



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dasatinib

Proprietary Product Name: Sprycel

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

January 2019

TGA Health Safety
Regulation

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
Allo-HCT	Allogeneic haematopoietic cell transplantation
ASA	Australian specific annex
ASCT	Allogeneic stem cell transplant
BCR-ABL	A protein tyrosine kinase
BM	Bone marrow
CHR	Complete haematologic response
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CR	Complete remission/response
CRD	Complete remission duration
DFS	Disease-free survival
DVT	Deep vein thrombosis
EB05	Empirical Bayesian 5%
EB95	Empirical Bayesian 95%
EBGM	Empirical Bayesian geometric mean
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
ESMO	European Society for Medical Oncology
EU	European Union
FAERS	Food and Drug Administration adverse event reporting system
FDA	Food and Drug Administration (US)
GI	Gastro intestinal

Abbreviation	Meaning
GU	Genital urinary
HCVAD	Hyper-CVAD chemotherapy: cyclophosphamide, vincristine, doxorubicin and dexamethasone
IGH PCR	Immunoglobulin heavy chain polymerase chain reaction
MedDRA	Medical dictionary for regulatory activities
MFC	Multi-parameter flow cytometry
MGPS	Multi-Item Gamma Poisson Shrinker
MMR	Major molecular response
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NR	Not recorded
OS	Overall survival
PAD	Peripheral arterial disease
PAH	Pulmonary arterial hypertension
PCR	Polymerase chain reaction
Ph ⁺ ALL	Philadelphia chromosome positive ALL
PBRER	Periodic benefit risk evaluation report
PSUR	Periodic safety update report
QD	Once daily
RFS	Relapse-free survival
RR	Risk ratio
SCT	Stem cell transplant
SIR	Standardised incidence ratio
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
triple IT	Triple intrathecal (intrathecal methotrexate/cytarabine/hydrocortisone)

Abbreviation	Meaning
UMRD	Undetectable minimal residual disease

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (new indication)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	7 March 2018
<i>Date of entry onto ARTG:</i>	9 March 2018
<i>ARTG numbers:</i>	125557, 125558, 125559, 125560, 125561, 125562, 157352 and 157356
<i>, Black Triangle Scheme</i>	No
<i>Active ingredient:</i>	Dasatinib
<i>Product name:</i>	Sprycel
<i>Sponsor's name and address:</i>	Bristol-Myers Squibb Australia Pty Ltd PO Box 1080 Mount Waverley VIC 3149
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	20 mg, 50 mg, 70 mg and 100 mg
<i>Containers:</i>	Bottle or blister pack
<i>Pack sizes:</i>	60 tablets (20 mg, 50 mg, 70 mg) or 30 tablets (100 mg)
<i>Approved therapeutic use:</i>	<i>Sprycel is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	Once daily. To achieve the recommended dose, Sprycel is available as 20 mg, 50 mg, 70 mg and 100 mg film coated tablets. Dose increase or reduction is recommended based on patient response and tolerability. For the full details please see the Product Information.

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Sprycel dasatinib 20 mg, 50 mg, 70 mg and 100 mg tablets for the following indication:

Sprycel is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy.

Acute lymphoblastic leukaemia (ALL) refers to a group of hematopoietic neoplasms involving cells committed to the lymphoid lineage.¹ Philadelphia chromosome positive ALL (Ph⁺ ALL) is a biologically and clinically distinct variant of ALL. Ph⁺ ALL accounts for approximately 20 to 30 percent of ALL in adults and 2 to 3 percent of ALL in children. This 'Philadelphia chromosome' results in a BCR-ABL fusion protein with deregulated tyrosine kinase activity.

When treated with chemotherapy alone, patients with Ph⁺ ALL have a uniformly poor prognosis with few survivors at five years after treatment.¹ Allogeneic hematopoietic cell transplantation (allo-HCT) provides better results, curing approximately 30 to 60 percent of patients with Ph⁺ ALL.¹ BCR-ABL fusion protein is one of the five tyrosine kinases antagonised by dasatinib. Incorporation of a tyrosine kinase inhibitor (TKI) of BCR-ABL1 (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) into the treatment regimen has resulted in superior response rates, thereby allowing more patients to proceed to allo-HCT.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 January 2007.

The approved indications at the time of submission were:

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph⁺) chronic myeloid leukaemia in the chronic phase.

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.

Sprycel is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

International regulatory status

This application is specific to Australia and is not planned to be submitted elsewhere in the world.

Product Information

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

¹ Larson, R., Lowenberg B., Rosmarin A. Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukaemia in adults. UpToDate. Feb 2017 (literature search current up until September 2017).

II. Registration time line

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

Table 1: Timeline for Submission PM-2016-04272-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	28 February 2017
First round evaluation completed	31 July 2017
Sponsor provides responses on questions raised in first round evaluation	1 August 2017
Second round evaluation completed	16 November 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	18 November 2017
Sponsor's pre-Advisory Committee response	12 January 2018
Advisory Committee meeting	1-2 February 2018
Registration decision (Outcome)	7 March 2018
Completion of administrative activities and registration on ARTG	9 March 2018
Number of working days from submission dossier acceptance to registration decision*	212

*Statutory timeframe for standard applications is 255 working days

Evaluations included under quality findings and nonclinical findings incorporate both the first and second round evaluations.

TGA guidance at pre-submission meetings is nonbinding and without prejudice.

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

The drug is a broad spectrum competitive inhibitor of 5 oncogenic tyrosine kinases/kinase families that transmit growth signals from the cell membrane to the nucleus: BCR-ABL, SRC, c-KIT, PDGFR and ephrin receptor kinases.

Dosage and administration

For the new indication proposed, that of newly diagnosed Philadelphia chromosome positive ALL (Ph⁺ ALL) in adults, integrated with chemotherapy, the dosage instructions are as follows:

The recommended starting dosage of Sprycel (dasatinib) for newly diagnosed Ph⁺ ALL is 100 mg administered orally once daily (QD) and should be taken consistently either in the morning or evening.

Proposed changes to the product documentation

Changes include updates to the Clinical Trials section to incorporate the supporting data for this proposed new indication, addition of the indication, additions to the Dosage and Administration section to manage the treatment for the new indication, and a small statement in Adverse Events to reflect that the safety profile seems no different in this expanded Ph⁺ ALL treatment population than that for the current Ph⁺ ALL indications, based upon the limited data set.

Information on the condition being treated

ALL is a group of haematopoietic neoplasms of cells committed to the lymphoid lineage. Ph⁺ ALL is a biologically distinct variant. About 350 cases of ALL in total are diagnosed in Australia each year. Of these, 40% are adults. Of these 40%, about 25% have Philadelphia chromosome positive (hereafter Ph⁺) disease.

This 'chromosome' results in a BCR-ABL fusion protein with deregulated tyrosine kinase activity and is the most common cytogenetic abnormality in adults with ALL or chronic myeloid leukaemia (CML). Note that this is one of the five tyrosine kinases antagonised by dasatinib.

In general, lymphoblastic neoplasms are grouped into either precursor B cell or precursor T cell. This is done mainly because prognosis and treatment differ between these two groups. What distinguishes the terms 'lymphoma' or 'leukaemia' are:

- A case is called lymphoma if there is a mass lesion in the mediastinum or elsewhere and < 25% blasts in the bone marrow.
- A case is classified as leukaemia if there are > 25% blasts in the bone marrow with or without a mass lesion.

So in this case, the disease state under study is Philadelphia chromosome positive (Ph⁺) acute lymphoblastic leukaemia (ALL).

Prognosis hinges on tumour and patient characteristics. Age at diagnosis and cytogenetic/genetic findings appear to be the strongest predictors of survival. Ph⁺ ALL is a poor prognosis form of precursor B cell ALL.²

² Up to Date 22 February 2017: Clinical manifestations, pathologic features and diagnosis of Precursor B acute lymphoblastic leukaemia/lymphoma

Current treatment options

In terms of current induction treatment, Ph⁺ ALL has a uniformly poor prognosis when treated with chemotherapy alone, with few survivors at 5 years. Allogeneic haematopoietic cell transplant (HCT) cures between 30 and 60% of Ph⁺ ALL patients, and literature suggests incorporation of a tyrosine kinase inhibitor (imatinib, dasatinib, nilotinib, bosutinib and ponatinib) into a chemotherapy treatment regimen results in superior response rates, thus allowing more patients to progress to allogeneic HCT. What is still uncertain is which provides better long term outcome: chemotherapy plus a tyrosine kinase (TK) inhibitor or allogeneic HCT in first remission.

- Induction aims to reduce leukaemia cell populations to below 10⁹ in the body.
- Consolidation (over 80% achieve a remission) occurs when treated with chemotherapy incorporating a TK inhibitor. Without additional cytotoxic therapy, however, despite continued TK inhibitor use, essentially all patients will relapse in weeks or months.
- Maintenance chemotherapy with a TK inhibitor for those who do not have HCT may be offered for two to three years. Some receive a TK inhibitor after HCT as well.

In central nervous system involvement

All current treatment regimens involved prophylaxis for this. Cranial irradiation plus intrathecal chemotherapy is the mainstay of treatment.

In older or frail patients

Typically a TK inhibitor plus a steroid is used for induction.

In young adults or adolescents

Some studies note that outcomes for those aged 16 to 21 can be better when treated on paediatric protocols. This is still under study.

In summary, current clinical treatment appears to support this submission, with recommendations for use of dasatinib or imatinib in patients with newly diagnosed Ph⁺ ALL. The best schedule and duration of TK inhibitor treatment is yet to be determined. Note that few survivors at 5 years is typical when chemotherapy alone is used.³

Clinical rationale

The rationale for the submission is to seek approval for treatment of newly diagnosed Ph⁺ ALL patients with dasatinib in combination with chemotherapy to achieve an initial remission. Approval already exists for refractory disease as monotherapy.

Evaluator's commentary on the background information

There appears to have been liaison with the TGA prior to submission to agree upon the method of substantiation of efficacy and safety. From the sponsor's cover letter, a study designated Study ALL5 has been included as a draft manuscript. This study was conducted by the Australian Leukaemia and Lymphoma Group. It has not been incorporated into the relevant summary documents of the submission. This study (n = 20) plus 4 other Phase II published studies are put forward as the 'pivotal' data to support the desired indication. There are 8 other publication abstracts submitted in support and four 'reports of analyses from more than one study' for review. Finally an 'other' study report examining the use of imatinib is submitted. This completes the trial data, with four periodic safety update

³ Source: Up to Date 22/2/17: Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukaemia in adults

reports (PSUR) then submitted as well as the same number of periodic benefit risk evaluation reports (PBRER). These will be examined as part of post-market data.

Orphan drug designation

Orphan status was granted on 12 October 2005 by the TGA for the treatment of chronic myeloid leukaemia in patients who are resistant to or intolerant of imatinib and for treatment of Philadelphia-positive acute lymphoblastic leukaemia (Ph⁺ ALL).

There appear to be no other orphan designations on the TGA website.

Guidance

A pre-submission meeting with TGA it was agreed that Phase II published trial data could be submitted in lieu of Phase III studies to try and support the desired indication. TGA guidance at pre-submission meetings is nonbinding and without prejudice.

Contents of the clinical dossier

Four studies are submitted as the pivotal data supporting the proposed indication. Ravandi et al. (presented as 3 papers, 2010, 2013, 2015); Yoon et al.; Rousselot et al.; and Foa et al.^{4,5,6,7,8,9} These papers collectively represent 247 adult patients treated with dasatinib as part of their first-line treatment.

The aforementioned ALL5 trial is present as Grigg et al. 2017 in draft.¹⁰ There are then six other supportive but non-pivotal papers presented for evaluation.

Four analyses of more than one study presented from the literature examine adverse reactions observed when tyrosine kinase inhibitors or specifically dasatinib is used clinically.

Paediatric data

The submission relates to adult Ph⁺ ALL for the most part. There are very few data incorporating children and none specific to children.¹¹

⁴ Ravandi F et al. 2010 First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph₊) acute lymphoblastic leukemia. *Blood* 2010; 116: 2070-2077

⁵ Ravandi F et al. 2013 Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. *Blood* 2013; 122: 1214-1221

⁶ Ravandi F et al. 2015 Long-Term Follow-Up of a Phase 2 Study of Chemotherapy Plus Dasatinib for the Initial Treatment of Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. *Cancer* 2015; 121: 4158-4164.

⁷ Yoon J-H et al 2016 Minimal residual disease-based effect and long-term outcome of first-line dasatinib combined with chemotherapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia. *Annals of Oncology* 2016; 27: 1081-1088

⁸ Rousselot P et al 2016 Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood* Prepublished online as Blood First Edition paper, April 27, 2016

⁹ Foa R et al 2011 Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2011; 118: 6521-6528

¹⁰ Grigg A et al. 2017 Dasatinib and Hyper-CVAD in Ph⁺ Acute Lymphoblastic Leukaemia leads to prolonged survival even in the absence of allogeneic stem cell transplantation

¹¹ Slayton W 2015 Outcomes of dasatinib plus intensive chemotherapy or stem cell transplant (SCT) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ ALL) on Children's Oncology Group AALL0622. Published on Meeting Library (<http://meetinglibrary.asco.org/content/150973-156>) (provided in the dossier)

Good clinical practice

Studies were conducted to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) standards.

Pharmacokinetics

No pharmacokinetic (PK) studies are presented in this submission.

Pharmacodynamics

No pharmacokinetic (PD) studies are presented in this submission.

Dosage selection for the pivotal studies

Any information on dosage selection will derive from the efficacy studies as they are themselves Phase II.

Efficacy**Studies providing efficacy data*****Ravandi studies***

- 2010: The first report of a Phase II study of dasatinib with hyper (cyclophosphamide, vincristine, doxorubicin and dexamethasone) (HCVAD) for initial treatment of Ph⁺ ALL.
- 2013: Detection of minimal residual disease (MRD) may predict outcome of Ph⁺ ALL for those treated with TK inhibitors plus chemotherapy.
- 2015: Long term follow up of the 2010 trial.

Evaluator's conclusions on efficacy

This evaluator makes the following overall conclusions on clinical efficacy:

- In terms of hierarchy of evidence, the data in this submission are of Level III evidence or lower.
- First line treatment regimens for Ph⁺ ALL that incorporate a TK inhibitor have been shown to result in very high initial complete remission (CR) success, with or without chemotherapy.
- Dasatinib has already been approved for treatment of this disease, in cases of resistance or intolerance to prior therapy.
- Comparative data for dasatinib versus use of other TK inhibitors for the same indication suggest similar efficacy but the true quantification of benefit in this regard in terms of comparison between different TK inhibitors is not fully circumscribed and would need Phase III trial data.
- The treatment regimens using dasatinib in this submission have varied considerably. These are summarised earlier in this report, but use of chemotherapy, dosage of dasatinib, and continuous or intermittent dosing, all vary across studies.
- Use of the drug is in any case limited by haematological toxicity. The draft PI contains information on dose modification in such instances.

- The indications statement in the annotated PI requires integration of dasatinib treatment with chemotherapy and this evaluator supports that as the most robust data are in combination with HCVAD.

Safety

Studies providing safety data

*Ravandi (2010)*⁴

Exposure in this study amounted to 35 individuals. Adverse effects amounted to 16 episodes of bleeding (11 gastro intestinal (GI), 2 genital urinary (GU), 1 soft tissue haematoma and 2 subdural haematomas) and 8 pleural effusions.

Other events included infection, deep vein thrombosis (DVT), pulmonary emboli, diarrhoea, and changes to serum chemistry values such as hypophosphataemia, hypokalaemia and hypocalcaemia. There were also elevated transaminases, hyperglycaemia and a reversible rise in creatinine that was considered unrelated to treatment. Events are summarised in Table 2.

Table 2: Treatment related toxicities encountered during induction and consolidation intensive chemotherapy cycles

	Induction number (%), n = 35		Subsequent cycles number (%), n = 31	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Infections	1 (3)	24 (69)	1 (3)	26 (84)
Pleural effusions	1 (3)	1 (3)	5 (16)	1 (3)
Hemorrhage	NA	4 (11)	1 (3)	11 (35)
Gastrointestinal	14 (40)	1 (3)	3 (10)	NA
Cardiac	3 (9)	1 (3)	2 (6)	1 (3)
Renal failure	NA	6 (17)	NA	4 (13)
Metabolic	22 (63)	21 (60)	9 (29)	11 (35)
Increased AST/ALT	4 (11)	3 (9)	2 (6)	1 (3)
Neurological	2 (6)	NA	2 (6)	1 (3)
DVT/PE	1 (3)	NA	3 (10)	4 (13)

AST/ALT indicates aspartate aminotransferase/alanine aminotransferase; DVT/PE, deep vein thrombosis/pulmonary embolism; and NA, not applicable.

*Ravandi (2013)*⁵

Safety was not addressed in this publication.

*Ravandi (2015)*⁶

Median times to neutrophil and platelet recovery were 18 and 22 days respectively. Grade 3 and 4 adverse events included bleeding (various), pleural effusions, pericardial effusions, reversible rises in creatinine, DVT, pulmonary emboli, diarrhoea, infections, hypophosphataemia, hypokalaemia, hypocalcaemia, hyperglycaemia and elevated transaminases.

Discontinuation of dasatinib occurred in 12 patients, with an alternative TK inhibitor commenced. Toxicities that led to the discontinuation of dasatinib were pleural effusions in 6 patients, pulmonary artery hypertension in 2 patients, gastrointestinal bleeding in 2 patients, skin cancer in 1 patient, and subdural bleeding in 1 patient.

Yoon (2016)⁷

No patient withdrew from treatment, but 6 discontinued for between 3 to 14 days during the first and subsequent dasatinib cycles, to recommence at 100 mg or 70 mg daily. Further information about adverse events was not provided.

Rousselot 2016⁸

Median exposure was 7.8 months (range 0.6 to 72.4 months). Thirty eight patients discontinued treatment as a result of either relapse or death. Fourteen patients discontinued as a result of adverse events and 7 because of receiving stem cell transplant. At the time of analysis, only 8 patients were still on the drug, of 22 remaining in the study. Others were receiving imatinib or nilotinib at the discretion of their investigator.

At induction, mean duration of neutropenia was 8.9 days. Thirteen patients developed bacteraemia or septicaemia.

Pleural effusions occurred in 7 patients. Three were receiving 130 mg dasatinib daily at the time and 4 100 mg daily. Four of these cases were associated with pneumonia and one with pericardial effusion.

Other serious adverse events included tumour lysis syndrome during induction (n = 2), renal failure (n = 6), subdural haemorrhage (n = 3, including 1 patient with concomitant acetyl salicylic acid therapy), digestive haemorrhage (n = 3), transaminase elevations (n = 5), pulmonary embolism (n = 3), atrial fibrillation (n = 4), and cardiac failure (n = 2).

Foa (2011)⁹

Safety was not analysed in this paper.

Grigg (2017)¹⁰

Six of the 20 patients received the complete 8 cycles of chemotherapy. Two received 7, 6 or 5 cycles with six receiving 4 cycles and two receiving 3 cycles. Two patients withdrew as a result of toxicity, two due to non-compliance and the remaining 8 who received less than 8 cycles were withdrawn to receive stem cell transplant. No deaths occurred on treatment and all patients experienced haematologic recovery within 42 days following induction cycles.

Seventeen of the 20 patients reported at least one Grade 3 or higher adverse event during the induction phase that was deemed associated with therapy. Haematologic toxicity was considerable which is consistent with the other pivotal studies using this regimen, and 95% of patients in this study experienced Grade 4 neutropaenia, 90% Grade 4 thrombocytopenia and 30% Grade 3 anaemia during the induction phase. Not surprisingly infection was the most common non-haematologic toxicity with febrile neutropaenia in 45%.

Solely considering dasatinib, two patients required dose reduction to 70 mg daily during the intensive chemotherapy phase. In maintenance therapy, six patients required dosage reduction.

Other studies

Other studies were comprised of the following: Caocci (2012); Gurman (2016); Lamanna (2012); Pastori (2015); Sasaki 2016; Slayton 2015; Tekgunduz 2016^{12 13 14 1516,17,18}

¹² Caocci G et al 2012 Prophylactic and Preemptive Therapy with Dasatinib after Hematopoietic Stem Cell Transplantation for Philadelphia Chromosome- Positive Acute Lymphoblastic Leukemia. *Biol Blood Marrow Transplant* 2012; 18: 652-654

¹³ Gurman G et al 2016 The efficacy of tyrosine kinase inhibitors with steroid in ph+ acute lymphoblastic leukemia. *J Clin Oncol* 2016; 34, (suppl; abstr e18531)

There was either minimal or no real safety data of utility in these studies as most were abstracts and did not go into safety and adverse events in any detail. By contrast the four publications presented as 'Reports of Analyses of Data from More than One Study' were all focussed on safety issues and are thus presented in the safety section of this report.

Studies that assessed safety as the sole primary outcome

Le Coutre (2016)¹⁹

This letter to the editor in the journal *Leukaemia* describes peripheral arterial disease as a potential side effect of TK inhibitors, and assessed dasatinib trials to identify this as an adverse event or indeed events related to peripheral arterial disease. A standardised ratio was attempted between rates in dasatinib trials and that in a similar population that did not receive the drug. The population was essentially those patients with CML in chronic phase or Ph⁺ ALL. The analysis included information on n = 2,712 adults with CML or Ph⁺ ALL treated with dasatinib in 11 clinical trials. Of these, n = 324 were in first line treatment. Median treatment was 19 months. The trials appear to have been sponsored by Bristol Myers Squibb, as the company safety database was used to gather the events. Event terms included arterial stenosis, arterial thrombosis, atherosclerosis, arterial stenosis limb, intermittent claudication, femoral artery occlusion, necrosis ischaemic and peripheral artery disease.

A comparison population was derived from 'Truven Health Analytics MarketScan Commercial Claims' and 'Medicare Supplementary Database'. MarketScan consists of information from several commercial health plans in the US.

Peripheral arterial disease (PAD) or PAD related events were detected in 11 patients during dasatinib treatment among 2,712 individuals with a cumulative dasatinib exposure of 6,421 patient-years, which corresponds to a cumulative incidence of 0.4% and an incidence rate (per 100 patient-years) of 0.2%. Of the 11 patients, all were previously treated with a TK inhibitor; 8 were resistant and 3 were intolerant to prior imatinib therapy. No cases of PAD or PAD related events were identified among the 258 patients treated with first-line dasatinib in dasatinib versus imatinib study in treatment naïve CML patients (the DASISION trial) (median duration of 60 months (range: 0.03 to 73 months)).

Standardised incidence ratio (SIR) analysis showed that the observed number of PAD or PAD related events (n = 11) in the pooled population did not exceed the expected number of events (n = 20) in the general population (SIR (95% confidence interval (CI)), 0.56 (0.31 to 1.01)). Similarly, the observed number of PAD or PAD-related events (n = 11) in the pooled population did not exceed the expected number (n = 43) based on rates in the

¹⁴ Lamanna N et al 2012 High Dose Cytarabine and Mitoxantrone in Combination with Dasatinib As Active Induction Therapy in Adult Patients with Philadelphia Chromosome Positive (ph+) Acute Lymphoblastic Leukemia (ALL) *Blood* 2012; 120: abstract 4293

¹⁵ Pastori G et al 2015 Fludarabine, Cytarabine, Daunoxome Plus Dasatinib Has High Efficacy with an Acceptable Toxicity Profile As Either Consolidation or Salvage Regimen in Adult Philadelphia Positive Acute Lymphoblastic Leukemia Patients *Blood* 2015; 126: abstract 4908

¹⁶ Sasaki K et al 2016 Propensity score analysis: Frontline therapy with hyper-CVAD (HCVAD) + ponatinib vs. HCVAD + dasatinib in patients (pts) with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). *J Clin Oncol* 2016; 34: (suppl; abstr 7025)

¹⁷ Slayton WB et al 2015 Outcomes of dasatinib plus intensive chemotherapy or stem cell transplant (SCT) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) on Children's Oncology Group AALL0622. *J Clin Oncol* 2015; 33: (suppl; abstr 10006)

¹⁸ Tekgunduz E et al 2016 Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Daily Practice: A Multicenter Experience. *Clinical Lymphoma, Myeloma & Leukemia*, 2016; 16: 2692-274

¹⁹ Le Coutre PD et al 2016 Low incidence of peripheral arterial disease in patients receiving dasatinib in clinical trials. *Leukemia* 2016; 30: 1593-1596

reference CML population (SIR (95% CI), 0.26 (0.14 to 0.46). No PAD or PAD related events were identified in newly diagnosed CML patients treated with dasatinib in the DASISION trial, which has the longest median exposure time to dasatinib of any study.

The utility of this publication with respect to this submission is minimal. It simply serves to raise the possibility that TK inhibitors vary in their adverse event profile and that it might be the case that dasatinib has less peripheral vascular adverse impact than some other TK inhibitors or indeed shows no real difference in comparison to an untreated population.

Cortes (2015)²⁰

This research article also examines cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors. The United States (US) Food and Drug Administration (FDA) adverse event reporting system (FAERS) was used to identify any adverse events associated with imatinib, dasatinib, and nilotinib.

Multi-Item Gamma Poisson Shrinker (MGPS) is a validated Bayesian method of providing an estimate of disproportionality called the empirical Bayesian geometric mean (EBGM), calculated by adjusting the observed frequency of the drug-event pair; the frequency of reports of the event of interest with all other drugs, and; the frequency of all other events reported for the drug of interest.

While these analyses do not establish causality or measure adverse event (AE) incidence, they measure association and thus can assist in determining if further investigation is warranted. Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT) of cardiac; respiratory, thoracic and mediastinal; and; vascular were examined for the three drugs. The analysis was for up to and including 30 September 2012. A second analysis focussed upon year by year analyses, and to evaluate AEs in different age groups, analyses were run for separate cohorts defined as 18 to 45 years, 46 to 64 years and 65 and over. Analyses were also run to make sure that differences in drug pair significance were not overlooked when different preferred terms were used to identify essentially the same adverse event. Various similar clinically preferred terms were combined to check this.

Nine hundred and fifty six unique preferred terms were identified and recorded as a drug-event 'pair' for one or more of the three drugs. The EBGM;²¹ 90% confidence interval was designated EB05 and EB95. $EB05 \geq 4$ was chosen to identify clinically relevant events (typically greater than or equal to two is used for drug event associations, per se). Hence the associations here were only those that were quite strong it would seem.

Twenty three terms reached EB05 of 4 or greater. Pleural effusion reached this threshold for all three agents which is not surprising given the adverse event profile noted in the pivotal studies in this submission. Furthermore it had a much higher EB05 with dasatinib (30.77 versus 5.65 for nilotinib and 5.59 for imatinib). Pericardial effusion was also higher for dasatinib (11.75 versus imatinib (4.57) and nilotinib (3.86).

²⁰ Cortes J et al 2015 Cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors: Data from the FDA Adverse Event Reporting System. *Am. J. Hematol.* 2015; 90: E66-E72

²¹ The EBGM is calculated by adjusting the observed frequency of the drug-event pair using b, the frequency of reports of the event of interest with all other drugs, and c, the frequency of all other events reported for the drug of interest. The EBGM 90% confidence interval (CI) is defined by EB05 and EB95. Although disproportionality analyses do not measure AE incidence or establish that a drug is causative, higher EBGM or EB05 values indicate higher probability of association, warranting further evaluation. Although $EB05 \geq 2$ is commonly used for identifying drug-event associations warranting further investigation, $EB05 \geq 4$ was chosen for this report to identify events more likely to be clinically relevant and potentially attributable to drug therapy.

Of interest to this submission, terms reaching the significance threshold for dasatinib also included those related to fluid retention, that is, chylothorax and malignant pleural effusion; pleural haemorrhage; pulmonary oedema, and; pulmonary arterial hypertension (PAH). Sub analyses did not reveal additional terms for dasatinib, merely differences in the strength of association, but all still over the threshold level.

The message to take from this publication is that while TK inhibitors appear to have class effect AEs, they can vary depending upon the specific drug in terms of association. The events related to fluid retention are already noted in the PI for dasatinib and have been reiterated by these data.

Egron (2015)²²

This publication attempted to assess the rate and character of 'preventable' or 'potentially preventable' serious adverse drug reactions with oral protein kinase inhibitors.

The French pharmacovigilance database was used to retrospectively study such serious adverse drug reactions (ADRs) recorded between 1 January 2008 and 31 December 2009. Dasatinib was one of the eight drugs studied.

Two hundred and sixty five spontaneous reports were noted. Preventability was assessed by one of the authors according to a scale of 1 to 4 where categories 1 and 2 were 'preventable' or 'potentially preventable'. Those considered preventable or potentially preventable numbered only one and three, respectively. The single preventable case was in fact with the use of dasatinib and was a subdural haematoma in a 15 year old boy treated for acute myeloid leukaemia (AML) off label.

These data provide little additional information of interest relevant to this submission. While dasatinib was one of the drugs studied, it was studied effectively in all uses, not simply Ph⁺ ALL.

Samad (2015)²³

This was a one page abstract of a retrospective analysis of the adverse event of pleural effusion in patients treated with dasatinib for haematological and solid tumour malignancies. It should also be noted some of the text was missing and not able to be assessed by the evaluator.

A retrospective analysis at a single centre (not specifically named) was carried out for all those who received dasatinib for this group of diseases between January 2006 and November 2014. Of 222 charts reviewed, 105 were excluded. Exclusion criteria included use in clinical trials where treatment could not be verified; treatment for less than one month; a pre-existing effusion before dasatinib treatment, or; developed a pleural effusion while not using dasatinib.

Of the 117 remaining patients, 27% developed a pleural effusion. Older age and presence of one or more comorbidities increased risk, while only coronary artery disease demonstrated increased risk of statistical significance (risk ratio (RR) 2.04; p = 0.046).

Obviously there are inherent issues with this study including concomitant medications that may also have such adverse events. While this evaluator is unsure of the methodology given the brevity of information, co-administration of ipilimumab was associated with increased frequency and rapidity of pleural fluid accumulation.

²² Egron A et al 2015 Preventable and potentially preventable serious adverse reactions induced by oral protein kinase inhibitors through a database of adverse drug reaction reports *Targ Oncol* 2015; 10: 229–234

²³ Samad R et al 2015 Dasatinib-Associated Pleural Effusion in Patients with Hematological and Solid Malignancies. *Am J Respir Crit Care Med* 2015; 191: A6385

In the context of this submission, this abstract adds little to consider. The adverse event is well known and in the PI. Of note is only that a prescriber should perhaps be more vigilant for this AE in the context of pre-existing coronary disease.

Post-marketing data

Four PSURs covering 28 December 2006 to 27 December 2008 and 28 June 2010 to 27 June 2012 were submitted. Also submitted were four PBERs covering 28 June 2012 to 27 June 2016.

In the latter two PSUR reports that each cover one year of time, the following additions of interest were made to the Company Core Data Sheet:

- 'Pulmonary arterial hypertension' added as an adverse event.

Other than this, updated figures on market and clinical trial exposure are of course made. There were 4754 patients in total now exposed to dasatinib in clinical trials as of end June 2012. Cumulative market exposure was estimated at 32,882 patients at the same cut-off date.

The PSURs verify that the constellation of ADRs present in the PI reflect those discovered up to that timeframe and are consistent with those noted in clinical trials and present in the PI.

Another point of note was found in the PBER dated 28 June 2015 to 27 June 2016, where the potential for reactivation of hepatitis B virus was added to the Company Core Data Sheet. This is also reflected in the PI document.

In summary the post-market data provide additional comfort (and in the view of this evaluator, the most robust information given the number of patients and nature of the trials in the publications submitted) that the safety profile derived from clinical trials is reflected in practical use of the drug. The PI reflects current knowledge of dasatinib in terms of clinical trial knowledge and most recent post-market considerations.

Evaluator's conclusions on safety

The sponsor summarises the safety population as 247 patients from 4 pivotal trials and 406 in total when adding supportive studies. Given the clinical overview was authored without Study ALL5, this includes a further 20 patients. The studies presented include different doses and dose regimens for dasatinib, slightly different inclusion and exclusion criteria, and different concomitant treatment for Ph⁺ ALL. There is no study that compares a chemotherapy regimen with chemotherapy plus dasatinib, therefore ADRs attributable to dasatinib alone are via biological plausibility and previously submitted data rather than being clearly apparent from this dossier's data.

The nature of the data presented is such that formal adverse event information is not presented for any study. Indeed some publications do not discuss adverse events at all. Given that context, the contribution of this dossier to further circumscribe the safety profile of dasatinib is, in the opinion of this evaluator, modest. The adverse events that are apparent are known ADRs for dasatinib and there do not appear to be additional serious adverse events revealed by these studies that are not already known to the sponsor and regulator. The nature of the data, several studies of relatively small populations with different designs and treatment regimens, makes it difficult or impossible to check the ADR frequencies in these data against those of the PI. It is the considered view of this evaluator that significant ADRs do not appear to have occurred at greater rates than the PI currently, but even if they did, these data would not necessarily readily identify that. Prima facie the data support the safety profile of the current PI document. Serious adverse events provided by the pivotal studies of this submission are summarised in Table 3.

Table 3: Serious adverse events reported in pivotal publications

Study	Serious Adverse Events (as reported by study authors)
Ravandi (2015)	Grade 3/4 adverse events reported (for details see m2.7.4, section 2.2) Events reported >20%: <ul style="list-style-type: none"> • infections • metabolic (hypophosphatemia, hypokalemia, hypocalcemia, hyperglycemia) • elevated transaminases. • acute renal failure Events reported <20%: <ul style="list-style-type: none"> • pleural effusion, pericardial effusion • bleeding (gastrointestinal, genitourinary, soft-tissue, and subdural hematomas) • vascular (deep vein thromboses, pulmonary emboli) • reversible rises in creatinine • diarrhea, nausea, vomiting • decreased fibrinogen
Yoon	No specific details of adverse events provided.
Rousselot	Serious adverse events reported were: <ul style="list-style-type: none"> • Pleural effusion (3 cases during induction, 1 case during maintenance, 1 case post-maintenance) • Subdural haemorrhage (3 cases) • digestive haemorrhage (3 cases) • pulmonary embolism (3 cases) • atrial fibrillation (4 cases) • cardiac failure (2 cases) • Tumour lysis syndrome during induction (2 cases) • Renal failure (6 cases) • transaminase elevations (5 cases)
Foa	Four patients discontinued treatment due to adverse events: <ul style="list-style-type: none"> • 1 due to weight gain, fever of unknown origin, and pleural effusion G1/G2 and superficial oedema G2; • 1 due to fever of unknown origin G2, nausea and vomiting G3); • 1 due to G3 proteinuria • 1 due to personal decision following G4 hypertransaminasemia 2 patients presented a serious adverse event, but did not discontinue treatment: <ul style="list-style-type: none"> • 1 due to a moderate pleural effusion • 1 due to mild fever of unknown origin

These events are encompassed by the PI. The post-market data reflect a patient experience in the estimated tens of thousands and the adverse events encountered are reflected in the PI. The most recent post-market information is that of a PBRER7 up to 27 June 2016.

First round benefit-risk assessment

It has been reported in this dossier and this evaluation report that clinical outcomes for those diagnosed with Ph⁺ ALL prior to the advent of TK inhibitors was poor on chemotherapy alone, and stem cell transplant remains the gold standard of care for eligible patients.

With the use of TK inhibitors including dasatinib, CR rates as well as event free survival (EFS) and overall survival (OS) have improved. This dossier supports very good CR outcomes for the use of dasatinib in first line treatment of Ph⁺ ALL, within the constraints of the patient numbers presented and acknowledged level of evidence of the data. While data are not yet fully generated to demonstrate whether or not long term use of TK inhibitors may offer comparable outcome data as that for stem cell transplants (SCTs), nonetheless the data presented here show that overall survival can be prolonged for many months in a sizeable proportion of patients treated with TK inhibitorss including dasatinib.

In that light, the drug, at the very least, allows prolonged survival which then increases chances for SCT.

The sponsor makes the point that despite the use of imatinib in first line treatment; outcomes can still be poor as a result of:

- Relapse with selection of point mutations in the BCR-ABL kinase domain.
- Evidence of other kinases involved in Ph⁺ ALL that are not blocked by imatinib (for example SRC kinases).

As a result, the availability of dasatinib as a first line treatment option would seem advantageous for clinicians.

Shortcomings of this dossier apart from the level of evidence of the data include the varying dosage regimens and strengths of dasatinib in the publications presented, and the varying accompanying chemotherapy regimen in most cases. An 'agreed' or ideal regimen does not exist and this remains an absent data set in terms of verifying Phase III trials. While treatment dose has been circumscribed largely based upon patient tolerance and toxicity, dosage regimen remains uncertain. Some regimens treat intermittently, others continuously. In the view of this evaluator this is really principally dependent upon patient tolerance of toxicity for the most part, including the toxicity of concomitant or peri-concomitant chemotherapy agents. The PI indication statement does include chemotherapy, where some of the data in this submission treated solely with dasatinib alone.

Furthermore, the safety data that this dossier encompasses are largely either brief in the context of a publication or absent entirely; therefore additional circumscribing of the safety profile of the drug for this indication has not been possible in a thorough sense other than via post-market information with its inherent limitations. There is no doubt the drug and TK inhibitors in general have a significant toxicity profile; this is offset favourably as a result of the limited treatment options for Ph⁺ ALL and the very poor outcome data without the use of TK inhibitors or stem cell transplant.

First round recommendation regarding authorisation

This evaluator recommends approval of the use of dasatinib for first-line treatment of Ph⁺ ALL in adults.

The question and second round evaluation related to PI issues and are considered beyond the scope of the AusPAR.

VI. Pharmacovigilance findings

Risk management plan

Summary of Risk management plan (RMP) evaluation²⁴

- The most recently evaluated EU-RMP was version 14.0 (dated 20 July 2016; data lock point (DLP) 12 November 2015) and Australian Specific Annex (ASA) version 4.0 (dated 7 September 2016). In support of the extended indications, the sponsor has submitted a revised version of the ASA (version 5.0, dated 22 February 2017). The EU-RMP has not been updated.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below. There are no new safety concerns related to the proposed extension of indications.

Table 4: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Myelosuppression	ü	-	ü	-
	Fluid Retention	ü	-	ü	-
	Bleeding Related Events	ü	-	ü	-
	QT Prolongation	ü	-	ü	-
	Pulmonary Arterial Hypertension (PAH)	ü	-	ü	-
	Pregnancy Related Malformative or Feto/Neonatal Toxicity	ü	-	ü	-
Important potential risks	Severe Hepatotoxicities	ü	-	ü	-
	Direct Cardiotoxic Effects (for example, Cardiomyopathy)	ü	-	ü	-
	Growth and development disorders and bone mineral metabolism disorders in the paediatric population	ü	-	ü	-

²⁴ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

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

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Toxic Skin Reactions	Ü	-	Ü	-
	CYP3A4 Drug Interactions	Ü	-	Ü	-
	HBV Reactivation	Ü	-	Ü	-
Missing information	Carcinogenicity	Ü	-	Ü	-
	Paediatric Population data	Ü	-	Ü	-
	Reproductive and lactation data	Ü	-	Ü	-
	Data in ethnic groups	Ü	-	-	-

- There are no additional pharmacovigilance or risk minimisation activities which is consistent with previous applications.

New and outstanding recommendations from second round evaluation

There are no outstanding issues.

Proposed wording for conditions of registration

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

The suggested wording is:

Implement EU-RMP (version 14.0 dated 20 July 2016; DLP 12 November 2015) with Australian Specific Annex (version 5.0, dated 22 February 2017) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Background

Acute lymphoblastic leukaemia (ALL) refers to a group of haematopoietic neoplasms involving cells committed to the lymphoid lineage.¹ Philadelphia chromosome positive ALL (Ph⁺ ALL) is a biologically and clinically distinct variant of ALL classified as ALL with t(9;22)(q34;q11.2);BCR-ABL1 in the World Health Organization classification system.²⁵ According to UpToDate, Ph⁺ ALL accounts for approximately 20 to 30 percent of ALL in adults and 2 to 3 percent of ALL in children.¹

²⁵ Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008

When treated with chemotherapy alone, patients with Ph⁺ ALL have a uniformly poor prognosis with few survivors at five years after treatment.¹ Allogeneic haematopoietic cell transplantation (allo-HCT) provides better results, curing approximately 30 to 60 percent of patients with Ph⁺ ALL.¹ Incorporation of a TK inhibitor of BCR-ABL1 (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) into the treatment regimen has resulted in superior response rates, thereby allowing more patients to proceed to allo-HCT. It remains uncertain whether treatment only with the combination of chemotherapy plus a TK inhibitor will provide long term survival results similar or better than allo-HCT in first remission.

Prognosis hinges on tumour and patient characteristics. Age at diagnosis and cytogenic/genetic findings appear to be the strongest predictors of survival. Ph⁺ ALL is a poor prognosis form of precursor-B ALL.¹

In Australia, imatinib is approved for use in first line Philadelphia chromosome positive ALL with the following wording of indication:

treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph⁺ ALL) integrated with chemotherapy.

The current approved PI for imatinib provides the following data set for imatinib in this setting: A randomised controlled study of imatinib as induction versus chemotherapy, with imatinib integrated with chemotherapy for consolidation (both arms), three studies integrating imatinib with historical data of chemotherapy alone and a paediatric dataset covering a total of 93 patients aged < 2 to 22 years (see Australian PI, Imatinib, dated 8 September 2017).

The sponsor makes the point that despite the use of imatinib in first line treatment outcomes can still be poor as a result of:

- Relapse with selection of point mutations in the BCR-ABL kinase domain.
- Evidence of other kinases involved in Ph⁺ ALL that are not blocked by imatinib (for example SRC kinases).

Dasatinib is a broad spectrum competitive inhibitor of 5 oncogenic tyrosine kinases/kinase families that transmit growth signals from the cell membrane to the nucleus: BCR-ABL, SRC, c-KIT, PDGFR and ephrin receptor kinases. Dasatinib is already registered as 20, 50, 70 and 100 mg film coated tablets, with indications of:

Treatment of adults 18 years or over with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase.

Treatment of adults 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.

Treatment of adults 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

Regulation (Australia)

The sponsor states that this submission is specific to Australia and is not planned for submission in other regulatory jurisdictions.

Question for sponsor: Is there any additional information available regarding the rationale for this application in Australia? Has any other regulator provided comment on this application?

The current approved indication in Australia for Ph⁺ ALL is as follows:

Sprycel is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

The current United States PI states the following indication for Ph⁺ ALL: '*adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ ALL) with resistance or intolerance to prior therapy*' (US PI; Revised November 2017).

The current EU Summary of Medical Product Characteristics (SmPC) states the following indication for Ph⁺ ALL: '*Sprycel is indicated for the treatment of adult patients with: Ph⁺ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy*'.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Overview of data

The pivotal data for this submission comprises a total of four Phase II studies. These are:

- Ravandi et al., (presented as 3 papers, 2010, 2013, 2015)^{4,5,6}
- Yoon et al.⁷
- Rousellot et al.⁸
- Foá et al.⁹

An additional paper by Grigg et al., (2017) was included in draft format.¹⁰ Together, these five pivotal papers collectively represent 267 adult patients treated with dasatinib as part of their first-line treatment of Ph⁺ ALL. A total of six supportive papers were also presented, in addition to four documents titled 'Reports of Analyses from more than one study' which examine adverse reactions observed when tyrosine kinase inhibitors or specifically dasatinib is used clinically. Four PSURs and four Periodic Benefit Risk Evaluation Reports (PBRERs) support the post-market data submission.

Pharmacology

No PK or PD data was submitted with this application.

Efficacy

There are no direct head-to-head or randomised controlled trials comparing the first-line use of imatinib and dasatinib in combination with chemotherapy for Ph⁺ ALL. The current dossier presented a total of 426 patients with newly diagnosed adult Ph⁺ ALL treated with dasatinib (integrated with chemotherapy) across 4 pivotal Phase II clinical trials and 7 supportive studies.

For ease of discussion in this overview, the literature has been approached from the following four perspectives:

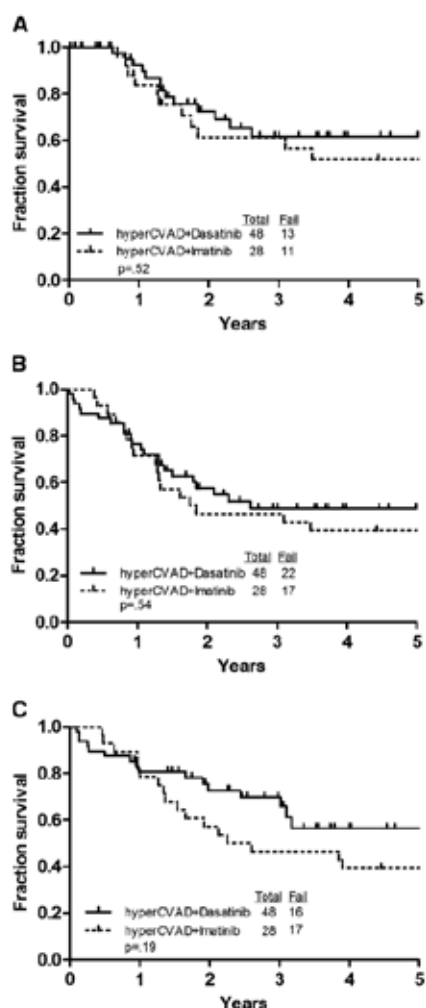
- dasatinib in comparison to imatinib;
- dasatinib in combination with high-dose chemotherapy;
- dasatinib in combination with low-dose chemotherapy; and
- supportive efficacy studies.

Dasatinib in comparison to imatinib

One pivotal study (Ravandi et al., 2013);⁵ compared patients treated with chemotherapy and dasatinib with historical data of chemotherapy and imatinib. The full results from these two trials have also been separately published and are discussed below.^{6,26} For context, it is important to note that the Ravandi et al., (2013) study was focused on the usefulness of MRD detection as a predictor of outcome for patients with Ph⁺ ALL treated with tyrosine kinase inhibitors plus chemotherapy, who do not receive allogeneic stem cell transplant (ASCT) after first CR. This was a Phase II single centre study using imatinib as a historical control via sequential protocols for each TK inhibitor. In total, 122 adult patients (aged 21 to 84 years) with newly diagnosed Ph⁺ ALL were treated with one of two front line regimens combining HCVAD with either imatinib (n = 54) or dasatinib (n = 68). Of the 76 patients who did not receive an ASCT in first CR, there was an overall trend for improved survival among the patients treated with dasatinib, however, this was not statistically significant (Ravandi et al., (2013) page 1216).⁵ Achieving major molecular response (MMR) or better was associated with longer EFS (HR 0.41; p=0.002).

²⁶ Daver N et al 2015. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica* 2015; 100: 653-661

Figure 1: Comparison of outcomes for the patients treated on the 2 regimens. (A) Complete remission duration; (B) Disease-free survival; (C) Overall survival



The Delegate agreed with the evaluator that while this study focussed primarily upon whether MMR or negative status for MRD as measured by multi-parameter flow cytometry (MFC) and immunoglobulin heavy chain polymerase chain reaction (IGH PCR) could predict outcome in a small population without stem cell transplant, for the purposes of this submission it provides data for 48 patients who responded to a combination of HCVAD and dasatinib therapy in first-line treatment of Ph⁺ ALL. It also demonstrates comparable outcomes compared with imatinib, and is one of the few studies presented in the dossier with a comparator.

Dasatinib in combination with high dose chemotherapy

Two pivotal studies investigated dasatinib for first line treatment of Ph⁺ ALL with high dose chemotherapy: Ravandi et al., (2010, 2013, 2015) and Yoon et al.^{4, 5, 6, 7} A total of 123 patients were treated across these studies with median follow up 67 months (range 33 to 97 months) and 54 months (40 to 63 months) respectively. The administration of dasatinib was similar across both studies, with dasatinib administered on selected days initially (100 mg daily on Days 1 to 14 of Cycle 1) then continuous thereafter. Study ALL5 provides additional data supporting dasatinib in combination with high-dose chemotherapy.¹⁰ Key treatment points and results are discussed below.

Ravandi et al., (2015) was a Phase II study that reported on a total of 72 newly diagnosed adult Ph⁺ ALL patients.⁶ Dasatinib 100 mg daily (administered as 50 mg twice daily doses or 100 mg daily) was administered on Days 1 to 14 of each of the 8 cycles of alternating

HCVAD and high dose cytarabine and methotrexate (induction/consolidation cycles). After the enrolment of the first 42 patients, the protocol was amended to administer 70 mg daily continuously from the second cycle. Overall, 69 of 72 patients (96%) achieved CR²⁷. Of these, 57 (83%) achieved cytogenetic CR after 1 cycle with 64(93%) achieving a major molecular response at a median of 4 weeks (range 2 to 38 weeks). 65 patients (94%) were negative for minimal residual disease at a median of 3 weeks (range 2 to 37 weeks). With a median follow-up of 67 months, 30 patients were in CR (43%); 33 (46%) were alive and 12 underwent ASCT. A total of 39 patients died (3 at induction, 19 after relapse, 7 after SCT performed during first CR and 10 during CR). The 5 year disease free survival was 44% and overall survival 46%. The median disease free survival and overall survival were 31 (range 0.3 to 97 months) and 47 months (range 0.2 to 97 months) respectively. Overall seven relapsed patients had BCR-ABL kinase domain mutations, including 4 with T3151.

Yoon et al., was a Phase II single cohort study of 51 adult patients with newly diagnosed Ph⁺ ALL (median age 46 years, range 19 to 64).⁷ The treatment regimen was a chemotherapy cycle, then as soon as neutrophil and platelet recovery had occurred (neutrophil at or greater than $1 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$), dasatinib 100 mg daily. Patients received up to four dasatinib cycles. The first dasatinib cycle integrated cyclophosphamide/vincristine/danorubicin/dexamethasone plus central nervous system (CNS) prophylaxis of intrathecal methotrexate/cytarabine/hydrocortisone (triple IT). The second dasatinib cycle was integrated with cytarabine/mitoxantrone, plus triple IT. This induction phase was followed by 2 years of maintenance with 100 mg dasatinib daily. The primary endpoint was the MMR rate;²⁸ at the end of the second dasatinib cycle. This could be assessed in all but two patients who died due to sepsis during chemotherapy. Forty-six (93.9%) of 49 assessable patients had persistent CR by the end of the second cycle (with 39 progressing to ASCT); 38 patients (77.6%) had MMR (n = 16; 32.7%) or undetectable minimal residual disease (UMRD) (n = 22; 44.9%). After a median follow-up of 54 months (range 40 to 63), the 4 year cumulative incidence of disease free survival (DFS) and OS rates were 52.0% and 51% respectively.

Study ALL5 (Grigg et al., 2017) narrates the results of a trial of dasatinib in combination with hyper CVAD chemotherapy in Ph⁺ ALL adult patients.¹⁰ Following a prophase therapy of dasatinib 70 mg BD for 7 days, subjects received 8 cycles of chemotherapy, starting with dexamethasone, doxorubicin, cyclophosphamide and vincristine and alternating with methotrexate, cytarabine and methylprednisolone. Each course was given with dasatinib 100 mg daily on Days 1 to 14 of each cycle. In terms of induction response rate, all patients attained complete haematologic response (CHR) after the first induction cycle. Fifteen attained a complete molecular response during the chemotherapy phase, and the remaining five attained MMR as their best response to treatment. Overall, 11 patients achieved a complete molecular response prior to three months of therapy. Thirteen patients proceeded to allogeneic stem cell transplantation. Median event free survival was 3.8 years (95% CI 2.9 to not recorded (NR)) with 12 events occurring, 10 being relapse. Median relapse free survival was 6.2 years (95% CI 3.2 to NR). Overall survival was 4.9 years for transplant recipients versus NR for non transplant recipients (p = 0.07). Approaching, but not, statistically significant between groups. Only two patients who did not receive a transplant in first remission died in the study period.

Overall, these three studies support the efficacy of dasatinib in combination with high dose chemotherapy. The data presented indicates that for a reasonable proportion of the

²⁷ In the studies by Ravandi *et al* (2010;2013;2015), a complete response was defined as fewer than 5% blasts in the bone marrow, with more than $1 \times 10^9/L$ neutrophils and more than $100 \times 10^9/L$ platelets in the peripheral blood and no extramedullary disease

²⁸ MMR was defined as a ratio of BCR-ABL1 to ABL1 of $\leq 0.1\%$ on the international scale for p210BCR-ABL1 or a reduction in BCR-ABL1 transcript level by at least 3-log from the standardised pooled baseline value for p190BCR-ABL1. Complete molecular response was defined as absence of detectable BCR-ABL1 transcripts by centralised PCR assays (4.5 log sensitivity).

patients studied; clinically relevant CR outcomes can be achieved with the use of dasatinib in first line treatment of Ph⁺ ALL.

Dasatinib in combination with low-dose chemotherapy

Two pivotal studies investigated dasatinib for first line treatment of Ph⁺ ALL with low dose chemotherapy: Rousellot et al and Foá et al.^{8,9} A total of 124 patients were studied in this setting with a median follow up of 32 months (range 2 to 88 months, with median follow-up for surviving patients 66 months (range, 21 to 88 months)) and 24.8 months (range, 8.9 to 35.3 months) respectively. The dose of dasatinib was similar between the studies at 140 mg/day in either a single or divided dose.

Rousellot et al., studied an older aged cohort, reporting on 71 patients aged over 55 years (median 69, range 59 to 83).⁸ Patients were treated with dasatinib 140 mg/day (dose reduction of 100 mg/day for patients aged over 70 years) plus intrathecal chemotherapy, vincristine and dexamethasone during induction. Consolidation therapy was dasatinib 100 mg daily with methotrexate on Day 1 and asparaginase on Day 2 for Cycles 1, 3 and 5. For Cycles 2, 4 and 6, cytarabine every twelve hours on Days 1, 3 and 5 was given. These cycles were 4 weeks in length. Maintenance therapy was dasatinib 100 mg daily, with 6-mercaptopurine and methotrexate weekly, every other month. Every two to three months dexamethasone/vincristine was given up to 2 years. After this, therapy was dasatinib alone 100 mg daily until relapse or death. Overall, 67 of the 71 patients achieved CR, 3 died during induction and 7 patients underwent ASCT. In total, 49 patients died, (69%), with 32 in relapse or refractory disease and 14 in CR. There were 6 deaths considered related to treatment. Twenty two patients were alive at the time of analysis. Of seven patients who underwent ASCT, 4 were alive in CR at 53, 56, 59 and 65 months. Of those achieving first CR (67), 55 were evaluable for MRD. After induction, 33 patients reached MMR. During consolidation, 36 patients reached MMR. The primary study endpoint of relapse free survival (RFS) at 12 months was 58% (95% CI 45, 69). At three years, RFS, EFS and OS were 33% (95% CI 22, 44), 31% (95% CI 21, 42) and 41% (95% CI 29, 52) respectively. At 5 years, RFS, EFS, and OS;²⁹ were 28% (95% CI, 18 to 39), 27%(95%CI, 17 to 37), and 36%(95%CI, 25 to 47), respectively. Median RFS, EFS, and OS were 19.1, 18.9, and 25.8 months, respectively.

The Delegate agreed with the evaluator that whilst there is no comparison group, outcomes are likely to be clinically significant in this group given typically poor outcomes for Ph⁺ ALL in the elderly population studied. The reported outcomes are less pronounced in comparison with other pivotal studies submitted, however the median age of the population in this study must be considered.

Foá et al., reported on 53 adult patients with newly diagnosed Ph⁺ ALL (median age 53.6 years, range 23 to 76 years) (reported as part of the GIMEMA LAL0201-B protocol study).⁹ Patients received 7 days of steroid treatment prior to dasatinib treatment, with increasing doses of 10 to 60 mg/m² per day. Patients then received dasatinib (70 mg twice daily) induction therapy for 84 days combined with steroids for the first 32 days and intrathecal chemotherapy. Post remission therapy was not specified. After the steroid phase, 86% showed a blast reduction of 75% or greater. Fourteen percent showed a blast reduction less than 75%. However during dasatinib treatment, 100% of patients achieved a CHR; 49 at the first bone marrow (BM) determination on Day 22, three at the second determination at Day 43, and one at the third determination on Day 57. Median time to CHR was 23 days. After treatment with dasatinib, a marked BM reduction of the leukemic clone was recorded: at Day 22, 9 of 44 patients (20.4%) were negative and 12 of 44 patients (27.3%) showed < 0.01% of disease; at Day 43, 19 of 47 patients (40.4%) were negative and 15 of

²⁹ Relapse free survival was defined as from the first date of therapy to the relapse date. Event free survival was time between inclusion and death under induction; haematologic relapse, or; death in the first CR. OS was calculated from date of initiation of therapy to death OR last contact.

47 (31.9%) showed < 0.01% of disease. The leukemic cell reduction was significant between Days 0 and 22, Days 22 and 43 ($p < 0.0001$), and Days 43 and 57 ($p = 0.0143$). No further significant reduction was observed between Days 57 and 85. A significant difference in disease free survival was observed between patients who showed at Day 22 a decrease in BCR-ABL levels of $< 10^{-3}$ compared with patients who never reached these levels during induction.

The results from Foá et al., support the efficacy of dasatinib plus steroids for first line Ph⁺ ALL therapy. The primary endpoint measures demonstrated significant and rapid removal of the neoplastic clone and this was statistically significant out to Day 57 of the analysis time points. Those patients with BCR-ABL+ status can achieve a rapid debulking of the disease using dasatinib alone without the use of combination chemotherapy in this patient population.

Supportive efficacy data

As stated by the sponsor, published efficacy data available in the form of abstracts or conference posters have been identified in the literature search. The publications have significant limitations due to the brevity of the information included. The available information is summarised in Table 5 to demonstrate a consistent trend with pivotal studies in outcomes for efficacy in newly diagnosed Ph⁺ ALL patients treated with dasatinib.

Table 5: Efficacy data from supportive studies

Study	Induction Treatment	CR	EFS/DFS/OS
Caocci et al	TKI* + chemotherapy	NR	NR
Gurman et al (11 patients)	Dasatinib + steroid (4 patients)	100%	Median 14 months (range 3-24 months): 9 patients alive, 6 in CMR
Pastori et al (10 patients)	Dasatinib + steroids	100%	NR
Sasaki et al (84 matched patients, 42 on each TKI)	Dasatinib + HCVAD or	95%	1-yr EFS: 73% 3-yr EFS: 50% 1-yr OS: 83% 3-yr OS: 60%
	Ponatinib +HCVAD	100%	1-yr EFS: 86% 3-yr EFS: 69% 1 yr OS: 89% 3-yr OS: 74%
Slayton et al (60 patients)	Dasatinib + Chemotherapy	NR	3-yr DFS: 79% 3-yr OS: 93%
Tekgündüz et al (46 patients)	TKI* + chemotherapy	93%	2-yr OS (dasatinib): 67% Median OS (dasatinib): 23 months
	TKI* monotherapy	100%	

*dasatinib or imatinib

The reported results from the available publications in newly diagnosed patients with Ph⁺ ALL does not include adequate detail to make a clear determination of efficacy in CNS involvement at initial diagnosis.

Paediatric patients

Paediatric data was not included in the current dossier.

Comparison of long term data from pivotal studies

The sponsor provided the information presented in Table 6 summarising the long term data from each of the pivotal studies.

Table 6: Comparison of reported long-term efficacy results

Study	Long-term efficacy results
Ravandi et al (2015, High-dose Chemotherapy)	<ul style="list-style-type: none"> • Median follow up: 67 months (range, 33-97) • 33 (46%) patients alive, with 30 (43%) in CR. • Median DFS: 31 months (range 0.3-97 months) • Median OS: 47 months (range, 0.2-97 months) • 2-year DFS: 49% • 2-year OS: 57% • 5-year DFS: 46% • 5-year OS: 46%
Daver et al (2015) – Imatinib treatment	<ul style="list-style-type: none"> • Median follow up: 130 months (range, 73-149) • 19 (35%) patients alive, 18 (33%) in CR • Median DFS: 22 months (range 3-148 months) • Median OS: 31 months (range, 0.6-149 months) • 2-year DFS: 49% • 2-year OS: 57% • 5-year DFS: 43% • 5-year OS: 43%
Yoon et al (High-dose Chemotherapy)	<ul style="list-style-type: none"> • Median follow up: 54 months (range, 40-63 months) • 26 (51%) patients alive and in CR • 4-year DFS (all patients): 52% • 4-year OS (all patients): 51% • 4-year DFS (SCT): 64% • 4-year OS (SCT): 64%
Rousselot et al (Low-dose Chemotherapy)	<ul style="list-style-type: none"> • Median follow up: 66 months (range, 21-88 months) • 22 (31%) patients alive (21 in CR) • 5-year EFS: 27% • 5-year OS: 36%
Foa et al (Steroid Chemotherapy)	<ul style="list-style-type: none"> • Median follow up: 25 months (range, 9-35 months) • 34 (64%) patients alive • Median DFS: 22 months • Median OS: 31 months • 20-month DFS: 51% (95%CI: 44-59%) • 20-month OS: 69% (95%CI: 61-79%)

The data demonstrates similarities in regards to durability of efficacy outcomes, with the exception of the Rousselot et al., study (this was an older patient cohort).

Safety

The clinical evaluator discusses the components of the dossier with safety data in the clinical evaluation report. Key findings include the following:

- The safety data presented in the current dossier is limited. No formal adverse event information is provided, with some publications excluding data regarding adverse events.

- The safety population comprises 247 patients from the 4 pivotal trials and a total of 406 patients when including supportive studies. A further 20 patients were included from Study ALL5 which was not included in the overview of clinical safety.
- The clinical evaluator states that the adverse events presented are known adverse drug reactions (ADR) for dasatinib. The evaluator further notes that the nature of the data, several studies of relatively small populations with different designs and treatment regimens, makes it difficult or impossible to check the ADR frequencies in these data against those of the PI. Overall, the evaluator considered that significant ADRs do not appear to have occurred at greater rates than the PI currently, but this conclusion is limited by the current data.

Serious adverse events provided by the pivotal studies of this submission are summarised as in Table 3 above.

The clinical evaluator concludes that the events presented above are encompassed by the PI.

Drug related adverse events leading to discontinuation in the pivotal studies occurred in a total of 60/247 patients (24%), with 54/247 (21.9%) permanently discontinued. The reason for discontinuation is shown in Table 7.

Table 7: Reported drug related adverse events leading to discontinuation

Study	Discontinuation (as reported by study authors)
Ravandi (2015)	Dasatinib was discontinued in 12 patients due to adverse events <ul style="list-style-type: none"> • pleural effusions in 6 patients, • pulmonary artery hypertension in 2 patients, • gastrointestinal bleeding in 2 patients, • skin cancer in 1 patient, and • subdural bleeding in 1 patient.
Yoon	Dasatinib was discontinued temporarily in 6 of 51 patients. No patient withdrew from the study at any time because of dasatinib-related serious adverse events
Rousselot	38 of 51 patients discontinued because of relapse or death 14 patients withdrew from the study due to adverse events or investigator decision Details of AEs causing withdrawal or discontinuation were not reported
Foa	Four patients discontinued treatment due to adverse events: <ul style="list-style-type: none"> • 1 due to weight gain, fever of unknown origin, and pleural effusion G1/G2 and superficial oedema G2; • 1 due to fever of unknown origin G2, nausea and vomiting G3); • 1 due to G3 proteinuria • 1 due to personal decision following G4 hypertransaminasemia

The sponsor proposed the following additional statement in the Adverse Effects section of the PI which was subsequently amended by the clinical evaluator (text in bold and strikethrough):

*'The safety profile of Sprycel in 4 Phase II clinical trials in newly diagnosed patients with Ph+ ALL, ~~indicated a similar~~ **was generally consistent with** the safety profile ~~compared with use in patients who were resistant or intolerant to prior therapy.'~~*

Given the limitations of the dossier presented, including the difficulties prosecuting literature based data, the following amendment is recommended:

'Newly diagnosed Ph+ ALL

No dedicated clinical trials have been conducted investigating the safety of dasatinib in newly diagnosed Ph+ ALL as a primary outcome. The safety profile of Sprycel in 4 Phase II clinical trials in newly diagnosed patients with Ph+ ALL, indicated a similar was generally consistent with the safety profile compared with use in patients who were resistant or intolerant to prior therapy.

Recommendation for sponsor: Please amend the statement under adverse effects as recommended above [inclusion of the full list of recommended PI changes is beyond the scope of this document].

Clinical evaluator's recommendation (if applicable)

The clinical evaluator recommends approval of the use of dasatinib for first-line treatment of Ph+ ALL in adults.

Risk management plan

There were no objections to approval from an RMP perspective and no outstanding issues remained.

The RMP evaluator recommended the following condition of registration:

Implement EU-RMP (version 14.0 dated 20 July 2016; DLP 12 November 2015) with Australian Specific Annex (version 5.0, dated 22 February 2017) and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

Dasatinib in combination with chemotherapy has been associated with notable toxicities and treatment discontinuation. Across the 4 pivotal studies, a discontinuation rate of approximately 24% was noted, with approximately 21.9% permanently discontinued. The safety data that this dossier encompasses are limited. Whilst the evaluator considered that the safety data that is presented reflects a known safety profile for dasatinib and is captured in the current PI, it must be noted that if differences do exist, this may not be identified in the current dossier.

Balanced against this, the Delegate agreed with the clinical evaluator that the data presented indicates that for a reasonable proportion of the patients studied; clinically relevant CR outcomes can be achieved with the use of dasatinib in first line treatment of Ph+ ALL. However, it is not possible based on these data to accurately determine how this compares to current therapy in Australia. The dossier draws historical comparison to imatinib in this setting via the Daver et al., (2015) study, demonstrating similar efficacy to imatinib.²⁶ Although this approach is reasonable, it is important to note that there have been other relevant publications in this field. For example, the recent article in the American Society of Hematology educational materials by Ravandi, December 2017 (see Table 8).³⁰ The rate of allo-HCT following dasatinib therapy is another important consideration. Whilst comparison to other therapies is difficult, the sponsor has been asked to comment on the paper by Ravandi 2017 which indicates that the rate of allo-HCT in the

³⁰ Ravandi F. Current Management of Philadelphia chromosome positive ALL and the role of stem cell transplantation. American Society of Hematology: Acute Lymphocytic Leukaemia: New Approaches in Management. December 2017

studies by Foá et al., and Ravandi et al., may be lower than that for other TK inhibitors in frontline therapy.

Table 8: Published selected trials in Ph+ ALL

Table 1. Published selected trials in Ph+ ALL

Study	N	Age, y, median [range]	Regimen	CMR rate	AlloHCT rate	RFS rate	OS rate
Imatinib							
Lee et al ³⁵	87	41 [16-71]	Intensive chemotherapy	66% (at remission)	68%	39% (5 y)	33% (5 y)
Yanada et al ³⁶	80	48 [15-63]	Intensive chemotherapy	50% (day 63)	49%	—	76% (1 y)
Vignetti et al ¹⁸	29	69 [61-83]	Corticosteroids	4%	—	48% (1 y)	74% (1 y)
Bassan et al ³⁷	59	45 [20-66]	Intensive chemotherapy	—	72%	39% (5 y)	38% (5 y)
Fielding et al ²	169	42 [16-64]	Intensive chemotherapy	—	72%	50% (4 y)	38% (4 y)
Daver et al ⁹	54	51 [17-84]	Intensive chemotherapy	45% (overall)	30%	43% (5 y)	43% (5 y)
Chalandon et al ²¹	133	45 [21-59]	Intensive chemotherapy	23% (2 cycles)	65%	—	46% (5 y)*
	135	49 [18-59]	Low-intensity chemotherapy	29% (2 cycles)	62%	—	46% (5 y)*
Wetzler et al ³³	34	45 [24-57]	Intensive chemotherapy	—	44%	46% (5 y)	51% (5 y)
Dasatinib							
Foá et al ¹⁹	53	54 [24-77]	Corticosteroids	15% (day 85)	42%	22% (20 mo)	31% (20 mo)
Ravandi et al ⁶	72	55 [21-80]	Intensive chemotherapy	65% (overall)	17%	44% (5 y)	46% (5 y)
Ravandi et al ¹⁵	97	44 [20-60]	Intensive chemotherapy	—	42%	62% (3 y)	69% (3 y)
Rousselot et al ²⁰	71	69 [55-83]	Low-intensity chemotherapy	24% (consolidation)	10%	28% (5 y)	36% (5 y)
Nilotinib							
Kim et al ¹⁴	90	47 [17-71]	Intensive chemotherapy	77% (3 mo)	63%	72% (2 y)	72% (2 y)
Ponatinib							
Jabbour et al ²⁸	37	51 [27-75]	Intensive chemotherapy	78% (overall)	24%	—	80% (2 y)

*Pooled data.

Other pertinent constraints of this dossier apart from the level of evidence and difficulties prosecuting literature based evidence; include the varying dosage regimens and strengths of dasatinib in the publications presented and the varying accompanying chemotherapy regimens. An 'agreed' or ideal regimen does not exist and this remains an absent data set in terms of verifying Phase three trials. While treatment dose has been circumscribed largely based upon patient tolerance and toxicity, dosage regimen remains uncertain.

Proposed indication

The indications statement in the annotated PI requires integration of dasatinib treatment with chemotherapy:

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy.

The Delegate agreed with the clinical evaluator that the most robust data presented in this submission are in combination with HCVAD.

Use of dasatinib with multi-agent regimens

No specific drug interaction studies between dasatinib and routinely used chemotherapy regimens have been presented. The sponsor discussed the implications for dasatinib integrated with chemotherapy. The sponsor states that in the Australian clinical setting, the drugs used in the HCVAD (cyclophosphamide/vincristine, doxorubicin/dexamethasone; or methotrexates/cytarabine) or low dose chemotherapy regimens (for example Vincristine, prednisolone/dexamethasone) will likely be the same irrespective of the TKI integrated with chemotherapy in the treatment of newly diagnosed patients with Ph+ ALL.

Cyclophosphamide, vincristine, doxorubicin and dexamethasone all have some evidence of interaction with CYP3A family or CYP3A4 metabolising enzymes.

In humans, the major enzyme responsible for the metabolism of dasatinib is CYP3A4 (see current approved dasatinib PI). The current PI includes statements under *Interactions with other medicines* which include paragraphs regarding the following:

- *CYP3A4 inhibitors: administration of a potent CYP3A4 inhibitor is not recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity.*
- *CYP3A4 inducers: concomitant use of potent CYP3A4 inducers is not recommended.*
- *CYP3A4 substrates: CYP3A4 substrates known to have a narrow therapeutic index should be administered with caution in patients receiving Sprycel.*

There is no specific mention of the chemotherapy agents listed above in the PI. The sponsor provides justification for this on the basis that the drug-drug interaction studies submitted with previous applications used potent CYP3A4 inhibitors and substrates, commonly used in clinical pharmacology studies, which represent a worst case scenario and dasatinib is not likely to interact differently to imatinib integrated with this commonly used chemotherapy regimen in Ph⁺ ALL.

Whilst the Delegate agrees with the sponsor's reasoning and current PI statements, prescribers may benefit from the addition of the statement '*No specific drug interaction studies between dasatinib and chemotherapy regimens routinely used in newly diagnosed Ph⁺ ALL have been performed.*' The Delegate would appreciate the Advisory Committee's clinical opinion on whether such a statement would assist prescribers.

Recommended dasatinib dose for newly diagnosed Ph⁺ ALL

The proposed draft PI for Australia recommends a starting dosage of dasatinib for newly diagnosed Ph⁺ ALL of 100 mg administered orally once daily (QD) and should be taken consistently either in the morning or evening. The PI states that 'in clinical studies, treatment with Sprycel was continued in the maintenance phase until disease progression or until no longer tolerated by the patient.' A further statement under Dose Escalation states '*In clinical studies in adult Ph⁺ ALL patients, dose escalation to 140 mg once daily (newly diagnosed patients) ...was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage.*'

A range of dose regimes were utilised in the clinical studies submitted as part of this application. The sponsor has provided the following summary of dasatinib dosing, as shown in Table 9.

Table 9: Summary of dasatinib dosing in the pivotal studies

Study	Dasatinib Dosing
Ravandi et al (High-dose Chemotherapy)	Induction/Consolidation Initially: 50 mg twice daily, later 100 mg once daily (amendment to protocol) After first 42 patients: 100 mg/day for first 14 days, then 70 mg/day from second cycle. After CR Initially 50 mg twice daily, later 100 mg/day.
Yoon et al (High-dose Chemotherapy)	Induction 100 mg once daily
Rousselot et al (Low-dose Chemotherapy)	Induction 140 mg/day or 100 mg/day (amendment to protocol) Consolidation/ Maintenance and post-maintenance 100 mg/day
Foa et al (Steroid Chemotherapy)	Induction 70 mg twice daily for 84 days. Dose reduction Permitted after non-haematologic toxicity. Post-induction treatment was not specified.

The sponsor states that based on the above, a dose regimen in newly diagnosed patients with Ph⁺ ALL is proposed as 100 mg administered orally daily, with dose increased or decreased based on individual patient response and tolerability. Although a range of different pre-treatments, induction, consolidation and maintenance treatments were included in the dossier, the dosage and administration section indicates this proposed dose of dasatinib as a starting dose and for the maintenance phase (see proposed changes to the dasatinib PI).

The Delegate agreed with the sponsor and clinical evaluator that the data presented does support a dose of 100 mg daily in this setting. Furthermore, it is reasonable to consider that individual patient response and tolerability will largely drive clinical dosing. However, the Delegate would appreciate the Advisory Committee's advice on this issue.

CNS involvement in the pivotal studies

The reported results from the available publications in newly diagnosed patients with Ph⁺ ALL does not include adequate detail to make a clear determination of efficacy in CNS involvement at initial diagnosis.

Mutation rates in the pivotal studies

Overall, the T315I mutation was more commonly reported after treatment with dasatinib compared to treatment with imatinib.²⁶ However, not all patients who relapsed underwent mutational analysis. The sponsor comments that compared to the results presented in Daver et al.;²⁶ the data suggests that treatment with dasatinib results in a narrower range of mutations than treatment with imatinib. The sponsor states that this would be expected as many of the mutations that are resistant to imatinib treatment are sensitive to dasatinib. Whilst the Delegate agreed that the top line view of the data (see Table 10) does support this suggestion; it is difficult to draw a clear conclusion at this stage based on the data presented.

Table 10: Comparisons of mutations in pivotal studies

Study	Observed mutations post-induction
Ravandi et al 2015, (High-dose Chemotherapy)	Twenty-two of 72 patients relapsed (31%) of which 8 had CNS-only relapse. Median time to relapse was 17 months (range 6-72 months). Thirteen relapsed patients underwent a mutational analysis - 7 had <i>ABL</i> mutations: <ul style="list-style-type: none"> • 4 x T315I • 1 x F359V and • 2 x V299L
Daver et al (Imatinib treatment) (High-dose Chemotherapy)	Seventeen of 54 patients relapsed (31%) with a median CR duration of 14.1 months (range 7.9-92.7). One or more <i>ABL</i> -kinase mutations were identified in 5 of 8 patients with relapsed disease in whom mutational analysis was performed. The mutations identified were F359V, E459K, V338, P309A, Y253F, and Y253H. No <i>ABL</i> -kinase mutations were detected in 3 patients.
Yoon et al (High-dose Chemotherapy)	Fifteen of 51 patients relapsed (29%) at a median CR duration of 12 months (range 2–24 months). Among these relapsed patients the mutations were: <ul style="list-style-type: none"> • 6 x T315I • 2 x E255K, and No mutations were detected in seven patients.
Rousselot et al (Low-dose Chemotherapy)	Ten patients were positive for the T351 mutation at diagnosis; eight of these patients relapsed, all with this mutation. In total, 36 of 71 patients relapsed (51%); median relapse-free survival was 19.1 months. 24 were tested for mutation by Sanger sequencing, and 18 (75%) were T315I-positive. Other detected mutations were: <ul style="list-style-type: none"> • 1 x F317L • 1 x V299L • 1 x compound mutation (F137I + F359I + F359C) No mutations were detected in three patients.
Foa et al (Steroid Chemotherapy)	Twenty-three of 53 patients relapsed (43%) at a median 5.9 months from first CHR (range, 2.8-23.6 months). Seventeen underwent mutational analysis and 13 mutations were detected: <ul style="list-style-type: none"> • 12 x T315I • 1 x E255K No mutations were detected in the other 4 patients.

Questions for sponsor

1. The sponsor states that this application is specific to Australia and is not planned for submission in other regulatory jurisdictions. Is there any additional information available regarding the rationale for this application in Australia? Has any other regulator provided comment on this application?
2. Whilst comparison to other therapies is difficult, please comment on the paper by Ravandi et al., (2017) which indicates that the rate of allo-HCT in the studies by Foá et al., and Ravandi et al., may be lower than that for other TK inhibitors in frontline therapy (note; the TGA acknowledges that the study by Rousselot et al., is an older cohort of patients, thus likely accounting for the lower rate of allo-HCT).

Summary of issues

1. Level of evidence in the current dossier supporting the safety and efficacy of dasatinib in the first line treatment of Ph⁺ ALL (discussed above).
2. Proposed wording of indication for first line Ph⁺ ALL in light of the limitations of the dossier presented (discussed above).
3. Acceptability of proposed dosage given diversity of dosage regimen given in clinical trials.
4. Limited availability of safety data in the proposed indicated population.

Proposed action

The Delegate was unable to provide a preliminary opinion regarding approval at this time. The Delegate sought the advice of the Advisory Committee on Medicines (ACM) regarding the issues raised in the overview

Request for ACM advice

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

1. Does the committee feel that there is a sufficient level of evidence for both safety and efficacy in the current dossier to support registration of dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph⁺ ALL) integrated with chemotherapy?
2. Balanced against the level of data presented in the current submission, limited data allowing direct comparison with imatinib, and limited safety dataset in the first line setting; is the committee satisfied with the wording of the current proposed indication? In particular, could the committee discuss whether there is sufficient evidence to support this indication versus including additional wording limiting dasatinib use for first line Ph⁺ ALL in patients who are ineligible for imatinib (or for whom imatinib is not clinically appropriate)?
3. Does the ACM consider that a specific statement under DRUG INTERACTIONS is required regarding dasatinib use with multi-agent chemotherapy regimens?
4. Does the committee consider that the propose dose of 100 mg dasatinib for the treatment of newly diagnosed Ph⁺ ALL is acceptable? Is the wording of the Dosage and Administration section of the PI appropriate in regards to first line treatment of Ph⁺ ALL for induction and consolidation/maintenance?

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

Response from sponsor

The sponsor welcomes the clinical evaluator's recommendation for 'approval of dasatinib for first line treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph⁺ ALL) in adults' and provides further clarifying information relating to the Delegate's request for advice from the ACM.

In addition to the currently approved indications, the proposed new indication is:

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy.

Ph⁺ ALL is a severe and rare disease which is orphan designated in Australia. It is even more rare in the subset of adult patients with less than 35 diagnosed annually in Australia. As such, the available evidence for efficacy and safety, based on published data in more than 400 adult patients of which 247 were in pivotal, Phase II trials, submitted in support of this application, provides a relatively large body of evidence to support this indication.

The submitted pivotal data demonstrates that dasatinib achieved similar, consistent and clinically meaningful efficacy outcomes when compared with the outcomes reported for imatinib and the safety profile was unchanged when compared to the currently registered safety profile of dasatinib. While the level of evidence is limited to Phase II, uncontrolled studies, there is established precedence for such data to be considered appropriate for registration of a rare indication, where the outcomes are considered clinically meaningful and consistent and the safety profile can be adequately managed by an experienced clinician.

The proposed indication is similar to that registered for imatinib and is considered appropriate for a therapeutic alternative to imatinib, given that dasatinib is a second generation, potent, broad spectrum inhibitor of several tyrosine kinases, including BCR-ABL (blocked by imatinib) and SRC (not blocked by imatinib). Dasatinib also effectively inhibits the growth of leukemic clones harbouring all known imatinib-resistant BCRABL kinase domain point mutations, with the exception of V299L, T315I, and F317L.

Neither the therapeutic basis, nor the clinical evidence presented, provides a rationale for limiting the indication further, to patients who are ineligible for imatinib, or for whom imatinib is inappropriate. Further, there are no clinically established criteria for identifying such patients. The proposed dosing regimen of 100 mg once daily is supported by the available evidence as stated by both the Delegate and clinical evaluator and allows for dose adjustment for management of toxicities.

Sponsor comments on advice sought by the TGA delegate from ACM

- 1. Does the committee feel that there is a sufficient level of evidence for both safety and efficacy in the current dossier to support registration of dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy?*

Ph⁺ ALL in adults is a very rare and severe condition, supported by its orphan designation (~ 35 patients diagnosed annually in Australia). As such the submitted body of evidence, based on published data, of over 400 newly diagnosed adult patients with Ph⁺ ALL treated with dasatinib is sufficient to enable an adequate assessment of the benefits and risks of the treatment and should be assessed in this context. It is acknowledged that the available pivotal efficacy studies in 247 newly diagnosed adult Ph⁺ ALL patients are limited to four Phase II uncontrolled studies, which have inherent design bias. However, there is well established precedent of regulatory approvals based on open label, single arm studies in the oncology setting for very rare diseases, where the achieved outcomes are clinically meaningful, and treatment is managed by experienced healthcare professionals with a significant knowledge of the available therapy options, their data limitations and strategies for managing the treatment risks.

The results of these 4 pivotal studies indicate a complete remission (CR) rate during induction of 96% to 100% in all studies, which is consistent if not slightly better than the CR reported with imatinib. The high CR rate enables eligible patients to be progressed to transplant where appropriate in accordance with the standard treatment protocols of the hospital and physician. Please also refer to the Response to questions raised by the Delegate to be addressed by the sponsor: Question 2, below.

The long-term survival estimates for patients treated with dasatinib integrated with a high dose chemotherapy regimen was a 4 year disease free survival (DFS) and

overall survival (OS) of 52% and 51% respectively reported by Yoon et al., (2016);⁷ and 5 year DFS and OS of 44% and 46% respectively reported by Ravandi et al., (2015).⁶ The long term survival estimates for patients treated with dasatinib integrated with low dose chemotherapy regimens was DFS and OS (after 20 months) of 51% and 69% respectively reported by Foa et al., (2015);⁹ and a 5 year event free survival (EFS) and OS of 27% and 36% respectively reported by Rousselot et al., (2016).⁸ The Rousselot data was generated in a predominantly elderly patient population with a median age of 69 and hence is a relatively good long-term outcome considering the advanced age and likely co-morbidities of this study population.

Additionally, the pivotal studies reported a narrower spectrum of mutations in patients with relapsed disease compared to that reported for imatinib. This result is consistent with dasatinib's well documented sensitivity to the majority of imatinib resistant mutations.³¹ The most commonly reported mutations in dasatinib resistant patients were T315I, V299L, F359V and E225K.³¹

The safety profile as described in the pivotal published studies, other supportive studies and case reports, in newly diagnosed Ph⁺ ALL patients treated with dasatinib integrated with chemotherapy is consistent with the known safety profile of dasatinib as monotherapy with no safety signals that would suggest a difference. Dasatinib has been demonstrated to be safe and efficacious when used first-line in newly diagnosed patients with chronic phase CML. Additionally, dasatinib has been approved for over 10 years for use second line in CML and Ph⁺ ALL patients who are resistant or intolerant to prior therapy. As such, there is a vast body of safety data collected over a 10 year post marketing period that helps characterise the risks as well as provide clinical strategies to mitigate and manage these risks.

- 2. Balanced against the level of data presented in the current submission, limited data allowing direct comparison with imatinib, and limited safety dataset in the first-line setting; is the committee satisfied with the wording of the current proposed indication? In particular, could the committee discuss whether there is sufficient evidence to support this indication versus including additional wording limiting dasatinib use for first-line Ph⁺ ALL in patients who are ineligible for imatinib (or for whom imatinib is not clinically appropriate)?*

The sponsor does not consider any additional wording is warranted to further clarify the indication as the evidence submitted demonstrates that the efficacy outcomes with dasatinib integrated with chemotherapy is consistent with the outcomes achieved with imatinib, regardless of imatinib eligibility/appropriateness. As such, it should be registered as an alternative therapy option to imatinib. Limitations in recruitment, given the rare nature of this disease and ethical considerations given the established outcomes with both agents, means that a direct comparison is not feasible.

Responses in Ph⁺ ALL using imatinib-based therapy are often short-lived, and marrow relapse is frequently associated with the selection of point mutations in the BCR-ABL kinase domain (KD), fostered by the high genetic instability of ALL cells.^{31,32} There is also evidence supported by literature that indicates that there are other kinases in addition to

³¹ Soverinin S. et al. 2014 Drug Resistance and BCR-ABL Kinase Domain Mutations in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia From the Imatinib to the Second-Generation Tyrosine Kinase Inhibitor Era. *Cancer* 2014: 1004 -1009.

³² Pfeifer H. et al. Kinase domain mutations of BCR-ABL frequently precede imatinib-based therapy and give rise to relapse in patients with de novo Philadelphia-positive acute lymphoblastic leukemia (Ph⁺ ALL). *Blood*. 2007; 110: 727-734.

BCR-ABL involved in the development of Ph⁺ ALL, particularly SRC kinases, which are not blocked by imatinib.³³

Dasatinib is a second generation, potent, broad spectrum inhibitor of several tyrosine kinases including BCR-ABL and SRC. In vitro, dasatinib has 325 fold greater potency than imatinib for inhibiting BCR-ABL by binding to both active and inactive conformations of c-ABL, whereas imatinib only binds to the inactive state⁴. Dasatinib effectively inhibits the growth of leukemic clones harbouring all known imatinib resistant BCRABL kinase domain point mutations, with the exception of V299L, T315I, and F317L.³⁴

Ph⁺ ALL with CNS involvement is a further treatment complexity, noting that imatinib does not penetrate the CNS where as dasatinib has been shown to penetrate the blood brain barrier in patients with CNS involvement.³⁵

Therefore, there is no plausible scientific reason for restricting the indication for dasatinib to only those patients' ineligible for imatinib.

Further, there are no established criteria for identifying newly diagnosed patients who may not be eligible for imatinib or for whom imatinib is not appropriate.

3. *Does the ACM consider that a specific statement under drug interactions is required regarding dasatinib use with multi-agent chemotherapy regimens?*

The sponsor acknowledges the Delegate's comment confirming acceptance of our reasoning on this issue and the current PI statements as stated in the Delegate's overview. The sponsor does not consider that further statements specific to use with multi agent chemotherapy regimens is warranted in the Sprycel PI for the reasons discussed below.

There is already experience with use of dasatinib with multi agent chemotherapy in newly diagnosed patients via the published dasatinib Ph⁺ ALL clinical studies included in this submission and in second line treatment where dasatinib may be co-administered with dexamethasone and vincristine.

Advice from experienced clinicians is that interactions, while relevant, are not primary clinical considerations in the treatment of newly diagnosed Ph⁺ ALL patients with dasatinib, since the chemotherapy agents to be co-administered with dasatinib first-line are the same as those already used with imatinib.

Both imatinib and dasatinib are primarily metabolised by CYP3A4;³⁶ and details of studies investigating the effects of potent CYP3A4 inhibitors and inducers are already included in the approved Sprycel and Glivec PI documents. Both imatinib and dasatinib are known to have their concentrations affected by CYP3A4 inhibitors and inducers.

Concentrations (AUC) of simvastatin (a CYP3A4 substrate) were increased by 3.5 fold by imatinib and 20% by dasatinib, suggesting imatinib may have a greater effect on CYP3A4 than dasatinib. Precautions regarding administration of imatinib and dasatinib with CYP3A4 substrates, particularly those with a narrow therapeutic index, are already included in the Australian PI documents for both drugs.

Therefore, although there is some evidence that cyclophosphamide, vincristine, doxorubicin and dexamethasone (the drugs comprising the HCVAD regimen) interact with the CYP3A family or CYP3A4 metabolising enzymes, the sponsor believes that the

³³ Hu Y. et al 2004 Requirement of Src kinases Lyn, Hck and Fgr for BCR-ABL1-induced Blymphoblastic leukemia but not chronic myeloid leukemia. *Nat Genet.* 2004; 36: 453-461.

³⁴ Lombardo LJ, et al. 2004 Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem* 2004; 47:6658-6661

³⁵ Porkka et al. 2008 Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood* 2008; 112: 1005-1012.

³⁶ CYP: Cytochrome P450

substantial clinical experience of their co-administration with imatinib, the clinical data included in this submission and the information and precautions already included in the dasatinib Product Information are adequate to address this issue.

Furthermore, no specific precautions are included in the Australian Glivec PI with respect to the use of imatinib together with chemotherapy agents, therefore it follows that no specific precautionary measures are considered necessary when dasatinib is used in the same setting.

A further statement specific to chemotherapy agents in the Sprycel PI is therefore considered unnecessary.

4. *Does the committee consider that the proposed dose of 100 mg dasatinib for the treatment of newly diagnosed Ph⁺ ALL is acceptable? Is the wording of the dosage and administration section of the PI appropriate in regard to first-line treatment of Ph⁺ ALL for induction and consolidation/maintenance?*

The sponsor agrees with the Delegate's statement that the data presented support a dose of 100 mg/day for the first-line treatment of Ph⁺ ALL, with dosing adjustments depending on patient response and tolerability. The clinical evaluator also supported a 100 mg daily as the starting dose, noting in addition that 'the simple truth of treatment with this drug is it will be titrated according to toxicity'. Doses of 100 mg/day (as either 50 mg twice daily or 100 mg once daily) were used as starting doses for both induction and maintenance in 3 of the 4 pivotal clinical studies supporting this application.

Doses of 50 mg twice daily were initially administered during the induction phase in the studies by Ravandi et al., but this was changed by an amendment to the study protocol to 100 mg once daily when further data on the best dose and schedule of dasatinib became available. After the enrolment of the first 42 patients, the protocol was further amended to 100 mg of dasatinib once daily in the first 14 days of the first cycle followed by 70 mg once daily continuously from the second cycle. Patients achieving complete remission continued to receive maintenance dasatinib; initially 50 mg orally twice daily and, after amendment, 100 mg daily. Further dose adjustments during the maintenance phase were made based on clinical effects and tolerability.

Yoon et al.;⁷ used 100 mg once daily during induction, with a dose reduction to 70 mg once daily permitted for significant drug related toxicity. Six of 51 enrolled patients temporarily discontinued therapy. Of these, 4 resumed the drug at 100 mg once daily and 2 resumed at the reduced 70 mg daily dose. Rousselot et al.;⁸ initially used 140 mg/day for all patients in their study, but after 15 months a protocol amendment reduced the dose for patients over 70 years to 100 mg/day to limit patient discontinuation. It was noted in the report that safety of the drug was acceptable, especially after the reduction of dasatinib daily dose from 140 mg to 100 mg/day for these older patients.

The Foa et al., study;⁹ used a dose of 70 mg twice daily co-administered with steroids; dose reduction was permitted for non-haematologic toxicity. Unlike the other studies provided, no systemic chemotherapy other than steroids was administered to patients in this study.

Each of the pivotal studies where treatment was integrated with high intensity systemic chemotherapy used a dasatinib starting dose of 100 mg/day for all or a number of the enrolled patients.

Consistent with the conclusions of the Delegate and the clinical evaluator, a starting dose of 100 mg/day is considered appropriate, allowing for dose adjustments taking into account a patient's clinical response or toxicity.

Response to questions raised by the Delegate to be addressed by the sponsor

1. *The sponsor states that this application is specific to Australia and is not planned for submission in other regulatory jurisdictions. Is there any additional information*

available regarding the rationale for this application in Australia? Has any other regulator provided comment on this application?

As clarified in the clinical overview to this application a global development program for dasatinib as first-line therapy is not planned, as patients in various other markets already have access to the treatment first line. For example, dasatinib is recommended for use as first line treatment in the EU via the European Society for Medical Oncology (ESMO) clinical practice guideline for ALL in adults and the US via the National Comprehensive Cancer Network (NCCN) guidelines and is reimbursed via relevant insurance schemes. As access in Australia is facilitated by TGA approval a regulatory application is required, as a first step, to ensure all Australian patients also have access to the medicine as a first-line treatment. Furthermore, this ensures appropriate approved prescribing information is available to clinicians.

As a similar application has not been submitted elsewhere at present, no other regulatory agency advice is available.

- 2. Whilst comparison to other therapies is difficult, please comment on the paper by Ravandi (2017) which indicates that the rate of allo-HCT in the studies by Foá et al., and Ravandi et al., may be lower than that for other tyrosine kinase inhibitors in frontline therapy (note: the TGA acknowledges that the study by Rousellot et al., is an older cohort of patients, thus likely accounting for the lower rate of allo-HCT).*

Firstly, it is relevant to note that the Ravandi (2017) publication is an educational paper presented at a recent American Society of Hematology (ASH) symposium. Its objective is to review the available published data on TK inhibitors for educational purposes and consider the available treatment options for minimising chemotherapy and allo-HCT where possible for optimal patient outcomes.

The role of transplantation in the current treatment algorithms and standard of care for Ph⁺ ALL is evolving and as stated in the Ravandi (2017) publication, clinicians are investigating alternative treatment options, especially in patients with a deep molecular response to induction therapy, those not eligible for transplantation and older adults.

It is not possible to draw conclusions from the tabulated summary of information on selected trials in the Ravandi (2017) publication (see Table 8, above) by comparing the percentage of patients progressing to allo-HCT in the listed trials. To progress to allo-HCT, patients not only need to be in remission but need to have a sibling or matched donor available and to be fit for transplant. In all of the trials listed, the inclusion criteria, patient demographics, treatment regimen (dosage, consolidation versus non consolidation), pre-trial treatment, transplant protocol and other factors impacting on the decision to progress to transplant (for example age, donor, BCR-ABL transcript) differ. An appropriate comparison would only be possible via a randomised clinical trial comparing the different TK inhibitors plus intensive/low-intensity or steroid backbone.

More importantly, the best assessment of efficacy based on the data reported in Table 8 of the Ravandi (2017) publication are the endpoints of relapse free survival (RFS) and overall survival (OS) over comparable follow up periods, regardless of transplantation status. This data is not intended to demonstrate a relationship between rate of progression to allo-HCT and long term RFS or OS for either imatinib or dasatinib nor does it appear to show one. At face value and taking into consideration the limitations of such a comparison as discussed above, the rate of allo-HCT in the Foa et al., and Ravandi et al., studies do not appear to translate to detrimental long term RFS or OS outcomes.

New information available via a recent paper by Yu et al., (2017);³⁷ provides further insight on the question raised by the Delegate. The publication reports on a single centre study comparing the efficacy of first and second generation TK inhibitors in combination with chemotherapy in the first line treatment of Ph⁺ ALL. Seventy-seven (77) patients were enrolled and treated first line with TK inhibitors. Patients were grouped based on first (imatinib) versus second generation (dasatinib, nilotinib) TK inhibitor treatment: 45 on imatinib (43 at the dose of 400 mg daily), 30 on dasatinib (20/30 at the dose of 100 mg daily) and 2 on nilotinib. Fifty-three of 77 patients received allo-HCT.

Compared to patients receiving the first generation TK inhibitor (imatinib), the authors noted a trend toward better disease free survival (DFS) in patients being treated with the second generation TK inhibitors (p = 0.088), although this difference was not statistically significant. The OS was comparable between the two groups (p = 0.210). The univariate and multivariate analysis further suggested that upfront treatment with the second generation TK inhibitors could improve long term survival (see Table 11; reproduced from Table 4 of the publication).

Table 11: The risk factors for DFS and OS in Ph+ ALL; reproduced from Yu G et al., (2017)³⁷

	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Univariate factors ^a						
Gender (male vs. female)	1.99	0.76-5.25	0.163	0.91	0.35-2.39	0.851
Age (≥35y vs. <35y)	1.30	0.58-2.92	0.523	2.50	1.01-6.18	0.048
WBC (≥1000×10 ⁹ /l vs. <100×10 ⁹ /l)	1.17	0.51-2.67	0.712	1.00	1.00-1.01	0.279
EGIL classification (BAL vs. ALL)	1.48	0.43-5.09	0.538	2.80	0.72-10.83	0.136
ACA (with vs. without)	0.81	0.37-1.78	0.598	1.20	0.50-2.90	0.687
BCR/ABL1 (P210 vs. P190)	0.65	0.24-1.76	0.394	0.60	0.21-1.75	0.352
ABL1 gene mutations (yes vs. no)	0.82	0.27-2.48	0.727	0.82	0.31-2.20	0.697
The generation of TKI (2 nd vs. 1 st)	0.34	0.12-0.92	0.034	0.42	0.42-3.56	0.069
Allo-HSCT (with vs. without)	0.31	0.13-0.75	0.010	0.38	0.16-0.93	0.034
Multivariate factors ^c						
The generation of TKI (2 nd vs. 1 st)	0.40	0.18-0.91	0.030	0.41	0.18-0.93	0.033
Allo-HSCT (with vs. without)	0.23	0.10-0.49	<0.001	0.24	0.11-0.51	<0.001

Pertinent to the question raised by the Delegate, for patients who underwent allo-HCT, there were better outcomes in both DFS (p = 0.050) and OS (p = 0.048) for patients treated first-line with the second generation TK inhibitors compared to those on the first generation TK inhibitors. The authors conclude, that first-line treatment of newly diagnosed Ph⁺ ALL patients with the second generation TK inhibitors, especially dasatinib, is as effective and safe as imatinib and that first line treatment of Ph⁺ ALL patients with second generation TK inhibitors might benefit patients with better survival when allo-HCT was incorporated as consolidation therapy following first complete remission.

In conclusion, the decision to progress patients to allo-HCT following first complete remission during induction, is a complex decision based on multiple factors and best explained in the expert statement provided by [Information redacted]. Dr [information redacted] states:

“The decision with respect to allogeneic stem cell transplantation in Ph⁺ ALL remains a complicated one, and should not be driven solely by the TK inhibitor received.

³⁷ Yu G et al., (2017) Upfront treatment with the first and second-generation tyrosine kinase inhibitors in Ph-positive acute lymphoblastic leukemia *Oncotarget* 2017; 8: 107022-107032

Factors such as age, patient fitness, donor availability, remission status (first versus second or subsequent) along with molecular response all drive the decision making for allogeneic stem cell transplant.

As patients with a deep molecular response may do well in the absence of transplantation, as the risks of allogeneic stem cell transplantation increase with age, it may be reasonable to withhold transplantation, in those who attain a deep molecular response, in first remission, and to consider it either at molecular relapse or in second remission.

This is irrespective of the TK inhibitor received, though what limited (and retrospective) data there is suggests that early molecular responses may be superior to imatinib with second generation tyrosine kinase inhibitor thus allowing more patients to potentially pursue this strategy.'

Advisory Committee Considerations³⁸

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

The ACM taking into account the submitted evidence of efficacy, safety and quality, the ACM considered the Sprycel tablet containing 20 mg, 50 mg, 70 mg and 100 mg of Dasatinib to have an overall positive benefit-risk profile for the newly proposed indication:

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy

While the current approved indications are as follows:

- *Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph⁺) chronic myeloid leukaemia in the chronic phase.*
- *Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.*
- *Sprycel is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.*

The Delegate was unable to provide a preliminary opinion regarding approval at this time and sought the advice of the ACM regarding the issues raised in this overview.

Proposed conditions of registration

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

³⁸ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

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

1. *Does the committee feel that there is a sufficient level of evidence for both safety and efficacy in the current dossier to support registration of dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy?*

Yes, the committee advised that there is a sufficient level of evidence for both safety and efficacy in the current dossier to support the registration of dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy. However, the committee noted the limited clinical data available for dasatinib from Phase II trials, and there is no data available as Phase III trials.

2. *Balanced against the level of data presented in the current submission, limited data allowing direct comparison with imatinib, and limited safety dataset in the first line setting; is the committee satisfied with the wording of the current proposed indication? In particular, could the committee discuss whether there is sufficient evidence to support this indication versus including additional wording limiting dasatinib use for first line Ph+ ALL in patients who are ineligible for imatinib (or for whom imatinib is not clinically appropriate)?*

The ACM was satisfied with the wording of the current proposed indication, as it is consistent with the level of data presented in the current submission, limited data allowing for direct comparison with imatinib, and limited safety dataset in the first line setting. Furthermore, the committee recommended first line use dasatinib to be provided as an option for patients with Ph+ ALL at the discretion of the clinician and the patient circumstances. The committee did not feel that it was appropriate to limit first line use of dasatinib to patients who are ineligible for imatinib, or for whom imatinib is not clinically appropriate.

3. *Does the ACM consider that a specific statement under drug interactions is required regarding dasatinib use with multi-agent chemotherapy regimens?*

The ACM agreed that there was merit in including a specific statement under drug interactions regarding dasatinib use with multi-agent chemotherapy regimens given the complexity of Ph+ ALL therapies and the deficiencies of safety data.

4. *Does the committee consider that the propose dose of 100 mg dasatinib for the treatment of newly diagnosed Ph+ ALL is acceptable? Is the wording of the Dosage and Administration section of the PI appropriate in regards to first line treatment of Ph+ ALL for induction and consolidation/maintenance?*

The ACM considers the proposed dose of 100 mg dasatinib for the treatment of newly diagnosed Ph+ ALL to be acceptable and supported by the available evidence. However the committee advised the inclusion of the phrase 'as clinically appropriate' in brackets to allow for the discretion of clinicians to modify dosing due to differences in patient characteristics. Furthermore, in relation to the dose escalation to 140 mg the committee proposes to remove the word 'once' from dosage scheduling to allow for split dosing where clinically appropriate.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sprycel dasatinib 20 mg, 50 mg, 70 mg and 100 mg tablet, indicated for:

Sprycel is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy

The full indications are now:

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase.

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.

Sprycel is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy.

Specific conditions of registration applying to these goods

- The Sprycel EU-Risk Management Plan (EU-RMP), version 14.0, dated 20 July 2016, DLP 12 November 2015 with Australian Specific Annex (version 5.0, dated 22 September 2017) included with submission PM-2016-04272-1-4, and any subsequent revisions, to be revised to the satisfaction of the TGA will be implemented in Australia.

Attachment 1. Product Information

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

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