Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for ibrutinib

Proprietary Product Name: Imbruvica

Sponsor: Janssen-Cilag Pty Ltd

March 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASA	Australian Specific Annex
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
BCR	B-cell antigen receptor
Btk	Bruton's Tyrosine Kinase
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukaemia
C_{max}	maximal concentration
CR	complete response
CT	computed tomography
del17p	deletion in the short arm of chromosome 17p13.1
DDI	drug-drug interaction
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core 30
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL Five-Dimension
ESMO	European Society for Medical Oncology

Abbreviation	Meaning
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue
FDA	Food and Drug Administration
Hb	Haemoglobin
HR	hazard ratio
IRC	Independent Review Committee
ITT	intent to treat
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NCCN	National Comprehensive Cancer Network
NE	not estimable
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PFS	progression-free survival
P-gp	permeability-glycoprotein
PK	pharmacokinetic
PR	partial response
PRL	partial response with lymphocytosis
SAE	serious adverse event
SD	stable disease/standard deviation
SLL	small lymphocytic lymphoma

Abbreviation	Meaning
SMQ	Standardised MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	Time to achieve maximal concentration
USA	United States of America
WM	Waldenström's macroglobulinaemia

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	15 April 2015
Date of entry onto ARTG	20 April 2015
Active ingredient:	Ibrutinib
Product name:	Imbruvica
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
Dose form:	Capsule
Strength:	140 mg
Container:	Bottle
Pack sizes:	90 and 120 capsules
Approved therapeutic use:	Imbruvica is indicated for the treatment of: • Patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy or as first line in patients with CLL with 17p deletion • Patients with mantle cell lymphoma who have received at least one prior therapy.
Route of administration:	Oral
Dosage:	MCL: 560 mg (four capsules) once daily CLL/SLL: 420 mg (three capsules) once daily
ARTG number :	228499

Product background

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

Imbruvica is indicated for the treatment of:

- *Patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy or as first line in patients with CLL with 17p deletion*
- *Patients with mantle cell lymphoma who have received at least one prior therapy*

Ibrutinib inactivates Bruton tyrosine kinase and thereby inhibits B cell antigen receptor (BCR) and chemokine receptor signalling pathways in malignant B cells, disrupts integrin dependent B cell migration and adhesion in vitro and promotes egress of malignant B cells from tissues and prevents homing of these cells to tissues in patient without clinically adverse effects on levels of normal B cells.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 April 2015.

Table 1: Imbruvica regulatory status in major countries

Country	Indication	Submission Date	Approval Date	Conversion to full approval
US	MCL who have received at least one prior therapy. Accelerated approval was granted for this indications based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.	28 Jun 2013	13 Nov 2013 (accelerated approval)	Pending on Phase III Study PCI – 32765MCL3002 as confirmatory
	CLL who have received at least one prior therapy	28 Jun 2013	12 Feb 2014 (accelerated approval)	28 Jul 2014
	CLL with del17p	7 Apr 2014	28 Jul 2014	N/A
	Waldenström's macroglobulinemia (WM)	17 Oct 2014	29 Jan 2015	N/A
EU	Treatment of adult patients with relapsed or refractory (MCL	30 Oct 2013	21 Oct 2014	N/A but Phase III Study PCI-32765MCL3001 is a post marketing requirement
	Treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of del17p or TP53 mutation in patients unsuitable for chemo-immunotherapy	30 Oct 2013	21 Oct 2014	N/A
	WM	12 Nov 2014	pending	
Canada	Imbruvica (ibrutinib) is indicated for the treatment of patients with CLL, including those with del17p, who have received at least one prior therapy, of for the frontline treatment	16 April 2014	17 Nov 2014	N/A

Country	Indication	Submission Date	Approval Date	Conversion to full approval
	of patients with CLL with del17p. Clinical effectiveness of Imbruvica in the frontline setting is based on the benefit observed in CLL paints with del17p who have received at least one prior therapy. Clinical trial data in the frontline setting are very limited.			
	MCL who have received at least one prior therapy	23 Oct 2014	pending	
Switzerland	Treatment of adult patients with MCL, characterised by translocation t (11,14) an/or expression of cyclin D1 in whom no partial response (PR) was achieved with prior therapy or progression after prior therapy	10 Jan 2014	10 Nov 2014 (accelerated approval)	N/A, but Phase III Study PCI-32765MCL3001 is a post-marketing requirement
	Treatment of adult patients with CLL who have received at least one prior therapy	30 Jun 2014	pending	

Product Information

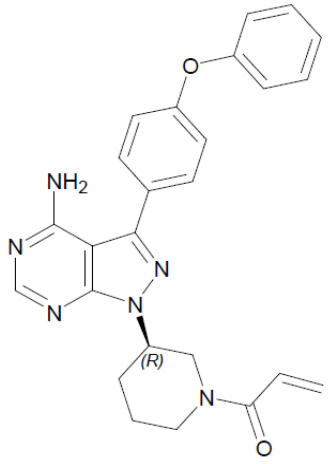
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

Ibrutinib has the following structure as shown in Figure 1.

Figure 1: Chemical structure of ibrutinib.



Ibrutinib is manufactured by chemical synthesis as a white to off-white solid. It contains one stereocentre and is synthesised as the *R* configuration. The electrophilic acryloyl group covalently interacts with a cysteine residue in the Btk active site (Cys-481).

Ibrutinib is practically insoluble in water across the physiological pH range. It has a pKa of 3.74 in aqueous solution containing methanol as a co-solvent. It is manufactured as the most thermodynamically stable polymorph, Form A. No conversion from Form A to other polymorphic forms was observed upon storage or during micronisation. The particle size is adequately controlled.

The drug substance specification includes limits for eight specified impurities. The enantiomer is controlled to not more that 1.0%. The specification also includes a test for residual diisopropylethylamine (DIPEA) base with a proposed limit of 80 ppm. This base is not specifically referred to in TGA adopted impurity/solvent guidelines. The proposed limit is not toxicologically qualified. This solvent has not been detected in batches synthesised with the proposed commercial process. All results were reported as < 16 ppm or < 60 ppm, depending on the limit of quantitation applied at the time of manufacture.

Ibrutinib exhibits good stability and the data provided supports a retest period of 24 months.

Ibrutinib is not subject to BP/Ph. Eur or USP monographs

Drug product

The drug product is an immediate release hard gelatin oral capsule containing 140 mg of ibrutinib.

The capsules are size 0, opaque white and marked with 'ibr 140 mg' in black ink. The excipients of the capsule fill are conventional for the dosage form.

The proposed commercial capsule fill is manufactured conventionally by dry granulation. Capsules manufactured by this process were used in the majority of the pivotal clinical studies.

The drug product specification includes control for three specified degradation products to limits that have been toxicologically qualified and any unspecified degradation products to limits in accord with TGA adopted guidelines. A dissolution limit of Q = 80% in 30 minutes is applied, using paddles at 75 rpm in 900 mL of 0.3% surfactant (SLS) in purified water.

Stability data generated under long term, intermediate and accelerated conditions support a shelf life of 24 months when stored below 30°C.

The drug product aspects are acceptable.

Biopharmaceutics

Ibrutinib has low water solubility at physiologically relevant pH and high permeability. It is classified as a 'Biopharmaceutic Classification System' Class II compound.

The following bioavailability and bioequivalence data have been submitted:

Study PCI-32765CLL1011 showed that the absolute oral bioavailability a 560 mg capsule dose (4 x 140 mg capsules) F_{abs} was 2.9% when administered under fasting conditions and had high inter subject variability. When ibrutinib was administered with a meal, with or without grapefruit juice, F_{abs} was approximately 16%, and 8%, respectively. Ibrutinib bioavailability is limited by extensive first pass metabolic clearance. The proposed Product

Information states that ibrutinib must not be taken with grapefruit juice; this could be extended to other naringin containing foodstuffs.

Study PCI-32765CLL1001 assessed the effect of food (and timing) on single oral doses of 420 mg ibrutinib (3 x 140 mg capsules) administered under fasting conditions or 30 minutes before, 30 minutes after or two hours after a high fat breakfast. Compared with fasted condition, ibrutinib C_{max} was 2.6, 3.2, and 3.9 fold higher when dosed 30 minutes before, 30 minutes after, or two hours after a high fat breakfast, respectively. AUC_{last} was 1.6, 1.9, or 1.8 fold higher. The company considers these results support the recommendation that the capsules may be administered with or without food.

Early development drug product capsule formulations were used in Phase I and Phase II clinical studies only. These were manufactured by different processes, with different formulations and at a different manufacturing site to the capsules used in the majority of the pivotal studies. Comparative dissolution data were provided to show that the capsules used in the earlier studies had similar dissolution profiles to the capsules used for the pivotal studies.

No formal relative bioavailability studies were conducted.

The capsule formulation used in the pivotal studies is the same as the proposed commercial formulation, apart from colour and imprinting. Comparative dissolution data showed that the differences in colour and imprinting did not change the dissolution profiles of the capsules and are not expected to affect bioavailability.

In summary, systemic exposure of ibrutinib after capsule dosing is variable.

Quality summary and conclusions

Registration is recommended in respect of chemistry, manufacturing and controls and biopharmaceutics aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical dossier was compliant with the relevant ICH guideline on the development of anti cancer pharmaceuticals. The overall quality of the dossier was high, with all pivotal safety studies conducted under GLP conditions.

Pharmacology

Primary pharmacology

Ibrutinib binds to the active site of Btk, an intracellular tyrosine kinase involved in BCR and chemokine receptor signalling in B cells. Binding of ibrutinib to the active site of Btk is through a stable covalent bond which leads to irreversible binding. In vitro studies have demonstrated that ibrutinib, which is the *R* enantiomer of PCI-31523, inhibits Btk with greater efficiency compared to the *S* enantiomer and dihydrodiol metabolite M37 (IC50s of ~0.4, 1.3 and 6.2 nM, respectively). Ibrutinib is a moderately selective Btk inhibitor but also inhibits other related Tec and Src/Abl family kinases, including Blk (B lymphocyte kinase, IC50 0.9 nM) and eight others (Bmx/Etk, Fgr, Lck, Yes/YES1, Tec, Csk, EGFR, Brk) with an IC50 of <10 nM. In addition, ErbB4/HER4 is inhibited by ibrutinib with an IC50 in

the sub-nanomolar range (IC50 0.64 nM). ErbB4/HER4 is inhibited by afatinib, which also forms a covalent bond with a cysteine present in the active site.[1]

In vitro cellular assays demonstrated ibrutinib inhibits B cell activation and Btk mediated cell signalling. Concentration dependent inhibition of phosphorylation of the Btk substrate, PLC-γ, was demonstrated in normal B cells and in MCL cell lines. Inhibition of PLC-γ phosphorylation, and phosphorylation of the downstream kinase, ERK was also demonstrated in a follicular lymphoma cell line (IC50 20 nM for PLC-γ and 15 nM for ERK). Ibrutinib also reduced BCR and chemokine-stimulated migration and adhesion to fibronectin and vascular cell adhesion molecule (VCAM)-1 in MCL cell lines and primary CLL cell cultures. Ibrutinib at 10 nM completely prevented upregulation of the early lymphocyte activation marker CD69 on B cells, while it inhibited the activation of T cells (which do not express Btk) only at a 1000-fold higher concentration (10 μM). In vitro, ibrutinib at 200 nM led to near complete occupancy of Btk in human PBMCs. Ibrutinib occupancy at the Btk active site correlates with inhibition of B cell activation. Complete or near complete occupancy of Btk in B-cells and splenocytes was achieved by IV, IP, SC and oral administration of ibrutinib, but a higher dose was required for the oral route. Occupancy rates decreased over 24 hours, which is likely due to Btk protein turnover as the binding of ibrutinib to Btk was shown to be irreversible.

The effect of ibrutinib on the growth of lymphoma cell lines was assessed in vitro, with variable inhibition observed. In primary CLL cells, growth was dose-dependently inhibited, by up to 69% following incubation with 1 μM ibrutinib. In DLBCL cell lines, ibrutinib inhibited growth in CARD11 wildtype cells with an EC50 of 1-2 nM. In contrast, much higher concentrations of ibrutinib were required to inhibit growth in a CARD11 mutated DLBCL cell line (EC50 12 μM). The effect of ibrutinib on growth of MCL cell lines varied from ≥50% growth inhibition at ibrutinib concentrations ≥100 nM in Mino cells, to <20% growth inhibition at the maximum ibrutinib concentration tested (10 μM) in Maver-1 cells. Mino cells appeared to develop resistance to ibrutinib following continuous culture, which was maintained after 16 days culture in the absence of ibrutinib. The sponsor proposed that the mechanism involved increased Mek activity. However, the western blot data did not provide conclusive evidence for this hypothesis, with the poor quality in terms of individual bands and presentation of the blots limiting interpretation of this data. Therefore, the clinical relevance of resistance to ibrutinib in this MCL cell line is unclear.

Daily dosing in dogs with spontaneous canine Non-Hodgkin lymphoma was associated with Btk occupancy in PBMC and lymph nodes up to 24 hours post-dose. Efficacy observed during the dog study was difficult to interpret because of the lack of a control group. In vivo mouse models of MCL, CLL, non-Hodgkin's lymphoma and DLBCL demonstrated efficacy of ibrutinib. In SCID mice inoculated with Mino cells (MCL cell line) ibrutinib (12 mg/kg/day) decreased clinical signs and disease progression. Similarly, treatment with ibrutinib (2.5 and 25 mg/kg/day) for one week suppressed CLL cell numbers in an adoptive transfer model in SCID mice using TCL1-192 cells (CLL cell line). In SCID mice with implanted DLBCL tumours, ibrutinib (3-12 mg/kg/day) dose-dependently decreased tumour growth. Similarly, in SCID mice bearing DOHH2 tumours, ibrutinib (30-90 mg/kg/day IV, 5-120 mg/kg/day IP or 20-50 mg/kg/day PO) dose-dependently inhibited tumour growth.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacology studies revealed ibrutinib (10 μM) also inhibits the dopamine transporter, sodium channel, tachykinin receptor and adenosine A2A receptor. Ibrutinib

[1] Nelson et al. *Afatinib: emerging next generation tyrosine kinase inhibitor for NSCLC.* OncoTargets and Therapy 2013: 6; 135-143.

inhibits the dopamine transporter with an IC50 of 0.5 μM, more than 1000× higher than the IC50 for Btk.

Specialised safety pharmacology studies covered the cardiovascular, respiratory and CNS systems. There was no effect of ibrutinib (2.5-150 mg/kg) in SD rats on the CNS and respiratory systems. Ibrutinib and its major metabolite, PCI-45227, inhibited hERG channels in vitro (IC50 0.97 and 9.6 μM, respectively, 96 and 415 fold higher than the clinical free fraction C_{max}). However, ibrutinib did not prolong QT interval in conscious telemetered beagle dogs (1.5-150 mg/kg). Instead, ibrutinib shortened QTcV interval, decreased heart rate, prolonged RR interval and increased pulse pressure at doses ≥24 mg/kg. Reduced heart rate and increased RR interval were also observed following repeated dosing of ≥30 and ≥60 mg/kg/day ibrutinib in female and male beagle dogs, respectively (relative exposures of ≥3.3 and ≥6.8 based on C_{max}). These effects were reversible but are of potential clinical significance given the relatively low exposure ratio.

Pharmacokinetics

Absorption

Ibrutinib was rapidly absorbed following oral, SC or IP administration in rodents. The speed of absorption was similar between rats (0.08-2.5 h), dogs (0.5-4 h) and humans (0.5-2 h). Oral bioavailability was generally low in rats and dogs (5-25%), with extensive first pass metabolism demonstrated in rats. Comparisons of ibrutinib concentration between portal and jugular vein plasma indicated that 34-73% of ibrutinib was absorbed from the gastrointestinal tract, but only 11-25% reached the systemic circulation. Exposure to ibrutinib was variable, and while exposure (as AUC) generally increased with dose, the increase was generally dose proportional only in male rats and not female rats or dogs. Exposures in female rats were generally higher than in male rats. In dogs, exposure was generally greater than dose proportional. In rats and dogs, exposure to ibrutinib increased with repeated dosing, indicating drug accumulation. Accumulation of ibrutinib was not apparent in humans. Systemic plasma half-life was similar between animals and humans, ranging from 1-6.4 h in rats and dogs, and 3-11 h in humans.

Distribution

Ibrutinib was highly bound to plasma protein from mice, rats, dogs and humans (96.2-99.5%), and showed higher binding affinity for human serum albumin compared to α1-acid glycoprotein. The extent of covalent binding to albumin, plasma, haemoglobin (Hb), liver and kidney S9 fractions and liver microsomes was relatively low compared to binding to Btk. The blood to plasma ratio indicated limited distribution into red blood cells. Following IV dosing in rats and dogs the volume of distribution was greater than body water indicating extravascular distribution of ibrutinib. This was consistent with tissue distribution studies in rats which demonstrated rapid and extensive distribution following oral dosing of radiolabelled ibrutinib. The tissues with greatest exposure to ibrutinib were the gastrointestinal tract wall, excretory organs (liver, kidney and urinary bladder) and adrenal gland. In contrast, ibrutinib penetration of the blood brain barrier was limited as evidenced by low levels of radioactivity in the brain and spinal cord.

Metabolism

Ibrutinib is extensively metabolised in vivo with over 40 metabolites identified in rats, dogs and humans. The major circulating metabolites were similar between humans, dogs and rats. The main metabolic pathways included hydroxylation of the distal phenyl moiety (M35), oxidative ring opening of the piperidine with subsequent reduction (M34, PCI-45752) or oxidation (M25, PCI-45741), and epoxidation of the ethylene on the acryloyl

moiety followed by hydrolysis (M37, PCI-45227). Concentration of PCI-45227 was similar in plasma from portal and jugular veins indicating a role of the gut in ibrutinib metabolism. Rapid metabolism was also observed in vitro, with only half the starting ibrutinib remaining following incubation with Caco-2 cells. CYP3A4/5 was identified as the primary CYP450 responsible for ibrutinib metabolism, but CYP2D6, to a much smaller extent, was also shown to metabolise ibrutinib in vitro.

Excretion

Ibrutinib and its metabolites were primarily excreted in the faeces in rats, dogs and humans (>80%). Urinary excretion was more prevalent in humans (~8%) and dogs (~3%) compared to rats (<2%). Significant biliary excretion was observed in rats (47%). Only minimal levels of unchanged drug were excreted (<3%) in all species.

Conclusion

Ibrutinib showed similar absorption, distribution, metabolism and excretion in rats, dogs and humans, with the pharmacokinetics (PK) most similar between dogs and humans. This similarity makes the animal studies performed suitable for assessing the toxicity of ibrutinib in humans.

Pharmacokinetic drug interactions

Both ibrutinib and PCI-45227 had weak inhibitory activity against a range of CYP450 enzymes (2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 for ibrutinib; 2B6, 2C8, 2C9 and 2D6 for PCI-45227). However, the IC50s were >25× the observed C_{max} in humans at the maximum recommended dose (ibrutinib C_{max} 164 ng/mL; PCI-45227 C_{max} 114 ng/mL). Coupled with the high protein binding (97%), it is unlikely that ibrutinib would inhibit CYP450s at clinically relevant doses. Ibrutinib did not induce CYP1A2, 2B6 or 3A4 activity, but did increase gene expression of CYP1A2 in hepatocytes at expected therapeutic concentrations based on C_{max} (relative exposure 1.3). However, given only <3% of ibrutinib is unbound; this effect is unlikely to be observed clinically. PCI-45227 also induced gene expression of CYP2B6 and 3A4, but only at concentrations >40× expected therapeutic concentrations based on C_{max}. Therefore, ibrutinib is unlikely to have any clinically relevant effect on the activity of CYP450 enzymes.

Ibrutinib was not a substrate of P-glycoprotein, but did inhibit P-glycoprotein with an IC_{50} of 2.2 μg/mL. This is >400× the expected maximum clinical unbound ibrutinib concentration, and therefore unlikely to be clinically relevant. The concentration of ibrutinib in the intestinal lumen is expected to be 224 μg/mL based on calculations in the EU guideline on drug interactions.[2] Inhibition of P-glycoprotein may occur in the intestinal tract following ibrutinib administration. In contrast to ibrutinib, PCI-45227 was a substrate but not inhibitor of P-glycoprotein. Ibrutinib and PCI-45227 are not substrates of the transporters, OATP1B1, OATP1B3 and OATP2B1. In human plasma, there was no effect of ibrutinib on the fraction of unbound warfarin.

Ibrutinib is extensively metabolised by CYP3A4/5. Therefore, inducers and inhibitors of CYP3A4/5 are likely to alter clinical exposure to ibrutinib.

[2] EMA guideline: CPMP/EWP/560/95/Rev. 1 Corr.* *Guideline on the Investigation of Drug Interactions.*

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice (PO) and rats (IV and PO), with limited observations performed. In mice, the maximum non lethal dose was 2000 mg/kg PO, but mice were observed for only 48 hours post dose and therefore delayed toxicity effects may not have been detected based on the outcomes of rat studies. In rats dosed orally, the maximum non lethal dose was 400 mg/kg in females and 1000 mg/kg in males. Mortality was observed in rats that received 2000 mg/kg after six or seven days, with the stomach a target organ in males. A bolus IV injection of ibrutinib was poorly tolerated in rats, with mortality observed following injection of ≥100 mg/kg. However, as ibrutinib is intended for oral administration in humans this is of limited relevance. By the oral route, ibrutinib has a moderate to low order of acute toxicity.

Repeat dose toxicity

Studies of up to 13 weeks duration were conducted in SD rats and beagle dogs. Pivotal, GLP compliant, studies of four and 13 weeks duration were conducted in both species, with each study including a recovery period of four (rat and dog), six (rat) or 13 (dog) weeks. Ibrutinib was administered orally by daily gavage, consistent with the route of administration in humans. Group sizes and study duration were adequate. The studies conducted were generally consistent with ICH guideline S9 (anticancer pharmaceuticals) and EU guideline on repeated dose toxicity. However, the omission of bone marrow smear evaluation in the pivotal repeat dose studies is considered a deficiency given that treatment-related changes are expected in bone marrow.

Relative exposure

Exposure ratios were calculated based on animal: human plasma AUC_{0-24} h for pivotal repeat-dose studies. Human reference values are from Clinical Study PCYC-1104-CA which administered ibrutinib at the maximum recommended human dose (560 mg/day) to patients with MCL. Clinical exposure in patients with CLL/SLL that received 420 mg/day was similar to or lower than that in MCL patients receiving the higher dose. Therefore, the exposure ratios presented below represent a conservative estimate.

High exposures were achieved in rats (exposure ratios up to 54), and exposure ratios in dogs were up to 16 in the four-week study and 13 in the 13-week study in dogs. In addition, exposure ratios for metabolite PCI-45227 were calculated, with exposure ratios of up to 14 achieved in rats, but only 1.2 in dogs. Metabolism studies identified three other major metabolites in human plasma. Exposure to these metabolites was not assessed in repeat dose toxicity studies. However, a separate evaluation of drug metabolites for drugs indicated for advanced cancer indications is generally not required for registration (ICH guideline S9), and the metabolites were detected in rat and dog plasma in the metabolism studies.

Table 2: Relative exposure to ibrutinib in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)		Exposure ratio[#]	
			♂	♀	♂	♀
Rat (SD)	Four weeks *[06-017-R-PO-TX]*	2.5	140	180	0.1	0.2
		40	2,800	4,000	2.9	4.2
		150 (♀); 300 (♂)	19,000	24,000	20	25
	Four weeks *[12-017-R-PO-IMTX]*	10	–	995	–	1.0
		30	–	4,984	–	5.2
		100	–	13,765	–	14
	13 weeks *[10-068-R-PO-TX]*	30	2,480	19,712	2.6	21
		100	5,506	20,661	5.8	22
		175 (♀); 300 (♂)	21,732	51,549	23	54
Dog (beagle)	Four weeks *[06-018-D-PO-TX]*	1.5	18.5	21.4	0.02	0.02
		24	1,536	1,853	1.6	1.9
		150	14,079	15,191	15	16
	13 weeks *[10-069-D-PO-TX]*	30	377	1,683	0.4	1.8
		80→60	3,414	2,211	3.6	2.3
		220→120	12,179	6,628	13	7.0
Human (MCL patients)	steady state *[PCYC-1104-CA]*	560 mg	953		–	

[#] = animal:human plasma AUC_{0-24h}.

Table 3: Relative exposure to PCI-45227 in repeat-dose toxicity studies

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)		Exposure ratio[#]	
			♂	♀	♂	♀
Rat (SD)	Four weeks *[12-017-R-PO-IMTX]*	10	–	1,027	–	0.8
		30	–	4,368	–	3.5
		100	–	10,162	–	8.0
	13 weeks *[10-068-R-PO-TX]*	30	1536	12,758	1.2	10
		100	3698	6872	2.9	5.4
		175 (♀); 300 (♂)	17,547	13,055	14	10
Dog (beagle)	13 weeks *[10-069-D-PO-TX]*	30	122	347	0.1	0.3
		80→60	768	352	0.6	0.3
		220→120	1,488	1,131	1.2	0.9
Human (MCL patients)	steady state *[PCYC-1104-CA]*	560 mg	1263		–	

[#] = animal:human plasma AUC_{0-24h}.

Major toxicities

The major target organs for ibrutinib were the gastrointestinal tract and lymphoid organs, with effects on pancreas, cornea, liver, bone, skin and pituitary observed in one of the animal species studied. Haematological changes were also observed, but were generally of small magnitude and were reversible. Elevated white blood cell counts were commonly observed at higher doses in pivotal studies, but this was probably a secondary effect of intestinal inflammation. Similarly, decreases in serum total protein, albumin and albumin to globulin ratios might be associated with gastrointestinal toxicity.

Gastrointestinal toxicity was observed in all pivotal repeat-dose toxicity studies, with clinical correlates of abnormal excreta in both species. Gastrointestinal inflammation, ulceration and or haemorrhage were present in rat and dog premature decedents. Inflammation and ulceration was observed in the ileum, cecum, colon and rectum in rats and dogs that received ≥120 mg/kg/day (exposure ratio ≥7). In addition, degeneration of the gastric smooth muscle was observed in female dogs that received ≥120 mg/kg/day for 13 weeks (exposure ratio 7). Other signs of gastrointestinal toxicity included stomach oedema, hyperplasia, epithelial atrophy and ulceration of the nonglandular stomach, dilatation of intestinal crypts and glands, as well as haemorrhage in the glandular stomach. These effects were only observed at the highest doses of ibrutinib in the 13 week studies. The adverse effects of ibrutinib on the gastrointestinal tract were reversible in both species.

Lymphoid depletion was observed in spleen, thymus, lymph nodes and Peyer's patch in rats and dogs that received ≥60 mg/kg/day (exposure ratio ≥2.3). In premature rat decedents, lymphoid depletion was more severe and bone marrow depletion also occurred. In surviving high dose dogs, lymphoid depletion was only observed in Peyer's patch. The effects of ibrutinib on the lymphoid system are an expected pharmacological effect and were reversible following cessation of dosing. Immunotoxicity is discussed below.

Acinar atrophy was observed in the pancreas of rats but not dogs. Acinar atrophy occurred in rats that received 12-300 mg/kg/day for two and 13 weeks, but was not observed in the

four week study which administered 2.5-300 mg/kg/day ibrutinib. These effects persisted after a six week recovery period, albeit the severity decreased during recovery. In the two week study, acinar atrophy in the pancreas was not associated with elevations in serum amylase and/or lipase levels. However, the duration of this study may have been insufficient for these markers of pancreatic injury to be expressed. Pancreatic acinar atrophy was more frequent in males than females; in the 13 week study it was observed in nearly all (87-100%) treated males at all dose levels, and in 7-30% of treated females (incidence not dose-dependent). Acinar atrophy was described as a combination of fibrosis, brown pigment (interpreted as hemosiderin and indicative of chronic haemorrhage), small acini with fewer zymogen granules, and mixed inflammatory cell infiltrate (predominantly neutrophils, lymphocytes and plasma cells, and consistent with chronic inflammation). The study author indicated that these pancreatic findings appear to be an exacerbation of a common lesion seen in ageing rats. A recent study of male Crl:CD(SD) rats, the same strain used in the repeat dose toxicity studies, reported similar lesions in 76% of untreated rats at approximately seven months of age.[3] Therefore, it is possible that ibrutinib may accelerate development of this lesion. The mechanisms involved in development of acinar atrophy in the pancreas are unclear. In response to a European Medicines Agency (EMA) question, the sponsor proposed that haemorrhage in the pancreas may be involved, based on the common presence of brown pigment in the lesion. Haemorrhage is a common adverse effect of tyrosine kinase inhibitors[4], and the sponsor is currently undertaking a study on the effects of ibrutinib on platelet function. Although the effect appears to be species-specific, it is unclear whether the same effect may occur in humans.

Corneal dystrophy was observed in dogs that received 150 mg/kg/day ibrutinib for four weeks (relative exposure 15-16). The finding was not reversed after four weeks recovery, and no causative factor was identified by histopathology. Mild corneal dystrophy/degeneration was also observed in one male dog during the 13 week study. Corneal dystrophy is commonly observed in beagle dogs, although the prevalence in these studies appeared to be treatment-related. Corneal atrophy was observed in repeat dose studies of afatinib, an ERbB inhibitor, in mice and pigs.[5] As ibrutinib also inhibited ErbB4/HER4 at clinically relevant concentrations, the corneal toxicity may be related to ErbB4/HER4 inhibition by ibrutinib. However, clinical trials of ibrutinib have not indicated adverse corneal effects. Together the data indicate that adverse corneal effect may be species-specific, but potential ocular effects in humans cannot be excluded.

Hepatic toxicity characterised by necrosis and alanine aminotransferase (ALT) elevation was evident in rats that received ≥40 mg/kg/day for four weeks (relative exposure ≥2.9). However, there were no indications of hepatotoxicity in the 13 week rat study at relative exposures up to 54 or in dogs. Serum ALT and GGT were decreased in mid- and high dose groups in the 13-week dog study. Together with the clinical data which have not shown adverse liver events it appears the hepatotoxicity observed in the four weeks rat study is of limited clinical relevance.

Decreased cortical and trabecular bone were observed in rats that received ≥100 mg/kg/day (female, relative exposure 22) and 300 mg/kg/day (male, relative exposure 23). These effects were reversed after six weeks recovery. Adverse bone effects were not observed in dogs. The absence of this effect in dogs, its reversibility and high relative exposure indicate limited clinical relevance of these observations.

[3] Chadwick et al. *Occurrence of Spontaneous Pancreatic Lesions in Normal and Diabetic Rats: A Potential Confounding Factor in the Nonclinical Assessment of GLP-1–Based Therapies.* Diabetes 2014;63:1303-1314.
[4] Cornelison et al. *Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with Chronic Myeloid Leukaemia: The role of the midlevel practitioner.* The Journal of Supportive Oncology 2012;10:14-24
[5] Afatinib AusPAR: http://www.tga.gov.au/auspar/auspar-afatinib-dimaleate

Inflammation, necrosis and squamous epithelium atrophy of skin was observed in rats that received ≥150 mg/kg/day ibrutinib (relative exposure ≥20). These effects were minimal in severity and were generally reversed following a recovery period. Adverse effects on skin are common for tyrosine kinase inhibitors. In clinical trials with ibrutinib skin rash was a reported adverse effect.

Cytoplasmic vacuolation in the pituitary was present at increased frequency in male rats that received 30-300 mg/kg/day for 13 weeks (relative exposure ≥2.6). The frequency decreased following six weeks recovery and the severity remained minimal. As this effect was observed only in male rats, the risk of adverse effects on the pituitary in humans is low.

Small but significant changes in haematological parameters were observed across studies, indicating ibrutinib treatment may lead to anaemia. Increased reticulocyte numbers associated with decreased red blood cells, Hb and haematocrit (in dogs) or decreased mean corpuscular volume, mean corpuscular Hb and mean corpuscular Hb concentration (rats) was observed in animals that received high dose ibrutinib for 13 weeks. Similar observations were made in studies of shorter duration. Effects were generally reversible, but increased reticulocyte numbers remained after six (rat) or 13 (dog) weeks recovery. An increased myeloid to erythroid cell ratio was also observed in the bone marrow of female rats that received ≥10 mg/kg/day for four weeks.

Increased neutrophils and/or large unstained cells were commonly observed in rats and dogs. Total white cell counts were more variable with some studies showing increased counts and others decreased. As indicated earlier, these effects may have been secondary to gastrointestinal toxicity. However, increased neutrophils were observed at study times and doses that were not associated with gastrointestinal toxicity.

Genotoxicity

The genotoxic potential of ibrutinib was tested in bacterial reverse mutation assays, in vitro chromosome aberration assays in Chinese hamster ovary cells, and an in vivo micronucleus test. This testing strategy was consistent with ICH guideline S2 (R1). The studies indicated that ibrutinib was not mutagenic or clastogenic. A single dose of 2000 mg/kg ibrutinib did not increase micronucleus formation in mice (relative exposure 49 based on C_{max}).

Carcinogenicity

No carcinogenicity studies were submitted which is acceptable for an anticancer pharmaceutical for the treatment of advanced cancer (ICH guideline S9).

Reproductive toxicity

Three embryofoetal development studies were conducted. In the pivotal study in rats, ibrutinib was administered daily for 12 days during organogenesis (gestation days 6 to 17). Caesarean sectioning was performed on gestation day 20 (n=25). Two non-GLP range-finding studies were also submitted. As the definitive study in rats found clear evidence of embryofoetal lethality a confirmatory study in rabbits was not conducted, which is acceptable (ICH guideline S9). Similarly, as ibrutinib is indicated for advanced cancer, studies of fertility and pre- post-natal development were not performed and are not required according to ICH guideline S9. Placental transfer and excretion into milk of ibrutinib were also not assessed.

Table 4: Relative exposure

Species	Study	Dose (mg/kg/day)	Ibrutinib		PCI-45227	
			AUC_{0-24h} (ng·h/mL)	Exposure ratio#	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
Rat (SD)	Embryofetal development *[10-063-R-PO-TTE]*	20	3,980	4.2	3,450	2.7
		200	27,700	29	29,200	23
Rat (SD)	Embryofetal development *[11-132-R-PO-TT]*	10 (NOAEL)	1,278	1.3	1,203	1.0
		40	5,348	5.6	5,110	4.0
		80	13,729	14	12,027	9.5
Rabbit (NZW)	Embryofetal development *[10-064-B-PO-TTE]*	10	565	0.6	1,670	1.3
		30	1,310	1.4	8,820	7.0
		100	21,000	22	38,500	31
Human (MCL patients)	steady state *[PCYC-1104-CA]*	560 mg	953	–	1,263	–

= animal:human plasma AUC_{0-24h}

Exposure to both ibrutinib and the dihydrodiol metabolite PCI-45227 at the lowest dose in the pivotal rat study was similar to expected clinical exposure. Exposure to ibrutinib was greater than dose proportional and the exposure at the highest dose was 14 fold higher than clinical exposure at 560 mg/day.

Fertility studies were not conducted. In the repeat dose studies there was some evidence of adverse effects of ibrutinib on reproductive organs. In rats, uterine weight was decreased in rats that received ≥100 mg/kg/day for 13 weeks, but there was no microscopic correlate for this observation. Degeneration of the testicular seminiferous tubules was observed in one male dog that was moribund sacrificed after it received 220/120 mg/kg/day ibrutinib. However, it was unclear if this was a direct effect of ibrutinib or if it was secondary to the poor condition of the animal. The available evidence indicates low risk of impairment of male and or female fertility.

Increased early resorptions were observed in SD rats that received ≥80 mg/kg during the period of organogenesis (relative exposure 14 for ibrutinib and 10 for the dihydrodiol metabolite). Foetal weight was decreased in offspring of dams that received ≥40 mg/kg/day (relative exposure 5.6 for ibrutinib and 4 for the dihydrodiol metabolite). Maternal body weight gain was reduced at >60 mg/kg/day. Visceral malformations and visceral and skeletal variations were observed in the offspring of dams that received 80 mg/kg/day ibrutinib. The malformations involved the heart and major blood vessels (dextrocardia, retroesophageal aortic arch, persistent truncus arteriosus, right sided aortic arch, interrupted aortic arch) and were related to ibrutinib treatment. Treatment related skeletal variations were unossified sternbrae 5 and 6, and reduced ossification of the 13th rib(s), which were also increased at 40 mg/kg/day. The skeletal effects might be secondary to reduced foetal growth. The NOAEL for embryofoetal development in rats was 10 mg/kg/day (relative exposure 1.3 and 1.0, for ibrutinib and its dihydrodiol metabolite, respectively). In NZW rabbits, early and late resorptions were increased and foetal weight was also decreased following administration of 100 mg/kg/day ibrutinib during organogenesis (relative exposure 22).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3. While the absence of data from pregnant women supports this categorisation, the severity of findings in animal studies indicates it may not be appropriate. Teratogenicity was evident in rats, albeit at a relative exposure of 14. Embryofoetal toxicity and lethality was observed in rats and rabbits at relative exposures ≥14. Therefore, a Pregnancy Category D is recommended as ibrutinib may be expected to cause human foetal malformations or irreversible damage to human foetuses. This category is also consistent with that of other small molecule tyrosine kinase inhibitors included in the TGA's Medicines in Pregnancy database.

Immunotoxicity

Immunophenotyping was performed in SD rats in the 13 week repeat-dose toxicity study, as well as in a dedicated four week immune-toxicity study. The immune-toxicity study was conducted in female rats only, on the basis that greater exposure to ibrutinib was seen in females in the 13 week study. The ICH guidance for immune-toxicity recommends the use of animals of both sex unless justified (ICH guideline S8). While the effect of gender on ibrutinib exposure was variable across species, in rats exposure was greater in females. Overall, the use of females appears justified as the immune phenotyping performed in the 13 week study did not find marked gender differences.

Expected pharmacological effects of decreased B cells and total lymphocyte numbers were observed in both studies. In the 13 week study, T lymphocytes also decreased in male rats that received 300 mg/kg/day (relative exposure 23) and female rats that received 175 mg/kg/day (relative exposure 54). In the immune toxicity study, T lymphocytes also decreased in female rats that received 100 mg/kg/day (relative exposure 14).

Other immune-toxic effects of ibrutinib were expected based on its pharmacological action. These effects included reduced total IgM and IgG levels. Similarly, induction of antigen-specific IgM and IgG was impaired by 100 mg/kg/day ibrutinib. While these effects were generally reversed following cessation of ibrutinib administration, antigen-specific IgM production remained reduced compared to controls. In addition, ibrutinib decreased plasma and lymphoid cells, and increased myeloid to erythroid ratio in bone marrow. Atypical lymphoid cells were also observed in bone marrow at all ibrutinib doses (relative exposure ≥1) and were still present in the high dose group after a 28 day non-dosing period. In the high dose group the atypical cells were generally lymphoblasts with aberrant nuclei more common in atypical lymphoid cells following recovery. While this is likely a pharmacological effect, the persistence following cessation of treatment suggests this may be an adverse effect of ibrutinib.

Phototoxicity

The phototoxicity of ibrutinib was assessed in a validated in vitro assay (3T3 Neutral Red uptake). The cytotoxicity of ibrutinib was not altered following exposure to UV-A light, indicating that ibrutinib is not phototoxic. No further testing for phototoxicity was performed which is consistent with ICH guidance (S10; Photo-safety evaluation of pharmaceuticals).

Impurities

The proposed specifications for four impurities in the drug substance, which include three degradation products in the drug product, are above ICH qualification thresholds (ICH guideline Q3a/B). The genotoxicity and repeat dose toxicity studies performed were adequate to qualify these impurities at the specified levels.

Paediatric use

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

Comments on the Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for ibrutinib detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the Nonclinical Evaluator. Comments on some toxicity findings were sought from the sponsor. While the responses adequately addressed some concerns of the nonclinical evaluator, the following are drawn to the attention of the RMP evaluator.

Human equivalent doses (HED) are described in mg/kg, which is inappropriate. The HED in mg/m^2, or where AUC or C_{max} data are available relative exposure based on AUC or C_{max} are more appropriate. The immune-toxicity study finding of atypical lymphoid cells in bone marrow following treatment with ibrutinib, which was not reversible, is also a key safety finding in addition to other findings described in SII. As indicated by the Sponsor, this finding may be associated with the pharmacological action of ibrutinib.

General safety pharmacology findings

Cardiovascular system

In the RMP, it states:

> *The no-observed-effect level (NOEL) was determined to be 1.5 mg/kg (HED= 0.81 mg/kg). The changes observed in RR interval, heart rate, and pulse pressure at the 24 mg/kg dose level (HED = 13 mg/kg) were considered to be non-adverse because of the relatively small magnitude of maximum or overall change. Thus, 24 mg/kg was considered to be the NOAEL.*

The TGA nonclinical evaluator does not agree with the sponsor's interpretation of the cardiovascular safety pharmacology study findings. The changes in cardiovascular parameters at 24 mg/kg (approximate increase of 23% for RR interval, decrease of 20% for heart rate, and increase of 12% for pulse pressure) are considered adverse by the TGA nonclinical evaluator. The NOAEL and NOEL was 1.5 mg/kg in the safety pharmacology study. Importantly, cardiac arrhythmia is identified as an important potential risk in the RMP.

Multiple dose toxicities

Exocrine pancreas

In the RMP, it states:

> *In rats dosed for two or 13 weeks, minimal to moderate acinar atrophy was observed in the pancreas of males and females. Acinar atrophy included a combination of fibrosis, brown pigment (interpreted as haemosiderin), small acini with fewer zymogen granules, and mixed inflammatory cell infiltrate (predominantly neutrophils, lymphocytes, and plasma cells, consistent with a chronic inflammatory infiltrate). These lesions were noted at doses ranging from 12 to 300 mg/kg/day and considered adverse (moderate severity or greater) at doses from 36 to 300 mg/kg/day (HED = 5.8 to 48 mg/kg/d).*

Acinar atrophy of the pancreas occurred at all doses (30-300 mg/kg/day) in males and also in treated females in the 13 week rat study, with no incidence in the control group. Acinar atrophy of the pancreas was also observed at all doses in male rats that received 12

to 120 mg/kg/day ibrutinib for two weeks. At lower doses (12 and 30 mg/kg/day) the changes were mild, but the lesion may progress to moderate to severe with longer treatment duration. Furthermore, moderate acinar atrophy of the pancreas was observed in rats that received 36 mg/kg/day for only two weeks duration. Thus, acinar atrophy at all doses is considered adverse. The NOAEL of 30 mg/kg/day described in the first paragraph is not supported by nonclinical data. Based on the observation at all doses, an NOAEL for acinar atrophy of the pancreas has not been established. In the S31 response to TGA questions, the Sponsor indicated that the mild atrophy seen at low doses was not considered adverse since the changes were not correlated with changes in clinical chemistry or other parameters/biomarkers consistent with functional perturbation. Importantly, exocrine pancreas was identified as a target organ in the RMP.

Lymphoid organs

The exposure margin for lymphoid depletion was low (approximately 2.3), suggesting moderate risk in humans. The TGA nonclinical evaluator does not agree with the sponsor's conclusion that "because of the margin where these findings occur, the risk to humans is considered low". As indicated above, the immune toxicity study finding (for example, atypical lymphoid cells in bone marrow) lends support to the potential risk of immune-toxicity in patients. This may be further addressed by the proposed long term repeat dose studies in rats and dogs.

Nonclinical summary

- While lymphoid depletion and decreased lymphocytes (peripheral and bone marrow) are expected pharmacological effects, toxicity findings including decreased plasma and lymphoid cells, increased myeloid to erythroid ratio and the presence of atypical lymphoid cells in bone marrow suggest potential adverse effects on bone marrow in patients. This is considered an important potential risk in addition to those (cardiac arrhythmia, severe gastrointestinal disorders, teratogenicity) already identified by the sponsor.
- The submitted dossier was compliant with the relevant ICH guideline on the development of anti-cancer pharmaceuticals. Consistent with this guideline, no carcinogenicity and only limited reproductive toxicity studies were conducted. The overall quality of the dossier was high, with all pivotal safety studies conducted under GLP conditions.
- Ibrutinib forms an irreversible covalent bond in the active site of Btk, thereby inhibiting BCR signalling and chemokine receptor mediated chemotaxis of B cells. In vitro, ibrutinib variably inhibited lymphoma cell line growth, and suppressed adhesion in an MCL cell line. In vivo, oral and parenteral administration achieved near complete or complete occupancy of the Btk active site in circulating B cells and splenocytes. Efficacy of ibrutinib was also demonstrated in a mouse model of MCL and CLL, and in tumour xenograft models using DLBCL cells.
- Ibrutinib has moderate selectivity and high affinity for Btk, but also binds Blk (a related kinase) and ErbB4/HER4 in the sub nanomolar range. Ibrutinib also inhibited other related kinases in the Tec and Src/Abl family with an IC_{50} of <10 nM for nine of these kinases. Inhibition of other receptors and transporters was observed, but not at clinically relevant concentrations.
- In vitro, ibrutinib and its dihydrodiol metabolite inhibited hERG channels, but with IC_{50} values ≥96 times the expected clinical concentration of ibrutinib (unbound). In dogs, ibrutinib decreased heart rate and QTcV interval, increased pulse pressure and prolonged RR interval at clinically relevant doses (relative exposure ≥3.3 based on C_{max}). There was no effect of ibrutinib on respiratory or central nervous system.

- Ibrutinib was rapidly absorbed but oral bioavailability was low due to extensive first pass metabolism in the gut and liver. Ibrutinib was highly bound to plasma protein of rats, dogs and humans. Wide tissue distribution was observed, with minimal retention of ibrutinib in any tissues. The plasma half-life was approximately two times longer in humans (three to 11 hours) compared to dogs and rats (one to six hours).
- Metabolism of ibrutinib was extensive, with the four main plasma metabolites identified in a human mass balance study also present in animals. However, except metabolite PCI-45227, the other main metabolites were not assessed for pharmacological activities or quantified in toxicity studies. Excretion was predominantly of metabolites via the biliary/faecal route.
- Based on in vitro studies, CYP3A was the main enzyme that metabolised ibrutinib. Therefore inhibitors and induces of CYP3A may alter ibrutinib exposure. At clinical exposure, ibrutinib is unlikely to cause systemic drug-drug interactions (DDIs) mediated by CYP450 or P-glycoprotein. However, following a therapeutic dose ibrutinib may inhibit intestinal P-glycoprotein.
- Single dose toxicity studies in mice and rats indicated a moderate to low order of acute toxicity.
- Pivotal repeat dose studies were conducted in rats and dogs, each for 4 and 13 weeks. An adequate exposure range was achieved in both species. Target organs for toxicity were the gastrointestinal tract (inflammation, ulceration, haemorrhage and in female dogs, smooth muscle degeneration) and lymphoid organs (lymphoid depletion in spleen, thymus, lymph nodes, bone marrow and/ or Peyer's patch). In addition, corneal dystrophy occurred in the four week dog study, while in rats, acinar atrophy in pancreas, decreased cortical and trabecular bone and inflammation, necrosis and atrophy of the skin were observed. Hepatotoxicity was an isolated observation in the four week rat study only.
- Ibrutinib was not mutagenic in bacterial reverse mutagenesis assays, and was not clastogenic in in vitro chromosome aberration assays or an in vivo micronucleus test. No carcinogenicity study was conducted which is acceptable.
- Reproductive toxicity studies were limited to an embryo-foetal development study in rats, with pilot studies in rats and rabbits. Ibrutinib was teratogenic (heart and major vessels) and embryofoetolethal at doses 14 times expected clinical exposures. Decreased maternal and foetal weights and increased incidences of skeletal variations (unossified sternebrae and reduced ossification of 13th rib) were observed at exposures ≥5.6 times expected clinical exposure.
- Ibrutinib was not phototoxic in a validated in vitro assay (3T3 Neutral Red uptake).
- Expected, pharmacological immuno-toxicity was observed in rats which included B and T lymphocyte depletion, decreased total IgM and IgG antibodies, and suppression of antigen-induced IgM and IgG antibody responses. These effects were generally reversible. However, atypical lymphoid cells (generally lymphoblasts and cells with aberrant nuclei) were observed in ibrutinib-treated rats at clinically relevant exposures, and this effect was not reversed following a four week recovery period.
- The proposed limits for four impurities in the drug substance and or drug product were adequately qualified by in silico, in vitro and in vivo genotoxicity studies, and a repeat-dose toxicity study.

Conclusions and Recommendation

- Overall, the nonclinical dossier was adequate, but the omission of bone marrow smear analysis in the 13 week repeat dose studies is considered a deficiency.

- The primary pharmacology studies support the use of ibrutinib for the proposed indications.
- Off-target inhibition of Blk and ErbB4/HER4 are likely at clinically relevant exposure. Inhibition of ErbB4/HER4 is potentially related to the adverse corneal effects observed in dogs, but adverse corneal effects have not been observed clinically. Adverse effects on cardiovascular system are possible based on decreased heart rate and RR interval at exposures similar to that expected clinically.
- As CYP3A is the main enzyme that metabolises ibrutinib, its inhibition or induction would likely alter clinical ibrutinib exposure.
- The main toxicities identified in repeat dose studies were gastrointestinal toxicity and lymphoid depletion in lymphoid organs. Gastrointestinal toxicity has been observed clinically. Lymphoid depletion is an expected pharmacological effect that is clinically as immunosuppression is associated with increased risk of infection. The skin and bone marrow toxicities observed in rats are also clinically relevant. Other toxicities of potential clinical relevance, but probably low risk, are acinar atrophy of pancreas and ocular effects.
- Ibrutinib does not pose a genotoxic hazard.
- Ibrutinib is teratogenic and causes embryofoetal toxicity and lethality in animals. Pregnancy Category D is recommended as ibrutinib may be expected to cause an increased incidence of human foetal malformations or irreversible damage.
- The immunosuppression demonstrated in the immune toxicity study is an expected pharmacological effect. However, the presence and persistence of atypical lymphoid cells in bone marrow warrants further investigation. The sponsor has indicated this will be addressed in two repeat dose studies that are currently underway (six month rat and nine month dog studies).
- Provided the above effects are adequately monitored or managed during clinical use and that the benefit/risk profile seems acceptable from a clinical perspective, there are no objections on nonclinical ground to the proposed registration of Imbruvica. The Sponsor is requested to provide the study reports for the rat six month and dog nine month repeat dose toxicity studies when these reports become available.
- The draft PI and RMP should be amended as directed.

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

Ibrutinib belongs to the pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE27.

“Ibrutinib inhibits BCR and chemokine-receptor signalling pathways in malignant B-cells, disrupts integrin-dependent B-cell migration and adhesion in vitro and promotes egress of malignant B cells from tissues and prevents homing of these cells to tissues in patients without clinically adverse effects on levels of normal B-cells.”

Ibrutinib forms a covalent bond with the cysteine residue (Cys-481) in the Btk active site, causing functional inactivation.

Contents of the clinical dossier

The submission contained the following clinical information:

- 10 clinical pharmacology studies
- two population PK analyses.
- one pivotal efficacy/safety study in CLL/SLL (Study 1112)
- one dose finding study (Study 04753)
- three supportive efficacy/safety studies.
- Integrated Summary of Efficacy, Integrated Summary of Safety

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical study reports contained in the submission included assurances that the studies had been conducted in accordance with ICH GCP guidelines, applicable country-specific requirements and the ethical principles outlined in the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each PK topic and the location of each study summary.

Table 5: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Number of subjects enrolled	Summary page
PK in healthy adults	Single dose Food-effect (healthy adults)	PCI-32765CLL1004 PCI-32765CLL1001	6 52	
PK in patients	Food effect (CLL/SLL patients) sub-study	PCYC-1102-CA	16	
Bioavailability	single oral/IV dose in healthy adults	PCI-32765CLL1011	8	
PK interactions	DDI with CYP3A4 inhibitor (ketoconazole) on PK of ibrutinib DDI of CYP3A4 inducer (Rifampicin) on Ibrutinib PK Effect of grapefruit on ibrutinib bioavailability (single oral/IV dose) in healthy adults	PCI-32765CLL1002 PCI-32765CLL1010 PCI-32765CLL1011	21 18 8	
Plasma protein binding studies		PCI-32765CLL1002 PCI-32765CLL1004	21 6	
PK in special populations	Hepatic impairment	PCI-32765CLL1006	Ongoing enrolment	
Population PK analyses	Target populations - MCL/CLL/SLL Model confirmation in CLL/SLL	Parent studies: 04753, 1102-CA, 1104-CA PCYC-1112-CA		

The sponsor developed the population PK model using data from subjects with three target conditions (MCL/CLL/SLL). This model was then used to confirm the summary data from Study 1112 in patients with CLL/SLL.

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

Evaluator's conclusions on pharmacokinetics

The absolute bioavailability of ibrutinib is low at 2.9% with high inter-subject variability. Orally administered ibrutinib is rapidly and almost completely absorbed, with a median time of maximal absorption of two hours.

The apparent volume of distribution of ibrutinib is 10000 L and apparent clearance is 1000 L/h.

Ibrutinib is highly protein bound at 97.3%. The blood to plasma ratio is approximately 0.7.

There is extensive first pass metabolism by CYP3A4. Ibrutinib exposure is substantially affected by inducers (28-fold) and inhibitors (10-fold) of CYP3A4. However, CYP2D4 metaboliser status does not appear to affect the exposure or metabolism of ibrutinib.

The primary metabolite of ibrutinib, PCI-45227 is a weak irreversible inhibitor of Btk and is not considered to exhibit a clinical effect, thereby in itself should not pose a safety concern.

There is rapid, and extensive, hepatobiliary excretion of ibrutinib within two days, and negligible urinary excretion: <10%. The mean terminal half life is 4 to 10 h as assessed by non compartmental analysis.

The accumulation of ibrutinib is less than two fold with repeated dosing.

The effect of ibrutinib on concomitant medication has not been studied.

Age and gender did not have any significant effect on the PK parameters of ibrutinib.

In subjects with mild or moderate categories of renal impairment, there was no significant effect on ibrutinib PK.

Pharmacodynamics

Studies providing pharmacodynamic data

No specific pharmacodynamic (PD) studies were performed.

Btk receptor binding results were obtained from studies in B cell malignancies and healthy subjects.

Evaluator's conclusions on pharmacodynamics

A clinically relevant degree of Btk occupancy of > 90% was observed following ibrutinib treatment at doses of either 420 mg/day or 840 mg/day within one week of commencement.

Dosage selection for the pivotal studies

No maximum tolerated dose was reached (based on Btk occupancy) in the Phase I clinical Study 04753 in which subjects received up to 12.5 mg/kg/day (1400 mg). There were no dose-limiting toxicities (DLTs) reported for the highest dose cohort in Study 04753, however, two DLTs were reported at lower doses (2.5 mg/kg/day and 8.3 mg/kg/day). These events were an interruption of treatment >seven days for Grade 2 neutropenia and a Grade 3 treatment related SAE of hypersensitivity.

The dose for the pivotal study in CLL/SLL patients was derived from the Phase I and II studies PK and PD sampling in Studies 04753 and 1102.

Efficacy

Studies providing efficacy data for the chronic lymphocytic leukaemia/small lymphocytic leukaemia

Pivotal efficacy study PCYC-1112-CA

This was a Phase III randomised, multicentre, open label study of ibrutinib versus ofatumumab in patients with relapsed or refractory CLL/SLL who had failed at least one prior systemic therapy and not considered appropriate candidates for treatment or retreatment with purine analogue based therapy.

The study was performed in the US, Europe and Australia.

Patient enrolment commenced on 22 June 2012 and the study was completed on 6 November 2013.

Supportive efficacy studies

Supportive efficacy data was supplied from three additional studies (Table 6).

Table 6: Supportive efficacy studies

Study ID	Phase, type	Study population	Aims
PCYC-04753	1, Open label, dose escalation	Recurrent B-cell lymphoma, CLL, WM	Safety and the maximum tolerated dose (MTD) of orally administered ibrutinib in patients with recurrent B-cell lymphoma PK of orally administered ibrutinib PD parameters, including drug occupancy of Btk, the target enzyme, and the effect on biological markers of B-cell function. Secondary objective of evaluation of tumour responses.
PCYC-1102-CA	1b/2, Open label	Treatment-naïve or relapsed/refractory CLL/SLL	The safety of a fixed-dose daily regimen of ibrutinib at 2 dose levels (420 mg and 840 mg) Preliminary efficacy, PK (including the effects of the fed-versus-fasted state), PD, and long-term safety of ibrutinib
PCYC-1104-CA	2, open label	Relapsed/refractory MCL	Primary objective - efficacy of ibrutinib in subjects with relapsed/refractory MCL, based on prior bortezomib exposure. Secondary objective - safety of a fixed daily dosing regimen (560 mg daily) of ibrutinib

Detailed information about the above pivotal and supportive studies is included in the Clinical Evaluation Report.

Evaluator's conclusions on efficacy of irbutinib for the treatment of CLL/SLL

The wording of the proposed indication is:

> *Imbruvica is indicated for the treatment of patients with CLL/SLL who have received at least one prior therapy.*

The proposed dose of ibrutinib for the treatment of CLL is 420 mg once daily.

The pivotal Phase III study comparing the efficacy of ibrutinib versus ofatumumab met its primary outcome of demonstrating a statistically significant improvement in progression-free survival (PFS) with ibrutinib for the whole study population. In sub-groups previously identified as having a poorer treatment response, such as del17p, the magnitude of PFS improvement was similar to the overall population studies. Indeed, given the known inferior response in patients with del17p to currently available therapies, consideration can be given to approve ibrutinib as first line therapy in this population. The secondary outcome of OS also demonstrated a statistically significant improvement with ibrutinib treatment over ofatumumab.

Whilst the efficacy response comparison of ibrutinib and ofatumumab is sufficiently robust in the randomised Trial 1112, it should be noted that the objective response rate (ORR) for the population of patients treated with ofatumumab with previously treated CLL was substantially lower (at 4.1%, as assessed by Cheson criteria) than the ORR reported for less heavily pre-treated relapsed subjects in the pivotal study seen in the currently

approved ofatumumab Australian product information (at 49%, (95%CI 36, 60), as assessed by International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria. However, these differences in assessment methodologies preclude between study comparisons for the two ofatumumab exposed populations.

The durability of response, as assessed by the proportion of subjects achieving a sustained haematological response was greater in the ibrutinib arm, for each of the parameters absolute neutrophil count (ANC), Hb and platelet count.

Evidence of efficacy from the three early phase studies is supportive of the findings from the pivotal study and for the dose regimen proposed in CLL patients.

Ibrutinib dose interruption of up to seven days is supported by the dosing regimen in Study 04753 of 28 days on treatment and 7 days off treatment demonstrates that the PD effect of ibrutinib is maintained in the off treatment period. This finding supports dose interruptions for up to seven days, where required.

Studies providing efficacy data for the Mantle Cell Lymphoma indication

Study PCYC-1104-CA

This was an open-label, multicentre, Phase II study of ibrutinib in relapsed or refractory Mantle Cell Lymphoma. Subjects were enrolled in parallel (nonrandomized) into 1 of 2 cohorts based on prior bortezomib exposure. Subjects having received ≥2 cycles of prior treatment with bortezomib, either as a single agent or as part of a combination therapy regimen, were considered to be bortezomib exposed. Subjects with <2 cycles of prior treatment with bortezomib were considered to be bortezomib-naïve.

The study was performed in the United States, Germany, Poland and United Kingdom. Patient enrolment commenced on 8 February 2011 and the clinical cut-off for the primary analysis was 26 December 2012.

Evaluator's conclusions on clinical efficacy for ibrutinib for the treatment of MCL

The wording of the proposed indication is:

> *Imbruvica is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.*

Efficacy data from the Phase II open label study of efficacy in MCL patients demonstrated a similar proportion of subjects achieving an ORR as assessed by the investigators (primary outcome) as compared to independent review (secondary outcome). The ORR of 67.6% reported for previously treated MCL subjects was comparable with the ORR seen in the CLL population. Prior bortezomib exposure did not have a demonstrable impact on the proportion of subjects achieving an ORR.

Given the nonrandomised nature of the study, additional efficacy endpoints in the subgroups analysed, though consistent with the overall response can only be considered exploratory.

The PFS data for this indication is currently immature, but demonstrated a median of 13.9 months; the sponsor should commit to providing an update to the PFS data for this study.

The selection of the dose for the MCL subjects is supported by the evidence from the clinical studies in this rarer population.

Development of lymphocytosis was shown to be associated with worse efficacy outcomes, however the baseline characteristics of patients were less favourable in those who developed lymphocytosis and may sufficiently explain these findings. In the absence of a study which stratifies by these baseline factors, this finding remains observational and

cannot absolutely predict the response to ibrutinib in individual patients treated with ibrutinib.

Safety

Studies providing safety data

Subjects that received at least one dose of ibrutinib were included in the safety analysis. The following studies provided evaluable safety data (Tables 7-8).

Table 7: Safety data in pivotal & supportive efficacy studies relating to proposed indications and dosage

Study population	Study	Study Phase	Study type	Monotherapy	Ibrutinib dose
Previously-treated MCL	1104	2	non-randomised	111 subjects	560 mg/day
Previously-treated MCL	04753	1	dose-escalation	9 subjects	560 mg/day
Previously-treated CLL/SLL	1112	3	RCT ibrutinib versus. ofatumumab	195 subjects	420 mg/day
Previously-treated CLL/SLL	1102	1b/2	non-randomised, open label	51 subjects	420 mg/day

Table 8: Studies providing supplementary safety data

Study population	Study	Study Phase	Study type	Monotherapy	Ibrutinib dose
Previously-treated CLL/SLL	04753	1	Dose-escalation	66 (16 CLL/SLL)	Variable
Previously-treated CLL/SLL	1102	2	Non-randomised, open label	34 subjects	840 mg/day
B-Cell malignancies & CLL	1103		Extension	197 (119 CLL)	Variable
CLL/SLL with del17p	1117	2	Open label single arm	145	420 mg/day
MCL	2001	2	Single arm, progression post-bortezomib	120	560 mg/day

Pivotal efficacy studies

For the MCL and CLL/SLL indications, treatment-emergent adverse events (TEAEs) were reported for fours subgroups according to: age (<65 and ≥65, <75 and ≥75 years); gender (male/female); baseline creatinine clearance (≥60, 30 to <60, <30 mL/min) and baseline liver abnormality (yes/no).

In the pivotal efficacy studies:

- The severity of AEs was assessed by CTCAE Version 3.0 to 4.03 depending on study number. Maximum severity was recorded in subjects with more than one occurrence of the event per Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). Grade 5 events have been reported separately from Grade 3 and 4 events.
- AEs of particular interest: CNS haemorrhagic events.
- Laboratory data were based on haematology and serum chemistry test results obtained up to 30 days after last dose or the safety follow-up visit, whichever was later. Laboratory parameters were graded using the NCI CTCAE except the CLL/SLL IWCLL 2008 guidelines[6] were used to grade Hb, platelet and ANC for CLL/SLL subjects.
- Treatment emergent events were defined as those that met the criteria of: occurring after the first dose of study drug, throughout the treatment phase and for 30 days following last dose; any event with missing onset date and a resolution date during treatment; any event that was considered study-drug related regardless of the start date of the event; any event that was present at baseline but worsened in severity or was subsequently considered drug related by the investigator. These events were classified according to MedDRA Version 15 to 16.1 depending on study number.

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies of safety.

Clinical pharmacology studies

Table 9: Four studies provided safety data

Study	Study Phase	Study Type	Number of subjects
1001	2	Non-randomised	52
1002	1	Dose-escalation	21
1004	3	RCT ibrutinib versus ofatumumab	6
1010	2	Non-randomised, open label	18

Patient exposure

Exposure has been reported separately for the population of each of the proposed indications.

CLL/SLL

In subjects with CLL/SLL enrolled in Studies 1112 and 1102, the median duration of ibrutinib treatment was 9.0 months (range 0.2 to 28.7 months). Overall, the median total cumulative dose was 110 g, with a median daily dose of 416 mg (range 140 mg to 430 mg), with a median pooled ibrutinib dose intensity of 99.2%. Dose reductions were required for

[6] Hallek M, et al. (2008) *Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines*. Blood 111: 5446-56.

16 subjects (6.5%) of the pooled ibrutinib exposure group, 14 (5.7%) requiring one dose reduction and two (0.8%) requiring two.

MCL

In the 120 subjects with MCL enrolled in Studies 1104 & 04753, the median duration of treatment was 8.3 months (range 0.7 to 24.8 months), at data cut off 15 May 2013. Overall, the median total cumulative dose was 125 g, with a median daily dose of 550 mg (range 80 mg to 708 mg), with a median dose intensity of 98.2%. Dose reductions were only permitted in Study 1104, with 11 subjects (10%) having one and seven subjects (6%) having two events.

Treatment related adverse events (adverse drug reactions)

MCL and CLL/SLL subjects

Categorised TEAEs in 357 MCL and CLL/SLL patients are shown below in Table 10, as presented in the SmPC for ibrutinib.

Table 10: Treatment-emergent adverse events in MCL, CLL and SLL patients

System organ class	Frequency (All grades)	Adverse drug reactions
Infections and infestations	Very common	Pneumonia*
		Upper respiratory tract infection
		Sinusitis*
	Common	Sepsis*
		Urinary tract infection
		Skin infection*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Other malignancies*
		Non-skin cancer*
		Skin cancer*
Blood and lymphatic system disorders	Very common	Neutropenia
		Thrombocytopenia
		Anaemia
	Common	Febrile neutropenia
		Leukocytosis
		Lymphocytosis
	Uncommon	Leukostasis
Metabolism and nutrition disorders	Common	Dehydration
		Hyperuricaemia
Nervous system disorders	Very common	Dizziness
		Headache
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage*
		Bruising*
		Petechiae
	Common	Subdural haematoma
		Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
		Vomiting
		Stomatitis*
		Nausea
		Constipation
	Common	Dry mouth
Skin and subcutaneous tissue disorders	Very common	Rash*
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
		Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia

* Includes multiple adverse reaction terms.

Note: For other malignancies, all events occurring during the study (including follow-up) are included.

CLL/SLL studies

Of the 246 subjects in the integrated CLL/SLL safety population receiving 420 mg per day ibrutinib, 99.6% experienced at least one TEAE of any grade, with 59.8% experiencing at least one event of Grade ≥3.

The listing of adverse events (AEs) in the CLL/SLL population is shown in Table 11.

The most common Grade 3 or 4 events were: neutropenia (15.9%), pneumonia (6.9%), and thrombocytopenia (6.5%)

Table 11: Treatment-emergent adverse events occurring in ≥10% of CLL/SLL safety population

	Study 1112				Study 1102		Pooled	
	Ibrutinib		Ofatumumab		Ibrutinib		Ibrutinib	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Analysis Set: Safety Population	195		191		51		246	
Subjects with TEAEs	194 (99.5%)	99 (50.8%)	187 (97.9%)	74 (38.7%)	51 (100.0%)	33 (64.7%)	245 (99.6%)	132 (53.7%)
MedDRA SOC/preferred term								
Gastrointestinal disorders	153 (78.5%)	17 (8.7%)	105 (55.0%)	7 (3.7%)	44 (86.3%)	3 (5.9%)	197 (80.1%)	20 (8.1%)
Diarrhoea	93 (47.7%)	8 (4.1%)	34 (17.8%)	3 (1.6%)	30 (58.8%)	2 (3.9%)	123 (50.0%)	10 (4.1%)
Nausea	51 (26.2%)	3 (1.5%)	35 (18.3%)	0	10 (19.6%)	1 (2.0%)	61 (24.8%)	4 (1.6%)
Constipation	30 (15.4%)	0	18 (9.4%)	0	11 (21.6%)	1 (2.0%)	41 (16.7%)	1 (0.4%)
Vomiting	28 (14.4%)	0	12 (6.3%)	1 (0.5%)	9 (17.6%)	1 (2.0%)	37 (15.0%)	1 (0.4%)
Stomatitis	21 (10.8%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	8 (15.7%)	0	29 (11.8%)	1 (0.4%)
Infections and infestations	137 (70.3%)	41 (21.0%)	104 (54.5%)	33 (17.3%)	37 (72.5%)	16 (31.4%)	174 (70.7%)	57 (23.2%)
Upper respiratory tract infection	31 (15.9%)	1 (0.5%)	20 (10.5%)	3 (1.6%)	20 (39.2%)	0	51 (20.7%)	1 (0.4%)
Sinusitis	21 (10.8%)	1 (0.5%)	12 (6.3%)	0	8 (15.7%)	3 (5.9%)	29 (11.8%)	4 (1.6%)
Pneumonia	19 (9.7%)	13 (6.7%)	13 (6.8%)	9 (4.7%)	6 (11.8%)	4 (7.8%)	25 (10.2%)	17 (6.9%)
General disorders and administration site conditions	113 (57.9%)	11 (5.6%)	104 (54.5%)	6 (3.1%)	34 (66.7%)	4 (7.8%)	147 (59.8%)	15 (6.1%)
Fatigue	54 (27.7%)	4 (2.1%)	57 (29.8%)	3 (1.6%)	17 (33.3%)	3 (5.9%)	71 (28.9%)	7 (2.8%)
Pyrexia	46 (23.6%)	3 (1.5%)	28 (14.7%)	2 (1.0%)	12 (23.5%)	1 (2.0%)	58 (23.6%)	4 (1.6%)
Oedema peripheral	22 (11.3%)	0	15 (7.9%)	0	4 (7.8%)	0	26 (10.6%)	0
Skin and subcutaneous tissue disorders	108 (55.4%)	7 (3.6%)	88 (46.1%)	4 (2.1%)	33 (64.7%)	3 (5.9%)	141 (57.3%)	10 (4.1%)
Petechiae	27 (13.8%)	0	2 (1.0%)	0	3 (5.9%)	0	30 (12.2%)	0
Musculoskeletal and connective tissue disorders	93 (47.7%)	8 (4.1%)	68 (35.6%)	3 (1.6%)	32 (62.7%)	4 (7.8%)	125 (50.8%)	12 (4.9%)
Arthralgia	34 (17.4%)	2 (1.0%)	13 (6.8%)	0	12 (23.5%)	0	46 (18.7%)	2 (0.8%)
Muscle spasms	25 (12.8%)	0	16 (8.4%)	0	9 (17.6%)	1 (2.0%)	34 (13.8%)	1 (0.4%)
Back pain	22 (11.3%)	2 (1.0%)	12 (6.3%)	1 (0.5%)	5 (9.8%)	1 (2.0%)	27 (11.0%)	3 (1.2%)
Pain in extremity	20 (10.3%)	1 (0.5%)	8 (4.2%)	0	5 (9.8%)	0	25 (10.2%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	93 (47.7%)	6 (3.1%)	83 (43.5%)	9 (4.7%)	29 (56.9%)	4 (7.8%)	122 (49.6%)	10 (4.1%)
Cough	38 (19.5%)	0	44 (23.0%)	2 (1.0%)	10 (19.6%)	0	48 (19.5%)	0
Dyspnoea	23 (11.8%)	4 (2.1%)	20 (10.5%)	1 (0.5%)	2 (3.9%)	0	25 (10.2%)	4 (1.6%)
Blood and lymphatic system disorders	98 (50.3%)	51 (26.2%)	67 (35.1%)	45 (23.6%)	21 (41.2%)	14 (27.5%)	119 (48.4%)	65 (26.4%)
Anaemia	44 (22.6%)	9 (4.6%)	33 (17.3%)	15 (7.9%)	7 (13.7%)	0	51 (20.7%)	9 (3.7%)
Neutropenia	42 (21.5%)	32 (16.4%)	28 (14.7%)	26 (13.6%)	7 (13.7%)	7 (13.7%)	49 (19.9%)	39 (15.9%)
Thrombocytopenia	33 (16.9%)	11 (5.6%)	22 (11.5%)	8 (4.2%)	7 (13.7%)	5 (9.8%)	40 (16.3%)	16 (6.5%)
Nervous system disorders	64 (32.8%)	2 (1.0%)	58 (30.4%)	1 (0.5%)	30 (58.8%)	3 (5.9%)	94 (38.2%)	5 (2.0%)
Headache	27 (13.8%)	2 (1.0%)	11 (5.8%)	0	9 (17.6%)	1 (2.0%)	36 (14.6%)	3 (1.2%)
Dizziness	22 (11.3%)	0	10 (5.2%)	0	10 (19.6%)	0	32 (13.0%)	0

Key: CLL = chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; SLL = small lymphocytic lymphoma; SOC = system organ class; TEAE = treatment-emergent adverse event
Note: A subject with multiple severity ratings for a given adverse event was counted only once under the maximum severity.
Adverse events are presented by descending frequency of SOC and preferred term within SOC within Any Grade and Pooled Ibrutinib, those with the same frequency are presented alphabetically.
Percentages are calculated with the number of subjects in safety population as denominators.
Adverse events were coded using MedDRA Version 16.1.
Study 1102 population was comprised of 51 subjects in study cohorts 1 and 4 (previously-treated disease) who received 420 mg/day ibrutinib.
Pooled ibrutinib population comprised of 195 subjects from Study 1112 and 51 subjects from Study 1102 (cohorts 1 and 4) with previously-treated CLL/SLL who received at least 1 dose of ibrutinib 420 mg/day.

Adverse drug reactions were only reported for the following criteria:

- AEs which occurred in ≥10% of subjects treated with ibrutinib and 5% greater in the ibrutinib group compared with the ofatumumab arm of Study 1112: diarrhoea, musculoskeletal pain, nausea, rash, pyrexia, anaemia, neutropenia, bruising, arthralgia, thrombocytopenia, stomatitis, upper respiratory tract infection, constipation, vomiting, headache, petechiae, dizziness, sinusitis, and vision blurred.
- Frequency of SAEs in ≥2% of subjects treated with ibrutinib and 2% greater in the ibrutinib group compared with ofatumumab in Study 1112: atrial fibrillation, pneumonia, and urinary tract infection.

- Biological plausibility: skin infections, sepsis, epistaxis, subdural haematoma, lymphocytosis, leucocytosis, and febrile neutropenia.

MCL studies

Of the 120 subjects in the integrated safety population, 99.2% experienced at least one TEAE of any grade, with 76.7% experiencing TEAE of Grade ≥3.

The listing of AEs in the MCL population is shown in Table 12.

Table 12: Treatment emergent adverse events in >10% of MCL monotherapy population

	All Subjects (N=120)	
System Organ Class MedDRA Preferred Term	Any Grade n (%)	Grade 3 + 4 n (%)
Subjects with an event	119 (99.2)	75 (62.5)
Blood and lymphatic system disorders	53 (44.2)	37 (30.8)
Thrombocytopenia	24 (20.0)	14 (11.7)
Neutropenia	22 (18.3)	20 (16.7)
Anemia	18 (15.0)	11 (9.2)
Gastrointestinal disorders	100 (83.3)	14 (11.7)
Diarrhea	63 (52.5)	6 (5.0)
Nausea	38 (31.7)	1 (0.8)
Constipation	32 (26.7)	0 (0.0)
Vomiting	28 (23.3)	0 (0.0)
Abdominal pain	21 (17.5)	6 (5.0)
Dyspepsia	14 (11.7)	0 (0.0)
Stomatitis	14 (11.7)	1 (0.8)
General disorders and administration site conditions	88 (73.3)	13 (10.8)
Fatigue	52 (43.3)	5 (4.2)
Oedema peripheral	34 (28.3)	2 (1.7)
Pyrexia	23 (19.2)	1 (0.8)
Asthenia	15 (12.5)	4 (3.3)
Infections and infestations	91 (75.8)	26 (21.7)
Upper respiratory tract infection	29 (24.2)	0 (0.0)
Sinusitis	17 (14.2)	1 (0.8)
Urinary tract infection	16 (13.3)	3 (2.5)
Pneumonia	14 (11.7)	6 (5.0)
Injury, poisoning and procedural complications	39 (32.5)	5 (4.2)
Contusion	21 (17.5)	0 (0.0)
Metabolism and nutrition disorders	65 (54.2)	16 (13.3)
Decreased appetite	28 (23.3)	2 (1.7)
Hyperuricemia	19 (15.8)	5 (4.2)
Dehydration	16 (13.3)	4 (3.3)
Musculoskeletal and connective tissue disorders	70 (58.3)	5 (4.2)
Muscle spasms	20 (16.7)	0 (0.0)
Myalgia	19 (15.8)	0 (0.0)
Arthralgia	16 (13.3)	0 (0.0)
Back pain	16 (13.3)	1 (0.8)
Pain in extremity	15 (12.5)	0 (0.0)
Nervous system disorders	50 (41.7)	3 (2.5)
Dizziness	18 (15.0)	0 (0.0)
Headache	15 (12.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	66 (55.0)	8 (6.7)
Dyspnea	31 (25.8)	4 (3.3)
Cough	24 (20.0)	0 (0.0)
Epistaxis	12 (10.0)	0 (0.0)
Oropharyngeal pain	12 (10.0)	0 (0.0)
Skin and subcutaneous tissue disorders	82 (68.3)	4 (3.3)
Rash	18 (15.0)	2 (1.7)

MCL = mantle cell lymphoma; MedDRA = Medical Dictionary for Regulatory Activities
Total ibrutinib population comprised of 111 subjects from Study 1104 and 9 subjects from Study 04753 with previously-treated MCL.

The most common Grade 3 or 4 AEs were: neutropenia (16.7%), thrombocytopenia (11.7%), anaemia (9.2%), diarrhoea (5.0%), abdominal pain (5.0%), and pneumonia (5.0%).

In the absence of comparative safety data, for the MCL safety population, adverse drug reactions were reported for all TEAEs with an incidence of 10% or higher (Table 13).

Table 13: Treatment-emergent adverse reactions reported in >10% of the MCL safety population treated with 560 mg ibrutinib

		Frequency	
System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Infections and infestations	Upper respiratory tract infection	26	0
	Urinary tract infection	14	3
	Sinusitis	14	1
	Pneumonia	12	5
Blood and lymphatic system disorders	Thrombocytopenia	21	12
	Neutropenia	19	17
	Anaemia	15	10
Metabolism and nutrition disorders	Decreased appetite	23	2
	Hyperuricaemia	17	5
	Dehydration	14	4
Nervous system disorders	Dizziness	14	0
	Headache	12	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	28	4
	Cough	18	0
	Epistaxis	11	0
Gastrointestinal disorders	Diarrhoea	53	5
	Nausea	32	1
	Constipation	28	0
	Vomiting	23	0
	Abdominal pain	18	5
	Stomatitis	13	1
	Dyspepsia	11	0
Skin and subcutaneous tissue disorders	Rash	16	2
Musculoskeletal and connective tissue disorders	Back pain	14	1
	Arthralgia	14	0
	Muscle spasms	14	0
	Myalgia	14	0
	Pain in extremity	12	0
General disorders and administration site conditions	Fatigue	43	5
	Oedema peripheral	30	2
	Pyrexia	19	1
	Asthenia	12	3
Injury, poisoning and procedural	Contusion	18	0

MCL= mantle cell lymphoma

Deaths and other serious adverse events

CLL/SLL

In the pooled ibrutinib safety population of 246 previously treated CLL/SLL subjects from Studies 1112 and 1102, 15 (6.1%) had TEAEs that led to death. This compares to 16 of 191 subjects (8.4%) of the ofatumumab arm of Study 1112. The listed causes of death are shown in Table 14. The causes of death in the ibrutinib safety population were generally consistent with known complications of the disease or concomitant conditions in an elderly population.

Table 14: Treatment emergent adverse events leading to death in CLL/SLL monotherapy safety population

	Study 1112		Study 1102	Pooled
	Ibrutinib	Ofatumumab	Ibrutinib	Ibrutinib
Analysis Set: Safety Population	195	191	51	246
Subjects with TEAEs	12 (6.2%)	16 (8.4%)	3 (5.9%)	15 (6.1%)
MedDRA Preferred Term				
Pneumonia	3 (1.5%)	2 (1.0%)	0	3 (1.2%)
CLL	2 (1.0%)	2 (1.0%)	0	2 (0.8%)
Sepsis	2 (1.0%)	0	0	2 (0.8%)
Cardiac arrest	1 (0.5%)	0	0	1 (0.4%)
Gastrointestinal carcinoma	1 (0.5%)	0	0	1 (0.4%)
Leukaemia	1 (0.5%)	0	0	1 (0.4%)
Malignant histiocytosis	0	0	1 (2.0%)	1 (0.4%)
Neutropenic sepsis	1 (0.5%)	1 (0.5%)	0	1 (0.4%)
Peripheral T-cell lymphoma unspecified	0	0	1 (2.0%)	1 (0.4%)
Richter's syndrome	1 (0.5%)	0	0	1 (0.4%)
Malignant histiocytosis	0	0	1 (2.0%)	1 (0.4%)
Neutropenic sepsis	1 (0.5%)	1 (0.5%)	0	1 (0.4%)
Peripheral T-cell lymphoma unspecified	0	0	1 (2.0%)	1 (0.4%)
Richter's syndrome	1 (0.5%)	0	0	1 (0.4%)
Systemic inflammatory response syndrome	0	0	1 (2.0%)	1 (0.4%)
Bacteraemia	0	1 (0.5%)	0	0
Bronchopneumonia	0	1 (0.5%)	0	0
Cardiac failure	0	1 (0.5%)	0	0
Influenza	0	1 (0.5%)	0	0
Metastatic squamous cell carcinoma	0	1 (0.5%)	0	0
Nocardiosis	0	1 (0.5%)	0	0

	Study 1112		Study 1102	Pooled
Pyrexia	0	1 (0.5%)	0	0
Renal failure acute	0	1 (0.5%)	0	0
Sepsis syndrome	0	1 (0.5%)	0	0
Squamous cell carcinoma	0	1 (0.5%)	0	0
Upper respiratory tract infection	0	1 (0.5%)	0	0

Of the 15 subjects that died within 30 days of their last ibrutinib dose, only two had events that were possibly related to ibrutinib: one event of systemic inflammatory response syndrome and one event of pneumonia. The remainder were considered not related or unlikely.

Serious SAEs were more common in the ibrutinib arm (41.5%) compared to ofatumumab arm (30.4%). In particular the events of atrial fibrillation and pneumonia and lung infection (combined) occurred more commonly with ibrutinib (Table 15).

Table 15: Serious adverse events with incidence ≥2% in Study 1112 safety population

System Organ Class MedDRA Preferred Term	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Number of subjects reporting at least one SAE	81 (41.5)	58 (30.4)
Blood and lymphatic system disorders	8 (4.1)	11 (5.8)
Febrile neutropenia	3 (1.5)	4 (2.1)
Anaemia	2 (1.0)	4 (2.1)
Cardiac disorders	13 (6.7)	6 (3.1)
Atrial fibrillation	6 (3.1)	1 (0.5)
General disorders and administration site conditions	12 (6.2)	4 (2.1)
Pyrexia	6 (3.1)	4 (2.1)
Infections and infestations	46 (23.6)	39 (20.4)
Pneumonia	17 (8.7)	12 (6.3)
Lung infection	5 (2.6)	0 (0.0)
Lower respiratory tract infection	4 (2.1)	2 (1.0)
Urinary tract infection	4 (2.1)	0 (0.0)
Upper respiratory tract infection	1 (0.5)	4 (2.1)

Adverse events are coded by MedDRA Version 16.1. N = number of subjects in the specified population.
Percentages are calculated by 100*n/N.
Subjects with multiple events for a given preferred term or system organ class are counted once only under each preferred term or system organ class, respectively.

MCL

Of the 120 MCL subjects in the safety population, 17 (14.2%) died during treatment or within 30 days of discontinuation. The most common cause of death was disease progression in eight subjects (seven with MCL and one malignant pleural effusion), with a further four having AEs directly related to disease progression. All subjects who died were from Study 1104 and had received the proposed ibrutinib dose for MCL of 560 mg daily. Three subjects died due to treatment-emergent infections; two of these had pneumonia as

a cause of death that was possibly related to ibrutinib, the remainder of all deaths were considered not related (Table 16).

Table 16: Causes of death in MCL safety population

Duration of Treatment Duration (Days)	Days from Last Dose	Cause of Death by Preferred Term	Relationship to Ibrutanib
74	5	Pneumonia	Possible
27	30	Dyspnoea	Not Related
672	21	Hypovolaemic shock	Not Related
78	13	Renal failure acute	Not Related
58	15	MCL	Not Related
56	26	Malignant pleural effusion	Not Related
103	5	Ileus paralytic	Not Related
168	15	*Pneumocystis jiroveci*	Possible
84	18	MCL	Not Related
123	1	MCL	Not Related
250	3	Respiratory failure	Not Related
167	13	MCL	Not Related
169	23	MCL	Not Related
224	9	Sepsis	Not Related
340	1	Cardiac arrest	Not Related
119	11	MCL	Not Related
49	12	MCL	Not Related

Overall, any SAE was reported for 59.2%, with 51.7% experiencing any Grade ≥3 event. For serious adverse events (SAEs) that were related, 24.2% had any grade, and 21.7% had Grade ≥3 events.

SAEs in Study 1104 were reported for 60.4% of subjects, the most commonly occurring events were: atrial fibrillation (6.3%), pneumonia (5.4%), urinary tract infection (3.6%), abdominal pain (2.7%), subdural haematoma (2.7%), febrile neutropenia (2.7%), acute renal failure (2.7%), peripheral oedema (2.7%) and pyrexia (2.7%).

Discontinuation due to adverse events

CLL/SLL

In the integrated safety population from 1112 & 1102, 21 of 246 (8.5%) had discontinued ibrutinib treatment due to a TEAE, of which 10 events (4.1%) were of Grade 3 or 4 severity.

Overall, the commonest reasons for discontinuation were disease progression (5.3%) and death (5.3%).

MCL

In the MCL safety population from Studies 1104 and 04753, 14 of 120 subjects (11.4%) discontinued treatment due to an AE, of which eight (6.7%) were Grades 3 or 4, and four

were Grade 5 Among the 14 subjects, six discontinued due to an AE related to disease progression. There were three events related to haemorrhage: two subjects with subdural haemorrhage, and one with splenic haematoma, none of which were fatal.

Laboratory tests

Liver function

CLL/SLL

In the ibrutinib arm of Study 1112, two subjects (1.0%) had a post-baseline increase in total bilirubin of Grade 3 or 4, one of whom had an autoimmune haemolytic anaemia with elevated baseline bilirubin.

In the pooled CLL/SLL data, no Grades 3 or 4 toxicities related to aspartate aminotransferase (AST) or ALT were reported.

MCL

None of the 120 subjects had a worst post-baseline toxicity of Grade 3 or 4 in ALT, AST or total bilirubin.

Kidney function

CLL/SLL studies

In the pooled ibrutinib population, there were: 25 of 244 (10.2%) subjects that experienced any grade increase in creatinine, none of which were Grades 3 or 4, and 44 of 244 (17.9%) events of decreased creatinine clearance, two of which were Grade 3 or 4.

Among the 244 subjects in the integrated ibrutinib CLL/SLL population with available data, 209 (85.7%) maintained their baseline grade, 18 (7.4%) changed from ≥60 mL/min to <60 mL/min, and 2 (0.8%) changed from 30 to <60 to <30 mL/min during treatment.

MCL studies

TEAEs of elevation of serum creatinine were reported for 40 of 120 (33.3%) of subjects, two of whom had Grade 3 or 4 decrease in creatinine clearance. Overall, 77.5% of subjects remained in the same category of creatinine clearance, 18.3% changed from ≥60 mL/min to between >60 and 30 mL/min, and 1.7% changed to <30 mL/min at some time during treatment.

Serum electrolytes

CLL/SLL

For subjects in the pivotal CLL/SLL study whose grade changed from baseline (prior to crossover for ofatumumab subjects), the worst toxicity grade in clinical chemistry parameters are shown in Table 17.

Table 17: Worst toxicity Grade in clinical chemistry parameter during treatment (safety population)

Chemistry Laboratory Parameter	Direction of Toxicity	Ibrutinib (N=195)		Ofatumumab (N=191)	
		Any Grade n (%)	Grade 3 + 4 n (%)	Any Grade n (%)	Grade 3 + 4 n (%)
Alanine Aminotransferase	High	23 (11.8)	0	20 (10.5)	0
Albumin	Low	31 (15.9)	0	18 (9.4)	2 (1.0)
Alkaline Phosphatase	High	16 (8.2)	1 (0.5)	17 (8.9)	0
Aspartate Aminotransferase	High	11 (5.6)	0	16 (8.4)	0
Bilirubin	High	24 (12.3)	2 (1.0)	11 (5.8)	0
Calcium	High	3 (1.5)	0	1 (0.5)	0
Calcium	Low	17 (8.7)	2 (1.0)	11 (5.8)	0
Creatinine	High	12 (6.2)	0	16 (8.4)	1 (0.5)
Creatinine Clearance	Low	31 (15.9)	2 (1.0)	33 (17.3)	7 (3.7)
Glucose	High	74 (37.9)	5 (2.6)	87 (45.5)	11 (5.8)
Glucose	Low	23 (11.8)	0	10 (5.2)	0
Phosphate	Low	17 (8.7)	2 (1.0)	15 (7.9)	1 (0.5)
Potassium	High	3 (1.5)	0	4 (2.1)	1 (0.5)
Potassium	Low	20 (10.3)	1 (0.5)	5 (2.6)	0
Sodium	High	11 (5.6)	0	9 (4.7)	0
Sodium	Low	29 (14.9)	6 (3.1)	14 (7.3)	1 (0.5)

In Study 1102, hypernatraemia of any Grade 1 and 2 was observed in 23.6% of all 116 subjects; no Grade 3 or 4 events were reported. Hyponatraemia was reported in 27 subjects (23.3%) with eight of these events being of Grade 3 severity.

Hyperkalaemia was reported in 31 subjects (26.7%) with four and one events being of Grade 3 and 4 respectively. Hyponatraemia was reported in 15 subjects (12.9%), of which two events were of Grade 3 severity.

Hypocalcaemia was reported in 84 subjects (72.4%), of which three events were of Grade 3 severity. Six events (5.2%) of hypercalcaemia were reported, one of which was Grade 4 severity.

Hyperkalaemia of Grade 3 and 4 were reported in four (3.4%) and one (0.9%) subjects respectively. Two events (1.7%) of Grade 3 hypokalaemia were reported.

MCL

In the integrated ibrutinib MCL population, Grade 3 or 4 decreases in calcium, magnesium, potassium, and sodium levels were observed for 0.8%, 0%, 0.8%, and 5.8%, respectively. No ibrutinib treated MCL subject had a treatment-emergent Grade 3 or 4 increase in these serum electrolytes.

Haematology

CLL/SLL

AEs of neutropenia, febrile neutropenia, anaemia and thrombocytopenia are detailed in Table 18.

Table 18: Summary of selected cytopenias in the CLL/SLL safety population

	Any AE		Grade 3 or 4 AE		SAE	
	Ibrutinib	Ofatumumab	Ibrutinib	Ofatumumab	Ibrutinib	Ofatumumab
Neutropenia	21.5%	14.7%	16.4%	13.6%	1.0%	1.6%
Febrile neutropenia	2.1%	2.6%			1.5%	2.1%
Anaemia	22.6%	17.3%	4.6%	7.9%	1.0%	2.1%
Thrombocytopenia	16.9%	11.5%	5.6%	4.2%	0	0

Among the subjects with febrile neutropenia, in one patient in the ofatumumab arm this lead to treatment discontinuation and no discontinuations occurred in the ibrutinib arm. One subject in the ibrutinib arm died had a fatal AE of neutropenic sepsis which was classified as unlikely related to study treatment, whereas one patient in the ofatumumab arm had a fatal AE of neutropenic sepsis which was possibly related to study treatment.

MCL

AEs of neutropenia, febrile neutropenia, anaemia and thrombocytopenia in the 120 subjects in the MCL monotherapy safety population are shown in Table 19 below.

Table 19: Summary of selected cytopenias in the MCL safety population

	Any AE	Grade 3 or 4 AE	SAE
Neutropenia	18.3%	16.7%	0.8%
Febrile neutropenia	4.2%	3.3%	3.3%
Anaemia	15.0%	9.2%	1.7%
Thrombocytopenia	20.0%	11.7%	0.8%

Febrile neutropenia of Grade 3 or 4 severity, occurred in 3.3% if the integrated safety population.

Electrocardiograph

Studies 04753 and 1102

No formal QT/QTc study has yet been performed. However, the sponsor has agreed to a Phase I thorough QT study (PCI-32765CLL1007) as a post-approval commitment, with a report anticipated to be submitted by the 4th quarter of 2016. The report of this study should also be submitted to the TGA in the event that ibrutinib is registered in Australia.

In two clinical studies (04753 and 1102) electrocardiogram (ECG) monitoring was performed, but did not include a time-matched control for comparison.

In Study 1102 QTcF intervals were reportedly not prolonged as compared to baseline screening, in either of the two ibrutinib dose groups (420 mg and 840 mg). However, ibrutinib was associated with: a mean numerical QTcF duration shortening of up to 8.9 ms compared to baseline, a reduction in mean HR of up to 6.8 bpm compared to baseline and a mild increase in PR interval. The shortening of QTcF and increase in PR interval was without evidence of dose-dependency.

With the exception of a single observation of 242 ms, there was no evidence of PR interval prolongation (>240 ms). The QRS duration was not affected by ibrutinib, regardless of dose or treatment group.

Exposure-response analysis using ibrutinib and PCI-45227 plasma concentrations did show significant correlations for both QTcF and PR, which translated in a slightly negative

and positive concentration-effect relationship for QTcF and PR, respectively, for both ibrutinib and the dihydrodiol metabolite PCI-45227. With slopes of maximally 2 ms for both QTc and PR per 100 ng/mL concentration increase over the extensive concentration ranges observed for both compounds. The sponsor makes the statement that "this is not considered clinically relevant".

Vital signs

Studies 1112, 1102, 1104 and 04753

The sponsor states that: "Review of vital signs (including weight) did not identify any safety signals in Studies 1112 and 1102. Given both the long duration of treatment in these studies and the complicated medical histories of these older subjects, transient and isolated abnormal vital signs readings over such long spans of time are not unexpected."

In regard to Studies 1104 and 04752 (MCL indication) the sponsor states: "Overall, no clinically meaningful safety signals were seen."

Renal adverse events

CLL/SLL studies

In Study 1112, there were two Grade 3 or 4 renal events, one of nephrolithiasis and one of renal failure. There was one fatal event of acute renal failure in this study.

Among the 246 subjects in the integrated CLL/SLL population, TEAEs in the SOC of renal and urinary disorders were reported for 13.0% of subjects. No events led to ibrutinib discontinuation.

MCL studies

TEAEs of the SOC of renal and urinary disorders were reported for 22 of 120 (18.3%) subjects. Of these, six events were classified as serious, including four events of renal failure or renal failure acute; none of the four events were considered related to ibrutinib due to concurrent confounding medical conditions.

Infections

CLL/SLL

In the CLL/SLL pivotal study, AEs of infections and infestations occurred more commonly in the ibrutinib arm (70.3%) as compared the ofatumumab arm (54.5%). However the proportion of subjects with Grades 3 or 4 infections was similar, with 21.0% and 17.3% occurring in the ibrutinib and ofatumumab arms respectively. Fatal infections occurred in 3.1% and 4.7% of the ibrutinib and ofatumumab arms respectively. None of the fatal infections were considered to be related to study treatment in either treatment arm.

Serious atypical infections occurred in nine subjects overall, five in the ibrutinib arm and four in the ofatumumab arm. Among the ibrutinib patients, there were three events of aspergillosis infection, one of *Pneumocystis jiroveci* pneumonia and one of fungal tonsillitis.

In Study 1102, the overall incidence of infections/infestations was 82.8%, with infection being a reason for treatment discontinuation in 6.9%. The sub-groups of infections included: 31.9% with upper respiratory tract infection, sinusitis in 18.1%, pneumonia in 17.2% and urinary tract infection in 12.1%. Grade 3 or 4 pneumonia-related events occurred in 11.2% and three events (2.6%) were fatal. One event of pneumonia was due to an atypical organism.

MCL

Overall, 94 of 120 (75.8%) of all subjects experienced at least one treatment emergent infection while on treatment. Grade 3 or 4 treatment emergent infection were reported in

21.7% of subjects, of which, pneumonia, cellulitis and urinary tract infection were the only infections reported for more than two subjects in 5%, 3.3% and 2.5% respectively.

Two subjects (1.7%) had serious atypical infections reported, one fatal event of *Pneumocystis jiroveci* pneumonia and one non-fatal event of ophthalmic herpes zoster.

Clinical pharmacology studies in healthy volunteers

Among the 97 subjects enrolled in the clinical pharmacology studies, one subject discontinued study treatment (ibrutinib plus rifampicin) due to a Grade 2 morbiliform rash. No other AEs or SAEs were considered clinically significant and no deaths occurred in this population.

Post marketing data

Ibrutinib received marketing authorisation by the FDA on 12 February 2014. In their summary of clinical safety, the sponsor states that: "Safety information obtained from post marketing sources for the period from 13 November 2013 through 12 February 2014 was reviewed. No new safety signals were observed based upon these post marketing reports, and there have been no regulatory actions taken for safety reasons."

Safety issues with the potential for major regulatory impact

Liver toxicity

No subjects in the MCL safety population developed hepatic toxicities that met the criteria for Hy's law. The MCL studies excluded patients with pre-existing hepatic impairment and no subjects experienced Grades 3 or 4 increases in AST, ALT or total bilirubin. Nine subjects (7.5%) experienced Grade 1 elevation of AST, ALT and/or bilirubin.

No subjects in the CLL/SLL safety population developed hepatic toxicities that met the criteria for Hy's law. Among the CLL/SLL subjects, there was one subject who experienced a Grade 3 elevation of bilirubin and there were no Grades 3 or 4 elevations of hepatic enzyme elevation. The event of increased bilirubin did not result in ibrutinib dose modification/interruption.

CNS haemorrhagic events

This was categorised as an AE of "clinical interest" due to events occurring early in the ibrutinib clinical development program. In total, there have been nine of 636 (1.4%) episodes of CNS haemorrhage up to 6 April 2013. The cumulative incidence has fallen over time, as new patients have been accrued into studies: at November 2011, six of 173 (3.5%) events were reported, whereas up to the end of 2012, nine of 527 (1.7%) events were reported.

In Study 1112, one subdural haematoma and one post procedural haemorrhage were reported in the ibrutinib arm, of which only the subdural haemorrhage event was considered possibly related to ibrutinib, leading to drug withdrawal.

Six events occurred in Study 1102, three of which were in subjects taking concomitant anticoagulant or anti platelet medication. One subject was taking concomitant ibuprofen and had a normal platelet count at the time of haemorrhage and a further subject had a history of von Willebrand disease.

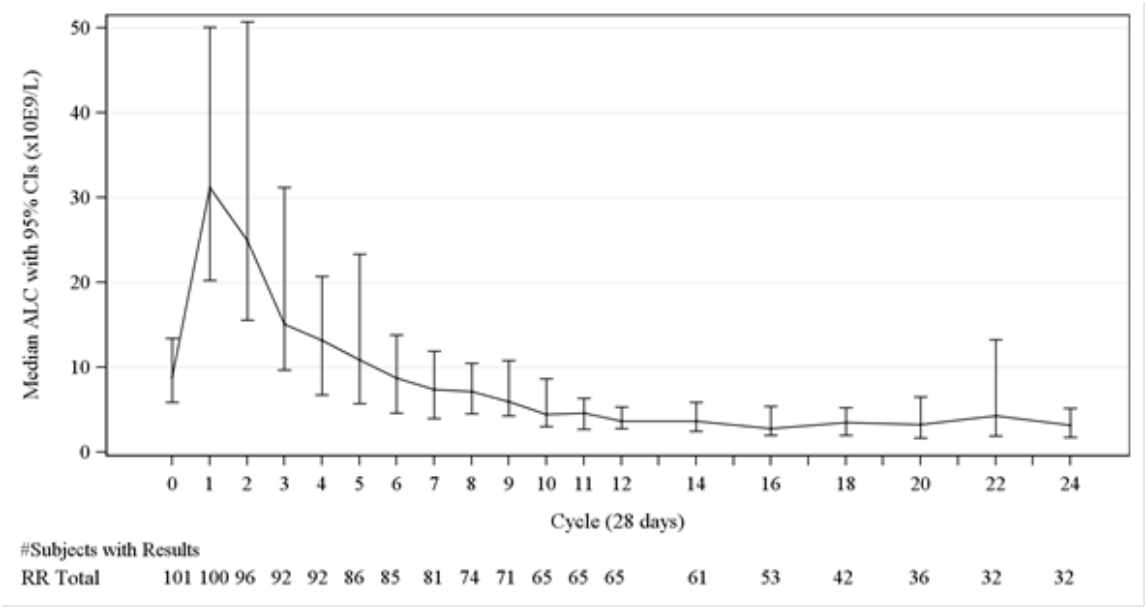
Haematological toxicity

In the CLL/SLL safety population, one subject in Study 1102 experienced Grade 4 leukostasis. This event was considered related to disease progression and was serious but

did not result in ibrutinib discontinuation. However, no subjects in the pivotal Study 1112 experienced leukostasis.

Over time, the median lymphocyte count in CLL/SLL subjects in Study 1102 showed an initial rapid increase in the first two cycles of treatment, followed by a progressive decline (Figure 2).

Figure 2: Median lymphocyte counts over time, in CLL/SLL subjects. Study 1102



In the MCL studies, one subject in Study 1104 had an event of leukostasis.

A further three cases of leukostasis have been reported in additional ibrutinib studies up to 3 January 2014.

Serious skin reactions

In the integrated CLL/SLL population 48 subjects (19.5%) experienced either: “rash”, “rash erythematous” or “rash maculopapular”. No serious rash related TEAEs were reported, and none led to ibrutinib discontinuation.

In Study 1117, a 71 year-old man experienced Grade 4 Stevens-Johnson syndrome which was histologically confirmed and was considered related to ibrutinib. This subject experienced oral ulceration and a maculopapular rash on first exposure and one re-challenge.

Cardiovascular safety

The SOC of cardiac disorders in Study 1112 are summarised in Table 20.

Table 20: Subjects with SOC of cardiac disorders, Study 1112

	Ibrutinib (n=195)		Ofatumumab (n=191)	
	Any grade (%)	Grade 3 & 4 (%)	Any grade (%)	Grade 3 & 4 (%)
Cardiac disorder	11.8	7.9	5.6	1.6
Atrial fibrillation	5.1	3.1	0.5	0
Atrial flutter	1	0	0	0
AV block	1	0	0	0
RBBB	0.5	0	0	0

Of the 11 subjects that were reported to have atrial fibrillation or flutter, five had previously received doxorubicin and five had concomitant infection at the time of diagnosis. Only two events were described as possibly related to ibrutinib.

Two subjects in the ibrutinib arm experienced events of AV block: one subject had pre-existing right bundle branch block at baseline, the second had a normal ECG at baseline.

The only event of right bundle branch block was observed at baseline in the ibrutinib arm.

In the 120 MCL subjects 11 (9.2%) events of atrial fibrillation occurred and 5.8% had serious TEAEs of atrial fibrillation.

In Study 1112, there were five subjects in the ibrutinib arm who had atrial fibrillation (all grades); three of these were Grade 3 or 4 events. In comparison in the ofatumumab arm one subjects had atrial fibrillation which was neither Grade 3 nor 4.

In the pooled ibrutinib safety population of 246 CLL/SLL subjects, 15 (6%) of subjects had atrial fibrillation of all grades and 10 (4%) had Grade 3 or 4 events.

In the CLL/SLL safety population, events of "sinus bradycardia", "bradycardia" and "heart rate decreased" were reported collectively in four of 246 (1.6%) of subjects. Events of "sinus tachycardia", atrial tachycardia", "heart rate increased" and "tachycardia" were reported collectively in five of 246 (2.0%) of subjects.

In their response to questions from the EMA, the sponsor confirms that all ibrutinib-exposed patients should be periodically monitored for atrial fibrillation.

Second malignancies

A description of the malignancies occurring in addition to the primary CLL/SLL in Study 1112 is shown in Table 21. Only data for ofatumumab patients before cross-over is included. The majority of second malignancies were of skin origin.

Table 21: Summary of second malignancies occurring in Study 1112 participants

	Ibrutinib (n=195)		Ofatumumab (n=191)	
	Any grade	Grade 3&4	Any grade	Grade 3&4
Skin cancers*	10 (5.1%)	1 (0.5%)	4 (2.1%)	0 (0%)
BCC	4 (2.1%)	0 (0%)	1 (0.5%)	0 (0%)
SCC	3 (1.5%)	0 (0%)	2 (1.0%)	0 (0%)
SCC of skin	2 (1.0%)	0 (0%)	0 (0%)	0 (0%)
Bowen's disease	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Skin cancer	1 (0.5%)	1 (0.5%)	0 (0%)	0 (0%)
Metastatic SCC	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
Gastrointestinal carcinoma	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Lung adenoma metastatic	1 (0.5%)	1 (0.5%)	0 (0%)	0 (0%)
Sarcoma	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Soft tissue neoplasm	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Squamous cell carcinoma of lung	1 (0.5%)	1 (0.5)	0 (0%)	0 (0%)
Myelodysplastic syndrome	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)
Tongue neoplasm	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)

*Events coded by MedDRA term.

Progressive multifocal leukoencephalopathy

Two cases of PML have been reported. One patient with CLL, who had received five prior rituximab containing regimens, developed neurological symptoms on Day 323 of ibrutinib warranting lumbar puncture, which confirmed presence of JC virus. This subject had received her last dose of rituximab 367 days prior to diagnosis.

Another patient with relapsed CLL, having not previously received rituximab, developed neurological symptoms following administration of rituximab, bendamustine and ibrutinib. Confirmation of the diagnosis of PML was made between Day 57 and 64 on study. The subject had received 15 doses of ibrutinib, two doses of rituximab and two doses of bendamustine and the investigator assessed the event as possibly related to ibrutinib. This PML event was fatal.

Eye disorders

In the MCL safety population, 37 subjects (30.8%) reported an event in the SOC of eye disorders.

In the CLL/SLL safety population from Study 1112, 36.4% in the ibrutinib arm and 18.8% of subjects in the ofatumumab arm developed an eye disorder; none of these events were Grade 3 or 4 severity. Blurred vision was reported by 10 of 195 subjects in the ibrutinib arm and three of 191 in the ofatumumab arm. The TEAE of blurred vision in the pooled CLL/SLL safety population was reported in nine subjects, with none of the events being Grade 3 or 4 severity. Five out of six subjects in the ibrutinib arm with cataracts observed during the course of the study did not have a prior history of the condition. The disorders of dry eye, increased lacrimation, reduced visual acuity, vitreous floaters, photophobia, eye irritation, eye pruritus, conjunctivitis and ocular hyperaemia were all more commonly reported in the ibrutinib treatment arm.

In the integrated CLL/SLL safety population, eye disorders were reported for 88 of 246 subjects (35.8%), all of which were Grade 1 or 2 severity. The incidence of blurred vision was 8.9% and dry eye 7.3%.

Unwanted immunological events

No events of anaphylaxis have been reported in the CLL/SLL or MCL safety populations.

One subject with a prior history of food and drug related allergy/anaphylaxis had four episodes of worsening of angioedema in Study 1112. None of these events were considered related to ibrutinib and did not result in dose modification/interruption.

Other safety issues

Safety in special populations

There have been no studies of ibrutinib use in human pregnancy or breast feeding. Preclinical studies in rats have demonstrated increased post implantation loss and malformations of the heart and major vessels with doses of between >40 to 80 mg/kg/day.

The sponsor has proposed ibrutinib to be Pregnancy Category B3.

Safety related to drug-drug interactions and other interactions

In vitro, ibrutinib is a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

The sponsor proposes to advise patients that a seven day off-treatment period is required when ibrutinib needs to be dosed with a strong CYP3A4 inhibitor.

In vitro studies demonstrated that ibrutinib is not a substrate for permeability glycoprotein (P-gp) but is an inhibitor. No clinical studies have been performed regarding the potential for DDIs with P-gp inhibition.

Overdose

There is no safety data pertaining to ibrutinib overdose. The maximum tolerated dose was not reached in the clinical development program. The highest daily dose administered was 1400 mg (12.5 mg/kg).

Drug abuse

The sponsor states there are no reports of abuse of, or dependence upon, ibrutinib. Given the pharmacological action of ibrutinib, it is not expected to have abuse potential.

Withdrawal & rebound

No studies of withdrawal or rebound have been conducted

Effect on immunisations

No studies of immunisation efficacy have been conducted.

Adverse drug reaction reports submitted to the TGA

As of the 11 November 2014, a total of six ADR reports were received by the TGA for Australian patients up to the date of this evaluation report.

One report was received for a subject with CLL in trial PCY-1112-CA. The subject was reported to have non-cardiac chest pain and recurrent urinary tract infections. The cause of the symptoms was recurrent pyelonephritis, and the dose of ibrutinib was not changed.

The investigator considered the causality between the non-cardiac chest pain and ibrutinib as possible. No assessment of causality between the recurrent UTI and ibrutinib was provided.

One report was received for a subject with MCL in trial PCI-32765MCL3002. The subject was reported to have lower abdominal pain. The cause of the symptoms was diverticulitis. The investigator considered the causality between ibrutinib and diverticulitis as “not related”.

One report was received for a subject with CLL in trial PCYC-1112-CA. The subject was reported to have a febrile illness (Grade 1), oral mucositis (Grade 3) and bacteroides bacteraemia (Grade 3).

The investigator considered the causality between oral mucositis, bacteroides bacteraemia and ibrutinib as “possible”.

One report was received for a subject with CLL in Study PCYC-1112-CA. The subject was reported to have had a Grade 2 post operative haemorrhage following removal of a non malignant skin lesion. No relevant laboratory data was provided.

The investigator considered the causality between the haemorrhage and ibrutinib as “possible”.

One report was received for a subject with refractory follicular lymphoma in Study PCI-32765FLR2002, being treated with ibrutinib. The subject was reported to have developed a malignant melanoma which was considered “possibly related” to ibrutinib exposure.

One report was received for a subject with MCL in Trial PCI-32765MCL3002. The subject developed axillary cellulitis and gout which was assessed as having “doubtful” causal association with the blinded study treatment.

Evaluator's conclusions on safety

Overall, cumulative exposure to ibrutinib was similar between the CLL/SLL and MCL populations, the former having a longer duration of exposure at the proposed lower dose.

Discontinuations due to reasons other than disease progression or death were comparable across the two indications.

The SOC of TEAEs was similar between the two indication populations, with events of infection occurring in subjects already at risk from their underlying disease states, in a typically elderly population. Atypical infections occurred during the ibrutinib studies but are not unusual in either disease state.

Cytopenias occurring in multiple cell lines were observed across the CLL/SLL and MCL patient populations.

In addition to observed cytopenias, serious CNS haemorrhagic events were specifically identified at being of clinical interest. The aetiology of the events is multifactorial, some occurring in patients not on anticoagulant or anti platelet therapies.

The effect of ibrutinib on heart rhythm does not appear readily predictable, nor does it have a typical direction of response on heart rate. Atrial fibrillation was observed across both indication populations, in particular occurring more commonly than with ofatumumab in the CLL/SLL population. In patients who develop atrial fibrillation while on ibrutinib, concomitant administration of anticoagulation should be carefully assessed on an individual basis given the observed risk of serious haemorrhage.

There is a potential for ibrutinib to be associated with a decrease in heart rate, which may have a disproportionate clinical effect in patients with increasing age, poor exercise tolerance or reduced cardiac reserve.

Progressive multifocal leukoencephalopathy was observed in two subjects with CLL, and is contained in the risk management plan under ongoing monitoring with routine pharmacovigilance activities and a targeted follow-up of AEs through a guided questionnaire.

The effect of ibrutinib on concomitant administration of immunisations has not been assessed. It should be recommended that patients receive immunisations prior to commencing ibrutinib or at least one month after ceasing therapy.

Second malignancies are a known risk for patients with haematological malignancies and in response to treatment modalities. In the randomised CLL/SLL subjects, the risk of second malignancies was higher with ibrutinib than with ofatumumab.

The sponsor has proposed ibrutinib to be Category B3. The evaluator considers this incorrect since there have been no studies in pregnant women and their offspring, which is a prerequisite for this categorisation. Given the preclinical evidence of foetal major heart and great vessel malformation Category D is the more appropriate pregnancy classification.

Among the CLL subjects, the pattern of causes of death was dissimilar for ibrutinib and ofatumumab; however, most of these events were typical of the underlying disease state or characteristics of the population. The incidence of Grade 3 or 4 cytopenias was similar among the ibrutinib and ofatumumab subjects.

Among the 120 MCL subjects studied, the causes of death were predominately due to disease progression, and only one atypical infection being possibly attributable to ibrutinib.

The incidence of Grades 3 or 4 cytopenias in the MCL subjects was similar to that seen in the CLL/SLL subjects.

First Round Benefit-Risk Assessment

First round assessment of benefit-risk balance

The benefit-risk balance of ibrutinib, given the proposed usage in both CLL/SLL and MCL populations is favourable.

First Round Recommendation Regarding Authorisation

The evaluator considers that given the efficacy and safety data presented, ibrutinib (Imbruvica) can be considered for approval for the sponsor proposed indications of:

> *Imbruvica is indicated for the treatment of patients with CLL/SLL who have received at least one prior therapy.*
>
> *Imbruvica is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.*

The following should be considered for conditions of registration by the Delegate:

- Presentation of the results of the formal QTc Study (CLL1007).
- Presentation of the results of Study CLL1006 in subjects with varying degrees of hepatic impairment.
- Completion of a pH study to establish the effects on ibrutinib absorption
- Commitment by the sponsor to provide an update to the efficacy data from Study 1104

Clinical Questions

Additional expert input

Not requested.

Clinical questions

Safety

1. The sponsor is kindly requested to provide any data it holds on the efficacy and safety of immunisations concurrently administered with ibrutinib.

Company response

Currently, the Company does not have any clinical data regarding the safety and efficacy of immunisations concomitantly administered with ibrutinib. Preclinical study in rats showed no adverse reactions from immunisations during concomitant ibrutinib administration at 100 mg/kg (human equivalent doses (HEDs) 16 mg/kg/day, AUC 13.8 μg·hr/mL); however, there was a dose dependent inhibition of IgM and IgG responses to immunisations of KLH at ≥ 10 mg/kg/day (HED ≥ 1.6 mg/kg/day, AUC ≥ 1 μg·hr/mL). This was considered non adverse as this was anticipated pharmacologic effect. Also, the genetic BTK deficiency in mice is associated with reduced response to immunisation. In summary, while there is no data regarding immunisation responses in people, preclinical data suggests immunoglobulin production in response to immunisation may be decreased in patients taking ibrutinib. This is consistent with the mechanism of action of ibrutinib. The company proposes to add the following statements in the 'Special populations' section of the PI:

Immunisations

There is no clinical data on the safety and efficacy of immunisations concomitantly administered with ibrutinib. Immunisations may be less effective in patients on ibrutinib therapy.

Evaluator response: This response and PI statement satisfactorily documents the current level of evidence and risk.

2. The sponsor should present any new safety signals arising from post marketing reports obtained outside Australia.

Company response

Cases of tumour lysis syndrome have been observed infrequently in clinical trials and postmarketing settings (four from monotherapy clinical trials out of 1730 subjects treated and seven from post-marketing out of 11,218 treated on commercial drug); none of the cases were fatal and all reported cases were confounded by underlying risk factors for tumour lysis syndrome. A definitive causal relationship between ibrutinib and tumour lysis syndrome cannot be established with the current data. However, since TLS is considered an important potential risk, the Company has added precautionary language in the Warning and Precautions section of the PI as described below.

Tumour lysis syndrome

Tumour lysis syndrome has been reported with Imbruvica therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

Tumour lysis syndrome is an important potential risk described in the EU Risk Management Plan and was also included in the Australian Specific Annex (ASA). The company will continue to routinely monitor reports of tumour lysis syndrome in association with the use of ibrutinib.

A full review of all reports of tumour lysis cases from worldwide clinical trials and post marketing sources is provided.

To date, there are no other new safety signals that have been identified from post-marketing surveillance.

Evaluator comment: This PI entry is satisfactory

Other matters

The sponsor has amended the indication of Ibrutinib in their response to TGA's request for further information, as proposed by the clinical evaluator in the Round 1 Evaluation, to:

Chronic Lymphocytic Leukaemia/Small Lymphocytic Leukaemia (CLL/SLL)

Imbruvica is indicated for the treatment of patients with CLL/SLL:

- Who have received at least one prior therapy
- Or for the frontline treatment of patients with CLL with 17p deletion

The amended indication is in line with that approved in the USA, EU and Canada. The proposed amended indication is still supported by the clinical evaluator.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The benefits from ibrutinib remain the same as at the first round evaluation.

Second round assessment of risks

The risks of ibrutinib therapy now include an observed risk of tumour lysis syndrome. This AE is expected in the clinical context, and is appropriately warned for. The clinical management of patients anticipated to experience tumour lysis is a standard of care in oncology patients.

This additional risk does not outweigh the benefits of ibrutinib.

Second round assessment of benefit-risk balance

The benefit-risk balance of ibrutinib, given the proposed usage in both CLL/SLL and MCL populations is favourable.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP: Ibrutinib EU-RMP (version 3.2, dated 30 July 2014) and Australian Specific Annex (ASA) (version 1.0, dated 13 August 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 22.

Table 22: Ongoing safety concerns

Important identified risks	• Leukostasis • Haemorrhage
Important potential risks	• DDI • Anaemia • Neutropenia • Thrombocytopenia • Infections • Cardiac arrhythmia • Severe GI disorders • Other malignancies • Hypersensitivity • Teratogenicity • Tumour lysis syndrome • Eye disorders • Renal failure • Hypertension
Missing information	• Off-label use in paediatric patients

	• Use during breastfeeding • Use in patients with severe cardiac disease • Use in patients with severe renal impairment • Use in patients with severe hepatic impairment • Long term use (>2 years)

OPR reviewer comment

The summary of ongoing safety concerns is consistent with that accepted in the EU as detailed in the ibrutinib EPAR. This is generally acceptable.

Although teratogenicity is listed as a potential risk, the sponsor should provide clarification as to why 'use in pregnancy' is not included as missing information.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine pharmacovigilance is proposed for all safety concerns. Routine pharmacovigilance includes a targeted follow up questionnaire for AEs relating to the important identified risks 'leukostasis' and 'haemorrhage' and important potential risk 'infections'. These questionnaires have been provided with the RMP.

Additional pharmacovigilance activities are proposed as described in the table which appears in the EU-RMP.

OPR reviewer's comment

The pharmacovigilance plan as represented in the EU-RMP is taken to apply in the Australian context whether or not the particular activities are to be conducted in Australia. Safety data accumulated through activities undertaken as commitments in the EU and US are considered generally applicable to the Australian context. Therefore, the sponsor is requested to clarify the following statement which appears in the ASA:

> *Any additional clinical trials listed in EU RMP v3.2 section SVIII.1 'Safety Concerns and Overview of Planned Pharmacovigilance Actions', under the 'Proposed routine and additional Pharmacovigilance activities' column, are exceptions in the Australian context – any clinical trials involving Australian sites are listed in section 2.2 of this ASA.*

Notwithstanding the above clarification, the pharmacovigilance plan presented is in accordance with what was deemed necessary and acceptable in the EU. Similarly, the plan is considered acceptable to monitor and inform the safety concerns in the Australian context and the evaluator has no objection to the proposed activities.

At the time of approval in the US the FDA determined that spontaneous post marketing AE reports would not be sufficient to assess the important identified risk of 'haemorrhage'. Therefore the sponsor was required to conduct Studies PCYC-PMR-2060-3 and PCYC-PMR-2060-4. Protocols of these studies should be submitted with the Section 31 response, if available. In particular the sponsor is requested to provide information on whether Australian patients will be included in either of these studies.

The additional pharmacovigilance activities will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke

applications to amend the Australian registration details. It is recommended that all study reports are provided to the TGA appropriately as required.

Risk minimisation activities

Evaluation of the need for risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor has concluded that routine risk minimisation (that is, product labelling) is sufficient to mitigate the risks attributed to ibrutinib. No additional risk minimisation activities are proposed.

Regarding off-label use the sponsor has provided the following information in SVI.5 of the EU-RMP:

> The current SmPC and Package Leaflet for ibrutinib clearly state the exact indication for which ibrutinib is authorised. The efficacy and safety in other malignancies have not been formally established and, for that reason, no dosing information for malignancies other than the indicated MCL and CLL conditions are presented in the product label. Ibrutinib could potentially be used as a treatment in unapproved oncology indications other than the approved indications.
>
> After ibrutinib is approved and available in the market in the EU, the potential exists that ibrutinib will be prescribed in a manner not consistent with the product label (for example, in patients with B-cell malignancies other than MCL, CLL) or at non recommended doses.

OPR reviewer comment

The risk of off label use is considered to be adequately mitigated by product labelling statements.

Risk minimisation plan

Planned actions

The sponsor has proposed routine risk minimisation (that is, product labelling) for all safety concerns.

No risk minimisation is proposed for the important potential risks 'other malignancies', 'tumour lysis syndrome', 'eye disorders' and 'hypertension' and missing information 'long term use (>2 years)'.

OPR reviewer comment

According to its proposed use, ibrutinib will be prescribed in Australia by specialist medical practitioners familiar with medicinal products that exhibit particular risks and may cause toxicity. This familiarity would tend to negate the requirement for additional risk minimisation activities in the absence of a particular risk that required specific mitigation. Therefore, the sponsor's proposal to not employ additional risk minimisation is considered acceptable at present.

The ASA does not refer to the specific wording in the PI attributed to each safety concern as routine risk minimisation. Instead the sponsor states that the safety concerns are equivalently addressed in the Australian labelling documents as detailed in the EU-RMP for the Summary of Product Characteristics (SmPC).

Therefore the draft Australian PI has been compared to the risk minimisation measures detailed in the EU-RMP. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:

- The sponsor should ensure that units quoted in the PI correspond to the units used by Australian laboratories. For instance the Leukostasis precaution includes a threshold for lymphocytes quoted as >400000/mcL. According to the Royal College of Pathologists of Australasia Manual, lymphocyte counts should be reported as cell count x 10^9/L. This and other units presented in the PI should be amended as appropriate.
- As routine risk minimisation for the identified risk 'leukostasis', the leukostasis precaution should be amended as follows to avoid ambiguity (addition underlined): *"Consider temporarily <u>with</u>holding ibrutinib".*
- As routine risk minimisation for the identified risk 'haemorrhage', the statement in the bleeding-related event precaution should be amended as follows to avoid ambiguity (addition underlined): "*Ibrutinib should be <u>with</u>held at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding*".
- As routine risk minimisation for the potential risk 'DDI', the EU SmPC contains the following contraindication: "*Use of preparations containing St. John's Wort is contraindicated in patients treated with Imbruvica*". A similar contraindication should be added to the draft PI that refers to the appropriate section regarding DDIs.
- As routine risk minimisation for the potential risk 'cardiac arrhythmia', the EU SmPC contains the following precaution which should be included in the Australian PI:

  Effects on the QT interval

  In a Phase II study, ECG evaluations showed Imbruvica produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (for example, Congenital Short QT Syndrome or patients with a family history of such a syndrome).
- As routine risk minimisation for the potential risk 'teratogenicity', the EU SmPc contains advice for women to avoid becoming pregnant for up to three months after treatment cessation whereas the Australian PI advises one month. This discrepancy should be corrected or justified with evidence.
- As routine risk minimisation for missing information 'use in patients with severe cardiac disease', the EU-RMP refers to a statement in the EU SmPC that "*patients with severe cardiovascular disease were excluded from Imbruvica clinical studies*". This omission is highlighted to the delegate.
- The EPAR revealed that medicines that increase stomach pH may decrease ibrutinib exposure. A study is planned for the important potential risk 'DDI' to investigate the potential interaction between PPIs and ibrutinib. Until these results are known, due to the expected co-administration of PPIs, it is recommended that the draft Australian PI include a statement similar to that which appears in the EU SmPC as follows:

  As ibrutinib solubility is pH dependent, there is a theoretical risk that medicinal products increasing stomach pH (for example, proton pump inhibitors) may decrease ibrutinib exposure. This interaction has not been studied in vivo.
- For missing information 'long term use (>two years)' the sponsor should provide justification why routine risk minimisation is not proposed.
- The overdose section should refer to the Australian Poisons Information centre telephone number.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to appropriately reflect PI changes made during the evaluation process.

Reconciliation of issues outlined in the RMP report

Table 23 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 23: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request 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 acknowledges the TGA request.	n/a
Although teratogenicity is listed as a potential risk, the sponsor should provide clarification as to why 'use in pregnancy' is not included as missing information.	The Sponsor initially included "use in pregnancy" as missing information in EU RMP. But this was removed based on PRAC suggestion that since teratogenicity is an important potential risk in the EU RMP, it is not necessary to include "use in pregnancy" as missing information.	This is acceptable from a RMP perspective.
The pharmacovigilance plan as represented in the EU-RMP is taken to apply in the Australian context whether or not the particular activities are to be conducted in Australia. Safety data accumulated through activities undertaken as commitments in the EU and US are considered generally applicable to	Section 2.3 of the Australian Specific Annex (attached ASA v1.1) is updated to correct the referencing to the relevant section of EU RMP. Routine pharmacovigilance activities will be	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
the Australian context. Therefore the sponsor is requested to clarify the following statement which appears in section 2.3 of the ASA: Any additional clinical trials listed in EU RMP v3.2 section SVIII.1 'Safety Concerns and Overview of Planned Pharmacovigilance Actions', under the 'Proposed routine and additional Pharmacovigilance activities' column, are exceptions in the Australian context – any clinical trials involving Australian sites are listed in section 2.2 of this ASA.	conducted in Australia as outlined in EU RMP, Part III Section III.1. 'Safety Concerns and Overview of Planned Pharmacovigilance Actions'. Safety data accumulated through activities described in Part III Section III.1 are applicable to the Australian context.	
At the time of approval in the US the FDA determined that spontaneous post-marketing AE reports would not be sufficient to assess the important identified risk of 'haemorrhage'. Therefore the sponsor was required to conduct studies PCYC-PMR-2060-3 and PCYC-PMR-2060-4. Protocols of these studies should be submitted with the section 31 response, if available. In particular the sponsor is requested to provide information on whether Australian patients will be included in either of these studies.	The study protocols of PCYC-PMR-2060-3 and PCYC-PMR-2060-4 are provided. Study PMR-2060-3 is an in vitro study. Study PMR-2060-4 is a PV assessment that will cover all company sponsored clinical trials and post-approval use in patients. Company-sponsored clinical studies that enrolled or will enrol Australian patients are listed in Table 2 of SECTION 2.2 of ASA.	This is acceptable from a RMP perspective. The evaluator has no objection to the studies conducted to address the risk of 'haemorrhage'. Results of these studies should be appropriately communicated to the TGA when available.
The additional pharmacovigilance activities will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. It is recommended that all study reports are provided to the TGA appropriately as required.	The Sponsor acknowledges the TGA request. The final CSR of Study PCYC-1104-CA, which was issued after the MAA submission, is enclosed with this response.	This is acceptable from a RMP perspective.
The sponsor should ensure that units quoted in the PI correspond to the units used by Australian laboratories. For instance the Leukostasis	The requested changes have been made in the revised PI.	This is acceptable from a RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
precaution includes a threshold for lymphocytes quoted as >400000/mcL. According to the Royal College of Pathologists of Australasia Manual, lymphocyte counts should be reported as cell count x 109/L. This and other units presented in the PI should be amended as appropriate.		
As routine risk minimisation for the identified risk 'leukostasis', the leukostasis precaution should be amended as follows to avoid ambiguity: "Consider temporarily withholding ibrutinib".	The requested change has been made in the revised PI.	This is acceptable from a RMP perspective.
As routine risk minimisation for the identified risk 'haemorrhage', the statement in the bleeding-related event precaution should be amended as follows to avoid ambiguity: "Ibrutinib should be withheld at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding".	The requested change has been made in the revised PI.	This is acceptable from a RMP perspective.
As routine risk minimisation for the potential risk 'DDI', the EU SmPC contains the following contraindication: "Use of preparations containing St. John's Wort is contraindicated in patients treated with Imbruvica". A similar contraindication should be added to the draft PI that refers to the appropriate section regarding DDIs.	The requested contraindication statement has been added to the revised PI.	This is acceptable from a RMP perspective.
As routine risk minimisation for the potential risk 'cardiac arrhythmia', the EU SmPC contains the following precaution which should be included in the Australian PI: Effects on the QT interval In a Phase II study, ECG evaluations showed Imbruvica produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of	The requested change has been made in the revised PI.	This is acceptable from a RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (for example, Congenital Short QT Syndrome or patients with a family history of such a syndrome).		
As routine risk minimisation for missing information 'use in patients with severe cardiac disease', the EU-RMP refers to a statement in the EU SmPC that "patients with severe cardiovascular disease were excluded from Imbruvica clinical studies". This omission is highlighted to the delegate.	Based on the recommendation of TGA clinical evaluator, the following statement has been added to the revised PI in the "special population" section in alignment with EU SmPC: *Severe cardiac disease* *Patients with severe cardiovascular disease were excluded from Imbruvica clinical studies.*	This is acceptable from a RMP perspective.
For missing information 'long term use (>two years)' the sponsor should provide justification why routine risk minimisation is not proposed.	There are ongoing studies that will collect long term use data. Thus, the Company considers that risk minimisation measures are not warranted for this missing information.	The sponsor's justification is not accepted. Long term use remains missing information (results from ongoing studies will be long awaited) and the absence of such data is clinically relevant. Limitations in long-term use data should be appropriately communicated in the PI.
The overdose section should refer to the Australian Poisons Information centre telephone number.	The Sponsor agrees to revise the Overdose section of the Product Information to add the Australian Poisons Information Centre	This is acceptable from a RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	telephone number. The specific proposed text is shown below. *Contact the Poisons Information Centre (telephone 131126) for advice on management of overdosage.*	

Summary of recommendations and sponsor's response

The sponsor's response in the RMP evaluation report is not accepted and therefore the following recommendation is outstanding:

- Long term use of ibrutinib remains missing information and the absence of such data is clinically relevant. It is recommended that limitations in long-term use data should be appropriately communicated in the PI/CMI.

Sponsor's response

For the following reasons, Janssen believes that no additional risk minimising activities, such as including text on limitations in long-term use, are needed other than routine pharmacovigilance:

The applicant has provided as part of the Pre-ACPM response Periodic Safety Update Reports (PSURs) covering a period of 13 November 2013 to 12 November 2014 with a cumulative patient exposure of 10,884 unique patients, representing 44,488 patient-months, in the post-marketing setting.

Janssen has agreed to provide the following additional studies to the TGA as soon as available after completion. In addition to the specific TGA requested commitments, Janssen will provide updated data for all submitted studies when that data becomes available:

- Update of Trial PCYC-1104CA to provide information about Progression-free survival (PFS) and overall survival (OS)
- The Phase III study in mantle-cell lymphoma (MCL) patients, PCI-32765MCL3001
- The Phase III study in MCL patients, (PCI-32765MCL3002)
- The Phase I thorough QT study (PCI-32765CLL1007)
- Completion of a study to establish the effects of drugs modifying gastric pH on ibrutinib absorption
- Study CLL1006 in subjects with varying degrees of hepatic impairment
- The in vitro drug interaction studies assessing the effect on enzymes and other drug transporters

The sponsor's current thinking is aligned with those of EMA, which did not feel it was necessary to require such additional statements to be included in the European Union (EU) Summary of Product Characteristics (SmPC) or EU RMP.

The following new recommendations are based on consideration of the ACSOM advice:

- ***It is recommended that the targeted follow-up questionnaires are appropriately amended to capture demographic information relevant to Australia.***

Sponsor's response

The targeted follow-up questionnaire (TFUQ) is a global form to solicit additional important safety information for certain significant SAEs, such as cases of progressive multifocal leukoencephalopathy (PML) reported for the sponsor's products. It is not unique to ibrutinib. The sponsor commits to collecting demographic information relevant to Australia as part of the routine AE reporting and follow-up process. Any potential safety signal observed in a specific ethnicity will be part of the routine signal detection and surveillance.

- ***The evaluator notes the ACSOM's concerns regarding the risk of 'paediatric off label use'. As missing information, it is expected that post market data regarding off label use will be appropriately monitored and captured in Periodic Safety Update Reports (PSURs).***

Sponsor's response

The sponsor includes off label use including paediatric off label use in the PSURs and will conduct routine assessment on these cases.

Considering the range of diseases in the literature for which Btk inhibitors are under investigation the sponsor considers there is minimum risk of off label use in paediatric patients for the following reasons:

- There is currently no paediatric formulation or clinical data demonstrating ibrutinib efficacy or safety in the paediatric population.
- The indications of CLL and MCL for which the company is seeking approval do not occur in children.
- Although there are no ongoing studies in adults with aggressive B cell lymphoma, there is currently no clinical data demonstrating ibrutinib activity in paediatric mature B cell non-Hodgkin lymphoma (NHL; predominately diffuse large B cell [DBL] and Burkitt lymphoma). In addition mature B cell lymphomas in children are rare (American Cancer Society 2014).
- Standard of care regimens in paediatric NHL patients result in very high cure rates in excess of 90%,[7] therefore it is unlikely that ibrutinib would be used off label in this setting in the absence of data demonstrating efficacy.
- The sponsor should provide information on how the effects of ibrutinib on bowel lymphatic tissue and the risk of bowel perforation will be investigated.

Ibrutinib was not associated with small intestinal perforations in the toxicology species tested. Furthermore, based on the available data observed from clinical trials and post-marketing experience, bowel perforation has not been a signal associated with ibrutinib use. Meanwhile, severe gastrointestinal event are Important Potential Risk defines in the RMP and under routine pharmacovigilance. Any SAEs related to bowel perforation will be included in PSURs and all cases will be medically reviewed. Case characteristics such as frequency and severity as well as risk factors will be analysed and provided in the PSURs.

- ***The conflicting PI statements regarding anticoagulation, as identified by ACSOM are highlighted for the Delegate's consideration.***

[7] Worch J, Rohde M, Burkhardt B. (2013) *Mature B-cell lymphoma and leukemia in children and adolescents-review of standard chemotherapy regimen and perspectives.* Pediatr Hematol Oncol. 30: 465-83.

Sponsor's response

The following additional text was added to the Precautions sub section Cardiac events as requested by the TGA clinical evaluator:

> *In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to Imbruvica should be considered. In patients who develop atrial fibrillation on therapy with Imbruvica a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to Imbruvica are non-suitable, tightly controlled treatment with anticoagulants should be considered.*

If TGA deem it necessary to modify the text, the sponsor suggests replacing the text with the following:

> *In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to Imbruvica should be considered. In patients who develop atrial fibrillation on therapy with Imbruvica a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to Imbruvica are non-suitable, and benefit-risk evaluation dictates the treatment with anticoagulants, patients should be closely monitored.*

- ***As routine risk minimisation for the identified risk 'haemorrhage' it is recommended that the CMI better emphasise that the patient should be alert to the possibility of bleeding events.***

Sponsor's response

The sponsor believes that possibility of bleeding is clearly emphasised in the current CMI. The warning provided under Side Effects in the current Australian CMI is as follows:

> *Bleeding: You may experience bruising or nosebleeds during treatment with Imbruvica. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine or brain may occur. Call your doctor or healthcare professional if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.*

> *It is recommended that as the sole risk minimisation tool, the product information (PI/CMI) should be amended to include clear information regarding the limitations of ibrutinib data. In the absence of an educational program, such information should aim to ensure health professionals and patients are aware of the limitations of the data when making choices about treatment, especially that it has not been demonstrated that ibrutinib improves symptoms or survival. Changes to the PI/CMI should include but not be limited to an additional PI statement in the MCL indication similar to the following found in the US product label.*

- ***Accelerated approval was granted for this indication based on ORR. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.***
  - ***The PI/CMI should include appropriate information that safety and efficacy data is not comprehensive and further evidence from Phase III trials is awaited.***
  - ***The above information should be clearly conveyed in any marketing material as well as approved product information.***
  - ***The PI/CMI should include information that safety in long term use has not been established.***

- ***The complete CMI should be included in every box of ibrutinib.***

Sponsor's response

The sponsor believes that even though the US label has such a statement a similar arrangement is not warranted on the Australian label because the EU RMP and EU SmPC which the TGA based their evaluation on does not contain this language and was considered acceptable by the EMA.

The sponsor believes that the safety data is comprehensive considering that two PSURs with greater than 10,000 patients cumulative exposure which provides a better idea of the safety profile have been provided to the TGA. The PI also states currently that the duration of response rate for the CLL Phase II Study 1102 was from four to greater than 214 months.

As the EMA did not require any additional statement be added to the EU SmPC for the MCL indication, we do not feel it is necessary to add this to the Australian Product Information or marketing materials.

The sponsor believes that inclusion of such text is not warranted considering that Janssen has provided as part of the Pre-SCPM response Periodic Safety Update Reports (PSURs) covering a period of 13 November 2013 to 12 November 2014 with a cumulative patient exposure of 10,884 unique patients, representing 44,488 patient-months, in the post-marketing setting and has agreed to provide additional studies to the TGA as Category 1 submissions as soon as available after completion. In addition to the specific TGA requested commitments, Janssen will also provide updated data for all submitted studies when that data becomes available.

The CMI will be provided on the sponsor's website, TGA's website and via a Data warehouse to pharmacists to give to their patients. Thus including a CMI in the box is not necessary and not done for any other Janssen products, as the version in the box may not be the most current version.

- ***Further, it is recommended that the TGA consider publishing information relating to ibrutinib on its website to:***
  - ***Advise health professionals of the limitations of safety and efficacy data.***
  - ***Encourage reporting of AEs to improve knowledge of the medicine's safety profile.***
  - ***Refer health professionals to the approved PI for pertinent safety information.***

Sponsor's response

The sponsor does not feel it is necessary to single out ibrutinib, when all products are initially approved with limited data. Other products have been approved by TGA for life-threatening conditions initially on more limited data packages because the benefit-risk ratio was positive for the disease condition as is the case for ibrutinib.

TGA already has general statements on its website encouraging doctors to report AEs for all products and there is no need to specifically single out ibrutinib.

The purpose of the PI document is to provide the prescribers with information on the safety and efficacy of the product as an aid in their decision whether to prescribe a product. This is something all physicians should already be doing for any prescription medicine.

- ***The following new recommendations are based on consideration of the nonclinical evaluation report:***
  - ***The evaluator supports the recommendations by the nonclinical evaluator regarding the inappropriate representation of human equivalent doses in the***

safety specification. The relevant sections of the RMP should be amended as recommended by the nonclinical evaluator.

Sponsor's response

Since the EU RMP which was provided to the TGA cannot be amended as requested, if TGA deems it necessary this information can be duplicated in the Australian Specific Annex in the requested format.

- ***The following new recommendations are based on consideration of the nonclinical evaluation report:***
  - ***'Atypical lymphoid cells in bone marrow', considered a key safety finding by the nonclinical evaluator should be added as a safety concern to the RMP/ASA unless an acceptable justification for its exclusion can be provided.***

Sponsor's response

Subsequent to submission the sponsor has completed the six month rat study. Top dose levels in that study were 100 mg/kg/day in males and 80 mg/kg/day in females. No bone marrow atypia was noted suggesting the findings in the immune-toxicity study were either not reproducible or transient and; therefore, do not represent a notable risk to patients. The final report will be provided to the TGA when it becomes available.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Following an assessment, the Pharmaceutical Chemistry evaluator had no objections to registration of ibrutinib. The following was highlighted:

Ibrutinib absolute bioavailability is limited by extensive first-pass metabolism, and affected by grapefruit juice; the PI currently mentions grapefruit and Seville orange products but no other naringin-containing products.

Delegate comment: the PI and CMI contain specific advice about grapefruit and Seville orange products likely to influence the bioavailability.

Nonclinical

The nonclinical evaluator had no objections on nonclinical grounds to registration of ibrutinib for the proposed indications.

- Overall, the submission was adequate, but the omission of bone marrow smear analysis in the 13 week repeat dose studies is considered a deficiency.
- The primary pharmacology studies support the use of ibrutinib for the proposed indications.
- Off target inhibition of Blk and ErbB4/HER4 are likely at clinically relevant exposure. Inhibition of ErbB4/HER4 is potentially related to the adverse corneal effects observed in dogs, but adverse corneal effects have not been observed clinically. Adverse effects on cardiovascular system are possible based on decreased heart rate and RR interval at exposures similar to that expected clinically.

Delegate comment: this correlates with the finding of a lower heart rate in some patients in the clinical studies.

- As CYP3A is the main enzyme that metabolises ibrutinib, its inhibition or induction would likely alter clinical ibrutinib exposure.
- The main toxicities identified in repeat–dose studies were gastrointestinal toxicity and lymphoid depletion in lymphoid organs. Lymphoid depletion is an expected pharmacological effect that is clinically observed as immunosuppression is associated with increased risk of infection. The skin and bone marrow toxicities observed in rats are also clinically relevant. Other toxicities of potential clinical relevance, but probably low risk, are acinar atrophy of pancreas and ocular effects.
- Ibrutinib does not pose a genotoxic hazard.
- Ibrutinib is teratogenic and causes embryo-foetal toxicity and lethality in animals. Pregnancy Category D is recommended as ibrutinib may be expected to cause an increased incidence of human foetal malformations or irreversible damage.
- The immunosuppression demonstrated in the immune-toxicity study is an expected pharmacological effect. However, the presence and persistence of atypical lymphoid cells in bone marrow warrants further investigation. The sponsor has indicated this will be addressed in two repeat dose studies that are currently underway (six month rat and nine month dog studies).
- Provided the above effects are adequately monitored or managed during clinical use and that the benefit/risk profile seems acceptable from a clinical perspective, there are no objections on nonclinical grounds to the proposed registration of Imbruvica. The sponsor is requested to provide the study reports for the rat six month and dog nine month repeat-dose toxicity studies when these reports become available.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- Ten clinical pharmacology studies
- Two population PK analyses
- One pivotal efficacy/safety study in CLL/SLL (Study 1112)
- One dose-finding study (Study 04753)
- Three supportive efficacy/safety studies
- Integrated Summary of Efficacy, Integrated Summary of Safety

In addition, the sponsor kindly provided their responses to the EMA Day 120 evaluation report, the Day 180 EMA evaluation report and the sponsor's responses to the Day 180 report.

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man
- Points to consider on application with 1. Meta-analyses; 2. One pivotal study.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for the registration of ibrutinib for the proposed indications can be considered for approval.

Paediatric data

The submission did not include paediatric data.

Pharmacokinetics/Pharmacodynamics

Ibrutinib is almost entirely absorbed from the GI tract, with extensive first pass metabolism. There is a marked variation in absolute bioavailability after overnight fasting (67%), modified fasting conditions rises 2.6 fold from 2.9% (90% CI 2.12, 3.94) to 7.6% after a meal. Inclusion of grapefruit juice with the meal further increased this to 15.8%. C_{max} was greatest after a high fat meal.

> *Delegate comment: the PI and CIM contain appropriate advice regarding avoiding grapefruit and Seville orange products. To be consistent with the Phase III clinical trial conditions, and taking into account the variability with food, the PI should state that ibrutinib should be taken before a meal.*

Summary of PK data

Ibrutinib is extensively metabolised by cytochrome P450 (CYP) 3A4-catalysed epoxidation of the acryloyl moiety, followed by hydrolysis to the dihydrodiol metabolite PCI-45227 (< 10% of total drug related compound in the circulation; 15 fold weaker and anti BK activity compared with parent compound). Three other metabolites were identified, but PCI-45227 demonstrated a more prolonged exposure than the other main metabolites.

Ibrutinib is mostly eliminated by biliary excretion, with small amounts of urinary and faecal excretion (together = 4.5%).

Pharmacokinetics in the target population

B cell histology was not a significant covariate in the PopPK analysis.

Pharmacokinetic/Pharmacodynamic interactions

Neither ibrutinib nor its major metabolite has a significant effect on CYP3A4 induction or inhibition. Ibrutinib is a P-gp inhibitor.

Effect of CYP3A4 induction

Rifampicin led to a significant reduction in C_{max}, $AUC_{0\text{-}24h}$ and AUC_{last} when co-administered with ibrutinib as compare to ibrutinib alone. There was a minor reduction in Btk receptor occupancy when co-administered.

Effect of CYP3A4 inhibition

Ketoconazole led to a marked increase in C_{max}, $AUC_{0\text{-}24h}$ and AUC_{last} with no effect on Btk occupancy.

> *Delegate comment: appropriate advice is included in the PI. A number of in vitro studies have been planned to investigate the effect of inhibitors of other CYP and drug transporting proteins, as a condition of registration, the sponsor is requested to submit as a Category 1 submission, any which identifies an effect that is likely to be clinically relevant in order to update the PI.*

Effect of antacids

The solubility of ibrutinib is pH dependent, and no formal study of the effects of antacids on ibrutinib AUC and C_{max} has been presented. Given the high likelihood of the use of such medications in the proposed population, the Delegate is in agreement with the clinical evaluator that a formal study should be undertaken (see Conditions of Registration).

Pharmacokinetic interactions demonstrated in human studies

Hepatic impairment

There were small numbers of patients with mild, moderate or severe hepatic impairment. Compared with six healthy matched controls, mean unbound exposure (AUC_{last}, unbound) in the mild, moderate and sever cohort is 4.0, 9.5 and 13 fold higher. There did not appear to be a risk for accumulation on repeated doing. A study in patients with varying degrees of hepatic impairment has been undertaken, and submission as a Category 1 application is a condition of registration (see Conditions of Registration).

Renal impairment

Mild or moderate renal impairment did not influence the PK of ibrutinib but severe renal impairment (creatinine clearance < 30 mL/min) has not been studied.

Pharmacodynamic effects

The median Btk occupancy at does from 420 mg to 840 mg/day in treatment naïve, relapsed and refractory CLL patients was > 90% for all cohorts. Concomitant administration with rifampicin (versus ibrutinib alone) lowered the occupancy from 91.2% to 80.8%, while concomitant ketoconazole exerted no effect.

A clinically relevant degree of Btk occupancy of > 90% was observed following ibrutinib treatment at doses of either 420 mg/day or 840 mg/day within one week of commencement.

Dose selection

In the absence of dose limiting toxicities up to 1400 mg/day, the dose for the pivotal study in CLL/SLL patients was derived from the Phase I and II studies PK and PD sampling in Studies 04753 and 1102. The sponsor indicated in the pre-submission meeting that the reason for choosing the higher dose level for MCL was because of the more resistant nature of that disease. Further comment from the sponsor is welcomed if deemed necessary.

Efficacy: CLL, PCYC-1112-CA

A Phase III randomised, multicentre, open-label study of ibrutinib (195 patients) versus ofatumumab (196 patients) in those with relapsed or refractory CLL/SLL who had failed at least one prior systemic therapy and not considered appropriate candidates for treatment or retreatment with purine analogue-based therapy.

Ibrutinib was administered as 420 mg orally daily, with 240 mL water, taken at least 30 minutes before food or at least two hours after a meal at approximately the same time each day.

> *Delegate comment: Given these were the conditions under which the trial was run, and the food effect on PK (see above), the PI should include advice that ibrutinib should be taken before a meal.*

Ofatumumab was administered according to an accepted regimen approved for CLL patients: Week 1 – 300 mg doses; Weeks 2–8 – 2000 mg weekly; Weeks 12, 16, 20 and 24 – 2000 mg every four weeks.

> *Delegate comment: this is an appropriate comparator.*

Inclusion and exclusion criteria

Two randomisation schemes were generated for US and non US based recruits. Under each scheme, randomisation was stratified according to: presence or absence or refractory

disease to purine analogue and anti CD20 containing regimen and presence/absence of del17p.

The intent to treat (ITT) population was used to assess all endpoints, and the safety population comprised all patients who had received at least one dose.

The primary efficacy outcome was:

- Independent Review Committee (IRC) blinded assessment of PFS

Secondary efficacy outcomes were:

- OS
- ORR
- Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-fatigue) score
- Sustained haematological improvement

The main safety end-point was the safety and tolerability of ibrutinib compared with ofatumumab.

Results for the primary efficacy outcome

The primary outcome of the study was met. After 146 PFS events, there was a statistically significant advantage for ibrutinib over ofatumumab (HR 0.215, 95% CI 0.146, 0.137), p < 0.0001. The median PFS was not met for ibrutinib whereas the median PFS in the ofatumumab arm was 8.1 months. The six month PFS estimates were 87.8% of subjects in the ibrutinib and 64.6% in the ofatumumab arm remained progression free (Table 24 and Figure 3). An improved response to ibrutinib compared with ofatumumab was seen for those with 17pdel. Re-testing to validate this 17pdel test occurred, with 86.2% concordance.

Table 24: Progression free survival PCYC-1112-CA ITT population

Progression-free Survival	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)	Ibrutinib vs. Ofatumumab
Events	35 (17.9%)	111 (56.6%)	146 (37.3%)	
Disease Progression	26	93		
Death	9	18		
Censored at cut-off	160 (82.1%)	85 (43.4%)	245 (62.7%)	
Progression-free Survival (Months) [1]				
Median	NE	8.1		
Min, Max	0.03+ , 13.96+	0.03+ , 13.77		
P-value				<0.0001
Hazard Ratio (95% CI)				0.215 (0.146, 0.317)
Kaplan-Meier point estimate for PFS rate at				
6 Months	87.8%	64.6%		
12 Months	65.7%	5.9%		
18 Months	-	-		
24 Months	-	-		

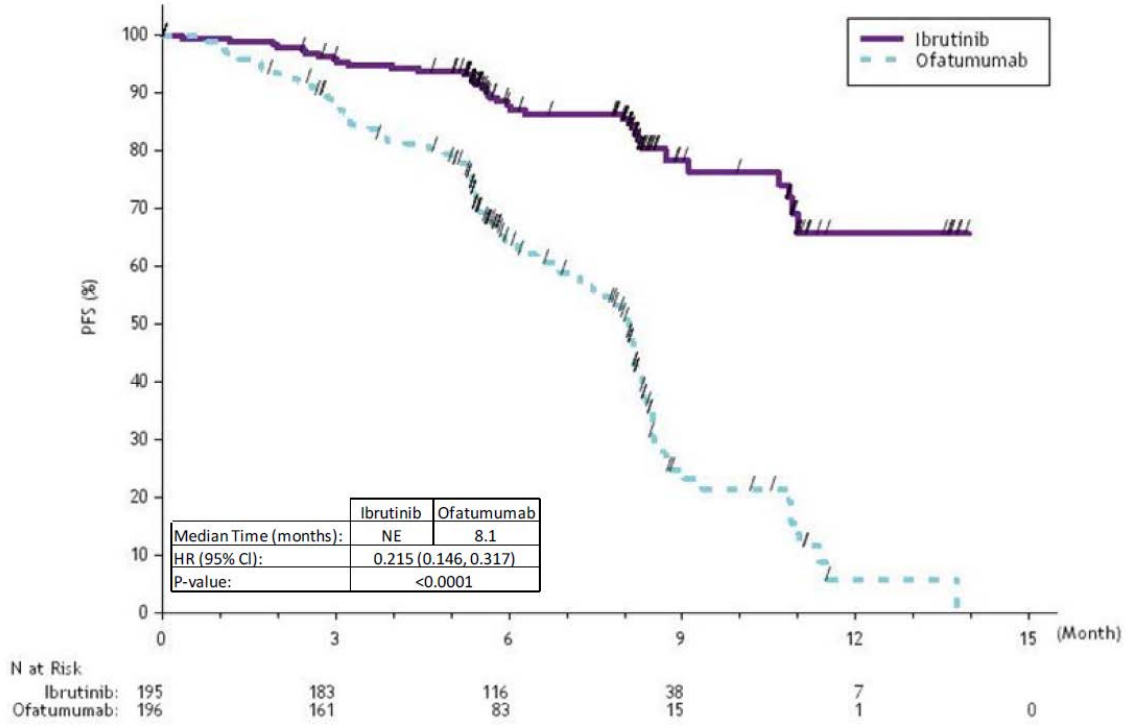
Analysis is based on IRC assessment and subjects are not censored for initiation of subsequent antineoplastic treatment

[1] P-value is based on a log-rank test stratified by the two randomization stratification factors reported in the IWRS at the time of randomization. Hazard ratio is based on Cox regression model (with treatment as the only covariate) stratified by the same factors as for the p-value and is relative to ofatumumab with <1 favoring ibrutinib.

+ Indicating censored observation

NE = Not estimable

Figure 3: Kaplan-Meier curve of progression-free survival – PCYC-1112-CA ITT population



Ibrutinib therapy does not appear to be an additional risk factor for Richter transformation, although the numbers in this trial were small. The favourable effect of ibrutinib was seen across all subgroup analyses.

The continuous dosing schedule supports the proposed usage in the application.

Results for other efficacy outcomes

OS: the primary analysis of OS demonstrated a statistically significant advantage is OS, including across the subgroups analysed, in the ibrutinib arm HR 0.434 (95% CI 0.238 0.789), however median survival had not been reached in either treatment arm.

ORR: independently assessed ORR, according to the IWCLL 2008 guideline was higher in the ibrutinib arm (42.6% compared with 4.1%). When allowing a PR in the presence of an isolated lymphocytosis (as per the IWCLL guideline modification in 2012). the ORR was 62.6% of the ibrutinib arm compared with 4.1% in the ofatumumab arm.

The analyses of ORR according to the pre-specified sub-groups of interest demonstrated a benefit from ibrutinib for all sub-populations.

QoL: there was no difference between the arms.

Haematological: consistent with the greater efficacy, sustained haematological response parameters were improved.

Supportive studies

Supportive data from three studies were provided: PCYC-04753, PCYC-1102-CA, PCYC-1104-C in a range of B cell malignancies including CLL/SLL, MCL, DLBCL (diffuse large B cell lymphoma and FL (follicular lymphoma) and WM.

Study PCYC-04753 was a Phase I dose-finding study in 66 patients with recurrent B-cell malignancies. Patients either took continuous daily doses, or followed a 28 days on, seven

days off regimen. Complete responses (CRs) were observed for some CLL/SLL, MCL, DLBCL and FL subjects with the majority of CRs in subjects receiving 8.3 mg/kg/day ibrutinib or less. The Kaplan-Meier estimate of PFS for the efficacy evaluable population was 10 months (95% CI 6.9, not estimable (NE)) after median follow-up of 8 months (range 0.8, 22.5). The duration of median PFS was 2.5 months DLCBL, 11.3 months or MCL, 13.4 months for FL and NE for CLL/CLL and WM.

> *Delegate comment: efficacy is seen in all cohorts, including continuous versus interrupted but the small numbers and variable histologies recruited to each precludes any conclusions being dawn to comparative efficacies or to support non-continuous dosing regimens.*

Study PCYC-1102-CA was a Phase Ib/II, open label comparison of safety, efficacy and PK of 420 mg versus 840 mg in 117 patients with treatment-naïve or relapsed/refractory CLL/SLL including those with 17pdel.

The response rates are summarised in Table 25 below.

Table 25: Summary of responses, and times to initial response, Study 1102

	Treatment-naïve (n=31)	Relapsed/refractory (n=85)
Overall best response, n (%)		
CR	4 (12.9)	2 (2.4)
Nodular PR	1 (3.2)	-
PR	17 (54.8)	62 (72.9)
PR + lymphocytosis	4 (12.9)	11 (12.9)
SD	3 (9.7)	4 (4.7)
PD	0 (0.0)	2 (2.4)
Missing	2 (6.5)	4 (4.7)
ORR, n (%) [95% CI]	22 (71.0) [52.0, 85.8]	64 (75.3%) [64.7, 84.0]
Time to initial response in those with ORR. Median (range), months	1.9 (1.5, 7.4)	1.8 (1.4, 12.2)

17delp status

ORR by del17p status was an exploratory endpoint. In the relapsed/refractory population, 29 subjects were del17p positive, with ORR (95% CI) 58.6% (38.9, 76.5) and 51 2343 del17p negative with an ORR (95% CI) 84.3% (71.4, 93.0).

In the treatment naïve population, two were del17p positive, with an ORR (95% CI) of 100% (66.4 100) and 29 were del17p negative, with an ORR (95% CI) of 69% (49.2, 84.7). For treatment naïve subjects with a median follow-up time of 22.1 months, the median duration of PFS was not met. At 24 months, the estimated proportion of subjects progression free was 96.3%.

Among the relapsed/refractory subjects, at an estimated 22.1 months of follow-up, 18 of 85 (21.2%) had died and 67 (78.8%) were censored. The median PFS duration could not be estimated for this group. The median survival time could not be estimated in the relapsed/refractory population. The median duration had not been met.

TP53 mutation status was not assessed and no data were presented in this submission.

> *Delegate comment: the data for 17p del CLL is drawn mostly from pre-treated patients, and a further Phase II open label single arm study (PCI-32765 1117) is underway in patients with 17delp CLL and SLL and should be submitted for evaluation to support the safety and efficacy of this usage.*
>
> *Data on responses in the presence of a TP53 mutation would be important to determine if there is an efficacy in this population.*

Efficacy: MCL pivotal study for MCL

Study PCYC-1104-CA was an open label, multicentre, Phase II study of ibrutinib 560 mg daily in two cohorts (bortezomib exposed or naïve) of patients with relapsed or refractory MCL. The primary efficacy endpoint was investigator-assessed ORR as per the IWG criteria for NHL. The secondary endpoints were DOR, PFS, OR and time to response. Independent review of ORR was an exploratory endpoint.

Of 115 patients, 63 of 65 bortezomib naïve subjects and 48 of 52 bortezomib-exposed subjects received ibrutinib. At the analysis point, 24 bortezomib naïve and 22 bortezomib-exposed subjects are continuing treatment, the remainder having discontinued. The ORR indicates efficacy of ibrutinib in patients with MCL 67.6% (96% CI: 58.9, 76.3) which was similar across all subgroups analysed and prior bortezomib exposure. DOR was 17.5 months overall, with a median not yet reached in those with a CR. The median time to response of 1.9 months (range 1.4, 13.7), and where attained, the median time to CR was 5.5 months (range 1.7 to 11.5 months). Median OS has not been reached at 15.3 months of follow-up.

There was a notable increase in lymphocyte count in the first two cycles of those with CLL, and in those with poorer prognostic features with MCL (tumour bulk, median tumour burden, bone marrow involvement). All the parameters of response were lower in those developing a lymphocytosis: PR, CR, ORR, PFS, death was lower in those with lymphocytosis.

Of those discontinuations, nine were due to an AE; four of these were possibly related to ibrutinib. The majority of discontinuations were due to death (41 subjects) and withdrawal of consent (eight subjects). Two subjects were lost to follow-up. IRC assessment of ORR was consistent with investigator assessments.

Table 26: ORR by investigator assessment, all treated population, Study 1104

	Bortezomib-naïve	Bortezomib-exposed	Combined
Population: all treated	63	48	111
Best response			
CR	12 (19.0%)	11 (22.9%)	23 (22.9%)
95% CI	(9.4%, 28.7%)	(11.0 %, 34.8 %)	(13.2%, 28.3%)
PR	31 (49.2%)	21 (43.8%)	52 (46.8%)
Stable disease (SD)	8 (12.7%)	8 (16.7%)	16 (14.4%)
Progressive disease (PD)	12 (19.0%)	7 (14.6%)	19 (17.1%)
Not evaluable	0	1 (2.1%)	1 (0.9%)
ORR (CR or PR)	43 (68.3%)	32 (66.7%)	75 (67.6%)
95% CI	(56.8%, 79.8%)	(53.3%, 80.0%)	(58.9%, 76.3%)

Efficacy summary

CLL

The efficacy of ibrutinib has been established for the treatment of those with pre-treated CLL/SLL with high quality randomised Phase III data. While lower response rates were observed in those with del17p compared with those without, there is still a good response rate in this population with treatment-resistant disease. The Delegate is in agreement with the clinical evaluator, and the subsequent modification of the proposed indication by the sponsor, and support registration as first line therapy in those with del17p given the poor response rate to other therapies. While there was PD evidence of ongoing efficacy and an ORR demonstrable in the earlier Phase I trials with a four weeks on, one week off regimen, dose interruptions are not recommended unless required to manage toxicities.

MCL

The Phase II open label study demonstrated an overall ORR to ibrutinib of 68% and CR of 21%, with the latter often occurring after prolonged exposure. PFS data are immature and not currently available. These responses were seen independent of prior bortezomib treatment. The appearance of an early lymphocytosis was associated with a poorer response, but these patients also had poor prognostic features therefore this cannot be considered predictive of a response to ibrutinib therapy until a trial appropriately stratified to examine this is undertaken. While there are limitations and potential biases arising within Phase II trials, this is a large treatment effect, which together with supportive evidence of activity in a range of B cell malignancies especially CLL/SLL supports registration for the proposed indication.

Although no separate data are presented, and it would be exceedingly uncommon for MCL to occur in an individual under the age of 18, it would be reasonable to extrapolate the efficacy to such an individual. It is noted the FDA indication in not restricted to adults.

Safety data

The data were presented separately for the two proposed indications, which is appropriate given the different dosages used. The safety population for each at the proposed usage is small: 246 patients with CLL, and 120 for MCL, although the latter is acceptable as it is a rare disease. Overall ibrutinib was well tolerated, with 6.5% and 16% requiring a dose reduction in the pivotal study CLL and MCL populations, respectively.

The high rates of TEAEs are consistent with the age of the patients at the stage and nature of the diseases being treated. The clearest information regarding what is attributable to ibrutinib is from the randomised Phase III trial. Deaths were observed at t a lower range in the ibrutinib arm (6.1% versus 8.4% for ofatumumab) and were consistent with known complications of the disease. Two of fifteen deaths were considered possibly related – a systemic inflammatory response syndrome and pneumonia. In the MCL population, two deaths from pneumonia may have been attributable to ibrutinib.

SAEs occurred more commonly with ibrutinib in the Phase III trial compared with ofatumumab (41.5% versus 30.4%) with the increase mostly due to cardiac events, especially atrial fibrillation (3.1% versus 0.5%) and respiratory infections (13.9% versus 9.4%). In the Phase II trials, 60.4% had an SAE, with 24% considered related and 21.7% had an event ≥ Grade 3. Atrial fibrillation and infections especially pneumonia were prominent, but also bleeding events including subdural and splenic haematomas, and acute renal failure were noted. Discontinuations due to AEs were 8.5% and 11.4%, in the CLL and MCL trials respectively.

In the CLL population, the most common Grade 3 or 4 events were: neutropenia (15.9%), pneumonia (6.9%), and thrombocytopenia (6.5%). In the MCL group, the most common Grade 3 or 4 adverse events were: neutropenia (16.7%), thrombocytopenia (11.7%), anaemia (9.2%), diarrhoea (5.0%) abdominal pain (5.0%) and pneumonia (5.0%).

Adverse events of special interest

Bleeding

Minor bleeding episodes such as petechiae and bruising are very common with ibrutinib. Serious and sometimes fatal haemorrhages were seen. There was no correlation with thrombocytopenia and the mechanism is not clearly understood. The need for anticoagulation antiplatelet therapy must be weighed against the risk of bleeding especially where there are other predisposing factors. Clear advice is included in the PI Precautions section, and this risk is included in the RMP.

Laboratory

Leukostasis

The median lymphocyte increased over the first two cycles in both CLL/SLL and MCL patients, with five cases of leukostasis reported to date. The PI contains appropriate management advice, including a definition of the term and condition leukostasis.

Haematological

Cytopenias were more frequent with ibrutinib than ofatumumab which may reflect the duration of exposure. Appropriate advice regarding monitoring and management is included in the PI.

Electrolytes, liver function tests

There did not appear to be adverse effects on liver function and while declines in renal function were observed these were similar to ofatumumab. Electrolyte disturbances were seen in both arms of the Phase III trial, but hypocalcaemia occurred more commonly

(8.7% versus 5.8%) and with greater severity (1% Grade 3 or 4 versus none) with ibrutinib. This is manageable with the standard monitoring of electrolytes in addition to the regular full blood counts, but needs to be included in the AE table for prescribers to be aware.

Cardiac

There was an increase in cardiac arrhythmias, mostly atrial fibrillation and flutter, with ibrutinib. PI indicates the increased risk of atrial fibrillation, especially where there are risk factors and includes appropriate cautionary about the risk of bleeding with anticoagulation.

No formal QT/QTc study was undertaken. Shortening of the QTCF duration was noted, decreases in heart rate and mild increase in PR interval. Cardiovascular effects were also noted in the animal studies. Submission of the Phase I thorough QT study (PCI-32765CLL1007) anticipated to be submitted by the fourth quarter of 2016 is a condition of registration.

Infections

Infections were more common with ibrutinib in the CLL population than ofatumumab, but the severity was similar. Similarly, infections were common in the MCL group. Infections are common in patients with CLL and MCL, and specialists are familiar with diagnosing and managing them. The PI contains appropriate advice.

Progressive multifocal leukoencephalopathy (PML)

Two patients with CLL developed PML; however, one had previously received treatment with rituximab, and the other had received rituximab concomitantly with ibrutinib, thus this remains possibly related to ibrutinib and should be included as a potential risk in the RMP.

Rash

19.5% of the integrated CLL/SLL population experienced a rash. None were serious nor led to discontinuation of ibrutinib. However, in Study 117, as case of Stevens Johnson syndrome (Grade 4) was attributed to ibrutinib. The sponsor has responded (Response to Delegate's overview, 26 February 2015) stating that this was the only case in what now includes more than 2000 patients in clinical trials, and with post marketing experience in 11,000. This is an area of ongoing pharmacovigilance.

Second malignancies

Ibrutinib appears to be associated with an increased risk of second malignancy. The majority were non-melanoma skin lesions occurring in those who had other risk factors. Given the high risk of the ageing Australian population, the sponsor agreed to include in the PI, advice to monitor regularly for the development of skin cancers. The other cancers did not demonstrate a consistent pattern and this is an area requiring ongoing pharmacovigilance.

Ocular

There was a high rate of ocular AEs, none of which exceeded Grade 2, in both the pivotal studies (CLL: ibrutinib 36.4% versus 18.8% in ofatumumab arm) and single arm MCL population (30.8%). Cataracts were noted to be newly developed in five of six CL patients but establishing the causality of this in an ageing population is somewhat difficult. In the integrated CLL population, 8.9% reported blurred vision. The off target effects in animals of ErbB4/HER4 inhibition indicate an increased risk of corneal opacities, so the role of ibrutinib and mechanism remain uncertain. This is included in the AE table in the PI so prescribers can inform (and at this stage, reassure patients) and this needs to be an area of ongoing pharmacovigilance.

Safety discussion

The main safety concerns in patients receiving ibrutinib for either indication are infection, cardiac arrhythmias, cytopenias and bleeding episodes. The PI informs appropriately about these. However, the total number of patients exposed to the proposed dosages was relatively low, and would not necessarily identify rarer events, especially when outside of a randomised, controlled trial setting. There are areas of uncertainty (for example, PML, hepatitis B reactivation) which required pharmacovigilance. There are Phase III trials planned in both populations, and it is a standard requirement that the TGA be information of any safety issues as they are identified; in addition, it is a requirement of the submission as a condition of registration that these Phase III studies be submitted for both confirmation of efficacy and evaluation of safety.

Risk-benefit analysis

Ibrutinib is efficacious in treating both CLL/SLL and MCL, and trials are ongoing to assess the safety and efficacy in these populations in combination with other treatments, or as monotherapy.

The safety profile is somewhat more difficult to characterise due to the high background rates of AEs seen in a generally older and often frail population (especially for CLL/SLL), combined with the underlying risks associated with the diseases themselves. The risks of treatment are generally manageable, and will be familiar to specialists experienced in the treatment of these diseases. While the Phase III study indicated a higher rate of AEs (although patients were on ibrutinib for a much longer time) than for ofatumumab, this was offset by the markedly higher efficacy. In the MCL population, there are two Phase III trials – one underway and one planned – to further characterise the efficacy and safety of use in this population.

The significantly better efficacy profile indicates a very positive benefit-risk equation for its use and registration is supported for the indications proposed.

To inform prescribers and patients better of the benefit-risk (both efficacy and safety) of treatment, the sponsor is required to provide several studies as Category 1 applications for evaluation as soon as available as a condition of registration (see Conditions of Registration).

RMP Evaluation

The Office of Product Review is considering the EU-RMP (version 3.2, dated 30 July 2014) and ASA (version 1.0, dated 13 August 2014).

The Delegate considers that PML should be added to the Safety Specifications of the RMP and hepatitis B reactivation as important potential risks.

Risk management plan

The opinion of the Advisory Committee for the Safety of Medicines (ASCOM) was sought on 20 February 2015. An extract from the minutes is below:

- ***Can the committee comment on the sufficiency of the pharmacovigilance plan? If considered insufficient can the committee comment on which additional Pharmacovigilance activities would be appropriate to monitor the risks in the Australian context?***

The committee advised that the activities outlined in the pharmacovigilance plan were essential to characterise the safety of the medicine; in particular, it was essential that more

clinical data including from placebo-controlled trials was obtained to look at AEs and to differentiate TEAEs as being due to the medicine or the disease.

The committee discussed that ibrutinib had undergone an 'accelerated approval' process in the USA. As a general comment, the committee expressed concern that where pre-market data was limited, the post-market monitoring and range of possible post-market obligations on sponsors and regulatory actions were of greater significance than with the more typical types of submissions considered.

Ibrutinib was the first such medicines that had been reviewed by the ACSOM as an 'accelerated approval' and there was a level of concern regarding the review of submissions of this type, as features of the current submission included:

- Difficulty in characterising the safety profile of the medicine because of the limited and preliminary nature of the data
- Difficulty in separating AEs related to the medicine from events related to the diseases, in the absence of placebo-controlled studies. Most of the reported 'AEs' could be due to the underlying disease or to the treatment. It was acknowledged that accounting for drug-free progression was an issue that was typical for most studies of oncology drugs
- The limited range and quantity of available safety data
- Lack of information on matters usually addressed in submissions (for example, absence of a dose ranging study and information on dose adjustments; absence of a clinical study in support of the proposed indication of ibrutinib as first-line treatment of patients with CLL with del17p).
- The wide range of missing information, including items not listed as Missing Information in the summary of ongoing safety concerns
- Pre-clinical drug interaction studies, and PK and PD studies, were still ongoing
- There was no biological mechanism proposed to explain most of the observed adverse effects, for example, infections (including sepsis, neutropenic sepsis, bacterial, viral or fungal infections) including fatalities from pneumonia and sepsis
- until more data was generated, the PI would not provide sufficient information to guide prescribers. It was important that all statements in the PI were supported by the studies undertaken and did not include extrapolations.

The medicines was likely to be used in elderly patients with concomitant medications and co-morbidities, there was a high potential for unexplored drug interactions in this vulnerable group.

Taking the above matters into consideration, the committee advised that the proposed pharmacovigilance plan was sufficient with respect to the indication for use in patients with MCL.

The committee advised that the proposed pharmacovigilance plan was less than sufficient with respect to the indication for use in patients with CLL. This indication applied to a larger patient group with a different prognosis. Therefore additional pharmacovigilance activities with larger trials with an appropriate comparator group and placebo-controlled arms for the CLL were appropriate.

Regarding the targeted follow-up questionnaire for AEs related to the Important Identified Risks ('leukostasis' and 'haemorrhage') and Important Potential Risk ('infections'), the questionnaire would need to be amended to capture demographic information relevant in Australia.

Off-label use in paediatric patients, identified as Missing Information, was likely to be an underestimate of the extent of off-label use, given the range of diseases in the literature for

which Btk inhibitors were under investigation. The potential for any off-label use was concerning when the overall safety profile of ibrutinib was not yet comprehensive.

Investigation of cardiac effects needed to proceed, especially QT shortening and consequential atrial fibrillation and any dose-effect relationships. The effects on bowel lymphatic tissue and risk of bowel perforation should also be investigated.

- ***Does the committee consider that the identified risks of leukostasis and haemorrhage are adequately communicated in the Product Information?***

Managing the risks of leukostasis would be improved if the PI provided clinicians with additional information on this obscure term. The PI lacked descriptive information on leukostasis and its clinical features; such information would be a useful addition to the PI, as patients will be managed on ibrutinib in an ambulatory clinical setting and many non-haematologists may be unfamiliar with the term 'leukostasis'.

The committee noted the Precautions in the PI that 'Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib' and that 'In patients at high risk [of atrial fibrillation] and where alternatives to Imbruvica are non-suitable, tightly controlled treatment with anticoagulants should be considered'. These statements were contradictory and confusing and inconsistent with approved information regarding the infeasibility of routine laboratory monitoring of the anticoagulant effects of new oral anticoagulants[8].

The PI advice that ibrutinib should be withheld 'at least three to seven days pre and post-surgery' to minimise the risk of bleeding appeared vague and reflected the lack of data.

The Consumer Medicine Information (CMI) should emphasise the importance of alertness to bleeding events.

Other

Ibrutinib has poor oral bioavailability that was affected by fasting, DDIs and hepatic disease. Absolute bioavailability in a fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Co-administration of ibrutinib and ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased exposure (Cmax and AUC) of ibrutinib by 29- and 24-fold, respectively. Unbound ibrutinib exposure was estimated to be four, 9, and 13 fold increases in subjects with mild, moderate, and severe hepatic impairment, respectively. It was not clear to the committee that the recommended dosage adjustments reflected these observations.

The PI should use units of measurement familiar to Australian clinicians.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the Office of Product Review.

Proposed action

The Delegate has no reason to say, at this time, that the application for ibrutinib should not be approved for the following modified indications:

Imbruvica is indicated for the treatment of

[8] For example 'Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity.' Source: Product Information for dabigatran etexilate (Pradaxa).

- *Patients with chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) who have received at least one prior therapy of as a first line in patients with CLL with 17p deletion.*
- *Patients with mantle cell lymphoma who have received at least one prior therapy.*

Data Deficiencies / Limitations

There are some outstanding PK/PD studies investigating the use of ibrutinib in hepatic impairment and a thorough QT study. It is also considered important to assess formally the effect of gastric pH altering drugs on ibrutinib absorption.

The risk of Hepatitis B reactivation with Imbruvica in unknown and it is recommended that patients be screened for hepatitis B prior to commencing Imbruvica. The sponsor has included this in the PI and the Safety Specification of the RMP.

Questions for the Sponsor

- Is there a study planned or underway to investigate the effect on ibrutinib PK of drugs altering gastric pH?

Conditions of registration: the following were proposed as conditions of registration:

- Implementation of the EU-RMP version 3.2 dated 20 July 2014 and Australian Specific Annex (version 1.0, dated 13 August 2014)
- Submission of the following clinical trial(s) as Category 1 submissions about PFS, and OS.
  - Update of Trial PCYC-1104CA to provide information about PFS, and OS.
  - The Phase III study in MCL patients, PCI-32765MCL3001
  - The Phase III study in MCL patients, PCI-32765MCL3002
  - The Phase I thorough QT study (PCI-32765CLL1007)
  - Completion of a study to establish the effects of drugs modifying gastric pH on ibrutinib absorption
  - Study Cll1006 in subjects with varying degrees of hepatic impairment

The sponsor has agreed to the above conditions of registration. The following condition of registration has been added:

- The in vitro drug interaction studies assessing the effect on enzymes and other drug transporters

Response from Sponsor

Questions for the sponsor

- ***Is there a study planned or underway to investigate the effect on ibrutinib PK of drugs altering gastric pH?***

Janssen Response

Yes. The draft protocol will be submitted to EMA by June 2015 as a Post Approval Commitment. The sponsor will provide the draft protocol or final protocol to TGA upon request.

Conditions of registration:

The following are proposed as conditions of registration:

- Implementation of the EU-RMP version 3.2 dated 30 July 2014 and Australian Specific Annex (version 1.0, dated 13 August 2014)
- Submission of the following clinical trial(s) as Category 1 submissions as soon as available after completion:
  - Update of Trial PCYC-1104CA to provide information about PFS, and OS.
  - The Phase III study in MCL patients, PCI-32765MCL3001.
  - The Phase III study in MCL patients, PCI-32765MCL3002.
  - The Phase I thorough QT study (PCI-32765CLL1007)
  - Completion of a study to establish the effects of drugs modifying gastric pH on ibrutinib absorption
  - Study CLL1006 in subjects with varying degrees of hepatic impairment.

Janssen Response

The sponsor accepts the above conditions proposed by TGA.

TGA proposed labelling revisions

- INDICATIONS

  TGA have also proposed simplifying the Indication statement to be*:*

  Imbruvica is indicated for the treatment of

  > *Patients with CLL/SLL who have received at least one prior therapy or as first line in patients with CLL with 17p deletion*
  >
  > *Patients with MCL who have received at least one prior therapy*

Janssen Response

The sponsor accepts the above indication statement revision.

TGA proposed revisions to Australian RMP

PML should be added to the Safety Specification of the RMP and hepatitis B as important potential risks.

Janssen Response

The sponsor agrees to include PML and hepatitis B reactivation in the "Infection Risks" section in the Australia Specific Annex of RMP in the Safety Specification and as important potential risks. Janssen will provide an amended Australian Specific Annex to the RMP coordinator. PML is already incorporated into the ASA and EI RMP version 3.2.

Advisory Committee Considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Imbruvica, capsules containing 140 mg of ibrutinib, to have an overall positive benefit-risk profile for the indication:

Imbruvica is indicated for the treatment of;

- *Patients with chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) who have received at least one prior therapy or for the frontline in patients with CLL with 17pdel mutation*
- *Patients with mantle cell lymphoma who have received at least one prior therapy*

Proposed conditions of registration

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

Proposed PI/CMI amendments

The ACPM agreed with the Delegate on the statements in the PI and CMI.

Specific advice

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

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

The ACPM was of the view that the Phase III trial in CLL was well designed and demonstrated clear efficacy of Imbruvica treatment. Despite limited trial data this is also true for MCL. While the trials safety data did provide reassurance, the submission, on completion of the studies outlined by the Delegate and the sponsor, should provide more certainty of the positive benefit-risk profile.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Imbruvica (ibrutinib) 140 mg capsules for oral administration, indicated for

> Imbruvica is indicated for the treatment of;
>
> - *Patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least one prior therapy or for the frontline in patients with CLL with 17pdel mutation*
> - *Patients with mantle cell lymphoma who have received at least one prior therapy*

Specific conditions of registration applying to these goods

- The Ibrutinib EU-RMP (version 3.2, dated 30 July 2014) plus ASA (version 1.1, dated 23 December 2014), to be revised to the satisfaction of the TGA, must be implemented in Australia.
- Submission of the following clinical trial(s) as Category 1 submissions as soon as available after completion:
  - Update of Trial PCYC-1104CA to provide information about PFS, and OS
  - The Phase III study in MCL patients, PCI-32765MCL3001
  - The Phase III study in MCL patients, PCI-32765MCL3002
  - The Phase I thorough QT study (PCI-32765CLL1007)
  - Completion of a study to establish the effects of drugs modifying gastric pH on ibrutinib absorption
  - Study CLL1006 in subjects with varying degrees of hepatic impairment
  - The in vitro drug interaction studies assessing the effect on enzymes and other drug transporters

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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