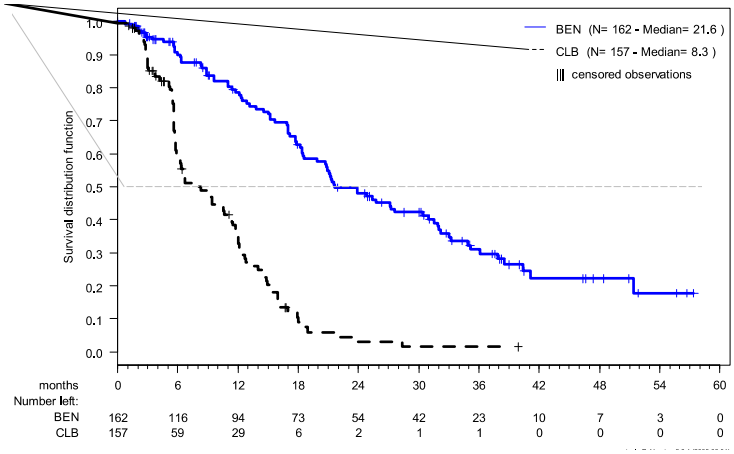
ORR was 67.9% for bendamustine versus 30.6% for chlorambucil. Complete responses were seen in 30.9% versus 1.9% respectively, and progressive disease was seen in 9.3% versus 33.8%. In those over 65 years of age, ORR was 63.5% for bendamustine versus 28.4% for chlorambucil (there were few patients >75 years of age). More stringent definitions of CR narrowed the CR difference between the two agents–it appears that the

[27] Cheson BD et al. National Cancer Institute - Sponsored working group guidelines for chronic lymphocytic leukemia: revises guidelines for diagnosis and treatment. Blood 1996;87:4990-4997.

'sensitivity analysis B' defined CR as, in part, 'lymph nodes ≤1.5 cm' which implies imaging to assess lymph nodes such as para-aortic and mediastinal that may not be palpated. The sponsor is invited to confirm this or clarify how definitions of CR differed from the primary analysis to 'sensitivity analysis B'.

Median PFS was 21.6 months (bendamustine) versus 8.3 months (chlorambucil) based on ICRA; the survival curve for PFS is shown below. The PFS difference was higher in males, lower in females; it was higher in those <65 years of age, lower in those over 65 years of age.

Figure 5: Study 02CLLIII – PFS based on ICRA – KM estimates; ITT population.



Secondary efficacy outcomes were broadly supportive for bendamustine. Regarding overall survival, 19.3% of bendamustine versus 26.1% of chlorambucil patients died in the observation period but statistical significance of any OS difference was not shown. The KM estimate of median OS was not available for bendamustine, versus 65.4 months for chlorambucil. A2010 follow-up revealed that 38% of the bendamustine arm versus 45% of the chlorambucil arm had died (not a statistically significant difference).

Regarding quality of life, results at the 'final' (as opposed to 'follow-up') analysis using a general cancer questionnaire favoured chlorambucil, strongly at times, for physical functioning, but bendamustine for cognitive functioning; no difference emerged in other domains (role/emotional/social functioning and global health status). The difference in physical functioning correlated with differences in symptomatic assessment that also favoured chlorambucil, especially after cycle 4, for the symptoms of nausea, vomiting, diarrhoea, loss of appetite and dyspnoea.

Anti-neoplastic therapy after EOT in the study was reported in 48.8% (bendamustine) versus 63.1% (chlorambucil).

Efficacy in previously untreated NHL and MCL

The sponsor nominates the paper by Rummel et al (2013)[24] as pivotal in support of efficacy in this indication. This paper reports the results of the StiL NHL 1-2003 study. An additional 11 studies are referenced by the sponsor in this context but the clinical evaluator does not consider any of these to be pivotal or supportive.

Study StiL NHL 1-2003 (Rummel et al 2013)

This was an open-label, randomised study of first-line treatment in patients with Stage III-IV, $CD20^+$ indolent NHL or MCL. It was conducted in Germany from 2003 to 2008, at 81 centres.

The types of B-cell lymphoma that could be studied are listed in the CER. The study group recommended alternative clinical trials incorporating Autologous Stem Cell Transplant

(ASCT) for patients <65 years with MCL, broadly consistent with the approach in Australia. The need to treat is described the CER (all MCLs were treated).

Patients were randomised to receive either:

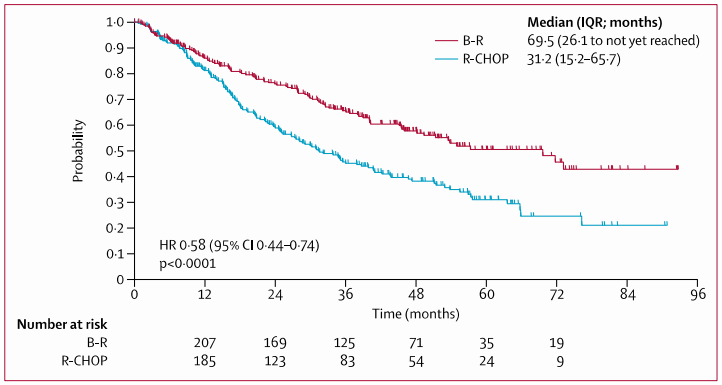
- Bendamustine (90 mg/m^2 by IV infusion over 30-60 minutes on Days 1 and 2 of a 4 week cycle for up to 6 cycles) + rituximab (B-R); or
- R-CHOP, comprising cyclophosphamide, doxorubicin, vincristine, predisone and rituximab

Dosing regimens are fully described in the CER. Treatment was stopped in the event of complete response or progressive disease. There was no consolidation or maintenance treatment; the clinical evaluator thought this a deficiency as '*it is currently unknown whether the significant PFS benefit seen with B-R induction therapy will be maintained, with or without subsequent maintenance treatment with rituximab*'. At least according to NCCN guidance, such subsequent therapy is optional (Table 3). The clinical evaluator considered R-CHOP an appropriate comparator in this setting.

Some 274 patients were randomised to B-R, 275 to R-CHOP. Median age was 63 to 64 years (range 31 to 83). Commoner subtypes were follicular lymphoma (54% of all subjects), MCL (18%) and marginal zone lymphoma (13%). Baseline characteristics were balanced.

The primary efficacy endpoint was PFS. PFS was estimated to be 69.5 months in the B-R arm, versus 31.2 months in the R-CHOP arm (hazard ratio 0.58, 95% CI 0.44-0.74). The KM curve is replicated below (Figure 6).

Figure 6: Kaplan Meier plot



The only common tumour subtype without a statistically significant PFS benefit with B-R was the marginal zone lymphoma. Given the difference in PFS, it is of note that ORR was similar across arms, although CR was higher in the B-R arm. Median OS had not been reached in either arm; 43 in the B-R arm versus 45 in the R-CHOP arm had died.

Efficacy in relapsed/refractory indolent NHL

The sponsor nominated four pivotal studies but the clinical evaluator considers only 2 to be influential (SDX-105-03, pivotal; SDX-105-01, supportive).

Study SDX-105-03 (pivotal)

This was an open-label, single-arm study in patients with indolent NHL, refractory to rituximab. Patients were also to have received 1 to 3 other prior chemotherapy regimes. The subtypes of indolent NHL eligible for inclusion are listed in the CER. The study was conducted from 2005 to 2007, in 24 centres across the USA and Canada.

- Patients received bendamustine 120 mg/m^2 by IV infusion over 60 minutes on Days 1 and 2 every 21 days, for a minimum of 6 and maximum of 8 cycles.

Some 102 patients were enrolled; 100 received study drug and were evaluable for efficacy and safety. 40/100 received <6 cycles; 60 received 6+ cycles. There was a minimum 6 months follow-up for patients.

Median age was 60 years (range 31-84 years); 65% were men; 88% were White. 62% had follicular lymphoma, 21% had B-cell CLL/ small lymphocytic lymphoma; 9% had extra-nodal marginal zone B-cell lymphoma; 7% had nodal marginal zone lymphoma; 1/100 had lymphoplasmacytic lymphoma. Some 8/100 were Ann Arbor Stage I, 16 were Stage II, 33 were Stage III and 43 were Stage IV. Some 16/100 patients had B symptoms. Further baseline characteristics are described in the CER.

The co-primary efficacy variables were ORR and duration of response. Response criteria are detailed in the CER.

An independent review committee (IRC) assessed responses. By IRC, ORR was 75% (14/100 complete responses, 3 unconfirmed complete responses, 58 partial responses). There was progressive disease in 7/100. Results were slightly better with investigator assessment. Median duration of response in those with IRC objective responses was 40.1 weeks. Median PFS was 40.3 weeks.

The clinical evaluator considered that ORR results and durability of response can, and do, show a clinically meaningful effect of treatment in this context.

Results were subjects to PK/PD analysis. The suggestion was that males had higher response rates than females (90% versus 77%) and that ORR was low in patients with WHO performance status of 2 (ORR = 33%). No PK exposure parameters were found to predict response.

Study SDX-105-01 (supportive)

This was an open-label, single-arm study of bendamustine monotherapy in 77 patients, mainly with indolent NHL refractory to rituximab (15/77 transformed NHL subjects were included, and 20/77 with a response to their most recent rituximab-containing regimen). The study was conducted from 2003 to 2006.

Patients were to have been treated with no more than 3 prior chemotherapy regimens (other than rituximab monotherapy) but the cohort can be considered as heavily pre-treated. Patients were given bendamustine 120 mg/m^2 IV infusion over 30 to 60 minutes on Days 1 and 2 of a 3 week cycle; patients with stable disease or better were given at least 6 cycles.

Some 77 patients were enrolled; 76 received study drug. Median age was 63 years (range 38-84 years); 89% were White; 54% were male.

The primary efficacy variable was ORR. ORR was 76.3% (primary analysis set, n=76), made up of 11/76 with a CR, 14/76 with unconfirmed CR and 33/76 with PR. There was progressive disease in 13/76. Median duration of response was 29 weeks. Median PFS was 31 weeks. In the subset with transformed disease, 10/15 obtained an objective response.

Other studies

These are described in the CER.

The Delegate agrees with the clinical evaluator that Study SDX-105-02, where bendamustine was used with rituximab, is not a pivotal study in support of bendamustine monotherapy. The relatively high ORR and CRR are noted but the study was uncontrolled.

The Delegate agrees with the clinical evaluator that Study 93BOP01, where bendamustine was used with vincristine + prednisone, is not a supportive study for bendamustine monotherapy. Results for ORR and 5 year survival were discordant (ORR was higher in the control arm, 5 year survival was higher in the bendamustine-containing arm).

Summary

The clinical evaluator considered that bendamustine at the proposed dose produces a clinically meaningful benefit in ORR, duration of response and PFS, but does note that no data demonstrate a survival benefit in this setting.

Safety

Safety in first-line CLL (Binet stage B or C)

Exposure in study 02CLLIII (bendamustine n=161 versus chlorambucil n=151) is described in the CER; 63-64% received 6 cycles. There is a summary of AEs in the CER, indicating a worse toxicity profile for bendamustine than for chlorambucil. For example, 11.2% of patients in the bendamustine arm withdrew due to unacceptable toxicity, versus 3.3% on chlorambucil but fewer patients in the bendamustine arm died (19.3% versus 27.2%).

Treatment with bendamustine led to more neutropenia (27.3% versus 13.9%), leukopenia (17.4% versus 3.3%) and pyrexia (24.8% versus 5.3%). Drug-related severe myelosuppression is tabulated in the CER. More patients used G-CSF in the bendamustine arm. This all translated into an imbalance in severe infections, for example, Grade 3-4 pneumonia was reported in 2.5% versus 0%.

Safety in previously untreated NHL and MCL

Exposure to bendamustine in this setting is less well characterised than in other settings, since the sponsor relies on one published paper (Rummel et al 2013[24]; B-R versus R-CHOP). The clinical evaluator notes that a definitive safety assessment cannot be made based on the information provided; various data limitations are listed.

Regarding haematological toxicity; B-R produces considerably less Grade 3-4 leukopenia and neutropenia than R-CHOP (and G-CSF usage was lower in the B-R arm), a similar amount of Grade 3-4 thrombocytopenia and anaemia, and considerably more Grade 3-4 lymphocytopenia.

For non-haematological toxicity, common AEs were broadly balanced across arms. There were significant imbalances for alopecia (0% for B-R; 100% for R-CHOP); paraesthesia (7% versus 29%); stomatitis (6% versus 19%); skin reactions (31% versus 15%); infectious episodes (37% versus 50%); and sepsis (<1% versus 3%). Severe pyrexia/ hills were more common with B-R than R-CHOP. Secondary malignancy was seen at similar rates across arms; in the B-R arm there was a case of myelodysplastic syndrome.

Safety in relapsed / refractory indolent NHL

Exposure to bendamustine in this setting is described in the CER; the clinical evaluator focused on the 176 patients in studies SDX-105-103 (single-arm; pivotal) and SDX-105-101 (single-arm; supportive); mean number of cycles was 5.3 and 4.8 respectively.

Bendamustine was toxic, with 35% discontinuing due to AEs (often haematological), and 37% having serious AEs. Gastrointestinal AEs, haematological AEs, fatigue, pyrexia and headache were common. Nausea was found to be predicted by higher Cycle 1 C_{max} but vomiting was not. In the pivotal study, there were 11 deaths, 4 of which were definitely or probably related to study drug. Pneumonia was a prominent serious AE, alongside febrile neutropenia. Infection was a significant issue; 20 patients in the pivotal study had fever or infection in combination with Grade 3-4 neutropenia. Secondary neoplasms were reported, for example 3 cases of myelodysplastic syndrome in 176 subjects. In the pivotal study, in those with WHO performance score of 0 at baseline (n=50), about half had a deterioration during the study; in those with a baseline of 1 (n=45), almost as many improved (n=9) as deteriorated (n=11).

Post-marketing experience

Over 100,000 patients have received bendamustine since 1994. Severe skin reactions have been identified in postmarketing pharmacovigilance.

Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's Office of Product Review (OPR), however the RMP Evaluator has asked for an updated Australian-Specific Annex to address several issues.

The Delegate proposes a condition of registration regarding the RMP as follows:

> *Implement bendamustine EU-RMP Version 2.0, dated 6 September 2013, with an Australian-Specific Annex considered acceptable by the TGA's RMP Evaluation Section, and any future updates. Before product launch, an updated Australian-Specific Annex must be accepted by the TGA's RMP Evaluation Section*.

Risk-benefit analysis

Delegate's considerations

Pharmacology – hepatic impairment

The clinical evaluator recommends patients with moderate to severe hepatic impairment avoid bendamustine, on the basis that the one study in hepatic impairment (98B03) did not include many patients with moderate or severe impairment. There is already a contraindication in patients with severe hepatic impairment (serum bilirubin >3 mg/dL). There is also a recommendation in the proposed PI to reduce the dosage by 30% in moderate hepatic impairment (serum bilirubin 1.2-3.0 mg/dL). *Can the sponsor clarify the basis for this recommendation, in the pre-ACPM response?*

Pharmacology – drug interactions

No in vivo studies were provided, despite in vitro evidence of the potential for drug-drug interactions mediated via P-gp and BCRP. The proposed PI notes a potential for interactions with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine; inducers (such as omeprazole) are not mentioned. Tobacco is also an inducer. There is no mention of risk around P-gp and BCRP interactions.

Efficacy – CLL

The clinical evaluator was concerned that the CLL study was in a younger patient group than may be seen in Australian practice. The sponsor argued that 'advanced age' did not alter PK of bendamustine (but too few elderly patients were sampled to draw firm conclusions). In SDX-105-103 (mainly indolent NHL; 21/100 had B-CLL), Cycle 1 AUC was similar across the age groups 16 to 64 years, 65 to 74 years and over 75 years. However, PK/PD correlations were weak in bendamustine studies, meaning similarity of PK across age groups does not provide strong evidence of similar efficacy. There remain few data about efficacy in CLL in elderly patients.

The clinical evaluator accepted comparison with chlorambucil. However, patients were young and there was no sign that this group had a very high burden of co-morbidities. A fludarabine-based comparator (such as FCR[28]) might be more relevant. FCR may produce better efficacy outcomes than chlorambucil. Comparison with chlorambucil may inflate the relative benefit of bendamustine in CLL. Even in the frail elderly where fludarabine-based

[28] FCR=fludarabine, cyclophosphamide and rituximab

therapy may not be feasible, both chlorambucil + rituximab and rituximab alone are preferred over chlorambucil alone (according to NCCN guidelines but not EviQ). See also discussion of indications below.

Regarding definition of CR, the relatively high values for bendamustine quoted in the proposed PI seem to be based on a clinical practice-based approach to assessment of response, for example no use of abdominal CT *(the sponsor should confirm this in the pre-ACPM response)*. Beyond ensuring that the PI communicates the exact definition of CR in a clear manner, the Delegate has no issue with this approach given the time when the protocol for the study was designed and also given the Delegate's understanding that imaging studies do not strongly influence the decision to treat relapsed disease.[29]

There was no assessment of eradication of minimal residual disease.

Efficacy – previously untreated indolent NHL, MCL

The sponsor notes:

Although Janssen are aware that the data to support iNHL is limited, an unmet clinical need was identified by clinicians in relation to this setting and submission of this data was in support of those clinicians who approached the company requesting access to bendamustine in this setting.

Despite the reliance on one published paper, the Delegate consider efficacy of B-R to be established in the setting of previously untreated indolent NHL and MCL, *relative to R-CHOP*. The study by Rummel et al[24] was large, apparently well-conducted and revealed a large effect. In the case of MCL, R-CHOP may be an appropriate comparator regimen only in a subset of patients. Likewise, treatment in indolent NHL is also individualised and R-CHOP may be appropriate first-line therapy only in a subset.

Safety – infection

Bendamustine is clearly immunosuppressive, with a risk of opportunistic infection. The significance of this depends on setting; in CLL the risk of infection is higher than with chlorambucil; in first line NHL the risk of infection is lower than with R-CHOP.

Safety – QT prolongation

There was a nonclinical signal that bendamustine may prolong the QT interval but there was no Thorough QT study. A Precaution in the proposed PI recommends that in patients with cardiac disorders, serum potassium (K+) should be >3.5 mEq/L and ECGs should be performed (no frequency is mentioned) – QT prolongation is not actually mentioned, except as an observed effect in overdose.

Safety in first-line indolent NHL/MCL

The Delegate agrees with the clinical evaluator that the information about safety in the 2013 paper published by Rummel[24] is not sufficient to allow risk-benefit assessment. However, in the Delegate's opinion the safety of bendamustine in first line indolent NHL/MCL can be informed by the toxicity profile observed in the two other settings, CLL and relapsed/refractory NHL. In addition, there is considerable postmarketing experience with bendamustine. Overall, and taking into account the magnitude of efficacy effect observed, the Delegate thinks that a risk-benefit assessment in first line indolent NHL/MCL can be made.

The toxicity profile of R-CHOP is in no small part from doxorubicin and R-CVP is also an available option. Risk-benefit can only be judged against a relatively toxic regimen.

[29] <http://www.uptodate.com/contents/evaluating-response-to-treatment-of-chronic-lymphocytic-leukemia?source=search_result&search=CLL+response+assessment&selectedTitle=14%7E150>

Indications

The wording of the CLL indication should reflect that the choice of comparator in 02CLLIII is more appropriate for an older cohort of patients, as per the EU approach:

> *First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.*

This is not an ideal solution in that bendamustine was not actually studied in an older/frail cohort and there is little experience of bendamustine in the elderly in the pivotal studies in this application. However, it is a reasonable compromise given the effect size observed in Study 02CLLIII.

There is discord between the proposed indication relating to relapsed/refractory indolent NHL and the dosage regimen applicable for that indication in that the dosage regimen specifies use in patients refractory to rituximab.

The clinical evaluator recommends that bendamustine be approved for the following indication in relapsed/refractory NHL:

> *Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.*

This is preferably to the sponsor's wording because it reflects the pivotal study's key inclusion criterion regarding refractoriness to rituximab.

In first-line NHL / MCL, the sponsor's proposed wording implies that CD20-negative patients could be treated with bendamustine monotherapy, which is not supported by the one pivotal study provided. Also, in the pivotal study, alternative clinical trials incorporating ASCT were recommended for patients <65 years with MCL. A supportable wording is:

> *Previously untreated indolent CD20-positive, Stage III-IV Non-Hodgkin's Lymphoma, in combination with rituximab.*
>
> *Previously untreated CD20-positive, Stage III-IV Mantle Cell Lymphoma, in combination with rituximab, in patients ineligible for autologous stem cell transplantation.*

Many patients who are candidates for ASCT were not studied in StiL NHL 1-2003. Also, it is unknown whether bendamustine treatment will affect ASC collection. While the same might be said for follicular lymphoma, use of ASCT in first-line therapy does not seem to be a widely established approach.

Use in children

The clinical evaluator notes that no paediatric data were submitted to the TGA, yet paediatric data were submitted to the European Medicines Agency (EMA) and the FDA. A paper about bendamustine in paediatric acute leukaemias has been published[30] but is not relevant to the current application.

Overall risk-benefit

The Delegate considers that the benefit-risk profile of bendamustine is favourable for the indications as modified above.

The advice of the Committee is requested. See below for specific questions.

[30] Fraser et al 2013, J Pediatr Hematol Oncol

Summary of delegate's issues

In the pivotal CLL study, comparison was with chlorambucil despite the study enrolling a relatively young group of patients without a high burden of co-morbidity.

Use in previously untreated indolent NHL and MCL is supported by one published study, with limited safety documentation. The comparator was R-CHOP but treatment is highly individualised in these conditions.

Proposed action

The Delegate had no reason to say that the application for bendamustine should not be approved for registration, in all indications requested (with some modification to the wording of all indications).

Request for ACPM advice

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

1. Should the CLL indication be modified to encompass only those 'first-line' patients for whom fludarabine-based treatment is not appropriate or can this be left to the discretion of the treating clinician?
2. Is there sufficient safety information in previously untreated indolent NHL and MCL, such as from the one published study and from bridging from other settings, to support registration?
3. In previously untreated indolent NHL and MCL, is the comparison with R-CHOP appropriate?
4. In what patient population, if any, is there a positive benefit/risk balance in MCL (that is, what is an appropriate wording for the indication?)

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.

Response from sponsor

Introduction

Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. It is currently registered in over 60 countries with various indications.

In Australia, bendamustine has been supplied intermittently under the Special Access Scheme (SAS) over a number of years with approximately 50 to 100 units supplied each month.

Janssen are seeking to register this New Chemical Entity for the treatment of Chronic Lymphocytic Leukaemia (CLL), Mantle Cell Lymphoma (MCL) and Indolent Non-Hodgkin's Lymphoma (iNHL).

The Delegate has recommended approval for use in all proposed indications, with some minor amendments to the wording.

This document has been prepared in response to the Delegate's Request for ACPM Advice dated 6 May 2014.

Issues raised by the delegate

Pharmacology - Hepatic impairment

The Delegate has requested clarification around the contraindication for use in patients with severe hepatic impairment and for a dose reduction in patients with moderate hepatic impairment. Janssen have contacted the owner of the clinical data and have been advised that there is currently no definitive data available in patients with severe hepatic impairment. However in the Study 98B03, the bendamustine pharmacokinetics was investigated in a group of patients with moderate to severe (30% to 70%) tumour or metastatic liver involvement as well as mild liver dysfunction (several fold increased plasma gamma-GT levels but normal or slightly elevated bilirubin) and a control group (without or small (that is, < 10%) tumour or metastatic liver involvement; bilirubin and gamma-GT remained at normal levels). There were no statistically significant differences in mean bendamustine pharmacokinetic parameters between the two groups. Therefore, a bendamustine dose reduction could not be recommended in patients with mild as well as moderate to severe (that is, up to 70 %) tumour or metastatic liver involvement and mild dysfunction of the liver.

In comparison, the pharmacokinetics of bendamustine has not been well investigated in patients with moderate to severe liver dysfunction/cholestasis. Dependency of AUC and total body clearance on serum bilirubin was determined in 32 patients (18 male, 14 female) in the Studies 98B03 and 20BEN D1 with a bendamustine hydrochloride dosage ranging from 120 mg/m^2 to 280 mg/m^2 to provide more complete data with respect to this problem. Patients with a normal renal function (creatinine clearance ≥ 60 mL/min) were included in the analysis. In previous investigations it was shown that neither age nor gender of tumour patients nor bendamustine dose significantly influenced total body clearance of bendamustine. AUC and total body clearance of bendamustine correlate significantly ($p < 0.05$) inversely with serum bilirubin in the investigated range of normal and elevated bilirubin serum levels. The data presented was in good accordance with the metabolic behaviour of bendamustine. Several pharmacokinetic studies showed that bendamustine underwent strong metabolisation by hydroxylation, N-dechloroethylation, N-demethylation, and glutathione S-conjugation. Numerous metabolites, mainly Phase II conjugates, were identified in the bile (Teichert J, Sohr R. et al. submitted in Drug Metab Disp). Hence, it was assumed that hepatic metabolic clearance and biliary excretion are decreased if moderate to severe liver dysfunction occurs.

Pharmacology drug interactions

The Delegate has requested comment on potential interaction with CYP1A2 inducers and P-gp/BCRP class products. The following data is available:

CYP1A2 inducers: Omeprazole inhibits CYP2C19 and CYP3A4. In vitro studies using primary cultures of human hepatocytes indicated that bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5 nor induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 (Study DM-2005-004). However the metabolism of bendamustine in the presence of substances selectively metabolised via the P450 enzyme system was studied in vitro in a GLPcompliant study (no. 99/37/KLG/01). Co-incubation of bendamustine (200 µM) with inhibitors (concentrations 0.1 µM, 1 µM, 50 µM) showed that the selective CYP1A2 inhibitor furafylline was the only P450 inhibitor to notably reduce M3 and M4 production at the lowest concentration of 0.1 µM. The inhibitors 4-methylpyrazole (CYP2E1), quinidine (CYP2D6), and sulfaphenazole CYP2C9/10) had no notable effect on M3 and M4 production. Ketoconazole (CYP3A4) and tranylcypromine (CYP2C19) showed inhibitory effects on M3 and M4 production only at the highest concentration (50 µM).

P-gp and BCRP interactions: The role of active transport systems in bendamustine distribution has not been fully evaluated. In vitro data suggest that P-glycoprotein, breast

cancer resistance protein (BCRP), and/or other efflux transporters may have a role in bendamustine transport.

In a study conducted in 2000 by Ribosepharm pharmacology (Study #0640.00.C7.02) the results showed that BCRP over expression resulted in a significant decrease in sensitivity to bendamustine (8.4 fold). In addition, the p-glycoprotein over expressing subline (MCF7 Ad2000) displayed a 7.6 fold increase in resistance to bendamustine compared to the parental cells. This value was not significant because the experiment was performed only once. However it does indicate that p-glycoprotein over expression might also confer resistance to bendamustine. These decreases in sensitivity to bendamustine are minor in comparison to the effect of these resistance mechanisms (p-gylcoprotein and BCRP) have on the sensitivity to their substrates doxorubicin and mitoxantrone (2772, 74 and 94 fold decrease, respectively).

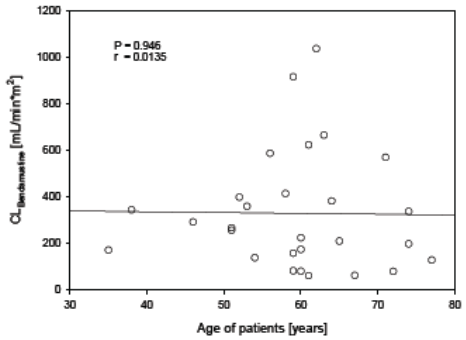
The following text has therefore been included in the PI

> *'The role of active transport systems in bendamustine distribution has not been fully evaluated.* In vitro*data suggest that P-glycoprotein, breast cancer resistance protein (BCRP), and/or other efflux transporters may have a role in bendamustine transport. Inhibitors of these transporters may increase the plasma concentration of bendamustine. Based on* in vitro*data, bendamustine is not likely to inhibit metabolism via CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.'*

Efficacy CLL

Adult patients the EU pharmacokinetic studies with bendamustine HCl included female and male patients with an age ranging from 35 to 84 years. There was no indication that advanced age of the patients changed the pharmacokinetic behaviour of bendamustine HCl.

Figure 7: Regression analysis between age of patients and clearance of bendamustin HCl in 28 tumour patients (Studies 98B02, 98B03, 20BEND1).



Although Janssen acknowledges the patient numbers are small (n=28), there is no reason to expect that this will not be representative of a larger group and the many years of clinical experience with the product in other countries (not quantifiable) has not provided any safety signal to indicate otherwise.

The definition of CR was defined according to when the following criteria were met for at least 8 weeks after first response was observed:

- Enlarged lymph nodes are no longer detectable by palpation (X-ray or ultrasound are optional);
- Absence of hepatomegaly or splenomegaly, confirmed by palpation. Computerized tomography (CT) and ultrasound were optional;
- No disease symptoms (B-symptoms);

- Blood counts:
  - Lymphocytes ≤ $4.0x10^9$/L
  - Neutrophils ≥ 1.5x109/L
  - Platelets > $100x10^9$/L
  - Haemoglobin > 11 g/dL (without blood transfusion)
- Bone marrow biopsy (histology and cytology) was to be performed 8 weeks after meeting the above criteria. The bone marrow had to be at least normocellular for age, with less than 30% lymphocytes.

Patients were assessed for response after three cycles of treatment. Two additional cycles were recommended for patients with complete response (CR) or partial response (PR), up to a maximum limit of six cycles in total. The response criteria according to the National Cancer Institute Sponsored Working Group guidelines for CLL had to be met for at least 8 weeks.

Janssen confirm that CT scan was not mandatory in the study but left to the discretion of the physician. A bone marrow biopsy was used for definitive confirmation.

Efficacy iNHL and MCL

The sponsor acknowledges and agrees with the Delegate's view that the efficacy of bendamustine in iNHL and MCL is established with the *Rummel et al* study as this was a large well designed and established published clinical trial.

Janssen also believe, like the Delegate, that although the published paper does not provide the normal level of safety information, safe use of the product in this group can be extrapolated from the results of the other studies provided.

In addition use of this product is well established in many countries and supply via SAS has been occurring intermittently in Australia since 2010.

Clinicians have also advised that the iNHL indication provides the greatest unmet need and is the reason why Janssen have submitted this data in support of those clinicians, even though the sponsor is aware this was an unconventional dataset.

Safety infection

Bendamustine has shown to display greater potency towards cells of the B-lineage (both normal and malignant) compared to other alkylators such as chlorambucil. This was evident in the greater potency of bendamustine relative to chlorambucil in the treatment of CLL (Cephalon study 02CLLIII). Despite a slightly higher infection rate in the bendamustine arm of the 02CLLIII study, it is noteworthy that the duration of neutropenia for patients in the bendamustine arm was 21 days which was considerably shorter compared to the 34 days in the chlorambucil arm.

R-CHOP is a more aggressive chemotherapy treatment and is well known for decreasing white blood cell count.

In a Rummel et al study[24]: NHL-2003 a greater number of infectious complications in the R-CHOP group compared to the BR group was seen, this is consistent with the greater number of hematologic adverse events and granulocyte count decrease (72% versus 54%) respectively reported. Fever and bacterial infection had a higher incidence in the R-CHOP treatment group. This higher incidence is related to the higher incidence of Grade 4 granulocyte count decreased in the R-CHOP treatment group (63% versus 24%). However it should be noted that the number of severe and life-threatening infections was similar between the 2 treatment groups and there was no marked difference in the number of severe infections.

Safety QT prolongation

Nonclinical data for bendamustine showed no effect on action potential parameters, including amplitude, resting potential, maximal rate of depolarization, and action potential duration under both normal (60 pulses per minute (ppm)) and slow (20 ppm) stimulation rates over a concentration range of 1.5 to 7.5 µg/mL (Sstudy 20010339 PECM). Bendamustine (20 µM and 200 µM) dose-dependently inhibited the potassium (hERG) tail channel current by 20% and 65%, respectively. It had no effect at 2 µM (refer to RCC Study No. 853896). These in vitro cardiovascular studies indicated that bendamustine had a low arrhythmogenic risk at concentrations equivalent to, or slightly greater than those being observed in patients (Study DP-2007-043). The C_{max} levels seen clinically are in the range of 5 to 7 µg/mL which is 12.5 to 17.5 micromolar. Therefore from the nonclinical data there was no suggestion of cardiac arrhythmic risk.

In a report done by Clinilabs Inc. on the 11th of November 2007, an analysis of the electrocardiographic effects of bendamustine was completed. Three studies were chosen and specific ECG recordings at particular times were done. Two of these studies were conducted in Belgium (20BEN D1 and 20BEN03) and one in Japan (2006001). In the setting of a drug with nonclinical data that does not suggest risk and clinical impact on a severe/life threatening condition (cardiac arrhythmia) a process for analysis of bendamustine effects on cardiac repolarisation consistent with standards for Thorough QT studies was applied. The data allowed the conclusion that there were no indicators of marked risk of cardiac repolarisation changes. The data showed no clear cut relationship between bendamustine administration and cardiac repolarisation. Assessments were made near the time of the peak plasma concentration (T_{max}) during each administration, allowing measurement at a total of 48 times for these 9 patients. There were no changes from pre-therapy for the group means at any time point nor were there changes noted at 3 weeks of follow up. This is data based on 9 patients treated with 2 cycles and 6 who underwent 3 cycles.

Indications

The following table summarises the sponsor's proposed and the TGA proposed indications.

Table 10: Summary of sponsor and TGA proposed indications

Proposed Janssen Indication	Proposed TGA Indication
First line treatment of Chronic Lymphocytic Leukaemia (Binet stage B or C)	First line treatment of Chronic Lymphocytic Leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
Previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients	Previously untreated indolent CD20-positive, stage III-IV Non-Hodgkin's lymphoma, in combination with rituximab Previously untreated CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation
Relapsed/Refractory indolent Non-Hodgkin's lymphoma.	Indolent Non-Hodgkin's Lymphoma that has progressed during or within six months of treatment with rituximab or rituximab-containing regimen.

The proposed changes to the indications suggested by the Delegate are acceptable to the sponsor.

Some concern has been raised by clinicians around the proposed restriction in patients with indolent Non-Hodgkin's lymphoma, to those who have progressed during or within six months. Janssen understand the Delegate's proposal to add this restriction to align with the trial definition of refractory patients, however the Janssen Clinical Advisory Board were consulted on the proposed wording and some concern was raised over the

number of patients that would be denied treatment by this restricted indication. A letter from a medical professional was enclosed with the sponsor's response.

As an alternative the sponsor counter-proposes to retain the original indication wording, but to include additional wording in the Clinical Trials section of the PI advising that refractoriness was defined as disease progression within a 6 month time of treatment with rituximab.

Use in children

The sponsor acknowledges that paediatric data was not submitted to TGA at the time of submission, as the data available was not aligned with the proposed indications. A report was subsequently submitted with the sponsor response for information purposes only.

Conclusion

Janssen supports the TGA recommendation to approve Ribomustin for use in CLL, MCL and iNHL and we look forward to providing clinicians and patients with these diseases, access to an alternative, efficacious and safe treatment option.

Advisory committee considerations

The submission seeks to register a new chemical entity.

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ribomustin powder for intravenous infusion containing 25 mg and 100 mg of bendamustine hydrochloride to have an overall positive benefit–risk profile for the amended indication**;**

> *First line treatment of chronic lymphocytic leukaemia (Binet stage B or C).*
>
> *Efficacy, relative to other first line agents than chlorambucil, has not been established*
>
> *First line therapy of indolent Non-Hodgkin's Lymphoma (iNHL) and Mantle Cell Lymphoma (MCL) where autologous stem cell transplantation is not clinically appropriate. Ribomustin should be used in combination with rituximab in CD20-positive patients.*
>
> *Relapsed / refractory indolent Non-Hodgkin's Lymphoma.*

In making this recommendation the ACPM noted the efficacy of treatment with bendamustine in combination with rituximab (B-R) for first-line treatment of indolent NHL and MCL in patients with CD20 positive Stage III/IV disease have been satisfactorily established in the one published study, Rummel et al (2013)[24]. The ACPM considered that sufficient bridging safety data exist and noted that there is little difference in the safety profile observed across the different indications.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Ddelegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

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

1. *Should the CLL indication be modified to encompass only those 'first-line' patients for whom fludarabine-based treatment is not appropriate, or can this be left to the discretion of the treating clinician?*

The ACPM advised that whilst fludarabine based regimens are currently the standard of care for those CLL patients who are 'fit' enough to undergo this therapy, this may not continue to be the case. The statement similar to that in the US PI that efficacy, relative to first line agents other than chlorambucil, has not been established would be appropriate.

2. *Is there sufficient safety information in previously untreated indolent NHL and MCL, e.g. from the one published study and from bridging from other settings, to support registration?*

The ACPM noted the concerns of the evaluator that complete safety information had not been provided and that regulatory requirements are such that registration (in the absence of a compelling clinical need) should not occur.

The ACPM was disappointed that a complete safety report from the single published study, Rummel et al (2013), for this indication was not provided. However, the ACPM noted that there is little difference in the safety profile observed across the different indications (for example CLL versus RRiNHL). Therefore the ACPM was of the view that sufficient bridging safety information exists in support of this indication.

3. *In previously untreated indolent NHL and MCL, is the comparison with R-CHOP appropriate?*

The ACPM advised that the R-CHOP regimen is considered to be an appropriate comparator for the B-R regimen for the first-line treatment of indolent NHL and MCL. R-CHOP has been the standard of care in untreated MCL, albeit not a very effective one. Similarly, R-CHOP is commonly used for untreated indolent NHL in cases where rapid response is considered desirable.

For patients younger than 65 years with MCL, where the intention is to proceed to autologous stem cell transplantation, alternative regimens are generally used and were recommended by the study group (NHL1-2003).

4. *In what patient population, if any, is there a positive benefit-risk balance in MCL (i.e. what is an appropriate wording for the indication?)*

The aggressive nature of MCL was noted. Positive benefit exists with the B-R combination for older patients as first line treatment and with single agent bendamustine in the setting of relapsed/refractory MCL. The ACPM noted the discouragement to enrol patients under the age 65 years from first line therapy Study NHL1-2003; however, alternative clinical trials incorporating autologous stem cell transplantation were recommended for these patients by the study group. The indication statement could be modified to

> *first line therapy of indolent NHL and MCL as first line therapy of iNHL and of MCL where SCT is not clinically appropriate*.

In addition, rituximab based immunochemotherapy regimens are the standard **initial** treatment of patients with symptomatic advanced indolent NHL and MCL.

R-CHOP is the most frequently used regimen for the treatment of indolent NHL. The variety of possible treatment regimens is noted. Most recent study (BRIGHT study) a comparison of R-CHOP, R-CVP and B-R has demonstrated non inferiority. The addition of rituximab maintenance therapy remains to be addressed (the MAINTAIN trial).

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ribomustin (bendamustine HCl) powder for infusion for injection containing bendamustine hydrochloride 25 mg and 100 omg for

> *First-line treatment of chronic lymphocytic Ieukaemia (Binet stage B or C). Efficacy relative to first-line the rapies other than chlorambucil has not been established.*
>
> *Previously untreated indolent CD20-positive, stage 111-IV Non-Hodgkin's lymphoma, in combination with rituximab.*
>
> *Previously untreated CD20-positive, stage 1/1-IV Mantle Cell Lymphoma in combination with rituximab, in patients in eligible for autologous stem cell transplantation.*
>
> *Relapsed/Refractory indolent Non-Hodgkin's lymphoma.*

Specific conditions of registration applying to these goods

The Ribomustin EU Risk Management Plan (EU-RMP), version 2.0, dated 6 September 2013, revised as specified by the Australian-Specific Annex (Version 2.1 dated 20 May 2014), and any future updates, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Ribomustin at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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