AUSTRALIAN PRODUCT INFORMATION

ICLUSIG® (PONATINIB HYDROCHLORIDE)

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, HYPERTENSION AND HEPATOTOXICITY

- **Arterial occlusive events (AOEs), including fatality, have occurred in ICLUSIG-treated patients. AOEs including 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 AOEs. Interrupt or stop ICLUSIG based on severity. Consider benefit-risk to guide decision to restart ICLUSIG**
- **Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or stop ICLUSIG based on severity.**
- **Heart Failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor cardiac function. Interrupt or stop ICLUSIG for new or worsening heart failure**
- **Hypertension, including hypertensive crisis, has been observed in ICLUSIG-treated patients.**
- **Hepatotoxicity, including liver failure and death have occurred in ICLUSIG-treated patients. Monitor hepatic function. Interrupt ICLUSIG based on severity.**

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 10, 15, 30, 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 for oral administration.

10 mg Tablet: White to off-white, biconvex, oval film-coated tablet with “NZ” debossed on one side.

15 mg Tablet: White, biconvex, round film-coated tablet with "A5" debossed on one side.

30 mg Tablet: White, biconvex, round film-coated tablet with “C7” debossed on one side.

45 mg Tablet: White, biconvex, round film-coated tablet 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 (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukaemia (CML) 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.

Dosage

ICLUSIG may be taken with or without food.

For dose adjustments to lower strengths, 10 mg or 15 mg film-coated tablets are available.

CP-CML

The recommended starting dosage of ICLUSIG is 45 mg once daily taken at the same approximate time each day with a reduction to 15 mg orally once daily upon achievement of molecular response (≤1% BCR-ABL1^{IS}). Patients with loss of molecular response can re-escalate the dose of ICLUSIG to a previously tolerated dosage of 30 mg or 45 mg orally once daily. Continue ICLUSIG until loss of response at the re-escalated dose or unacceptable toxicity.

Consider discontinuing ICLUSIG if haematologic response has not occurred by 3 months.

AP-CML, BP-CML, and Ph+ ALL

The recommended starting dose of ICLUSIG is 45 mg once daily, taken at the same approximate time each day. Consider reducing the dose of ICLUSIG for patients with accelerated phase (AP) CML who have achieved a major cytogenetic response. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

Consider discontinuing ICLUSIG if response has not occurred by 3 months.

Dose adjustments or modifications for Adverse Reactions

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

For a dose of 30 mg,15 mg or 10 mg once daily, 15 mg and 10 mg film-coated tablets are available.

Recommendations for dose modifications of ICLUSIG for the management of adverse reactions are summarised in Table 1 and recommended dose reductions of ICLUSIG for adverse reactions are presented in Table 2.

Table 1 Recommended ICLUSIG dose modifications for adverse reactions

Adverse Reaction	Severity	Dose Modification
AOE: cardiovascular or cerebrovascular	Grade 1	Interrupt ICLUSIG until resolved, then resume at the same dose.
	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 3 or 4	Discontinue ICLUSIG
AOE: peripheral vascular and other OR VTE	Grade 1	Interrupt ICLUSIG until resolved, then resume at the same dose.
	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at the same dose. If recurrence, interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose.
	Grade 3	Interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 4	Discontinue ICLUSIG.
Heart Failure	Grade 2 or 3	Interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 4	Discontinue ICLUSIG.
Hepatic Toxicity	AST or ALT greater than 3 times ULN	Interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose.

	AST or ALT at least 3 times ULN concurrent with bilirubin greater than 2 times ULN and alkaline phosphates less than 2 times ULN	Discontinue ICLUSIG.
Pancreatic and Elevation of Lipase / Amylase	Asymptomatic Grade 2 pancreatitis and/or Grade 2 elevation of lipase/amylase	Consider interrupting ICLUSIG until resolution then resume at the same dose.
	Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x ULN) only	Interrupt ICLUSIG until ≤ Grade 1 (less than 1.5 times ULN) then resume at the next lower dose.
	Grade 3 pancreatitis	Interrupt ICLUSIG until complete resolution of symptoms and after recovery of lipase elevation ≤ Grade 1, then resume at the next lower dose.
	Grade 4 pancreatitis	Discontinue ICLUSIG.
Myelosuppression	ANC less than 1.0 x 10^9/L or platelets less than 50 x 10^9/L	Interrupt ponatinib until ANC at least 1.5 × 10^9/L and platelets at least 75 × 10^9/L, then resume at same dose. If recurrence, interrupt ponatinib until resolution, then resume at next lower dose.
Other Non-haematologic Adverse Reactions	Grade 1	No intervention
	Grade 2	Interrupt ICLUSIG until ≤ Grade 1, then resume at the same dose. If recurrence, interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose.
	Grade 3 or 4	Interrupt ICLUSIG until ≤ Grade 1, then resume at the next lower dose. Discontinue ICLUSIG if recurrence.

Grading based on the National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0
ANC = absolute neutrophil count
ULN = upper limit of normal

Table 2 Recommended dose reductions for ICLUSIG for Adverse Reactions

Dose reductions	***Dosage for patients with CP-CML***	***Dosage for patients with AP-CML, BP-CML, & Ph+ ALL***
First	***30 mg once daily***	***30 mg once daily***
Second	***15 mg once daily***	***15 mg once daily***
Third	***10 mg once daily***	***Permanently discontinue ICLUSIG in patients unable to tolerate 15 mg once daily***
Subsequent reductions	***Permanently discontinue ICLUSIG in patients unable to tolerate 10 mg once daily***	

Patients with Hypertension

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.

Patients with Hepatic impairment

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

Patients with Renal impairment

ICLUSIG has not been studied in patients with severe renal impairment. Although renal excretion is not a major route of ponatinib elimination the potential for severe renal impairment to affect the pharmacokinetics of ponatinib has not been determined. No dose adjustment of ICLUSIG is recommended for patients with mild or moderate renal impairment (creatinine clearance 30-89 mL/min). Caution is recommended when administering ICLUSIG to patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease.

Concomitant Treatment

Avoid concurrent use of ICLUSIG and strong CYP3A inhibitors. If co-administration of a strong CYP3A inhibitors cannot be avoided, reduction of the starting dose of ICLUSIG to 30 mg should be considered with concurrent use of ICLUSIG and strong CYP3A inhibitors. Avoid concurrent use of ICLUSIG and strong CYP3A inducers unless the benefit outweighs the possible risk of decreased ponatinib exposure (see Section 4.5 Interactions with other Medicines and other forms of Interactions - Substances that may increase ponatinib serum concentrations).

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.

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 Occlusive Events

Arterial Occlusive Events (AOEs), including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease (sometimes resulting in amputation), and the need for urgent revascularisation procedures, have occurred in ICLUSIG-treated patients (see Section 4.8 Adverse Effects). Some patients experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced AOEs. 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.

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 an AOE (see Section 4.2 Dose and Method of Administration). A benefit–risk consideration should guide a decision to restart ICLUSIG therapy after the occurrence of an AOE.

Venous Thromboembolism Events

Venous thromboembolism events (VTEs) have occurred in ICLUSIG-treated patients (See Section 4.8 Adverse Effects).

Events reported include retinal venous occlusion and retinal vein thrombosis with vision loss, deep vein thrombosis, and pulmonary embolus, and superficial thrombophlebitis. The incidence of thromboembolic events is higher in patients with Ph+ALL or BP-CML than those with AP-CML or CP-CML.

Monitoring for evidence of thromboembolism and vascular occlusion should be performed and ICLUSIG should be interrupted immediately in case of a VTE (see Section 4.2 Dose and Method of Administration). A benefit–risk consideration should guide a decision to restart ICLUSIG therapy after the occurrence of a VTE.

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 aneurysms.

Heart Failure

Fatal and serious heart failure or left ventricular dysfunction occurred in ICLUSIG-treated patients (see Section 4.8 Adverse Effects). Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of ICLUSIG. Consider dose modification of ICLUSIG in patients who develop heart failure (see Section 4.2 Dose and Method of Administration). Consider discontinuation of ICLUSIG in patients who develop serious heart failure.

Hypertension

Hypertension (including hypertensive crisis) has occurred in ICLUSIG-treated patients (see Section 4.8 Adverse Effects).

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. Hypertension may also contribute to renovascular disorders, most commonly observed as renal artery stenosis. Monitoring for significant or unexplained hypertension is recommended as it may contribute to renal vascular disease.

Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Hypertension may contribute to the development of AOEs.

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-ABL1 inhibitors. Measurement of baseline QT is recommended prior to commencing ICLUSIG.

Haemorrhage

Haemorrhage and bleeding events have occurred in ICLUSIG-treated patients (see Section 4.8 Adverse Effects). Some fatal haemorrhage events have been reported. 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 3 or grade 4 thrombocytopenia. Interrupt ICLUSIG for serious or severe haemorrhage and evaluate; discontinuation may be required (see Section 4.2 Dose and Method of Administration – Myelosuppression).

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 ≥ grade 3 thrombocytopenia, neutropenia, and anaemia. Most commonly reported events included neutropenia, thrombocytopenia, and anaemia (see Section 4.8 Adverse Effects). Of the patients who developed grade 3 or 4 myelosuppression, most developed it within the first 3 months of treatment. The frequency of these events is greater in patients with AP-

CML or BP-CML/Ph+ ALL than in patients with 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

In PACE, fluid retention adverse events occurred in 31.6% of 449 ICLUSIG-treated patients with 4.2% experienced serious fluid retention. These events included peripheral oedema, pericardial effusion, pleural effusion, and ascites. One instance of brain oedema was fatal.

In OPTIC, fluid retention adverse events occurred in 5.3% of 94 ICLUSIG-treated CP-CML patients who received 45 mg. The most frequent fluid retention events were peripheral oedema and pleural effusion.

Patients should be monitored for fluid retention. Interrupt, reduce or discontinue ICLUSIG as clinically indicated.

Neuropathy

In PACE, 20% of 449 patients experienced a peripheral neuropathy event of any grade (1.8%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4.5%), paraesthesia (5.3%), hypoesthesia (3.6%), and hyperesthesia (1%). Cranial neuropathy developed in 3% of patients (0.7% grade 3/4). Cases of ataxia and convulsion were also reported.

In OPTIC, peripheral neuropathy occurred in 6% of patients. The most frequently reported peripheral neuropathies were hypoesthesia (2.1%), muscular weakness (2.1%), and paraesthesia (2.1%). Cranial neuropathy developed in 2 patients.

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, 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 (see Section 4.8 Adverse Effects). Most patients who reported an event of hepatoxicity had their first event in the first year of treatment. Isolated cases of fatal hepatic failure have occurred in ICLUSIG treated patients. Monitor liver function tests (LFTs) and transaminase level measurements 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

Pancreatitis and acute pancreatitis have occurred in ICLUSIG-treated patients (see Section 4.8 Adverse Effects). Elevation of serum lipase and amylase have also been reported.

Pancreatitis developed in the majority of the patients within the first 2 months of ponatinib use. Check serum amylase/lipase every 2 weeks for the first 2 months and then regularly thereafter. Dose modification may be required (see Section 4.2 Dose and Method of Administration).

If lipase elevations are accompanied by abdominal symptoms, ICLUSIG should be immediately withheld and patients evaluated for evidence of pancreatitis. 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

In PACE, tumour lysis syndrome (TLS) occurred in 3 patients (0.7%) with advanced CML treated with ICLUSIG-treated patients (see Section 4.8 Adverse Effects). Hyperuricemia also occurred in ICLUSIG-treated 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.

Of the 94 CP-CML patients who received a starting dose of 45 mg in OPTIC, serious TLS developed in 1.1% of patients. Hyperuricemia occurred in 2.1% of patients.

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-ABL1 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 severe renal impairment. Caution is recommended when administering ICLUSIG to patients with severe renal impairment or end-stage renal disease. (see Section 4.2 Dose and Method of Administration).

Use in the elderly

Patients aged ≥65 years or older are more likely to experience adverse reactions including vascular occlusion, decreased platelet count, peripheral oedema, increased lipase, dyspnoea, asthenia, muscle spasm, and decreased appetite. In general dose selection for elderly patients should be

cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant medical conditions or medications.

Of the 449 patients in the PACE study who received 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 six (51/155) percent of patients ≥ 65 years had arterial occlusive events.

Of the 94 patients with CP-CML who received ICLUSIG at a starting dose of 45 mg in OPTIC, 16 (17%) were ≥65 years. Patients aged ≥65 had a lower ≤ 1% BCR-ABL1^{IS} rate at 12 months (27%) as compared with patients less than 65 years of age (47%). Nineteen (3/16) percent of patients ≥65 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 thromboembolic 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, paraesthesia, 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 is 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. Avoid 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 $AUC_{0-\infty}$ and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone. Coadministration of ponatinib with strong CYP3A inhibitors (e.g. boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole and grapefruit juice) increases ponatinib plasma concentrations, which may increase the risk of ponatinib adverse reactions. Avoid co-administration of ICLUSIG with strong CYP3A inhibitors. If co-administration of a strong CYP3A inhibitor cannot be avoided, reduce the ICLUSIG dosage as recommended in Table 3. After the strong CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume

the ICLUSIG dosage that was tolerated prior to initiating the strong CYP3A inhibitor (see Section 5.2 Pharmacokinetic Properties).

Table 3 Recommended ICLUSIG Dosage for Co-administration with Strong CYP3A Inhibitors

Regular ICLUSIG Dosage	Recommended ICLUSIG Dosage with a Strong CYP3A Inhibitor
45 mg orally once daily	30 mg orally once daily
30 mg orally once daily	15 mg orally once daily
15 mg orally once daily	10 mg orally once daily
10 mg orally once daily	Avoid coadministration of ICLUSIG with a strong CYP3A inhibitor

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 $AUC_{0\text{-}inf}$ 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 decreased ponatinib exposure. Monitor patients for reduced efficacy. Selection of concomitant medications with no or minimal CYP3A induction potential is recommended (see Section 5.2 Pharmacokinetic Properties).

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 pre-treatment, 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 monitoring 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), ovaries (increased follicular atresia) and uterus (endometrial atrophy) as well as reduced ovarian weight were evident in monkeys that received daily oral doses of ponatinib (5 mg/kg) for 28 days, with exposure at the no effect level approximately equivalent to the clinical AUC. In the 6-month monkey study, there were variable increases and decreases in ovarian weights without a consistent direction of change, dose dependency, or microscopic correlates.

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 and men being treated with ICLUSIG should be advised not to father a child during treatment. 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. 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, blurred vision, visual impairment, mental status changes, and confusion have been associated with ICLUSIG. Therefore, patients should be advised not to drive or operate machines if they experience any of these symptoms while taking ICLUSIG.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Previously Treated CML or Ph+ ALL (PACE Study)

PACE is a single-arm, open-label, international, multi-centre study that included adult patients (N=449) with CML or Ph+ ALL in two eligible categories: those who were resistant or intolerant to prior dasatinib or nilotinib therapy, and those with T315I mutation. All patients received a starting dose of 45 mg ICLUSIG once daily and were entered into I of 6 cohorts based on disease phase diagnosis (CP-CML, AP-CML, or blast phase CML [BP-CML]/Ph+ALL). They were also divided into those who were resistant or intolerant to dasatinib or nilotinib (i.e., they did not have a detectable T315I mutation) or those who had the T315I mutation. The primary endpoint of this trial was major

cytogenetic response (MCyR) by 12 months for CP-CML and major haematologic response (MaHR) for advanced phase patients by 6 months.

Tabulated List of Adverse Reactions

Adverse reactions reported in Table 4 are listed by system organ class, preferred term and frequency. 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 CML and Ph+ ALL patients who received ICLUSIG in PACE (N=449)

System organ class	Frequency	Adverse reactions
Infections and infestations	Very common	upper respiratory tract infection
	Common	Pneumonia*, folliculitis, sepsis, cellulitis, conjunctivitis
Blood and lymphatic system disorders	Very common	anaemia
	Common	febrile neutropenia, pancytopenia,
Endocrine disorders	Common	hypothyroidism
Metabolism and nutrition disorders	Very common	decreased appetite
	Common	hypokalaemia, hyperuricaemia, hyperglycaemia, hypocalcaemia, hypophosphataemia, hyponatraemia, dehydration, 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, lethargy, migraine, cerebral infarction, paraesthesia, cerebrovascular accident*, carotid artery stenosis, syncope, transient ischemic attack.
	Uncommon	cerebral artery stenosis, cerebral haemorrhage, cerebral ischaemia, burning sensation, peripheral sensory neuropathy
Eye disorders	Common	dry eye, blurred vision, conjunctivitis, periorbital edema, eyelid edema, conjunctival haemorrhage, eye pain, blepharitis cataract, ocular hyperaemia, visual impairment
	Uncommon	retinal vein thrombosis and occlusion, eye swelling, retinal artery occlusion, conjunctival hyperaemia
Cardiac disorders	Common	angina pectoris, atrial fibrillation, pericardial effusion, palpitations, atrial flutter, acute myocardial infarction*/myocardial infarction*, coronary artery disease, cardiac failure congestive*, acute coronary syndrome, cardiac failure, coronary artery occlusion, tachycardia, bradycardia, sinus bradycardia

System organ class	Frequency	Adverse reactions
	Uncommon	cardiac discomfort, ventricular tachycardia, myocardial ischemia, ischemic cardiomyopathy, left ventricular dysfunction
Vascular Disorders	Very common	Hypertension
	Common	peripheral arterial occlusive disease, peripheral artery stenosis, peripheral ischaemia*, intermittent claudication, flushing, hot flush, deep vein thrombosis, peripheral artery occlusion, peripheral vascular disorder, hematoma
	Uncommon	embolism venous, hypertensive crisis, poor peripheral circulation, splenic infarction,
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,
	Common	dry mouth, pancreatitis, abdominal distension, dyspepsia, stomatitis, gastro-oesophageal reflux disease, abdominal discomfort, gastrointestinal haemorrhage*/upper gastrointestinal haemorrhage, gingival bleeding, ascites, haemorrhoidal haemorrhage
Hepatobiliary disorders	Uncommon	hepatotoxicity, hepatic failure*, jaundice, hepatocellular injury
Skin and subcutaneous tissue disorders	Very common	rash, dry skin, pruritus
	Common	erythema, rash pruritic, skin exfoliation, exfoliative rash, alopecia, night sweats, hyperhidrosis, petechiae, ecchymosis, hyperkeratosis, pain of skin, dermatitis exfoliative, 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, chest pain, non-cardiac chest pain, influenza-like illness, malaise, peripheral swelling, localised edema
Investigations	Very common	platelet count decreased, lipase increased, neutrophil count decreased, alanine aminotransferase increased, aspartate aminotransferase increased
	Common	amylase increased, blood alkaline phosphate increased, gamma-glutamyl transferase increased, white blood cell count increased, weight decreased, blood cholesterol increased, ejection fraction decreased, blood bilirubin increased, blood creatinine increased, lymphocyte count decreased, electrocardiogram QT prolongation
	Uncommon	transaminases increased

System organ class	Frequency	Adverse reactions
Renal and Urinary Disorders	Uncommon	renal artery stenosis
Injury, poisoning and procedural complications	Common	contusion

ADRs included as preferred terms are based on MedDRA version 21.0
* Includes fatal events

Previously Treated CP-CML (OPTIC Study)

The safety of ICLUSIG was evaluated in OPTIC is patients with CP-CML whose disease was considered to be resistant to at least two prior kinase inhibitors or who have the T315I mutation. Patients received one of three starting doses of ICLUSIG: 45 mg orally once daily (n=94), 30 mg orally once daily (n=94) or 15 mg orally once daily (n=94). Patients who received a starting dose of ponatinib 45 mg or 30 mg orally once daily had a mandatory dose reduction to 15 mg once daily upon achievement of ≤1% BCR-ABL1^{IS}. (see Section 5.1 Pharmacodynamic Properties).

Adverse reactions reported in CP-CML patients from OPTIC were generally similar to those reported for CP-CML patients from PACE.

Description of selected adverse reactions

The description of selected adverse reactions observed in the phase 2 studies PACE and OPTIC (45 mg cohort) is presented below:

Arterial Occlusive Events
In PACE, AOEs, including fatal cases, occurred in 25% of ICLUSIG-treated patients (n=449). Cardiovascular, cerebrovascular, and peripheral vascular AOEs occurred in 13%, 9% and 11% of patients respectively.

In OPTIC (45 mg cohort), AOEs occurred in 10% of ICLUSIG-treated patients. Cardiovascular, cerebrovascular, and peripheral vascular AOEs occurred in 4.3%, 2.1%, and 3.2% of patients, respectively.

(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 Thromboembolic Events
Venous thromboembolic events occurred in 6% of ICLUSIG-treated patients in PACE.

Of the 94 patients in OPTIC (45 mg cohort), 1 patient experienced a VTE (Grade 1 retinal vein occlusion).

(see Section 4.4 Special Warnings and Precautions for Use – Arterial Occlusion and Venous Thromboembolism and Section 4.2 Dose and Method of Administration).

Heart Failure
Heart failure or left ventricular dysfunction, including fatal cases, occurred in 9% of ICLUSIG-treated patients in PACE.

Heart failure or left ventricular dysfunction occurred in 3.2% of ICLUSIG-treated in OPTIC (45 mg cohort).

(see Section 4.4 Special Warnings and Precautions for Use – Heart Failure and Section 4.2 Dose and Method of Administration).

Hepatotoxicity
Events of hepatoxicity occurred in 30% (n=449) of ICLUSIG-treated patients in PACE.

Events of hepatoxicity occurred in 28% (n=94) of ICLUSIG-treated patients in OPTIC (45 mg cohort).

(see Section 4.4 Special Warnings and Precautions for Use – Hepatotoxicity and Section 4.2 Dose and Method of Administration).

Hypertension
Hypertension occurred in 32% (n=449) of ICLUSIG-treated patients from PACE study.

Hypertension occurred in 32% (n=94) of ICLUSIG-treated patients from OPTIC study (45 mg cohort).

(see Section 4.4 Special Warnings and Precautions for Use – Hypertension and Section 4.2 Dose and Method of Administration).

Pancreatitis and Serum Lipase
Pancreatitis and acute pancreatitis have occurred in 7% (n=449) of ICLUSIG-treated patients from PACE. Elevation of serum lipase and amylase have also been reported in 22% and 7% of patients, respectively.

Pancreatitis and acute pancreatitis have occurred in 2.1% (n=94) of ICLUSIG-treated patients from OPTIC (45 mg cohort). Elevations of serum lipase and amylase have also been reported in 20% and 5% of patients, respectively.

(see Section 4.4 Special Warnings and Precautions for Use – Pancreatitis and Serum Lipase and Section 4.2 Dose and Method of Administration).

Haemorrhage
Haemorrhage and bleeding events, including fatal cases, have occurred in 28% (n=449) of ICLUSIG-treated patients from PACE.

Haemorrhage has occurred in 12% (n=94) of ICLUSIG-treated patients from OPTIC (45 mg cohort).

(see Section 4.4 Special Warnings and Precautions for Use – Haemorrhage and Section 4.2 Dose and Method of Administration).

Myelosuppression
Myelosuppression events were reported in 60% (n=449) of ICLUSIG-treated patients from PACE. Most commonly reported events included neutropenia, thrombocytopenia, and anaemia occurring in 25%, 44%, and 25% of ICLUSIG-treated patients, respectively.

Myelosuppression events were reported in 63% (n=94) of ICLUSIG-treated patients from OPTIC (45 mg cohort). Most commonly reported events included neutropenia, thrombocytopenia, and anaemia occurring in 30%, 44%, and 21% of ICLUSIG-treated patients, respectively.

(see Section 4.4 Special Warnings and Precautions for Use – Myelosuppression and Section 4.2 Dose and Method of Administration).

Hepatitis B virus reactivation
Hepatitis B virus reactivation has been reported in association with BCR-ABL1 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

The following adverse drug reactions, which are not mentioned above, have been observed in the post-marketing setting:

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES)

Skin and Subcutaneous Tissue Disorders: Severe cutaneous reaction (e.g. erythema multiforme, Stevens-Johnson Syndrome), panniculitis (including erythema nodosum)

Vascular Disorders: Arterial dissections and aneurysms

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.

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-ABL1 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-ABL1 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-ABL1. In preclinical studies, 40 nM was determined as the concentration of ponatinib sufficient to inhibit viability of cells expressing all tested BCR-ABL1 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-ABL1 inhibition, in peripheral blood mononuclear cells. The clinical utility of CRKL phosphorylation as a biomarker has not been established.

<u>Cardiac electrophysiology</u>

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

Previously Treated CML or Ph+ ALL (PACE Study)

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[a], 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 (PFS), and overall survival (OS).

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. The median duration of follow-up on all patients was 37.3 months (range: 0.07 months to 73.1 months). Baseline demographic characteristics are described in Table 5 below.

[a] In PACE, a month is defined as 30.43 days for all calculations.

Table 5 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	31 (7%)
2	155 (35%)
≥3	263 (59%)
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-ABL1 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.

The median duration of ICLUSIG treatment was 32.2months in CP-CML patients, 19.4 months in AP-CML patients, 2.9 months in BP-CML patients, and 2.7 months in Ph+ ALL patients. Efficacy results are summarised in Table 6 and Table 7.

Table 6 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)	40% (35-47)	35% (28-42)	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-ABL1 to ABL transcripts on the International Scale (IS) (i.e., ≤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, 79% (15/19), 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 within the first year 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-ABL1 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 2.8 months (range: 1.6 to 11.3 months) and in patients who achieved MMR, the median time to MMR was 5.5 months (range: 1.8 to 55.5 months). The median durations of MCyR and MMR had not yet been reached at data cut-off. Of the CP-CML patients who achieved MCyR and MMR, 82.4% (95% CI: 74.1-88.2) and 61.0 (95% CI: [50.6% - 69.8%]), respectively, were estimated to maintain their response after 5 years.

Table 7 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) % (95% CI)	57% (45-68)	57% (44-69)	56% (31-79)	34% (25-45)	35% (22-51)	33% (20-48)
Complete[b] (CHR) % (95% CI)	51% (39-62)	49% (37-62)	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 0.7 months (range: 0.4 to 5.8 months), 1.0 month (range: 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months), respectively.

The median duration of MaHR for patients with AP-CML (median duration of treatment: 19.4 months), BP-CML (median duration of treatment: 2.9 months), and Ph+ ALL (median duration of treatment: 2.7 months) patients was estimated as 12.9 months (range: 1.2 to 68.4 months), 6.0 months (range: 1.8 to 59.6 months), and 3.2 months (range: 1.8 to 12.8 months, respectively.

Previously Treated CP-CML (OPTIC Study)

The efficacy of ICLUSIG was evaluated in OPTIC, a dose-optimisation trial. Eligible patients had CP-CML whose disease was considered to be resistant to at least 2 prior kinase inhibitors or who have the T315I mutation. Resistance in CP-CML while on a prior kinase inhibitor was defined as failure to achieve either a complete haematologic response (by 3 months), a minor cytogenetic response (by 6 months), or a major cytogenetic response (by 12 months), or development of a new BCR-ABL1 kinase domain mutation or new clonal evolution. Patients were required to have >1% BCR-ABL1^{IS} (by real-time polymerase chain reaction) at trial entry. Patients received one of three starting dosages: 45 mg orally once daily, 30 mg orally once daily, or 15 mg orally once daily. Patients who received a starting dose of 45 mg or 30 mg had a dose reduction to 15 mg once daily upon achieving ≤1% BCR-ABL1^{IS}. The primary efficacy endpoint was a molecular response based on the achievement of ≤1% BCR-ABL1^{IS} at 12 months[a]. All patients reached the 12-month time point (primary endpoint) by the data cut-off. The median duration of follow-up for the 45 mg cohort (N=94) was 31.1 months (95% CI: 24.1, 36.0). Only the efficacy results for the recommended starting dose of 45 mg are described below.

[a] In OPTIC, a month is defined as 28 days (cycle of treatment for ponatinib) for all calculations.

A total of 282 patients received ICLUSIG: 94 received a starting dose of 45 mg, 94 received a starting dose of 30 mg, and 94 received a starting dose of 15 mg. Baseline demographic characteristics are described in Table 8 for patients who received a starting dose of 45 mg.

Table 8: Demographic and Disease Characteristics for OPTIC

Patient Characteristics at Entry	ICLUSIG 45 mg → 15 mg (N = 94)
Age	
Median years (range)	46 (19 to 81)
Sex, n (%)	
Male	50 (53%)
Race, n (%)	
White	73 (78%)
Asian	16 (17%)
Other/Unknown	4 (4%)
Black or African American	1 (1%)
ECOG Performance Status, n (%)	
ECOG 0 r 1	93 (99%)
Disease History	
Median time from diagnosis to first dose, years (range)	5.5 (1 to 21)
Resistant to Prior Kinase Inhibitor, n (%)	92 (98%)
Presence of one or more BCR-ABL1 kinase domain mutations, n (%)	41 (44%)

Number of Prior Kinase Inhibitors, n (%)	
1	1 (1%)
2	43 (46%)
≥3	50 (53%)
T315I mutation at baseline	25 (27%)
Comorbidities	
Hypertension	29 (31%)
Diabetes	5 (5%)
Hypercholesterolemia	3 (3%)
History of ischaemic heart disease	3 (3%)

Efficacy results are summarised in Table 9. The primary endpoint was met in patients who received a starting dose of 45 mg. Overall, 44% of patients had one or more BCR-ABL1 kinase domain mutations at study entry with the most frequent being T315I (27%). The subgroup analysis based on baseline T315I mutation status showed similar ≤1% BCR-ABL1^{IS} rates at 12 months in patients with and without T3151 (see Table 9 below). No mutations were detected at study entry for 54% of the patients who received the starting dose of 45 mg.

Table 9: Efficacy Results in Patients with CP-CML Who Received ICLUSIG at Starting Dose of 45 mg in OPTIC

	ICLUSIG 45 mg → 15 mg (N = 93)[a]
Molecular Response at 12 months[b]	
Overall ≤1% BCR-ABL1^{IS} Rate % (n/N) (98.3% CI)[c]	44% (41/93) (32%, 57%)
Patients with T315I mutation % (n/N) (95% CI)	44% (11/25) (24%, 65%)
Patients without T315I mutation % (n/N) (95% CI)	44% (29/66)[d] (32%, 57%)
Cytogenetic Response by 12 months	
Major (MCyR)[e] % (n/N) (95% CI)	48% (44/91)[f] (38%, 59%)
Patients with T315I mutation % (n/N) (95% CI)	52% (13/25) (31%, 72%)
Patients without T315I mutation % (n/N) (95% CI)	46% (30/65)[g] (34%, 59%)

[a] ITT population (N=93) defined as patients who had b2a2/b3a2 BCR ABL1 transcripts.

(b) Primary endpoint was ≤1% BCR-ABL1^{IS} rate at 12 months.[i] Defined as a ≤1% ratio of BCR ABL to ABL transcripts on the International Scale (IS) (i.e., ≤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).

(c) 98.3% CI is calculated using the binomial exact (Clopper-Pearson) method.

(d) Of the 93 patients, two patients did not have a baseline mutation assessment and were excluded from the response by mutation analysis.

(e) Secondary endpoint was MCyR by 12 months which combines both complete (no detectable Ph+ cells) and partial (1% to 35% Ph+ cells in at least 20 metaphases) cytogenetic responses

(f) Analysis is based on ITT cytogenetic population (N = 91) defined as patients who had a cytogenetic assessment at baseline with at least 20 metaphases examined. One patient who had a complete cytogenetic response at baseline was excluded from the analysis.

(g) Of the 91 patients, one patient did not have a baseline mutation assessment and was excluded from the response by mutation analysis.

The secondary efficacy endpoints included complete cytogenic response (CCyR) at 12 months, major molecular response (MMR) at 12 and 24 months, complete hematologic response at 3 months, time to response, duration of response, maintenance of response, progression free survival (PFS), and overall survival (OS). In addition, additional assessment included the rates of molecular response at each patient visit at 3-month intervals for 36 months based on the achievement of ≤1% BCR-ABL1^{IS}.

- At 12 months, 34% (31/91) and 17% (16/93) of patients achieved CCyR, and MMR, respectively. At 24 months, 24% (18/75) of patients achieved MMR. The median duration of MMR had not yet been reached.
- Eighty seven percent (95% CI: 79% - 93%) patients achieved or maintained a complete hematologic response at 3 months.
- A response of ≤1% BCR-ABL1^{IS} was achieved as early as 2.9 months. The median time to response was 6 (95% CI: 3.1, 6) months.
- The median duration of ponatinib treatment was 21 months,
- Of the 45 patients who had a dose reduction after achieving ≤1% BCR-ABL1^{IS}, 28 patients (62%) maintained their response at the reduced dose for at least 90 days. Of the 28 patients, 18 patients (64%) maintained the response for at least one year. Median duration of response (MR2) was not reached at data cut-off.
- Long-term outcomes (PFS and OS) were favourable. The PFS rates were 92% at 12 months and 80% at 24 months. The OS rates were 98% at 12 months and 92% at 24 months.
- The rates of efficacy response ≤1% BCR-ABL1^{IS} analysed by patient visits at prespecified timepoints were 22% (3 months), 41% (6 months), 47% (9 months), 52% (12 months), 56% (18 months), 56% (24 months), 56% (30 months) and 56% (36 months).
- The molecular response rates (measured by achievement of ≤1% BCR-ABL1^{IS}) at 12 months was lower among patients who had received treatment with ≤2 prior TKIs compared with patients who had received ≥3 prior TKIs (40% vs 48%), respectively).

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 (10 mg to 60 mg), ponatinib exhibited dose proportional increases in both C_{max} and AUC. The geometric mean (CV%) C_{max} and $AUC_{(0-T)}$ 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 severe renal impairment (creatinine clearance <30 mL/min). Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) did not have a clinically meaningful effect on the pharmacokinetics of ponatinib based on a population pharmacokinetic analysis (see Section 4.2 Dose and Method of Administration – Patients with Renal Impairment).

Hepatic impairment

A single dose of ponatinib 30 mg was administered to subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, there was no trend of increased ponatinib exposure in subjects with hepatic impairment. ICLUSIG has not been studied in patients with hepatic impairment (Child-Pugh Classes A, B and C) at doses above 30 mg. There was an increased incidence of adverse reactions in subjects with hepatic impairment compared subjects with normal hepatic function (see Section 4.2 Dose and Method of Administration – Hepatic Toxicity). Therefore, it is recommended that patients with hepatic impairment begin on a starting dose of 30 mg.

Intrinsic factors affecting ponatinib pharmacokinetics

No specific studies have been performed to evaluate the effects of age, sex, race, or body weight on ponatinib pharmacokinetics. Based on an integrated population pharmacokinetic analysis, age, sex, race, and body weight do not have clinically meaningful effect on the pharmacokinetics of ponatinib.

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 28% 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

15 mg, 30 mg, and 45 mg tablets: Store below 30°C

10 mg tablets: Store below 25°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;
10 mg: 30 film-coated tablets*
15 mg: 30 or 60 film-coated tablets
30 mg: 30 film-coated tablets*
45 mg: 30 film-coated tablets

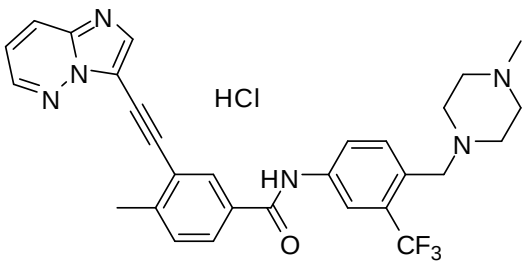
*Not marketed.

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

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9 DATE OF FIRST APPROVAL

ICLUSIG 15 mg and 45 mg film-coated tablets: 26 November 2014

ICLUSIG 10 mg and 30 mg film-coated tablets: 16 September 2022

10 DATE OF REVISION

03 April 2024

Summary table of changes

Section changed	Summary of new information
4.8	Addition of panniculitis (including erythema nodosum)
6.5	Addition of information on non-marketed strengths

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