AUSTRALIAN PRODUCT INFORMATION

ICLUSIG® (PONATINIB HYDROCHLORIDE)

WARNING: ARTERIAL OCCLUSION, VENOUS THROMBOEMBOLISM, HEART FAILURE, HYPERTENSION AND HEPATOTOXICITY

- **Arterial occlusions have occurred in 23% of ICLUSIG-treated patients at 4 years follow-up in the pivotal trial, resulting in fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease (sometimes resulting in amputation), vision loss, and the need for urgent revascularisation procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of arterial occlusion. Interrupt or stop ICLUSIG immediately for arterial occlusion**
- **Venous thromboembolism has occurred in 6% of ICLUSIG-treated patients at 4 years follow-up in the pivotal trial. Monitor for evidence of thromboembolism. Interrupt or stop ICLUSIG immediately for vascular occlusion**
- **Heart Failure, including fatalities, occurred in 9% of ICLUSIG-treated patients at 4 years follow-up in the pivotal trial. Monitor cardiac function. Interrupt or stop ICLUSIG for new or worsening heart failure**
- **Hypertension, including hypertensive crisis, has been observed in ICLUSIG-treated patients (31% overall, 12% grade 3 or 4) at 4 years follow-up in the pivotal trial**
- **Hepatotoxicity and fatal hepatic failure have occurred in ICLUSIG-treated patients. Monitor hepatic function. Interrupt ICLUSIG if hepatotoxicity is suspected**

See Section 4.4 Special Warning and Precautions for Use – Arterial Occlusion, Venous Thromboembolism, Heart Failure, Hypertension and Hepatotoxicity

1 NAME OF THE MEDICINE

Ponatinib (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ponatinib hydrochloride equivalent to 15 or 45 mg ponatinib.

Excipients with known effect: Lactose monohydrate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ICLUSIG tablets are available as white, round, film-coated tablets for oral administration.
15 mg film-coated Tablet: White, biconvex, round film-coated tablet that is approximately 6 mm in diameter, with "A5" debossed on one side.

45 mg film-coated Tablet: White, biconvex, round film-coated tablet that is approximately 9 mm in diameter, with "AP4" debossed on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ICLUSIG is indicated for the treatment of adult patients with:

- Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia whose disease is resistant to, or who are intolerant of at least two prior tyrosine kinase inhibitors; or where there is a T315I mutation.

- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) whose disease is resistant to, or who are intolerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or where there is a T315I mutation.

Therapy with ICLUSIG should be initiated and monitored by a haematologist with expertise in managing adult leukaemias.

4.2 DOSE AND METHOD OF ADMINISTRATION

The following laboratory tests and observations are recommended to monitor for haematologic and non-haematologic adverse reactions that would require dose modifications while taking ICLUSIG.

Monitor the following	**Monitoring Recommendation**
Complete Blood Counts	Obtain every 2 weeks for the first 3 months and then monthly or as clinically indicated and adjust the dose as recommended.
Serum Lipase	Check every 2 weeks for the first 2 months and then regularly thereafter.
Liver function	Monitor at baseline, at least monthly, or as clinically indicated.
Thromboembolism	Monitor for evidence of thromboembolism and vascular occlusion, including ocular toxicities.
Cardiac Function	Monitor cardiac function and monitor patients for signs and symptoms consistent with heart failure and treat as clinically indicated. Measurement of a baseline QT is recommended prior to commencing ICLUSIG.
Cardiovascular status	Monitor cardiovascular status and optimise cardiovascular therapy during treatment.
Hypertension	Monitor blood pressure at every visit and treat hypertension to normalise blood pressure.
Haematological and cytogenetic response	Monitor patients for major or complete haematological response to therapy.

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with ICLUSIG.

The recommended starting dose of ICLUSIG is 45 mg once daily, taken at the same approximate time each day. ICLUSIG may be taken with or without food. For the standard dose of 45 mg once daily, a 45 mg film-coated tablet is available. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

Caution should be exercised and a reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A inhibitors (see Section 4.5 Interactions with other Medicines and other forms of Interactions - Substances that may increase ponatinib serum concentrations).

A starting dose of 30 mg is recommended in patients with hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use – Hepatic Impairment and Section 4.2 Dose and Method of Administration – Patients with Hepatic Impairment).

Consider reducing the dose of ICLUSIG to 30 mg or 15 mg for chronic phase (CP) CML patients who have achieved a major cytogenetic response, especially in subjects at risk of vascular adverse events.

Although late responses may be observed, consider discontinuing ponatinib if a haematologic response has not occurred by 3 months (90 days) especially in subjects at risk of vascular adverse events.

Concomitant use of ICLUSIG with anticoagulants and/or anti-platelet agents should be approached with caution in patients who may be at risk of bleeding. Formal clinical studies evaluating the co-administration of ICLUSIG with these medications have not been conducted.

Dose adjustments or modifications

Dose modifications should be considered for the management of treatment toxicity. For a dose of 30 mg or 15 mg once daily, 15 mg film-coated tablets are available.

Myelosuppression

Haematologic support, such as platelet transfusion and haematopoietic growth factors, can be used during treatment if clinically indicated.

Dose modifications for neutropenia (ANC* < 1.0 x 10^9/L) and thrombocytopenia (platelets < 50 x 10^9/L) that are unrelated to leukaemia are summarised in Table 1.

Table 1 Dose modifications for myelosuppression

ANC* < 1.0 x 10^9/L or platelets < 50 x 10^9/L	First occurrence: • Withhold ICLUSIG and resume initial 45 mg dose after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
	Second occurrence: • Withhold ICLUSIG and resume at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L
	Third occurrence: • Withhold ICLUSIG and resume at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L

*ANC = absolute neutrophil count

Non-haematological adverse reactions

If a severe non-haematological adverse reaction occurs, treatment should be withheld. After the event is resolved or attenuated in severity, ICLUSIG may be resumed at the same dose or at a reduced dose according to initial grade of the adverse reaction.

Arterial occlusion and Venous thromboembolism

In a patient suspected of developing an arterial occlusive event or venous thromboembolism, ICLUSIG should be immediately interrupted. A benefit-risk consideration should guide a decision to restart ICLUSIG therapy (see Section 4.4 Special Warnings and Precautions for Use – Arterial Occlusion and Venous Thromboembolism) after the event is resolved.

Hypertension may contribute to risk of arterial thrombosis and occlusions, including renal artery stenosis. ICLUSIG treatment should be temporarily interrupted if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

Pancreatitis and/or elevated serum lipase

Recommended modifications for pancreatic adverse reactions are summarised in Table 2.

Table 2 Dose modifications for pancreatitis and elevation of lipase/amylase

Asymptomatic Grade 2 pancreatitis and/or elevation of lipase/amylase	Continue ICLUSIG at the same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN*) only	Occurrence at 45 mg:

	• Withhold ICLUSIG and resume at 30 mg after recovery to ≤ grade 1 (≤ 1.5 x ULN) Occurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 (≤ 1.5 x ULN) Occurrence at 15 mg: • Consider discontinuing ICLUSIG
Grade 3 pancreatitis	Occurrence at 45 mg: • Withhold ICLUSIG and resume at 30 mg after recovery to ≤ grade 1 Occurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 Occurrence at 15 mg: • Consider discontinuing ICLUSIG
Grade 4 pancreatitis	Discontinue ICLUSIG

*ULN = Upper Limit of Normal

For patients whose adverse reactions are resolved, escalation of the dose back to the patient's former dose should be considered, if clinically appropriate.

Hepatic Toxicity

Recommended modifications for hepatic toxicity are summarised in Table 3.

Table 3 Recommended Dose Modifications for Hepatic Toxicity

Elevation of liver transaminase > 3 x ULN* (grade 2, persistent (> 7 days) grade 2 or higher)	Occurrence at 45 mg: • Interrupt ICLUSIG and monitor hepatic function • Resume ICLUSIG at 30 mg after recovery to ≤ grade 1 (≤ 3 x ULN) Occurrence at 30 mg: • Interrupt ICLUSIG and resume at 15 mg after recovery to ≤ grade 1 Occurrence at 15 mg: • Discontinue ICLUSIG
Elevation of AST or ALT ≥ 3 x ULN concurrent with an elevation of bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	Discontinue ICLUSIG

*ULN = Upper Limit of Normal for the lab

Patients with Hepatic impairment

Caution is recommended when administering ICLUSIG to patients with moderate to severe hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use – Hepatic Impairment). Doses above 30 mg have not been tested in patients with hepatic impairment. Therefore, a starting dose of 30 mg is recommended.

Patients with Renal impairment

ICLUSIG has not been studied in patients with renal impairment. Renal excretion is not a major route of ponatinib elimination. The potential for moderate or severe renal impairment to affect renal elimination has not been determined. Caution is recommended when administering ICLUSIG to patients with moderate to severe renal impairment (i.e. an estimated Glomerular Filtration Rate [eGFR] < 60 mL/min/1.73m^2) or end-stage renal disease (i.e. on dialysis, or eGFR of <15 mL/min/1.73m^2 not on dialysis).

Missed Dose

If a dose is missed, the patient should not take an additional dose. In this case, the patient should take the usual dose at the next scheduled time.

Method of administration

The tablets should be swallowed whole. Patients should not crush or dissolve the tablets. ICLUSIG may be taken with or without food.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Arterial Occlusion

Arterial occlusions, resulting in fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease (sometimes resulting in amputation), vision loss, and the need for urgent revascularisation procedures, have occurred in ICLUSIG-treated patients. Renal artery stenosis, associated with worsening, labile or treatment-resistant hypertension, has occurred in some ICLUSIG-treated patients. In the pivotal study, patients with recent (i.e., within the past 3 months) myocardial infarction or unstable angina were excluded from the trial. Patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced arterial occlusive events. Arterial occlusion and occlusive events were more frequent with increasing age and in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia. The dose intensity-safety relationship indicated that there are significant increases in adverse events over the dose range of 15 to 45 mg once-daily, including vascular occlusion and arterial thrombosis. In the phase 2 trial, with a minimum of 48 cycles (1 cycle = 28 days) follow-up for all ongoing patients, arterial occlusive adverse reactions have occurred in 23% (104/449) of patients, and serious arterial occlusive adverse reactions occurred in 18% (83/449) of patients. In a phase 1 trial in patients with advanced leukaemia 28/81 patients (35%) experienced arterial or venous occlusive adverse events, and 22/81 (27%) of these were serious (treatment-emergent frequencies). In both trials, some patients experienced more than 1 type of event. Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment emergent frequencies) occurred in 13% (56/449), 9% (39/449), and 9% (40/449) of ICLUSIG-treated patients in the phase 2 trial, respectively. Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 9% (41/449), 7% (31/449), and 7% (31/449) of ICLUSIG- treated patients in the phase 2 trial, respectively. In the phase 2 study, the incidence of arterial occlusive events increased over the course of the study, while the ongoing study population decreased. The incidence of arterial occlusive events at 6 months follow-up was 9.6 % (43/449) and 23.2% (104/449) after 4 years follow-up. When adjusted for exposure, the incidence of first arterial occlusive events was greatest in the first two years of follow-up and declined with decreasing dose intensity. Based on the incidence of arterial occlusive events per unit exposure, the rate of arterial occlusive events/100 patient-years was 15.54 in year 1 of the study, 15.05 after 2 years follow-up, and 14.09 after 4 years follow-up. The incidence of arterial occlusive events is generally stable over time.

Ocular toxicities, including retinal arterial occlusions leading to vision loss, have occurred in ICLUSIG-treated patients. If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed and ICLUSIG should be interrupted if vascular occlusion is suspected.

ICLUSIG should not be used in patients with a history of myocardial infarction, prior revascularisation or stroke, unless the potential benefit of treatment outweighs the potential risk.

Before starting treatment with ICLUSIG, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and any cardiovascular therapy optimised during treatment with ICLUSIG.

Monitoring for evidence of arterial occlusion should be performed and ICLUSIG should be interrupted immediately in case of arterial occlusion. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy.

Venous Thromboembolism

Venous thromboembolism, including retinal venous occlusions with vision loss, deep vein thrombosis, and pulmonary embolus, have occurred in ICLUSIG-treated patients. The incidence of thromboembolic events is higher in patients with Ph+ALL or BP-CML than those with AP-CML or CP-CML. In the phase 2 trial, with a minimum of 48 cycles (1 cycle = 28 days) follow-up for all ongoing patients, venous thromboembolic treatment-emergent adverse events occurred in 6% (25/449) of patients. Serious venous occlusive treatment-emergent adverse events occurred in 5% (22/449) patients.

Monitoring for evidence of thromboembolism and vascular occlusion should be performed and ICLUSIG should be interrupted immediately in case of vascular occlusion. A benefit–risk consideration should guide a decision to restart ICLUSIG therapy.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating ponatinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Heart Failure

Fatal and serious heart failure or left ventricular dysfunction occurred in ICLUSIG-treated patients. In the phase 2 trial, with a minimum of 48 cycles (1 cycle = 28 days) follow-up for all ongoing patients, cardiac failure events occurred in 9% (39/449) of ICLUSIG-treated patients, 6% (28/449) were serious. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of ICLUSIG. Consider discontinuation of ICLUSIG in patients who develop grade 4 heart failure.

Hypertension

During ICLUSIG treatment, hypertension (including hypertensive crisis) has been observed. In the phase 2 trial, with a minimum of 48 cycles (1 cycle = 28 days) follow-up for all ongoing patients, treatment-emergent hypertensive events were reported in 31% of patients; 12% of those events were grade 3 or 4. In post marketing use, elevations in blood pressure have been observed in patients with and without risk factors (age [years]: median 59, range: 14 to 89) and as early as 1 day after initiating treatment. Hypertension may contribute to risk of arterial thrombotic and occlusive events, including renal artery stenosis.

During ICLUSIG treatment, all patients should be monitored for blood pressure elevations at each clinic visit and managed as clinically indicated. Hypertension should be treated to normalise blood pressure. ICLUSIG treatment should be temporarily interrupted if hypertension is not medically controlled. In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.

QT prolongation

The QT interval prolongation potential of ICLUSIG was assessed in 39 leukaemia patients and no clinically significant QT prolongation was observed (see Section 5.1 Pharmacodynamic Properties). However, due to design limitations of this study a clinically significant effect on QT cannot be excluded. The pivotal clinical study excluded subjects with a prolonged QT interval at baseline, and those receiving medicines known to be associated with torsades de pointes. QT prolongation has been observed with some other BCR-ABL inhibitors. Measurement of baseline QT is recommended prior to commencing ICLUSIG.

Haemorrhage

Severe bleeding events and haemorrhage, including fatalities, occurred in ICLUSIG-treated patients. The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal haemorrhage and subdural hematoma were the most commonly reported grade 3 or 4 bleeding events. Most haemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia (see Section 4.4 Special Warning and Precautions for Use – Myelosuppression). Interrupt ICLUSIG for serious or severe haemorrhage and evaluate (see Section 4.2 Dose and Method of Administration – Myelosuppression). Grade 3 or 4 thrombocytopenia was reported in 36% (160/449) of patients.

Concomitant use of ICLUSIG with anticoagulants and/or anti-platelet agents should be approached with caution in patients who may be at risk of bleeding. Formal clinical studies evaluating the co-administration of ICLUSIG with these medications have not been conducted.

Myelosuppression

ICLUSIG is associated with severe (National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or 4) thrombocytopenia, neutropenia, and anaemia. The frequency of these events is greater in patients with accelerated phase CML (AP-CML) or blast phase CML (BP-CML)/Ph+ ALL than in chronic phase CML (CP-CML). A complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding ICLUSIG temporarily or reducing the dose (see Section 4.2 Dose and Method of Administration – Myelosuppression).

Fluid Retention

Fluid retention adverse events occurred in 31% (4% grade 3 or greater) of patients treated with ICLUSIG. These events included peripheral edema, pericardial effusion, pleural effusion, and ascites. One instance of brain edema was fatal. Patients should be monitored for fluid retention. Interrupt, reduce or discontinue ICLUSIG as clinically indicated.

Neuropathy

Peripheral and cranial neuropathies occurred in ICLUSIG-treated patients. Overall, 20% (90/449) of ICLUSIG-treated patients experienced a peripheral neuropathy event of any grade (2%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4%, 19/449), paresthesia (5%, 19/449), hypoesthesia (3%, 15/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 2% (10/449) of ICLUSIG-treated patients (<1% grade 3/4). Cases of ataxia and convulsion were also reported.

Of the patients with neuropathy, 26% (23/90) occurred during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting ICLUSIG and evaluate if neuropathy is suspected.

Hepatotoxicity

ICLUSIG may result in severe drug induced liver injury. ICLUSIG may result in elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase. Isolated cases of fatal hepatic failure have occurred in ICLUSIG treated patients. Monitor liver function tests (LFTs) at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue ICLUSIG as clinically indicated (see Section 4.2 Dose and Method of Administration – Hepatic Toxicity).

Pancreatitis and serum lipase

ICLUSIG is associated with pancreatitis. In clinical studies, pancreatitis was observed in 7% of the patients (8% of the CP-CML patients, 8% of the AP-CML patients and 3% of the BP-CML/Ph+ ALL patients) with 6% of patients experiencing serious pancreatitis. Pancreatitis developed in the majority of the patients within the first 2 months of ponatinib use. Check serum lipase every 2 weeks for the first 2 months and then regularly thereafter. Dose interruption or reduction may be required. If lipase

elevations are accompanied by abdominal symptoms, ICLUSIG should be withheld and patients evaluated for evidence of pancreatitis (see Section 4.2 Dose and Method of Administration – Pancreatitis and/or elevated serum lipase). Caution is recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe or very severe hypertriglyceridemia should be appropriately managed to reduce the risk of pancreatitis.

Tumour Lysis Syndrome

Tumour lysis syndrome occurred in 2 patients (<1%) with advanced CML treated with ICLUSIG. Hyperuricemia occurred in 31 patients (7%), most of whom were CP-CML patients. Ensure adequate hydration and high uric acid levels should be corrected prior to initiating therapy with ICLUSIG.

Reversible posterior leukoencephalopathy syndrome (RPLS)

Post-marketing cases of Reversible posterior leukoencephalopathy syndrome (RPLS) also known as Posterior Reversible Encephalopathy Syndrome (PRES), have been reported in ICLUSIG-treated patients. RPLS is a neurological disorder with signs and symptoms such as seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances.

If diagnosed, interrupt ICLUSIG treatment and resume treatment only once the event is resolved and if the benefit of treatment outweighs the risk of RPLS.

Hepatitis B virus reactivation

Reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with ICLUSIG. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with ICLUSIG should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see Section 4.8 Adverse Effects).

Lactose

ICLUSIG contains lactose. Inform patients who have or may have intolerance to lactose.

Use in hepatic impairment

Hepatic elimination is a major route of excretion for ICLUSIG. Single doses of ponatinib 30 mg were administered to patients with mild, moderate and severe hepatic impairment (Child-Pugh Classes A, B, and C) and to control healthy subjects. Overall, no major differences in ponatinib PK were observed in patients with varying degrees of hepatic impairment as compared to healthy subjects. ICLUSIG has not been studied in patients with hepatic impairment (Child-Pugh Classes A, B and C) at doses above 30 mg. Therefore, it is recommended that patients with hepatic impairment begin on a starting dose of 30 mg. Caution is recommended when administering ICLUSIG to patients with moderate to severe hepatic impairment (see Section 4.2 Dose and Method of Administration – Patients with Hepatic Impairment).

Use in renal impairment

ICLUSIG has not been studied in patients with renal impairment. Renal excretion is not a major route of ponatinib elimination. Caution is recommended when administering ICLUSIG to patients with moderate to severe renal impairment (i.e. an estimated Glomerular Filtration Rate [eGFR] < 60 mL/min/1.73 m^2) or endstage renal disease (i.e. on dialysis, or eGFR of <15 mL/min/1.73 m^2 not on dialysis).

Use in the elderly

Of the 449 patients in the clinical study of ICLUSIG, 155 (35%) were ≥65 years of age at entry. In patients with CP-CML, patients of age ≥ 65 years were less likely to achieve a major cytogenetic response than those younger than 65 years. Compared to patients <65 years, patients older than 65 years may be more likely to experience adverse reactions. Thirty (47/155) percent of patients ≥ 65 years had arterial occlusive events.

Paediatric use

The safety and efficacy of ICLUSIG in patients less than 18 years of age have not been studied.

Effects on laboratory tests

No data available.

Patient Counselling Information

Advise patients of the following and provide a copy of the Consumer Medicine Information:

Arterial Occlusion and Venous Thromboembolism

Inform patients that serious arterial occlusive events (including fatal myocardial infarction, stroke, severe peripheral vascular disease, and arterial stenosis sometimes requiring revascularisation) and venous thromboembolism events have occurred. Advise patients to immediately contact their health care provider with any symptoms suggestive of a blood clot such as chest pain, shortness of breath, weakness on one side of the body, speech problems, leg pain, leg swelling, or decreased or blurred vision.

Heart Failure and Cardiac Arrhythmias

Inform patients of the possibility of heart failure, and abnormally slow or fast heart rates. Advise patients to contact their health care provider if they experience symptoms such as shortness of breath, chest pain, palpitations, fluid retention, dizziness, or fainting.

Fluid Retention

Inform patients of the possibility of developing fluid retention and to contact their health care provider for symptoms such as leg swelling, abdominal swelling, weight gain, or shortness of breath.

Neuropathy

Inform patients of the possibility of developing peripheral or cranial neuropathy while being treated with ICLUSIG. Advise patients to report symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness.

Hepatotoxicity

Inform patients of the possibility of developing liver function abnormalities and serious hepatic toxicity. Advise patients to immediately contact their health care provider if signs of liver failure occur, including jaundice, anorexia, bleeding or bruising.

Hypertension

Inform patients of the possibility of new or worsening of existing hypertension. Advise patients to contact their health care provider for elevated blood pressure or if symptoms of hypertension occur including headache, dizziness, chest pain, or shortness of breath.

Pancreatitis

Inform patients of the possibility of developing pancreatitis that may be accompanied by nausea, vomiting, abdominal pain, or abdominal discomfort, and to promptly report these symptoms.

Haemorrhage

Inform patients of the possibility of serious bleeding and to immediately contact their health care provider with any signs or symptoms suggestive of haemorrhage such as unusual bleeding or easy bruising.

Myelosuppression

Inform patients of the possibility of developing low blood cell counts; inform patients to report immediately should fever develop, particularly in association with any suggestion of infection.

Embryo-Fetal Toxicity

Inform patients that ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise women of the potential hazard to a fetus and to avoid becoming pregnant.

Aneurysms and artery dissections

Inform patients that ICLUSIG in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections.

Instructions for Taking ICLUSIG

Advise patients to take ICLUSIG exactly as prescribed and not to change their dose or to stop taking ICLUSIG unless they are told to do so by their health care provider. ICLUSIG may be taken with or without food. ICLUSIG tablets should be swallowed whole. Patients should not crush or dissolve the tablets. Patients should not take two doses at the same time to make up for a missed dose.

Lactose

Inform patients that ICLUSIG contains 121 mg of lactose monohydrate in a 45 mg daily dose.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ponatinib is metabolised by esterases and/or amidases, CYP3A4 and to a lesser extent by CYP2C8 and CYP2D6. Caution should be exercised with concurrent use of ICLUSIG and strong CYP3A inhibitors and strong CYP3A inducers.

In vitro studies indicate that clinical medicinal product interactions are unlikely to occur as a result of ponatinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A or CYP2D6. An *in vitro* study in human hepatocytes indicated that clinical medicinal product interactions are also unlikely to occur as a result of ponatinib-mediated induction of the metabolism of substrates for CYP1A2, CYP2B6, or CYP3A.

At therapeutic serum concentrations, ponatinib did not inhibit OATP1B1 or OATP1B3, OCT1 or OCT2, organic anion transporters OAT1 or OAT3, or bile salt export pump (BSEP) *in vitro*. Therefore, clinical medicinal product interactions are unlikely to occur as a result of ponatinib-mediated inhibition of substrates for these transporters.

Based on *in vitro* data, inhibition of P-glycoprotein and breast cancer resistance protein (BCRP) are possible (see Section 4.5 Interactions with other Medicines and other forms of Interactions - Substances that may have their serum concentrations altered by ponatinib).

Substances that may increase ponatinib serum concentrations

CYP3A inhibitors

Co-administration of a single 15 mg oral dose of ICLUSIG in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, resulted in modest increases in ponatinib systemic exposure, with ponatinib $AUC0_{-\infty}$ and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone.

Caution should be exercised and a reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.

Substances that may decrease ponatinib serum concentrations

CYP3A inducers

Co-administration of a single 45 mg dose of ponatinib (on day 7) in the presence of rifampicin (600 mg daily for 9 days), a strong CYP3A inducer, resulted in decreases in ponatinib systemic exposure, with ponatinib AUC0-inf and C_{max} values that were 62% and 42% lower, than those seen when ponatinib was administered alone. Co-administration of ponatinib with strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure.

Elevated gastric pH

The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. In 18 healthy subjects, the effect of gastric pH on ponatinib exposure was investigated by administration of a single 45 mg dose of ponatinib following multiple doses of a potent inhibitor of gastric acid secretion (lansoprazole 60 mg daily for 2 days). On average, following lansoprazole pretreatment, ponatinib C_{max} decreased by 25%, overall systemic exposure ($AUC_{0\text{-}inf}$) decreased by 6%, and median T_{max} was increased by 1 hour, respective to when ponatinib was administered alone.

ICLUSIG may be administered concurrently with drugs that raise gastric pH without the need for adjustment of ICLUSIG dose or separation of administration.

Substances that may have their serum concentrations altered by ponatinib

Transporter substrates

In vitro, ponatinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine) and may increase their adverse reactions. Close clinical surveillance is recommended when ponatinib is administered with these medicinal products.

Drug-Food Interactions

Administration of ICLUSIG with a high- or low-fat meal, or without food, does not change the pharmacokinetics of ponatinib (see Section 5.1 Pharmacodynamic Properties and Section 5.2 Pharmacokinetic Properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of ICLUSIG on male and female fertility in humans is unknown. Animal data indicate potential impairment of fertility in both sexes. Ponatinib decreased fertility in female rats at an oral dose of 1.5 mg/kg/day, associated with exposure levels (plasma AUC) less than half that of patients. No effect on fertility was observed in male rats, but the highest tested dose produced exposure only two-thirds of the clinical AUC. Microscopic changes in the testes (minimal germ cell degeneration) were evident in monkeys that received daily oral doses of ponatinib (5 mg/kg), with exposure at the no effect level approximately equivalent to the clinical AUC.

Use in pregnancy (Category D)

There are no adequate data from the use of ICLUSIG in pregnant women. Based on studies in animals, ponatinib may cause fetal harm. A rat embryofetal development study showed that ponatinib causes embryofetal toxicity. Embryofetal lethality (increased post-implantation loss), embryofetal toxicity (reduced fetal weights and whole body edema) and teratogenicity (multiple soft tissue and skeletal abnormalities) were seen in rats that received oral doses of ponatinib (≥1 mg/kg/day; approximately 25% of the AUC in patients) during the period of organogenesis.

Women of childbearing age being treated with ICLUSIG should be advised not to become pregnant. An effective method of contraception should be used during treatment. ICLUSIG should be used

during pregnancy only when clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus. It is unknown whether ICLUSIG affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used.

Use in lactation

It is unknown whether ponatinib is excreted in human milk. Available data cannot exclude potential excretion in human milk. Breast-feeding should be stopped during treatment with ICLUSIG.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse reactions such as lethargy, dizziness, and blurred vision have been associated with ICLUSIG. Therefore, caution should be recommended when driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse reactions described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 CML and Ph+ ALL patients who were resistant or intolerant to prior TKI therapy including those with a BCR-ABL T315I mutation. All patients received a starting dose of 45 mg ICLUSIG once daily. Dose adjustments to 30 mg once daily or 15 mg once daily were allowed for the management of treatment toxicity. With a minimum follow-up of 48 cycles (1 cycle = 28 days) for all ongoing patients, the median duration of treatment with ICLUSIG was 979 days in CP-CML patients, 590 days in AP CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 29 mg/day in CP-CML patients; median dose intensity was greater in advanced disease states. With a minimum follow-up of 48 cycles (1 cycle = 28 days) for all ongoing patients, 71% (318/449) of patients experienced a dose interruption of more than three days and 68% (304/449) experienced a dose reduction. The dose intensity-safety relationship indicated that there are significant increases in adverse events ≥ grade 3 with higher doses over the dose range of 15 to 45 mg once-daily, including pancreatitis, thrombocytopenia, ALT increase, AST increase, rash, arthralgia, arterial thrombosis, cardiac failure, vascular occlusion, and hypertension.

With a minimum follow-up of 48 cycles (1 cycle = 28 days) for all ongoing patients, the most common serious adverse drug reactions (treatment related events ≥ 1%, displayed as treatment-emergent incidences) were: neoplasm progression (8.9%), pneumonia (7.1%) pancreatitis (5.8%), pyrexia and abdominal pain (4.5% each), myocardial infarction and atrial fibrillation (4% each), peripheral arterial occlusive disease (3.8%), anaemia (3.6%), angina pectoris (3.3%), platelet count decreased (3.1%), febrile neutropenia (2.9%), hypertension (2.7%), cardiac failure congestive, cerebrovascular accident and coronary artery disease (2.4% each), sepsis (2.2%), lipase increased (2%), acute kidney injury, cellulitis, dehydration and urinary tract infection (1.8% each), cardiac failure, cerebral infarction, deep vein thrombosis, dyspnoea, non-cardiac chest pain, pleural effusion, and pulmonary embolism (1.6% each), diarrhoea, hypotension, neutrophil count decreased, pancytopenia, pericardial effusion and peripheral artery stenosis (1.3% each) and acute coronary syndrome, bacteremia, carotid artery stenosis, clostridium difficile colitis, constipation, hyponatraemia, squamous cell carcinoma of the skin and syncope (1.1% each). Overall, the most common adverse reactions (≥ 20%) were platelet count decreased, abdominal pain, rash, constipation, headache, dry skin, fatigue, hypertension, pyrexia, arthralgia, nausea, neutrophil count decreased, anaemia, diarrhoea, lipase increased, vomiting, myalgia, and pain in extremity.

Seventy-two patients discontinued due to adverse events of which 67 discontinued due to adverse events that were considered treatment-related. Platelet count decreased was the most common adverse event leading to discontinuation. The rates of treatment-emergent adverse events resulting in discontinuation were 19% (50/270) in CP-CML, 11% (10/85) in AP-CML and 14% (12/94) in BP-CML/Ph+ ALL.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be

compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Tabulated List of Adverse Reactions

Adverse reactions reported in all CML and Ph+ ALL patients are presented in Table 4. Frequency categories are very common (≥ 1/10), common (≥1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4 Adverse reactions observed in >1% CML and Ph+ ALL patients – frequency reported by incidence of treatment emergent events

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	upper respiratory tract infection
	Common	pneumonia, folliculitis, sepsis
Blood and lymphatic system disorders	Very common	thrombocytopenia (platelet count decreased), neutropenia (neutrophil count decreased), anaemia
	Common	febrile neutropenia, leukopenia (white blood cell count decreased), pancytopenia, lymphopenia (lymphocyte count decreased)
Endocrine disorders	Common	hypothyroidism
Metabolism and nutrition disorders	Very common	decreased appetite
	Common	weight decreased, hypokalaemia, hyperuricaemia, hyperglycaemia, hypocalcaemia, hypophosphataemia, hyponatraemia, dehydration, blood cholesterol increased, hypertriglyceridaemia, fluid retention
	Uncommon	tumour lysis syndrome
Psychiatric disorders	Very common	insomnia
	Common	confusional state
Nervous system disorders	Very common	headache, dizziness
	Common	peripheral neuropathy, including paraesthesia, hypoaesthesia, hyperaesthesia, cerebral ischaemic events (e.g. cerebrovascular accident, cerebral infarction, transient ischaemic attack), lethargy, migraine
	Uncommon	cerebral artery stenosis, cerebral haemorrhage
Eye disorders	Common	dry eye, blurred vision, conjunctivitis, periorbital edema, eyelid edema
	Uncommon	visual impairment, retinal vein thrombosis and occlusion, retinal artery occlusion, vision loss

System organ class	Frequency	Adverse reactions
Cardiac disorders	Common	cardiac ischaemic events (e.g. angina pectoris, myocardial infarction, coronary artery disease, myocardial ischaemia, acute coronary syndrome, ischaemic cardiomyopathy), cardiac failure (e.g. cardiac failure congestive, ejection fraction decrease, left ventricular dysfunction), atrial fibrillation, pericardial effusion, palpitations, atrial flutter
	Uncommon	cardiac discomfort
Vascular Disorders	Very common	Hypertension *
	Common	peripheral arterial occlusive and stenotic disease (including peripheral ischaemia, intermittent claudication, poor peripheral circulation, splenic infarction), flushing, hot flush, deep vein thrombosis
	Uncommon	embolism venous, hypertensive crisis, renal artery stenosis
Respiratory, thoracic and mediastinal disorders	Very common	cough, dyspnoea
	Common	pleural effusion, epistaxis, dysphonia, pulmonary hypertension, pulmonary embolism
Gastrointestinal disorders	Very common	abdominal pain, constipation, nausea, diarrhoea, vomiting, lipase increased
	Common	blood amylase increased, dry mouth, pancreatitis, abdominal distension, dyspepsia, stomatitis, gastro-oesophageal reflux disease, abdominal discomfort, gastrointestinal haemorrhage
Hepatobiliary disorders	Very common	alanine aminotransferase increased, aspartate aminotransferase increased
	Common	blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood bilirubin increased,
	Uncommon	hepatotoxicity, hepatic failure, jaundice
Skin and subcutaneous tissue disorders	Very common	rash (e.g. erythema, pruritic rash, exfoliative dermatitis/skin exfoliation), dry skin
	Common	pruritus, alopecia, night sweats, hyperhidrosis, petechiae, ecchymosis, hyperkeratosis, pain of skin, skin hyperpigmentation
Musculoskeletal and connective tissue disorders	Very common	arthralgia, myalgia, pain in extremity, back pain, bone pain, muscle spasms
	Common	musculoskeletal pain, neck pain, musculoskeletal chest pain
Reproductive system and breast disorders	Common	erectile dysfunction
General disorders and administrative site conditions	Very common	fatigue, pyrexia, oedema peripheral, asthenia, pain
	Common	chills, non-cardiac chest pain, influenza-like illness, malaise

*For hypertension - the timeframe for onset of hypertension was generated from post-marketing data (see Section 4.4 Special Warnings and Precautions for Use).

Description of selected adverse reactions

Arterial Occlusion

Serious arterial occlusion occurred in patients treated with ICLUSIG: cardiovascular events in 9%, cerebrovascular events in 7%, and peripheral vascular events in 7% of patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Arterial occlusion and occlusive adverse events were more frequent with increasing age and

in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia. (see Section 4.4 Special Warnings and Precautions for Use – Arterial Occlusion and Venous Thromboembolism and Section 4.2 Dose and Method of Administration).

Venous Thromboembolism
Serious venous occlusive treatment-emergent adverse events occurred in 5% (22/449) patients. The incidence of thromboembolic events is higher in patients with Ph+ALL or BP-CML than those with AP-CML or CP-CML. (see Section 4.4 Special Warnings and Precautions for Use – Arterial Occlusion and Venous Thromboembolism and Section 4.2 Dose and Method of Administration).

Hepatitis B virus reactivation
Hepatitis B virus reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see Section 4.4 Special Warnings and Precautions for Use – Hepatitis B reactivation).

Post-marketing experience

In addition to clinical trial observations, the following adverse reactions have been identified during post-marketing use of ICLUSIG: urinary tract infection, chest pain, dehydration, peripheral swelling, and severe cutaneous reaction (e.g. Erythema multiforme, Stevens-Johnson syndrome). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypothyroidism
Hypothyroidism was reported in 2.9% of clinical trial patients, and as of February 2017, a further 15 reports have been seen with post-marketing use.

Abnormal Haematologic and Clinical Chemistry Findings
Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 thrombocytopenia, neutropenia, and anaemia was higher in patients with AP-CML and BP CML/Ph+ ALL than in patients with CP-CML (see Table 5). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities. Discontinuation due to myelosuppression was infrequent (thrombocytopenia 3.8%, neutropenia and anaemia < 1% each).

Vascular disorders
Cases of aneurysms and artery dissections, sometimes fatal, have been reported with VEGFR pathway inhibitors.

Table 5 Incidence of Clinically Relevant Grade 3/4* Laboratory Abnormalities in ≥ 2% of Patients in Any Disease Group from the Phase 2 Trial (N=449): Minimum Follow-up of 48 Cycles (1 cycle = 28 days) for All Ongoing Patients

Laboratory Test	All Patients (N=449) (%)	CP-CML (N=270) (%)	AP-CML (N=85) (%)	BP-CML/Ph+ ALL (N=94) (%)
Haematology				
Thrombocytopenia (platelet count decreased)	40	35	49	46
Neutropenia (ANC decreased)	34	23	52	52
Leukopenia (WBC decreased)	25	12	37	53
Anaemia (Hgb decreased)	20	8	31	46
Lymphopenia (lymphocytes decreased)	17	10	25	28
Biochemistry				
Lipase increased	13	13	13	14
ALT increased	6	4	8	7
Phosphorus decreased	10	9	13	9
Glucose increased	7	7	12	1
Sodium decreased	5	5	6	2
AST increased	4	3	6	3
Potassium increased	2	2	1	3
Alkaline phosphatase increased	2	2	4	2
Potassium decreased	2	<1	6	2
Bilirubin increased	1	<1	2	1
Amylase increased	3	3	4	3
Calcium decreased	1	< 1	2	1

ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, Hgb=haemoglobin, WBC=white blood cell count.
*Reported using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Reporting suspected adverse effects

'Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.'

4.9 OVERDOSE

Overdoses with ICLUSIG were reported in clinical trials. One patient was accidentally administered the entire contents of a bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of ICLUSIG. Two hours after the overdose, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 and 400 ms. The patient died 9 days after the overdose from pneumonia and sepsis. Another patient accidentally self-administered 165 mg on cycle 1 day 2. The patient experienced fatigue and non-cardiac chest pain on day 3. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and a moderate pericardial effusion.

In the event of an overdose of ICLUSIG, the patient should be observed and appropriate supportive treatment given.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01XE24.

Mechanism of action

Ponatinib is a BCR-ABL tyrosine kinase inhibitor. *In vitro*, ponatinib inhibited the tyrosine kinase activity of ABL and T315I mutant ABL with IC50 values of 0.4 and 2.0 nM, respectively. Ponatinib inhibits the *in vitro* activity of other kinases, including RET, FLT3, and KIT and members of the FGFR, PDGFR, VEGFR, EPH and SRC families of kinases with IC50 values below 20 nM. In cellular assays, ponatinib reduced the viability of cells expressing various BCR-ABL mutants, including those resistant to imatinib, dasatinib, and/or nilotinib. Ponatinib elicited tumour shrinkage and prolonged survival in mice bearing tumours expressing native or T315I mutant BCR-ABL. In preclinical studies, 40 nM was determined as the concentration of ponatinib sufficient to inhibit viability of cells expressing all tested BCR-ABL mutants by >50% (including T315I). In the phase 1 study, plasma steady-state trough concentrations of ponatinib typically exceeded 21 ng/mL (40 nM) at doses of 30 mg or greater. At doses of 15 mg or greater, 32 of 34 patients (94%) demonstrated a ≥50% reduction of CRKL phosphorylation, a biomarker of BCR-ABL inhibition, in peripheral blood mononuclear cells. The clinical utility of CRKL phosphorylation as a biomarker has not been established.

Cardiac electrophysiology

The QT interval prolongation potential of ICLUSIG was assessed in 39 leukaemia patients who received 30 mg, 45 mg, or 60 mg ICLUSIG once daily. Serial ECGs in triplicate were collected at baseline and at steady state to evaluate the effect of ponatinib on QT intervals. No clinically significant changes in the mean QTc interval (i.e., > 20 ms) from baseline were detected in the study. In addition, the pharmacokinetic-pharmacodynamic models show no exposure-effect relationship, with an estimated QTcF mean change of –6.4 ms (upper confidence interval –0.9 ms) at C_{max} for the 60 mg group (111.34 ng/mL). However, due to limitations in the design of this study, the possibility of QT prolongation due to ponatinib has not been excluded (see Section 4.4 Special Warnings and Precautions for Use – QT prolongation).

Clinical trials

The safety and efficacy of ICLUSIG in chronic myeloid leukaemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) patients who were resistant or intolerant to nilotinib or dasatinib, or who had the T315I mutation were evaluated in a single-arm, phase 2, open-label, international, multicentre trial. All patients were administered 45 mg of ICLUSIG once-daily with the possibility of dose de-escalations and dose interruptions followed by dose resumption and re-escalation. Patients were assigned to one of six cohorts based on disease phase (chronic phase (CP)-CML; accelerated phase (AP)-CML; or blast phase (BP)-CML/Ph+ ALL), resistance or intolerance (R/I) to dasatinib or nilotinib, and the presence of the T315I mutation. Although not an entry requirement, 96% of patients in the phase 2 trial had experienced failure of prior imatinib therapy.

Resistance in CP-CML was defined as failure to achieve either a complete haematological response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months) while on dasatinib or nilotinib. CP-CML patients who experienced a loss of response or development of a kinase domain mutation in the absence of a complete cytogenetic response or progression to AP-CML or BP CML at any time on dasatinib or nilotinib were also considered resistant. Resistance in AP-CML and BP CML/Ph+ ALL was defined as failure to achieve either a major haematological response (AP-CML by 3 months, BP-CML/Ph+ ALL by 1 month), loss of major haematological response (at any time), or development of kinase domain mutation in the absence of a major haematological response while on dasatinib or nilotinib.

Intolerance was defined as the discontinuation of dasatinib or nilotinib due to toxicities despite optimal management in the absence of a complete cytogenetic response for CP-CML patients or major haematological response for AP-CML, BP-CML, or Ph+ ALL patients.

The primary efficacy endpoint in CP-CML was major cytogenetic response (MCyR) by 12 months, which included complete and partial cytogenetic responses (CCyR and PCyR). The secondary efficacy endpoints in CP-CML were complete haematological response (CHR) and major molecular response (MMR).

The primary efficacy endpoint in AP-CML and BP-CML/Ph+ ALL was major haematological response (MaHR) by 6 months, defined as either a complete haematological response (CHR) or no evidence of leukaemia (NEL). The secondary efficacy endpoints in AP-CML and BP-CML/Ph+ ALL were MCyR and MMR.

For all patients, additional secondary efficacy endpoints included: confirmed MCyR, time to response, duration of response, progression free survival, and overall survival.

The trial enrolled 449 patients of which 444 were eligible for analysis: 267 CP-CML patients (R/I Cohort: n=203, T315I Cohort: n=64), 83 AP-CML patients (R/I Cohort: n=65, T315I Cohort: n=18), 62 BP-CML (R/I Cohort: n=38, T315I Cohort: n=24), and 32 Ph+ ALL patients (R/I Cohort: n=10, T315I Cohort: n=22). A response of MCyR or better (MCyR, MMR, or CMR), or MMR or better (MMR or CMR) to the most recent course of dasatinib or nilotinib treatment was only achieved in 26% and 3% of the patients in the CP-CML cohorts respectively. A prior MaHR or better (MaHR, MCyR, MMR, or CMR) was only achieved in 21% and 24% of patients in the AP-CML and BP-CML/Ph+ALL cohorts, respectively. At the time of analysis, patients had a minimum follow-up of 48 cycles (1 cycle = 28 days). The median duration of follow-up on all enrolled patients was 37.3 months (range: 0.07 months to 58.5 months. Baseline demographic characteristics are described in Table 6 below.

Table 6 Demographics and disease characteristics

Patient characteristics at entry	Total safety population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)
Resistant to Prior TKI Therapy*, n (%)	375 (83.5%)
Experienced failure of prior imatinib, n (%)	431 (96%)
Prior TKI therapy– number of regimens, n (%)	
1	32 (7%)
2	155 (35%)
≥3	262 (58%)
BCR-ABL mutation detected at entry, n (%)	
None	198 (44%)
1	192 (43%)
≥2	54 (12%)

* of 427 patients reporting prior TKI therapy with dasatinib or nilotinib

Overall, 55% of patients had one or more BCR-ABL kinase domain mutation at entry with the most frequent being: T315I (29%), F317L (8%), E255K (4%) and F359V (4%). In 67% of CP-CML patients in the R/I cohort, no mutations were detected at study entry.

With a minimum follow-up of 48 cycles (1 cycle = 28 days) for all ongoing patients, the median duration of ICLUSIG treatment was 979 days in CP-CML patients, 590 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. Efficacy results are summarised in Table 7 and Table 8.

Table 7 Efficacy of ICLUSIG in resistant or intolerant chronic phase CML patients

	Overall (N=267)	**Resistant or Intolerant**	
		R/I Cohort (N=203)	**T315I Cohort (N=64)**
Cytogenetic Response			
Major-(MCyR) [a] % (95% CI)	 55% (50-62)	 51% (44-58)	 70% (58-81)
Complete (CCyR) % (95% CI)	 46% (40-52)	 40% (33-47)	 66% (53-77)
Major Molecular Response [b] % (95% CI)	 39% (33-46)	 34% (27-40)	 58% (45-70)
[a] Primary endpoint for CP-CML Cohorts was MCyR by 12 months, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses. [b] Measured in peripheral blood. Defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (ie, ≤0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).			

CP-CML patients who received fewer prior TKIs attained higher cytogenetic, haematological, and molecular responses. Of the CP-CML patients previously treated with one, two, or three, or four prior TKIs, 75% (12/16), 68% (66/97), 44% (63/142), and 58% (7/12) achieved a MCyR while on ICLUSIG, respectively. CP-CML patients who achieved MCyR or MMR by 3 months had statistically significantly improved progression-free and overall survival compared to those patients who did not meet those treatment milestones.

Of the CP-CML patients with no mutation detected at entry, 49% (66/136) achieved a MCyR.

There were 27 different types of BCR-ABL mutation detected in the CP-CML cohort at baseline. Of these, the following 15 mutations were seen in more than one patient: T315I, F317L, E255K, F359V, G250E, Y253H, V299L, E255V, M244V, F359C, H396R, F359I, E355A, E459K and L248V. At least one patient with each of these 15 mutations achieved a MCyR following treatment with ICLUSIG.

In CP-CML patients who achieved MCyR, the median time to MCyR was 84 days (range: 49 to 343 days) and in patients who achieved MMR, the median time to MMR was 168 days (range: 55 to1428 days). With a minimum of 48 cycles (1 cycle = 28 days) follow-up for ongoing patients, the median durations of MCyR (2.7-50.3+ months) and MMR (1.7-50.3+ months) had not yet been reached. Of the patients who achieved MCyR 82.3% (95% CI: 74.0-88.2) were estimated to maintain their response after 48 months.

Table 8 Efficacy of ICLUSIG in resistant or intolerant advanced phase CML patients

	Accelerated Phase CML			**Blast Phase CML/Ph+ ALL**		
	Overall (N=83)	**Resistant or Intolerant**		**Overall (N=94)**	**Resistant or Intolerant**	
		R/I Cohort (N=65)	**T315I Cohort (N=18)**		**R/I Cohort (N=48)**	**T315I Cohort (N=46)**
Haematological Response Rate						
Major[a] (MaHR)	57%	57%	56%	34%	35%	33%

	Accelerated Phase CML			Blast Phase CML/Ph+ ALL		
	Overall (N=83)	Resistant or Intolerant		Overall (N=94)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)		R/I Cohort (N=48)	T315I Cohort (N=46)
% (95% CI)	(45-68)	(44-69)	(31 - 79)	(25-45)	(22-51)	(20-48)
Complete[b] (CHR) % (95% CI)	51% (39-62)	48% (35-61)	56% (31-79)	26% (17-36)	27% (15-42)	24% (13-39)
Major Cytogenetic Response[c] % (95% CI)	39% (28-50)	34% (23-47)	56% (31-79)	31% (22-41)	27% (15-42)	35% (21-50)

[a] Primary endpoint for AP-CML and BP-CML/Ph+ ALL Cohorts was MaHR by 6 months, which combines complete haematological responses and no evidence of leukaemia.
[b] CHR: WBC ≤ institutional ULN, ANC 1 x 10^9/L platelets ≥100 x 10^9/L no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).
[c] MCyR combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

The median time to MaHR in patients with AP-CML and BP-CML/Ph+ ALL among responders was 21 days (range: 12 to 176 days) and 26 days (range: 11 to 168 days), respectively. The median duration of MaHR for patients with AP-CML and BP-CML/Ph+ ALL was 392 days (range: 35 to 1590 days) and 129 days (range: 54 to 1440 days), respectively.

Dose Escalation Study

The anti-leukaemic activity of ICLUSIG was also evaluated in a phase 1 dose escalation study that included 65 CML and Ph+ ALL patients; the study is ongoing. Of 43 CP-CML patients, 31 CP-CML patients achieved a MCyR with a median duration of follow-up of 42.5 months (range: 1.7 to 59.1 months). At a median follow-up duration of 47.2 months, 24 CP-CML patients were ongoing with median duration of MCyR (8 to >248 weeks) and MMR (12 to >214 weeks) not yet reached.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Peak concentrations of ponatinib are observed approximately 4 hours after oral administration. Within the range of clinically relevant doses evaluated in patients (15 mg to 60 mg), ponatinib exhibited dose proportional increases in both C_{max} and AUC. The geometric mean (CV%) C_{max} and $AUC_{(0-\tau)}$ exposures achieved for ponatinib 45 mg daily at steady state were 77 ng/mL (50%) and 1296 h•ng/mL (48%), respectively. The absolute bioavailability of ponatinib has not been determined. Following either a high-fat and low-fat meal, plasma ponatinib exposures (C_{max} and AUC) were not different versus fasting conditions. ICLUSIG may be administered with or without food.

Distribution

Ponatinib is highly bound (>99%) to plasma proteins *in vitro*. The blood/plasma partition ratio of ponatinib is 0.96. *In vitro* studies suggested that ponatinib is either not a substrate or is a weak substrate for both P-gp and breast cancer resistance protein BCRP. Ponatinib is not a substrate for the human organic anion transporting polypeptides OATP1B1 and OATP1B3 or the organic cation transporter OCT-1.

Metabolism

Ponatinib undergoes extensive metabolism with 74% of the circulating drug-related material consisting of metabolites. Ponatinib is metabolised to an inactive carboxylic acid by esterases and/or amidases, and to oxidative metabolites by CYP3A4 and to a lesser extent by CYP2C8 and CYP2D6.

Excretion

Following single and multiple 45 mg doses of ICLUSIG, the terminal elimination half-life of ponatinib was 22 hours, and steady-state conditions are typically achieved within 1 week of continuous dosing. With once-daily dosing, plasma exposures of ponatinib are increased by approximately 1.5-fold between first-dose and steady-state conditions. Ponatinib is mainly eliminated via faeces. Following a single oral dose of [^{14}C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the faeces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and <1% of the administered dose in faeces and urine, respectively, with the remainder of the dose excreted as metabolites.

Renal impairment

ICLUSIG has not been studied in patients with renal impairment. Renal excretion is not a major route of ponatinib elimination. Caution is recommended when administering ICLUSIG to patients with moderate to severe renal impairment (ie. an estimated Glomerular Filtration Rate [eGFR] <60 mL/min/1.73m^2) or end-stage renal disease (ie. on dialysis, or eGFR of <15 mL/min/1.73m^2 not on dialysis). (see Section 4.2 Dose and Method of Administration – Patients with Renal Impairment).

Hepatic impairment

Hepatic elimination is a major route of excretion for ICLUSIG. Single doses of ponatinib 30 mg were administered to patients with mild, moderate and severe hepatic impairment (Child-Pugh Classes A, B, and C) and to control healthy subjects. Overall, no major differences in ponatinib PK were observed in patients with varying degrees of hepatic impairment as compared to healthy subjects. ICLUSIG has not been studied in patients with hepatic impairment (Child-Pugh Classes A, B and C) at doses above 30 mg. Therefore, it is recommended that patients with hepatic impairment begin on a starting dose of 30 mg. Caution is recommended when administering ICLUSIG to patients with moderate to severe hepatic impairment.

Intrinsic factors affecting ponatinib pharmacokinetics

No specific studies have been performed to evaluate the effects of gender, age, race, or body weight on ponatinib pharmacokinetics. An integrated population pharmacokinetic analysis completed for ponatinib suggests that age may be predictive of variability for ponatinib apparent oral clearance (CL/F). Gender, race and body weight were not predictive in explaining ponatinib pharmacokinetic intersubject variability.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ponatinib was not mutagenic in a bacterial mutagenicity assay, was not clastogenic in a chromosome aberration assay in human lymphocytes, nor was it clastogenic in an *in vivo* mouse micronucleus test.

Carcinogenicity

The carcinogenic potential of ponatinib was investigated in a study in male and female rats involving oral administration for 92–100 weeks. No carcinogenic activity was evident in males up to the highest dose tested (0.2 mg/kg/day), but systemic exposure at this dose was low (4% of the plasma AUC in patients at 45 mg/day). Female rats showed increases (compared to both concurrent and historical controls) in the incidence of ovarian mixed sex cord stromal benign tumours at doses ≥0.4 mg/kg/day and of squamous cell carcinoma of the clitoral gland at 0.8 mg/kg/day. Carcinogenic doses in female

rats are associated with low multiples of the clinical plasma AUC (10% and 29% at 0.4 mg/kg/day and 0.8 mg/kg/day, respectively). The clinical relevance of these findings is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet also contains: lactose monohydrate, microcrystalline cellulose, sodium starch glycollate, colloidal silicon dioxide, magnesium stearate and a tablet coating. The tablet film coating consists of talc, macrogol 4000, polyvinyl alcohol, and titanium dioxide.

6.2 INCOMPATIBILITIES

Not Applicable. Please refer to Section 4.5 - Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original container in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

ICLUSIG film coated tablets are supplied in high density polyethylene (HDPE) bottles with desiccant canister and foil induction sealed child resistant, screw-top closures.

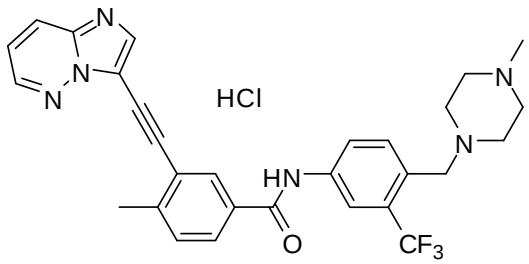
Each bottle contains either;
15 mg: 30 or 60 film-coated tablets
45 mg: 30 film-coated tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Name: {Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl])}

Molecular Weight: 569.02 g/mol (HCl salt)

Molecular Formula: $C_{29}H_{28}ClF_3N_6O$ (HCl salt)

Ponatinib HCl is an off-white to yellow powder with pKa of 2.77 and 7.8. The solubility of ponatinib in pH 1.7, 2.7, and 7.5 buffers is 7790 mcg/mL, 3.44 mcg/mL, and 0.16 mcg/mL, respectively, indicating a decrease in solubility with increasing pH.

CAS number

1114544-31-8 (HCl salt)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

26 November 2014

10 DATE OF REVISION

15 February 2021

Summary table of changes

Section changed	Summary of new information
4.4	New precaution added
4.8	New 'Post-marketing experience' added