ICLUSIG ™

WARNING: VASCULAR OCCLUSION AND HEART FAILURE

- **Vascular Occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 23% of ICLUSIG-treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, 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 thromboembolism and vascular occlusion. Interrupt or stop ICLUSIG immediately for vascular occlusion (see Precautions, Vascular Occlusion)**
- **Heart Failure, including fatalities, occurred in 8% of ICLUSIG-treated patients. Monitor cardiac function. Interrupt or stop ICLUSIG for new or worsening heart failure (see Precautions, Heart Failure)**

Name of Medicine

Active Ingredient: ponatinib *(as hydrochloride*)

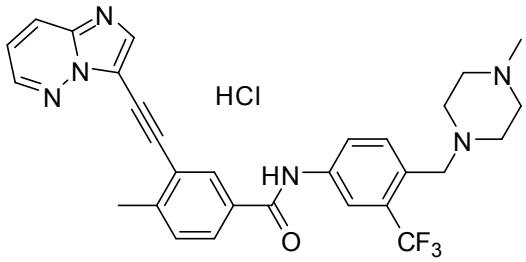
Chemical Name: *{Benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]}*

CAS Registry No: 1114544-31-8 (HCl salt)

Molecular Weight: 569.02 g/mol (HCl salt)

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

Chemical Structure:



Description

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.

ICLUSIG tablets are available as white, round, film-coated tablets for oral administration. Each tablet contains ponatinib hydrochloride equivalent to 15 or 45 mg ponatinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide, magnesium stearate and a tablet coating. The tablet film coating consists of talc, macrogol 4000, polvvinyl alcohol, and titanium dioxide.

Pharmacology

Pharmacodynamic properties

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

Ponatinib is a BCR-ABL tyrosine kinase inhibitor. *In vitro*, ponatinib inhibited the tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50} 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 IC_{50} 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. However, due to limitations in the design of this study, the possibility of QT prolongation due to ponatinib has not been excluded (**see Precautions**).

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 ng•hr/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, OATP1B3 and 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 comprising metabolites.

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 (See **Dosage and Administration**).

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, & 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. Based on these single dose pharmacokinetics data, a reduction of the starting dose of ponatinib in patients with hepatic impairment is not necessary.

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, and 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.

Clinical Studies

Clinical efficacy and safety
The safety and efficacy of ICLUSIG in chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (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% percent 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), 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), 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 prior MCyR or better (MCyR, MMR, or CMR) to dasatinib or nilotinib was only achieved in 26% patients with CP-CML and a prior MaHR or better (MaHR, MCyR, MMR, or CMR) was only achieved in 21%, and 24% of AP-CML, and BP-CML/Ph+ALL patients, respectively. At the time of analysis, patients had a minimum follow-up of 6 months (median follow-up: 10 months). Baseline demographic characteristics are described in Table 1 below.

Table 1 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 (%)	374 (88%)
Experienced failure of prior imatinib, n (%)	430 (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.

At the time of analysis, median duration of ICLUSIG treatment was 281 days in CP-CML patients, 286 days in AP-CML patients, 86 days in BP-CML/Ph+ ALL patients. Efficacy results are summarised in Table 2 and Table 3.

Table 2 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)	54% (48-60)	49% (42-56)	70% (58-81)
Complete (CCyR) % (95% CI)	44% (38-50)	37% (31-44)	66% (53-77)
Major Molecular Response [b] % (95% CI)	30% (24-36)	23% (18-30)	50% (37-63)

[a] Primary endpoint for CP-CML Cohorts was MCyR, 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 prior TKIs, 81% (13/16), 61% (65/107), and 46% (66/143) achieved a MCyR while on ICLUSIG, respectively.

Of the CP-CML patients with no mutation detected at entry, 46% (63/136) achieved a MCyR.

For every BCR-ABL mutation detected in more than one CP-CML patient at entry, a MCyR was achieved following treatment with ICLUSIG.

In CP-CML patients who achieved MCyR, the median time to MCyR was 84 days (range: 49 to 334 days) and in patients who achieved MMR, the median time to MMR was 167 days (range: 55 to 421 days). At the time of reporting, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 93% (95% CI: [85%–97%]) of CP-CML (median duration of treatment: 281 days) patients who achieved a MCyR and 84% (95% CI: [71%- 91%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 12 months.

Table 3 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)	59% (46-71)	50% (26 - 74)	34% (25-45)	35% (22-51)	33% (20-48)
Complete[b] (CHR) % (95% CI)	47% (36-58)	46% (34-59)	50% (26-74)	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, 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 289 days (range 35 to 538 days) and 108 days (range 30 to 429 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 25.3 months (range: 1.7 to 38.4+ months). At the time of reporting, 25 CP-CML patients were in MCyR (median duration of MCyR had not been reached).

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.

Contraindications

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

Precautions

Vascular occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularisation procedures, deep vein thrombosis, and pulmonary embolus, have occurred in 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 age 50 years or younger, experienced these events. Vascular occlusion particularly arterial adverse 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 adverse events over the dose range of 15 to 45 mg once-daily, including vascular occlusion and arterial thrombosis.

In the phase 2 trial, arterial and venous occlusive adverse reactions (treatment-emergent frequencies) have occurred in 23% (101/449) of patients, and serious arterial and venous occlusive adverse reactions (treatment-emergent frequencies) occurred in 18% (81/449) of patients. In a phase 1 trial in advanced leukemia patients arterial and venous occlusive adverse reactions (treatment-emergent frequencies) have occurred in 35% (28/81) of patients, and serious arterial and venous occlusive adverse reactions (treatment-emergent frequencies) occurred in 26% (21/81) of patients. 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 10% (43/449), 7% (33/449), and 7% (31/449) 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 7% (30/449), 6% (25/449), and 4% (20/449) of ICLUSIG- treated patients in the phase 2 trial, respectively.

Venous occlusive reactions (treatment-emergent frequencies) occurred in 5% (24/449) of patients in the phase 2 trial. Serious venous occlusive reactions

(treatment-emergent frequencies) occurred in 4% (20/449) of patients in the phase 2 trial.

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 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.

Cardiac Failure

Fatal and serious heart failure or left ventricular dysfunction occurred in ICLUSIG-treated patients. In the phase 2 trial, cardiac failure events occurred in 8% (37/449) of ICLUSIG-treated patients, 5.1% (23/449) 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 serious heart failure.

Hypertension

Hypertension may contribute to risk of arterial thrombotic events. During ICLUSIG treatment, blood pressure elevations should be monitored and managed. Hypertension should be treated to normalise blood pressure. ICLUSIG treatment should be temporarily interrupted if hypertension is not medically controlled.

Treatment-emergent hypertension occurred in ICLUSIG-treated patients. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.

Haemorrhage

Serious bleeding events and haemorrhage, including fatalities, occurred in ICLUSIG-treated patients. The incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Cerebral haemorrhage and gastrointestinal haemorrhage were the most commonly reported serious bleeding events. Most haemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia (see **Precautions**, Myelosuppression). Interrupt ICLUSIG for serious or severe haemorrhage and evaluate (see **Dosage and Administration**, **Myelosuppression**). Grade 3 or 4 thrombocytopenia was observed in 39.9% (179/449) of patients.

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 **Dosage and Administration**).

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.

Pancreatitis and serum lipase

ICLUSIG is associated with pancreatitis. In clinical studies, pancreatitis was observed in 7.4% (7% of the CP-CML patients, 6% of the AP-CML patients and 3% of the BP-CML/Ph+ ALL patients) with 5.8% 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 **Dosage and Administration**). 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.

QT prolongation

The QT interval prolongation potential of ICLUSIG was assessed in 39 leukaemia patients and no clinically significant QT prolongation was observed (see 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.

Lactose

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

Special populations

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, & 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. Based on these single dose pharmacokinetics data, a reduction of the starting dose of ponatinib in patients with hepatic impairment is not necessary. Caution is recommended when administering ICLUSIG to patients with moderate to severe hepatic impairment (See **Dosage and Administration**).

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.

Effects on Fertility
The effect of ICLUSIG on male and female fertility is unknown. Based on animal data, impairment of fertility is possible. Microscopic changes in the ovaries (increased follicular atresia and endometrial atrophy) and testes (minimal germ cell degeneration) were evident in monkeys that received daily oral doses of ponatinib (5 mg/kg). Exposure (AUC) at the no effect level is 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 foetal harm. Embryofoetal lethality (increased post-implantation loss), embryofetal toxicity (reduced fetal weights and whole body oedema) and teratogenicity (multiple soft tissue and skeletal abnormalities) were seen in rats that received oral doses of ponatinib (≥1 mg/kg/day; approximately 30% 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 foetus. 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.

Paediatric Patients (<18 years of age)
The safety and efficacy of ICLUSIG in patients less than 18 years of age have not been established.

Elderly Patients (≥65 years of age)

Of the 449 patients in the clinical study of ICLUSIG, 155 (35%) were ≥65 years of age. In patients with CP-CML, patients of age ≥ 65 years had a lower major cytogenetic response rate (38%) as compared with patients < 65 years of age (64%). In patients with AP-CML, BP-CML, and Ph+ ALL, patients of age ≥ 65 years had a higher major haematologic response rate (47%) as compared with patients < 65 years of age (40%). Compared to patients <65 years, patients older than 65 years may be more likely to experience adverse reactions. Thirty (46/155) percent of patients ≥ 65 years had vascular occlusion events.

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
Carcinogenicity studies have not been performed with ponatinib.

Effects on ability to drive and operate machinery
Adverse reactions such as lethargy, dizziness, and vision blurred have been associated with ICLUSIG. Therefore, caution should be recommended when driving or operating machines.

Interactions with Other Medicines

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 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.

Caution should be exercised 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 in the presence of rifampin (600 mg daily for 9 days), a strong CYP3A inducer, resulted in decreases in ponatinib systemic exposure, with ponatinib AUC_{0-inf} and C_{max} values that were 62% and 42% lower, respective to 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.

Administration of a single 45 mg dose of ponatinib following multiple doses of a potent inhibitor of gastric acid secretion (lansoprazole 60 mg QD for 2 days) resulted in a minor reductions in ponatinib C_{max} (25%) without a change in overall systemic exposure (AUC_{0-inf}), respective to those seen when ponatinib was administered alone. Median T_{max} was increased by 1 hour when ponatinib was administered following lansoprazole pretreatment.

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 Pharmacodynamics and Pharmacokinetics).

Adverse 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. At the time of reporting, the median duration of treatment with ICLUSIG was 281 days in CP-CML patients, 286 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 37 mg or, 83% of the expected 45 mg dose. The events of vascular disorders, cardiac failure, and peripheral neuropathy reported in Table 4 below include data from an additional 13 months of follow-up (median duration of treatment CP-CML: 672 days, AP-CML: 590 days, BP-CML: 89 days, Ph+ ALL: 81 days).

The most common serious adverse drug reactions (> 1%) were pancreatitis (5.1%), abdominal pain (1.8%), platelet count decreased (1.8%), lipase increased (1.3%), anaemia (1.3%), cardiac failure (1.3%), coronary artery disease (1.1%), diarrhoea (1.1%), neutrophil count decreased (1.1%), febrile neutropenia (1.1%), pancytopenia (1.1%), and pyrexia (1.1%). Overall, the most common adverse reactions (≥ 20%) were platelet count decreased, rash, dry skin, and abdominal pain.

Fifty-three patients discontinued due to adverse events of which 40 discontinued due to adverse events that were considered treatment-related. Platelet count decreased was the most common treatment-related event leading to discontinuation.

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 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, sepsis, folliculitis
Blood and lymphatic system disorders	Very common	anaemia, platelet count decreased, neutrophil count decreased
	Common	pancytopenia, febrile neutropenia, white blood cell count decreased
Metabolism and nutrition disorders	Very common	decreased appetite
	Common	dehydration, fluid retention, hypocalcaemia, hyperglycaemia, hyperuricaemia, hypophosphataemia, hypertriglyceridaemia, hypokalaemia, weight decreased
	Uncommon	tumour lysis syndrome
Psychiatric disorders	Very common	insomnia
Nervous system disorders	Very common	headache, dizziness
	Common	cerebrovascular accident, cerebral infarction, neuropathy peripheral, lethargy, migraine, hyperaesthesia, hypoaesthesia, paraesthesia, transient ischaemic attack
	Uncommon	cerebral artery stenosis
Eye disorders	Common	vision blurred, dry eye, periorbital oedema, eyelid oedema
	Uncommon	retinal vein thrombosis, retinal vein occlusion, retinal artery occlusion, visual impairment
Cardiac disorders	Common	cardiac failure, myocardial infarction, cardiac failure congestive, coronary artery disease, angina pectoris, pericardial effusion, atrial fibrillation, ejection fraction decreased

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

System organ class	Frequency	Adverse reactions
	Uncommon	myocardial ischemia, acute coronary syndrome, cardiac discomfort, ischemic cardiomyopathy, arteriospasm coronary, left ventricular dysfunction, atrial flutter
Vascular Disorders	Very common	hypertension
	Common	peripheral arterial occlusive disease, peripheral ischaemia, peripheral artery stenosis, intermittent claudication, deep vein thrombosis, hot flush, flushing
	Uncommon	poor peripheral circulation, splenic infarction, embolism venous, venous thrombosis
Respiratory, thoracic and mediastinal disorders	Very common	dyspnoea, cough
	Common	pulmonary embolism, pleural effusion, epistaxis, dysphonia, pulmonary hypertension
Gastrointestinal disorders	Very common	abdominal pain, diarrhoea, vomiting, constipation, nausea, lipase increased
	Common	pancreatitis, blood amylase increased, gastrooesophageal reflux disease, stomatitis, dyspepsia, abdominal distension, abdominal discomfort, dry mouth
	Uncommon	gastric haemorrhage
Hepatobiliary disorders	Very common	alanine aminotransferase increased, aspartate aminotransferase increased
	Common	blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased
	Uncommon	hepatotoxicity, jaundice
Skin and subcutaneous tissue disorders	Very common	rash, dry skin
	Common	rash pruritic, exfoliative rash, erythema, alopecia, pruritis, skin exfoliation, night sweats, hyperhidrosis, petechia, ecchymosis, pain of skin, dermatitis exfoliative
Musculoskeletal and connective tissue	Very common	bone pain, arthralgia, myalgia, pain in extremity, back pain, muscle spasms

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

System organ class	Frequency	Adverse reactions
disorders	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, asthenia, oedema peripheral, pyrexia, pain
	Common	chills, influenza like illness, non-cardiac chest pain, mass, face oedema

Description of selected adverse reactions

Vascular occlusion (see **Precautions** and **Dosage and Administration**).
Serious vascular occlusion occurred in patients treated with ICLUSIG: cardiovascular events in 7%, cerebrovascular events in 6%, peripheral vascular events in 5%, and venous thrombotic events in 4% of patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

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 3.6%, neutropenia and anaemia < 1% each).

Table 5: Incidence of Clinically Relevant Grade 3/4 * Laboratory Abnormalities in ≥ 2% of Patients in Any Disease Group

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)	39	34	47	45
Neutropenia (ANC decreased)	33	23	47	52
Leukopenia (WBC decreased)	25	12	33	53
Anaemia (Hgb decreased)	20	9	26	48
Lymphopenia	15	9	24	28
Biochemistry				
Lipase increased	10	11	9	5
ALT increased	8	6	8	12
Phosphorus decreased	7	6	8	9
Glucose increased	5	6	7	0
Sodium decreased	4	4	6	2
AST increased	3	3	2	3
Potassium increased	2	2	1	3
Alkaline phosphatase increased	2	1	1	4
Potassium decreased	2	<1	4	2
Bilirubin	1	<1	4	1
Amylase decreased	<1	0	0	2

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.

Dosage and Administration

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.

Consider reducing the dose of ICLUSIG to 30mg or 15mg 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 event.

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 (platelet < 50 x 10^9/L) that are unrelated to leukaemia are summarised in Table 6.

Table 6 Dose modifications for myelosuppression

ANC* < 1.0 x 10^9/L or platelet < 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 platelet ≥ 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 platelet ≥ 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 platelet ≥ 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.

Vascular occlusion
In a patient suspected of developing an arterial or venous occlusive event, ICLUSIG should be immediately interrupted. A benefit-risk consideration should guide a decision to restart ICLUSIG therapy (see **Precautions**) after the event is resolved.

Hypertension may contribute to risk of arterial thrombotic events. ICLUSIG treatment should be temporarily interrupted if hypertension is not medically controlled.

Pancreatitis and/or elevated serum lipase
Recommended modifications for pancreatic adverse reactions are summarised in Table 7.

Table 7 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 IULN*) only	Occurrence at 45 mg: • Withhold ICLUSIG and resume at 30 mg after recovery to ≤ Grade 1 (≤ 1.5 x IULN) Recurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to ≤ Grade 1 (≤ 1.5 x IULN) Recurrence at 15 mg: • Consider discontinuing ICLUSIG
Grade 3 pancreatitis	Occurrence at 45 mg: • Withhold ICLUSIG and resume at 30 mg after recovery to < Grade 2 Recurrence at 30 mg: • Withhold ICLUSIG and resume at 15 mg after recovery to < Grade 2 Recurrence at 15 mg: • Consider discontinuing ICLUSIG
Grade 4 pancreatitis	Discontinue ICLUSIG
*IULN = institution 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.

Patients with Hepatic impairment
Caution is recommended when administering ICLUSIG to patients with moderate to severe hepatic impairment (see **Precautions**).

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.

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.

Overdosage

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).

Patient Counselling Information

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

Vascular Occlusions
Inform patients that serious arterial thromboses (including 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, or leg swelling (see **Precautions**).

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 (see **Precautions**).

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 (see **Precautions**).

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 (see **Precautions**).

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 (see **Precautions**).

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 (see **Precautions**).

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 (see **Precautions**).

Embryo-Foetal Toxicity
Inform patients that ICLUSIG can cause foetal harm when administered to a pregnant woman. Advise women of the potential hazard to a foetus and to avoid becoming pregnant (see **Precautions**).

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.

Presentation and Storage Conditions

Presentation:

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.

ICLUSIG film coated tablets are supplied in high density polyethylene (HDPE) bottles with child resistant, screw-top closures.

Each bottle contains either;

- 60 15 mg film-coated tablets, or
- 30 45 mg film-coated tablets.

Storage:

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

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Poison Schedule of the Medicine:

Prescription Only Medicine (S4)

Date of First Inclusion in the ARTG

26 November 2014

Date of the Most Recent Amendment