6.20 PONATINIB
Tablet 15 mg (as hydrochloride),
Tablet 45 mg (as hydrochloride),
Iclusig®, Specialised Therapeutics Australia Pty Ltd.

1 Purpose of Application

1.1 The minor submission requested Authority Required listing for ponatinib for patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in patients who have failed or are intolerant to dasatinib but do not have the T315I mutation.

2 Background

2.1 Ponatinib was recommended for listing at the July 2015 PBAC meeting for

- the treatment of chronic myeloid leukaemia (CML) in (i) Patients who have failed first line therapy with imatinib or dasatinib or nilotinib and whose CML has the T315I mutation; (ii) Patients with CML where both nilotinib and dasatinib have failed or where one of nilotinib or dasatinib has failed and the patient is intolerant of the other drug; and
- the treatment of relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in patients whose ALL has the T315I mutation. The PBAC considered that the cost-effectiveness of ponatinib would be acceptable when benchmarked against the costs of dasatinib and nilotinib, with adjustments required to account for the toxicity of the treatments. The equi-effective doses were considered to be ponatinib 30.2 mg daily, dasatinib 102 mg daily and nilotinib 797 mg daily.

2.2 The submission considered at the July 2015 PBAC meeting had requested listing for treatment of adult patients with relapsed or refractory BCR-ABL positive acute lymphoblastic leukaemia (Ph+ ALL), with or without the T315I mutation. The PBAC considered that there was a clinical need for treatments of Ph+ ALL patients without the T315I mutation however, based on the evidence provided, the PBAC considered that they could not recommend approval for ponatinib in Ph+ ALL without the T315I mutation. The PBAC noted that they would welcome additional quality evidence of the benefit of ponatinib in Ph+ ALL patients without the T315I mutation to facilitate any future reconsideration.

3 Requested listing

3.1 The minor submission requested the following listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PONATINIB				
15 mg tablet, 60	60	2	$5758.13	Iclusig Specialised Therapeutics Australia Pty Ltd
45 mg tablet, 30	30	2	$6477.57	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Acute
Condition:	Lymphoblastic leukaemia
PBS Indication:	Acute lymphoblastic leukaemia
Treatment phase:	Initial
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have failed treatment with PBS-subsidised dasatinib for this condition; *OR* Patient must have developed intolerance to PBS-subsidised dasatinib of a severity requiring treatment withdrawal
Prescriber Instructions	Failure of treatment is defined as either: 1. Failure to achieve a complete morphological and cytogenetic remission after a minimum of 2 months treatment with intensive chemotherapy and imatinib AND dasatinib; 2. Morphological or cytogenetic relapse of leukaemia after achieving a complete remission induced by chemotherapy and imatinib AND dasatinib; 3. Morphological or cytogenetic relapse or persistence of leukaemia after allogeneic haemopoietic stem cell transplantation. Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (greater than 5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission.

Administrative Advice	The authority application must be made in writing and must include: 1. a completed authority prescription form; and 2. a completed Acute Lymphoblastic Leukaemia ponatinib PBS Authority Application - Supporting Information Form; and 3. a signed patient acknowledgement; and 4. a pathology report demonstrating that the patient has active acute lymphoblastic leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of BCR-ABL transcript. The date of the relevant pathology report(s) need(s) to be provided Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	Acute
Condition:	Lymphoblastic leukaemia
PBS Indication:	Acute lymphoblastic leukaemia
Treatment phase:	Continuing
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must not have progressive disease.
Administrative Advice	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

For more detail on PBAC's view, see section 5 PBAC outcome

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments emphasised the clinical need for ponatinib in patients who do not respond to current PBS-listed treatments.

Current situation

4.3 The current minor submission did not present new data for the use of ponatinib in the treatment of refractory Ph+ALL, but considered that further scrutiny of existing data demonstrated that the treatment benefit in patients with and without the T315I mutation is comparable.

4.4 The minor resubmission noted that the uptake of ponatinib has been below what was forecast in the July 2015 submission (see table 6 of the minor resubmission), and provided the following estimate of utilisation for Ph+ ALL patients without the T315I mutation in Table 1.

Table 1. Estimated utilisation of Iclusig for Ph+ ALL patients without the T315I mutation

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Population eligible for treatment					
New Ph+ ALL patients diagnosed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients failing 2nd line TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Refractory Patients (excluding T315I)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Patients receiving Iclusig	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS Services for Iclusig					
Total 15 mg scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total 45 mg scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of prescriptions/packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS for Iclusig					
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 7, p10 of the minor resubmission

The redacted table shows that at year 5, the net cost to the PBS would be less than $10 million per year.

5 PBAC Outcome

5.1 The PBAC recommended amending the current ponatinib restriction for relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) to include patients without the T315I mutation who have failed or are intolerant to dasatinib noting that the patient population of the requested extension is small.

5.2 The PBAC reiterated its view that there is a clinical need for treatments of Ph+ ALL patients without the T315I mutation.

5.3 The PBAC noted that the submission did not provide any new data for the use of ponatinib in the treatment of refractory Ph+ ALL. However, the PBAC considered that there is emerging evidence in the public domain confirming the activity of ponatinib in Ph+ ALL irrespective of T315I mutation expression.

5.4 The PBAC noted that while ponatinib was associated with a higher frequency of cardiovascular events compared with other tyrosine kinase inhibitors, it considered that clinicians are well aware of these risks. The PBAC were therefore satisfied that ponatinib would be prescribed appropriately to patients with limited treatment options, such as after the failure of dasatinib.

5.5 In light of its consideration of extending the current ponatinib restriction, the PBAC considered that the proposed restriction no longer aligned with current treatment guidelines. The PBAC further noted that the ponatinib restriction was based on the dasatinib restriction for Ph+ ALL. The PBAC advised that both the ponatinib and dasatinib restrictions should be updated to align with current treatment guidelines and their respective places in therapy. The PBAC requested that the Department seek advice from the Haematology Society of Australia and New Zealand (HSANZ) regarding the appropriate place in therapy for dasatinib in the treatment of Ph+ ALL to ensure that the restriction properly captures the intended patient population. The PBAC can finalise the wording of the restriction for ponatinib after receiving this advice, and making appropriate adjustments to the dasatinib restriction.

5.6 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Amend existing listing as follows:

Restrictions to be finalised

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

Specialised Therapeutics wishes to thank the members of the PBAC for considering our application. This positive recommendation will be well received by all patients with Ph+ ALL disease who will now have a new treatment available to them.

Addendum to the November 2017 PBAC Minutes:

12. PONATINIB Tablet 15 mg (as hydrochloride), Tablet 45 mg (as hydrochloride), Iclusig®, Specialised Therapeutics Australia Pty Ltd.

9 Current situation

9.1 The HSANZ's advice was subsequently received in early March 2018 and was considered by the PBAC at its April 2018 Special Meeting. The HSANZ welcomed and endorsed the PBAC recommendation to extend the listing of ponatinib for relapsed/refractory Ph+ALL to include all patients, regardless of T315I mutation status, who have failed or are intolerant to dasatinib. The HSANZ considered that the proposed alteration of the ponatinib listing, in addition to implied agent sequencing, appeared concordant with current NCCN clinical guidelines.

9.2 The HSANZ also requested a number of changes in their advice as follows:

a. That the restriction of imatinib to be in combination with intensive chemotherapy be broadened to chemotherapy or corticosteroid therapy.
b. That the limit of 2 years for continuing treatment with imatinib be removed.
c. The requirement for second line TKI therapy to be the sole-PBS therapy be removed
d. That consideration be given to allow the use of a second generation TKI in the setting of initial therapy for Ph+ acute lymphoblastic leukaemia, depending on comparative drug cost.

10 PBAC recommendation

10.1 The PBAC reiterated its view from the November 2017 meeting that there is a clinical need for treatments of Ph+ ALL patients without the T315I mutation. The PBAC

considered that ponatinib can be used as a second or third line therapy in the treatment of Ph+ ALL.

10.2 The PBAC thanked HSANZ for their helpful summary of guidelines and suggested general changes that would better align restrictions for currently listed TKIs for this condition with guidelines. With respect the restriction for imatinib in first line, the PBAC agreed to the requested change of an inclusion of corticosteroid therapy in the current restriction wording for imatinib for the Ph+ ALL indication. This should now state that 'The treatment must be in combination with chemotherapy or corticosteroids'.

10.3 The PBAC noted that not all the HSANZ requests provided adequate levels of evidentiary support to enable the PBAC to make recommendations, particularly extending the use of very high cost TKIs indefinitely following 2 years of first line therapy. The PBAC therefore did not agree to the requested removal of the limit of 2 years for continuing treatment with a TKI as first line therapy for ALL, but welcomes evidence that could inform further consideration of its cost-effectiveness. The PBAC also did not agree to the requested removal of the requirement for second line TKI therapy to be as the sole PBS therapy.

10.4 The PBAC noted that the sponsor of ponatinib had requested a grandfather arrangement for ponatinib for Ph+ ALL patients without the T315I mutation in correspondence to the Department. The PBAC noted that the sponsor forecasted fewer than [redacted] patients would need to be grandfathered. The PBAC recommended a grandfather arrangement with the same PBS restriction criteria as the PBS population.

10.5 Regarding the requested change of allowing use of a second generation TKI in the first line setting for Ph+ ALL, the PBAC considered that the evidence did support the use of dasatinib in combination with chemotherapy as an alternative to the use of imatinib plus chemotherapy. In this setting, a price reduction for dasatinib would be required for it to be cost effective. The PBAC requested that the Department to write to the sponsor of dasatinib to invite a submission with a proposal on dosing and price for first line therapy in Ph+ ALL, in combination with chemotherapy or corticosteroid therapy.

10.6 The PBAC further considered that changes would need to be made to the Ph+ ALL restrictions for imatinib, dasatinib and ponatinib in a coordinated fashion in order to minimise clinical confusion for prescribers and patients should dasatinib, in combination with chemotherapy or corticosteroid therapy, be approved for use as first line therapy in Ph+ALL.

11 Recommended listing

11.1 Extend the listing of ponatinib to include the following new indication:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PONATINIB				
15 mg tablet, 60	60	2		Iclusig Specialised Therapeutics Australia Pty Ltd
45 mg tablet, 30	30	2		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Acute
Condition:	Lymphoblastic leukaemia
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Initial treatment
Restriction Level / Method:	☒Authority Required - In Writing
Clinical criteria:	The condition must be expressing the Philadelphia chromosome; OR The condition must have the transcript BCR-ABL, AND Patient must have failed prior treatment with PBS-subsidised dasatinib for this condition OR Patient must have developed intolerance to PBS-subsidised dasatinib of a severity requiring treatment withdrawal AND The treatment must be the sole PBS-subsidised therapy for this condition
Prescriber Instructions	Failure of treatment with dasatinib is defined as either: 1. Failure to achieve a complete morphological and cytogenetic remission after a minimum of 2 months treatment with PBS-subsidised dasatinib for this condition; or 2. Morphological or cytogenetic relapse of leukaemia after achieving a complete remission induced by PBS-subsidised dasatinib for this condition; or 3. Rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (greater than 5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission; Or rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. The authority application must be made in writing and must include: 1. a completed authority prescription form; and 2. a completed Acute Lymphoblastic Leukaemia ponatinib PBS Authority Application -

	Supporting Information Form; and 3. a signed patient acknowledgement; and 4. a pathology report demonstrating that the patient has active acute lymphoblastic leukaemia, manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of BCR-ABL transcript. The date of the relevant pathology report(s) need(s) to be provided; or 5. pathology reports documenting rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. The date of the relevant pathology report(s) need(s) to be provided
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Acute
Condition:	Lymphoblastic leukaemia
PBS Indication:	Acute lymphoblastic leukaemia (ALL)
Treatment phase:	Initial treatment – grandfather treatment
Restriction Level / Method:	☒Authority Required - In Writing
Clinical criteria:	Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to 1 month year. AND The condition must be expressing the Philadelphia chromosome; OR The condition must have the transcript BCR-ABL, AND Patient must have failed prior treatment with PBS-subsidised dasatinib for this condition OR Patient must have developed intolerance to PBS-subsidised dasatinib of a severity requiring treatment withdrawal

	AND The treatment must be the sole PBS-subsidised therapy for this condition
Prescriber Instructions	Failure of treatment with dasatinib is defined as either: 1. Failure to achieve a complete morphological and cytogenetic remission after a minimum of 2 months treatment with PBS-subsidised dasatinib for this condition; or 2. Morphological or cytogenetic relapse of leukaemia after achieving a complete remission induced by PBS-subsidised dasatinib for this condition; or 3. Rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (greater than 5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission; Or rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. The authority application must be made in writing and must include: 1. a completed authority prescription form; and 2. a completed Acute Lymphoblastic Leukaemia ponatinib PBS Authority Application - Supporting Information Form; and 3. a signed patient acknowledgement; and 4. a pathology report demonstrating that the patient had active acute lymphoblastic leukaemia, manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of BCR-ABL transcript at the time treatment with ponatinib was initiated. The date of the relevant pathology report(s) need(s) to be provided; or 5. pathology reports documenting rising levels of BCR-ABL1 transcript on two consecutive occasions in a patient in complete remission while being treated with PBS-subsidised dasatinib for this condition. The date of the relevant pathology report(s) need(s) to be provided.
Administrative Advice	Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Acute
Condition:	Lymphoblastic leukaemia
PBS Indication:	Acute lymphoblastic leukaemia
Treatment phase:	Continuing treatment
Restriction Level / Method:	☒Authority Required - Telephone
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must not have progressive disease while being treated with this drug for this condition.
Administrative Advice	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

11.2 Amend the listing of imatinib for ALL to allow combination use with chemotherapy or corticosteroids as follows:

Replace the clinical criteria of:
"The treatment must be in combination with chemotherapy."

With the clinical criteria:
"The treatment must be in combination with chemotherapy ***or corticosteroids***"

12 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

13 Sponsor's Comment

The sponsor had no comment.