Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Iclusig 15 mg coated tablets
Iclusig 30 mg coated tablets
Iclusig 45 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Iclusig 15 mg film-coated tablets
Each film-coated tablet contains 15 mg of ponatinib (as hydrochloride).

Excipients with known effect
Each film-coated tablet contains 40 mg of lactose monohydrate.

Iclusig 30 mg film-coated tablets
Each film-coated tablet contains 30 mg of ponatinib (as hydrochloride).

Excipients with known effect
Each film-coated tablet contains 80 mg of lactose monohydrate.

Iclusig 45 mg film-coated tablets
Each film-coated tablet contains 45 mg of ponatinib (as hydrochloride).

Excipients with known effect
Each film-coated tablet contains 120 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Iclusig 15 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 6 mm in diameter, with "A5" debossed on one side.

Iclusig 30 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 8 mm in diameter, with "C7" debossed on one side.

Iclusig 45 mg film-coated tablets
White, biconvex, round film-coated tablet that is approximately 9 mm in diameter, with “AP4” debossed on one side.

WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY
See full prescribing information for complete boxed warning
Vascular Occlusion: Arterial and venous thrombosis and occlusions have occurred in at least 27% 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 revascularization procedures.
Patients with and without cardio vascular 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.
Heart Failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure.
Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Iclusig is indicated in adult patients with

- chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

See sections 4.2 for the assessment of cardiovascular status prior to start of therapy and 4.4 for situations where an alternative treatment may be considered.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia. Haematologic support such as platelet transfusion and haematopoietic growth factors can be used during treatment if clinically indicated.

Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with ponatinib.

Posology
The recommended starting dose is 45 mg of ponatinib once daily. 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.

Patients should be monitored for response according to standard clinical guidelines.

Discontinuing ponatinib should be considered if a complete haematologic response has not occurred by 3 months (90 days).

The risk of arterial occlusive events is likely to be dose-related. Reducing the dose of Iclusig to 15 mg should be considered for CP-CML patients who have achieved a major cytogenetic response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to cytogenetic response, and BCR-ABL transcript levels (see sections 4.4 and 5.1). If dose reduction is undertaken, close monitoring of response is recommended.

Management of toxicities

Dose modifications or interruption of dosing should be considered for the management of haematological and non-haematological toxicities. In the case of severe adverse reactions, treatment should be withheld.

For patients whose adverse reactions are resolved or attenuated in severity, Iclusig may be restarted and escalation of the dose back to the daily dose used prior to the adverse reaction may be considered, if clinically appropriate.

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

Myelosuppression
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 summarized in Table 1.

Table 1 Dose modifications for myelosuppression

ANC* < 1.0 x 10^9/L or platelet < 50 x 10^9/L	First occurrence: • Iclusig should be withheld and resumed at the initial 45 mg dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Second occurrence: • Iclusig should be withheld and resumed at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Third occurrence: • Iclusig should be withheld and resumed at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
*ANC = absolute neutrophil count	

Arterial occlusion and venous thromboembolism
In a patient suspected of developing an arterial occlusive event or a venous thromboembolism, Iclusig should be immediately interrupted. A benefit-risk consideration should guide a decision to restart Iclusig therapy (see sections 4.4 and 4.8) after the event is resolved.

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

Pancreatitis
Recommended modifications for pancreatic adverse reactions are summarized in Table 2.

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

Grade 2 pancreatitis and/or asymptomatic elevation of lipase/amylase	Iclusig should be continued at the same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x IULN*) only	Occurrence at 45 mg: • Iclusig should be withheld and resumed at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 30 mg:

	• Iclusig should be withheld and resumed at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 15 mg: • Iclusig discontinuation should be considered
Grade 3 pancreatitis	Occurrence at 45 mg: • Iclusig should be withheld and resumed at 30 mg after recovery to < Grade 2 Recurrence at 30 mg: • Iclusig should be withheld and resumed at 15 mg after recovery to < Grade 2 Recurrence at 15 mg: • Iclusig discontinuation should be considered
Grade 4 pancreatitis	Iclusig should be discontinued
*IULN = institution upper limit of normal	

Hepatic toxicity
Dose interruption or discontinuation may be required as described in Table 3.

Table 3 Recommended dose modifications for hepatic toxicity

Elevation of liver transaminase > 3 × ULN* Persistent grade 2 (longer than 7 days) Grade 3 or higher	Occurrence at 45 mg: • Iclusig should be interrupted and hepatic function should be monitored • clusig should be resumed at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN), or recovery to pre-treatment grade Occurrence at 30 mg: • Iclusig should be interrupted and resumed at 15 mg after recovery to ≤ Grade 1, or recovery to pre-treatment grade Occurrence at 15 mg: • Iclusig should be discontinued
Elevation of AST or ALT ≥ 3 × ULN concurrent with an elevation of bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN	Iclusig should be discontinued

*ULN = Upper Limit of Normal for the lab

Elderly patients
Of the 449 patients in the clinical study of Iclusig, 155 (35%) were ≥ 65 years of age. Compared to patients < 65 years, older patients are more likely to experience adverse reactions.

Hepatic impairment
Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with hepatic impairment (see sections 4.4 and 5.2).

Renal impairment
Renal excretion is not a major route of ponatinib elimination. Iclusig has not been studied in patients with renal impairment. Patients with estimated creatinine clearance of ≥ 50 mL/min should be able to safely receive Iclusig with no dosage adjustment. Caution is recommended when administering Iclusig to patients with estimated creatinine clearance of < 50 mL/min, or end-stage renal disease.

Paediatric population
The safety and efficacy of Iclusig in patients less than 18 years of age have not been established. No data are available.

Method of administration
Iclusig is for oral use. The tablets should be swallowed whole. Patients should not crush or dissolve the tablets. Iclusig may be taken with or without food.

Patients should be advised not to swallow the desiccant canister found in the bottle.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Important adverse reactions

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

Arterial occlusion
Arterial occlusions, including fatal myocardial infarction, stroke, retinalarterial occlusions associated in some cases with permanent visual impairment or vision loss, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, renal artery stenosis (associated with worsening, labile or treatment-resistant hypertension), and the need for urgent revascularization procedures have occurred in Iclusig-treated patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Arterial occlusion adverse events were more frequent with increasing age and in patients withhistory of ischaemia, hypertension, diabetes, or hyperlipidaemia.

The risk of arterial occlusive events is likely to be dose-related (see sections 4.2 and 5.1).

In the phase 2 trial (with a minimum of 64 months follow-up), arterial occlusive adverse reactions have occurred in25% of patients (treatment-emergent frequencies). Some patients experienced more than 1 type of event. Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 13%, 9%, and 11% of Iclusig-treated patients, respectively.

In the phase 2 trial, serious arterial occlusive adverse reactions occurred in 20% of patients (treatment-emergent frequencies). Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 10%, 7%, and 9% of Iclusig treated patients, respectively (see section 4.8).

The median time to onset of the first cardiovascular, cerebrovascular, and peripheral vascular arterial occlusive events was 351, 611, and 605 days, respectively.

Iclusig should not be used in patients with a history of myocardial infarction, prior revascularization or stroke, unless the potential benefit of treatment outweighs the potential risk (see sections 4.2 and 4.8). In these patients, alternative treatment options should also be considered before starting treatment with ponatinib.

Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively

managed. Cardiovascular status should continue to be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with ponatinib.

Monitoring for evidence of arterial occlusion should be performed and if decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed. Iclusig should be interrupted immediately in case of arterial occlusion. A benefit -risk consideration should guide a decision to restart Iclusig therapy (see sections 4.2 and 4.8).

Venous thromboembolism
In the phase 2 trial (with a minimum of 64 months follow-up), venous thromboembolic adverse reactions have occurred in 6% of patients (treatment-emergent frequencies). Serious venous thromboembolic adverse reactions occurred in 5% of patients (treatment-emergent frequencies) (see section 4.8).

Monitoring for evidence of thromboembolism should be performed. Iclusig should be interrupted immediately in case of thromboembolism. A benefit -risk consideration should guide a decision to restart Iclusig therapy (see sections 4.2 and 4.8).

Retinal venous occlusions associated in some cases with permanent visual impairment or vision loss have occurred in Iclusig-treated patients. If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed.

Hypertension
Hypertension may contribute to risk of arterial thrombotic events, including renal artery stenosis. During Iclusig treatment, blood pressure should be monitored and managed at each clinic visit and hypertension should be treated to normal. Iclusig treatment should be temporarily interrupted if hypertension is not medically controlled (see section 4.2).

In the event of significant worsening, labile or treatment-resistant hypertension, treatment should be interrupted and evaluation for renal artery stenosis should be considered.

Treatment-emergent hypertension (including hypertensive crisis) occurred in Iclusig-treated patients. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.

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 Iclusig, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Congestive heart failure
Fatal and serious heart failure or left ventricular dysfunction occurred in Iclusig-treated patients, including events related to prior vascular occlusive events. Patients should be monitored for signs or symptoms consistent with heart failure and they should be treated as clinically indicated, including interruption of Iclusig. Discontinuation of ponatinib should be considered in patients who develop serious heart failure (see sections 4.2 and 4.8).

Pancreatitis and serum lipase
Iclusig is associated with pancreatitis. The frequency of pancreatitis is greater in the first 2 months of use. Check serum lipase every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required. If lipase elevations are accompanied by abdominal symptoms, Iclusig should be withheld and patients evaluated for evidence of pancreatitis (see section 4.2). 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.

Hepatotoxicity
Iclusig may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Most patients who had an event of hepatotoxicity had their first event during the first year of treatment. Hepatic failure (including fatal outcome) has been observed. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated.

Haemorrhage
Severe haemorrhage, including fatalities, occurred in Iclusig-treated patients. The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML and Ph+ ALL. Gastrointestinal haemorrhage and subdural hematoma were the most commonly reported grade 3/4 bleeding events. Most haemorrhagic events, but not all, occurred in patients with grade 3/4 thrombocytopenia. Iclusig should be interrupted and patient evaluated for serious or severe haemorrhage.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.
Patients should be tested for HBV infection before initiating treatment with Iclusig. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Iclusig should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Posterior Reversible Encephalopathy Syndrome
Post-marketing cases of Posterior Reversible Encephalopathy Syndrome (PRES) have been reported in Iclusig-treated patients.
PRES is a neurological disorder that can present 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 continued treatment outweighs the risk of PRES.

<u>Medicinal product interactions</u>
Caution should be exercised with concurrent use of Iclusig and moderate and strong CYP3A inhibitors and moderate and strong CYP3A inducers (see section 4.5).

Concomitant use of ponatinib with anti-clotting agents should be approached with caution in patients who may be at risk of bleeding events (see “Myelosuppression” and “Haemorrhage”). Formal studies of ponatinib with anti-clotting medicinal products have not been conducted.

<u>QT prolongation</u>
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). However, a thorough QT study has not been performed; therefore a clinically significant effect on QT cannot be excluded.

<u>Special populations</u>

Hepatic impairment
Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with hepatic impairment (see sections 4.2 and 5.2).

Renal impairment
Caution is recommended in when administering Iclusig to patients with estimated creatinine clearance of < 50 mL/min or end-stage renal disease (see section 4.2).

Lactose
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Substances that may increase ponatinib serum concentrations

CYP3A inhibitors
Ponatinib is metabolized by CYP3A4.
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 and a reduction of the starting dose of Iclusig to 30 mg should be considered with concurrent use of strong CYP3A inhibitors such as 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 Iclusig in the presence of rifampin (600 mg daily), a strong CYP3A inducer, to 19 healthy volunteers, decreased the $AUC_{0-\infty}$ and C_{max} of ponatinib by 62% and 42%, respectively, when compared to administration of ponatinib alone.

Co-administration of strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort with ponatinib should be avoided, and alternatives to the CYP3A4 inducer should be sought, unless the benefit outweighs the possible risk of ponatinib underexposure.

Substances that may have their serum concentrations altered by ponatinib

Transporter substrates
In vitro, ponatinib is an inhibitor of P-gp and 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 therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is administered with these medicinal products.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
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. It is unknown whether ponatinib affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used.

Pregnancy
Based on limited human data (less than 50 known pregnancy outcomes), cases of congenital

megacolon (Hirschsprung's disease) have been reported in children born to women exposed to ponatinib during the first trimester. Studies in animals have shown reproductive toxicity (see section 5.3). Iclusig should not be used during pregnancy unless the clinical condition of the woman requires treatment with ponatinib. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.

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

Fertility
No human data on the effect of ponatinib on fertility are available. In rats, treatment with ponatinib has shown effects on female fertility and male fertility was not affected (see section 5.3). The clinical relevance of these findings to human fertility is unknown.

4.7 Effects on ability to drive and use machines

Iclusig has minor influence on the ability to drive and use machines. Adverse reactions such as lethargy, dizziness, and vision blurred have been associated with Iclusig. Therefore, caution should be recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
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 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. Additionally, after approximately 2 years of follow-up, all patients who were still taking a 45 mg daily dose were recommended to undergo a dose reduction, even in the absence of adverse events, in response to the continued occurrence of vascular occlusive events in the clinical trial. At the time of reporting, all ongoing patients had a minimum follow-up of 64 months. The median duration of treatment with Iclusig was 32.2 months in CP-CML patients, 19.4 months in AP-CML patients, and 2.9 months in BP-CML/Ph+ ALL patients. The median dose intensity was 28 mg/day in CP-CML patients or, 63% of the expected 45 mg dose; median dose intensity was greater in advanced disease states (32 mg/day in the AP-CML patients and 44 mg/day in the BP CML/Ph+ ALL patients).

The most common serious adverse reactions > 2% (treatment-emergent frequencies) were pneumonia (7.3%), pancreatitis (5.8%), abdominal pain (4.7 atrial fibrillation (4.5%), pyrexia (4.5%), myocardial infarction (4.0%), peripheral arterial occlusive disease (3.8%), anaemia (3.8%), angina pectoris (3.3%), platelet count decreased (3.1%), febrile neutropenia (2.9%), hypertension (2.9%), coronary artery disease (2.7%), cardiac failure congestive (2.4%), cerebrovascular accident (2.4%), sepsis (2.4%), cellulitis (2.2%), acute kidney injury (2.0%), urinary tract infection (2.0%) and lipase increased (2.0%).

Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 10%, 7%, and 9% of Iclusig treated patients, respectively. Serious venous occlusive reactions (treatment-emergent frequencies) occurred in 5% of patients.

Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 13%, 9%, and 11% of Iclusig-treated patients, respectivelyOverall arterial occlusive adverse reactions have occurred in 25% of Iclusig-treated

patients from the phase 2 trial, with serious adverse reactions occurring in 20% of patients. Some patients experienced more than one type of event.

Venous thromboembolic reactions (treatment-emergent frequencies) occurred in 6% of patients. The incidence of thromboembolic events is higher in patients with Ph+ ALL or BP-CML than those with AP-CML or CP-CML. No venous occlusive events were fatal.

After a minimum follow-up of 64 months, the rates of adverse reactions resulting in discontinuation were 20% in CP-CML, 11% in AP-CML, 15% in BP-CML and 9% in Ph+ ALL.

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 < 1/1,000), 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, cellulitis
Blood and lymphatic system disorders	Very common	anaemia, platelet count decreased, neutrophil count decreased
	Common	pancytopenia, febrile neutropenia, white blood cell count decreased, lymphocyte count decreased
Endocrine disorders	Common	hypothyroidism
Metabolism and nutrition disorders	Very common	decreased appetite
	Common	dehydration, fluid retention, hypocalcaemia, hyperglycaemia, hyperuricaemia, hypophosphataemia, hypertriglyceridaemia, hypokalaemia, weight decreased, hyponatraemia
	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, cerebral haemorrhage, haemorrhage intracranial, posterior reversible encephalopathy syndrome *
Eye disorders	Common	vision blurred, dry eye, periorbital oedema, eyelid oedema, conjunctivitis, visual impairment
	Uncommon	retinal vein thrombosis, retinal vein occlusion, retinal artery occlusion

System organ class	Frequency	Adverse reactions
Cardiac disorders	Common	cardiac failure, myocardial infarction, cardiac failure congestive, coronary artery disease, angina pectoris, pericardial effusion, atrial fibrillation, ejection fraction decreased, acute coronary syndrome, atrial flutter
	Uncommon	myocardial ischemia, cardiac discomfort, ischemic cardiomyopathy, arteriospasm coronary, left ventricular dysfunction,
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, hypertensive crisis, renal artery stenosis
	Not Known	Aneurysms and artery dissections
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, 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, hepatic failure, jaundice
Skin and subcutaneous tissue disorders	Very common	rash, dry skin, pruritus
	Common	rash pruritic, exfoliative rash, erythema, alopecia, skin exfoliation, night sweats, hyperhidrosis, petechia, ecchymosis, pain of skin, dermatitis exfoliative, hyperkeratosis, skin hyperpigmentation
	Rare	panniculitis(including erythema nodosum)
Musculoskeletal and connective tissue disorders	Very common	bone pain, arthralgia, myalgia, pain in extremity, back 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, asthenia, oedema peripheral, pyrexia, pain
	Common	chills, influenza like illness, non-cardiac chest pain, mass, face oedema

* Spontaneous reports from post-marketing experience

Description of selected adverse reactions

Vascular occlusion (see section 4.2 and 4.4).
Serious vascular occlusion has occurred in patients treated with Iclusig, including cardiovascular, cerebrovascular and peripheral vascular events, and venous thrombotic events. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Arterial occlusive adverse events were more frequent with increasing age and in patients with history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

Myelosuppression
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 4%, neutropenia and anaemia < 1% each).

Hepatitis B reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Severe Cutaneous Adverse Reactions (SCARs)
Severe skin reactions (such as Stevens-Johnson Syndrome) have been reported with some BCR-ABL Tyrosine Kinase Inhibitors. Patients should be warned to immediately report suspected skin reactions, especially if associated with blistering, peeling, mucosal involvement or systemic symptoms.

Table 5 Incidence of clinically relevant grade 3/4* laboratory abnormalities in ≥ 2% of patients in any disease group from the Phase 2 Trial (N=449): minimum follow-up of 64 month for all ongoing patients

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

Hgb=haemoglobin, WBC=white blood cell count.
*Reported using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Isolated reports of unintentional overdose with Iclusig were reported in clinical trials. Single doses of 165 mg and an estimated 540 mg in two patients did not result in any clinically significant adverse reactions. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and asymptomatic, moderate pericardial effusion. Treatment was interrupted, the events resolved, and Iclusig was restarted at 45 mg, once daily. In the event of an overdose of Iclusig, the patient should be observed and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EA05

Ponatinib is a potent pan BCR-ABL inhibitor with structural elements, including a carbon-carbon triple-bond, that enable high affinity binding to native BCR-ABL and mutant forms of the ABL kinase. Ponatinib inhibits the tyrosine kinase activity of ABL and T315I mutant ABL with IC_{50} values of 0.4 and 2.0 nM, respectively. In cellular assays, ponatinib was able to overcome imatinib, dasatinib, and nilotinib resistance mediated by BCR-ABL kinase domain mutations. In preclinical mutagenesis 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) and suppress the emergence of mutant clones. In a cell-based accelerated mutagenesis assay, no mutation in BCR-ABL was detected that could confer resistance to 40 nM ponatinib.
Ponatinib elicited tumour shrinkage and prolonged survival in mice bearing tumours expressing native or T315I mutant BCR-ABL.
At doses of 30 mg or greater plasma steady state trough concentrations of ponatinib typically exceed 21 ng/mL (40 nM). At doses of 15 mg or greater, 32 of 34 patients (94%) demonstrated a ≥ 50% reduction of CRK-like (CRKL) phosphorylation, a biomarker of BCR-ABL inhibition, in peripheral blood mononuclear cells.
Ponatinib inhibits the activity of other clinically relevant kinases with IC_{50} values below 20 nM and has demonstrated cellular activity against RET, FLT3, and KIT and members of the FGFR, PDGFR, and VEGFR families of kinases.

Clinical efficacy and safety
The safety and efficacy of Iclusig in CML and Ph+ ALL patients who were resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy were evaluated in a single-arm, open-label, international, multicenter 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 (CP-CML; AP-CML; or BP-CML/Ph+

ALL), resistance or intolerance (R/I) to dasatinib or nilotinib, and the presence of the T315I mutation. The trial is ongoing.

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. Also, post-hoc analyses to assess the relationship of shorter-term cytogenetic (MCyR) and molecular (MMR) response outcomes with longer-term outcomes of PFS and OS, maintenance of response (MCyR and MMR) after dose reductions, and PFS and OS by Arterial Occlusive Event status were conducted.

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. Baseline demographic characteristics are described in Table 6 below.

Table 6 Demographics and disease characteristics

Patient characteristics at entry	Total safety population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease history	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)

Resistant to Prior TKI Therapy [a] *, n (%)	374 (88%)
Prior TKI therapy– number of regimens, n (%)	
1	32 (7%)
2	155 (35%)
≥ 3	262 (58%)
BCR-ABL mutation detected at entry, n (%)[b]	
None	198 (44%)
1	192 (43%)
≥ 2	54 (12%)
[a]* of 427 patients reporting prior TKI therapy with dasatinib or nilotinib [b] Of the patients with one or more BCR-ABL kinase domain mutations detected at entry, 37 unique mutations were detected.	

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 E359V (4%). In 67% of CP-CML patients in the R/I cohort, no mutations were detected at study entry.

Efficacy results are summarized in Table 7, Table 8, and Table 9.

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

	Overall (N=267)	**Resistant or Intolerant**	
		R/I Cohort (N=203)	**T315I Cohort (N=64)**
Cytogenetic Response			
Major (MCyR) [a] % (95% CI)	 55% (49-62)	 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, 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). Database cutoff date 06 February 2017			

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, three or four prior TKIs, 75% (12/16), 68% (66/97), 44% (63/142), and 58% (7/12)) achieved a MCyR while on Iclusig, respectively.

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

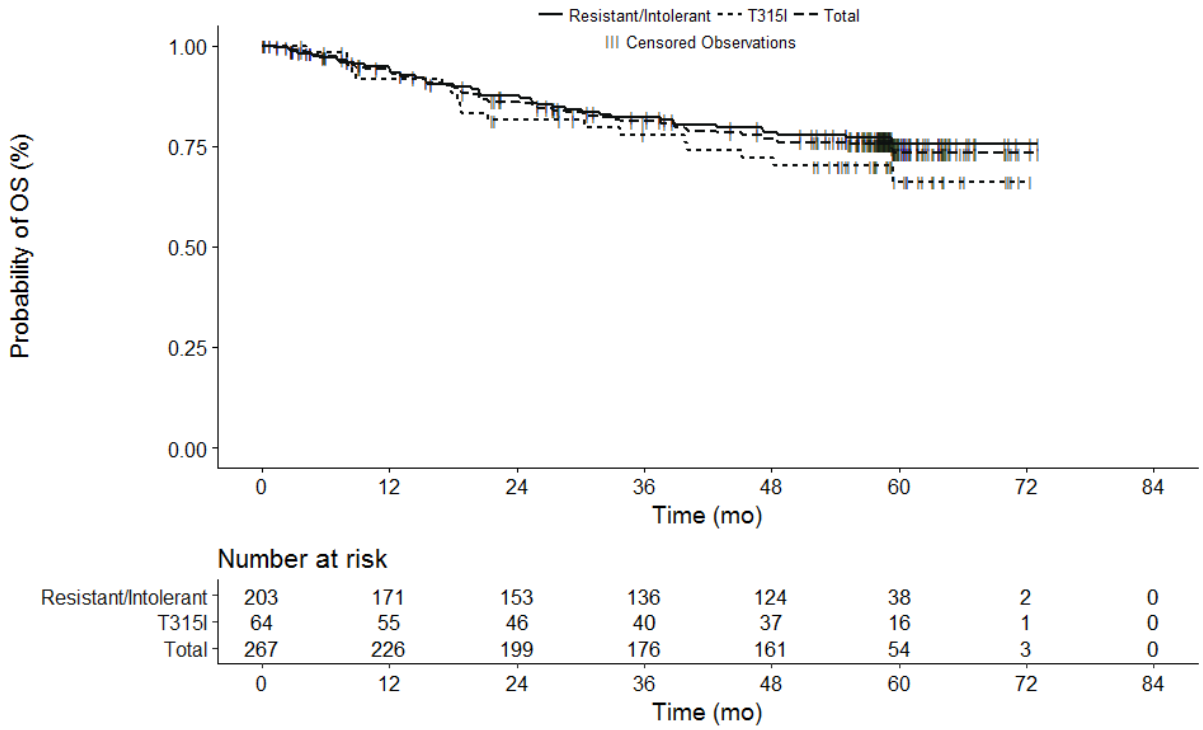
In CP-CML patients who achieved MCyR, the median time to MCyR was 2.8 months (range: 1.6 to 11.3 months) and in patients who achieved MMR, the median time to MMR was 5.5 months (range: 1.8 to 55.5 months). At the time of updated reporting with minimum follow-up for all ongoing patients of 64 months, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 82% (95% CI: [74%–88%]) of CP-CML (median duration of treatment:

32.2 months) patients who achieved a MCyR are projected to maintain that response at 48 months; and 61% (95% CI: [51%- 70%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 36 months. The probability of all patients with CP CML maintaining MCyR and MMR did not change further when the analysis was extended out to 5 years.

With a minimum follow-up of 64 months, 3.4% (9/267) of CP-CML patients experienced transformation of their disease to AP-CML or BP-CML.

For CP-CML patients overall (N=267), as well as for CP-CML R/I Cohort A patients (N=203) and T315I Cohort B patients (N=64), the median OS has not yet been reached. For the overall CP-CML disease group, the probability of survival at 2, 3, 4, and 5 years is estimated as 86.0%, 81.2%, 76.9%, and 73.3%, respectively, as shown in Figure 1.

Figure 1- Kaplan-Meier estimates for overall survival in the CP-CML population (Treated Population)



CP -CML patients who achieved MCyR or MMR response within the first year of treatment had statistically significantly improved progression-free (PFS) and overall survival (OS) compared to those patients who did not meet the treatment milestones. A MCyR at the 3-month landmark correlated strongly and statistically significantly with PFS and OS ($p<0.0001$ and $p=0.0006$, respectively). Statistical significance was achieved in the correlation of PFS and OS with a MCyR at the 12-month landmark ($p=<0.0001$ and $p=0.0012$, respectively).

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

	Accelerated Phase CML			Blast Phase CML		
	Overall (N=83)	Resistant or Intolerant		Overall (N=62)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)		R/I Cohort (N=38)	T315I Cohort (N=24)
Haematological Response Rate						
Major[a] (MaHR) % (95% CI)	57% (45-68)	57% (44-69)	56% (31-79)	31% (20–44)	32% (18–49)	29% (13–51)
Complete[b] (CHR) % (95% CI)	51% (39-62)	49% (37-62)	56% (31-79)	21% (12-33)	24% (11-40)	17% (5-37)
Major Cytogenetic Response[c] % (95% CI)	39% (28-50)	34% (23-47)	56% (31-79)	23% (13-35)	18% (8-34)	29% (13-51)

[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 ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, 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.
Database cutoff date 06 February 2017

Table 9 Efficacy of Iclusig in resistant or intolerant Ph+ ALL patients

	Overall (N=32)	Resistant or Intolerant	
		R/I Cohort (N=10)	T315I Cohort (N=22)
Haematological Response Rate			
Major[a] (MaHR) % (95% CI)	41% (24-59)	50% (19-81)	36% (17-59)
Complete[b] (CHR) % (95% CI)	34% (19-53)	40% (12-74)	32% (14-55)
Major Cytogenetic Response[c] % (95% CI)	47% (29-65)	60% (26-88)	41% (21-64)

[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 ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, 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.
Database cutoff date 06 February 2017

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 0.7 months (range: 0.4 to 5.8 months), 1.0 months (range: 0.4 to 3.7 months), and 0.7 months (range: 0.4 to 5.5 months),

respectively. At the time of updated reporting with minimum follow-up for all ongoing patients of 64 months, the median duration of MaHR for 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 12.8months), respectively.

For all patients in the phase 2 trial, the dose intensity-safety relationship indicated that there are significant increases in grade ≥ 3 adverse events (cardiac failure, arterial thrombosis, hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression, arthralgia) over the dose range of 15 to 45 mg once-daily.

The analysis of the dose intensity-safety relationship in the phase 2 trial concluded that after adjusting for covariates, the overall dose intensity is significantly associated with an increased risk of vascular occlusion, with an odds ratio of approximately 1.6 for each 15 mg increase. In addition, results from logistic regression analyses of data from patients in the phase 1 trial, suggest a relationship between systemic exposure (AUC) and occurrence of arterial thrombotic events. A reduction in dose is therefore expected to reduce the risk of vascular occlusive events, however, the analysis suggested that there may be a 'carry over' effect of higher doses such that it might take up to several months before a dose reduction manifests in risk reduction. Other covariates that show a statistically significant association with the occurrence of vascular occlusive events in this analysis are medical history of ischemia and age.

Dose reduction in CP-CML patients

In the phase 2 trial, dose reductions were recommended following adverse events; in addition in October 2013 new recommendations for prospective dose reduction in all CP-CML patients in the absence of adverse events were introduced in this trial with the aim of reducing the risk of vascular occlusive events.
With a minimum follow-up of 48 months, and approximately 2 years after the recommendation for prospective dose reduction, there were 110 CP-CML patients ongoing. A majority of these ongoing patients (82/110 patients; 75%) were reported to be receiving 15 mg at the last dose, while 24/110 patients (22%) were receiving 30 mg, and 4/110 (4%) were receiving 45 mg. At the time of study closure initiation (minimum follow-up of 64 months, and more than 3 years after the recommendation for prospective dose reduction), 99 CP-CML patients were ongoing and 77 (78%) of these patients received 15 mg as their last dose on study.

Safety
In the phase 2 trial, 86 CP-CML patients achieved MCyR at a dose of 45 mg, 45 CP-CML patients achieved MCyR after a dose reduction to 30 mg, mostly for adverse events.
Vascular occlusive events occurred in 44 of these 131 patients. Most of these events occurred at the dose at which the patient achieved MCyR; fewer events occurred after dose reduction.

Table 10 Vascular occlusive first adverse events in CP-CML patients who achieved MCyR at 45 mg or 30 mg (data extraction 7 April 2014)

	Most recent dose at onset of first vascular occlusive event		
	45 mg	**30 mg**	**15 mg**
Achieved MCyR at 45 mg (N=86)	19	6	0
Achieved MCyR at 30 mg (N=45)	1	13	5

The median time to onset of the first cardiovascular, cerebrovascular, and peripheral vascular arterial occlusive events was 351, 611, and 605 days, respectively. When adjusted for exposure, the incidence of first arterial occlusive events was greatest in the first two years of follow-up and declined with decreasing daily dose intensity (following recommendation for prospective dose reduction). Factors other than dose may also contribute to this risk of arterial occlusion.

Efficacy
Data from the phase 2 trial are available on the maintenance of response (MCyR and MMR) in all CP-CML patients who underwent dose reduction for any reason. Table 11 shows these data for patients who achieved MCyR and MMR at 45 mg; similar data are available for patients who achieved MCyR and MMR at 30 mg.
The majority of patients who underwent dose reduction maintained response (MCyR and MMR) for the duration of currently available follow-up. A proportion of patients did not undergo any dose reduction, based on an individual benefit-risk assessment.

Table 11 Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45 mg dose (data extraction 06 February 2017)

	Achieved MCyR at 45 mg (N=86)		**Achieved MMR at 45 mg (N=63)**	
	Number of patients	**Maintained MCyR**	**Number of patients**	**Maintained MMR**
No dose reduction	19	13 (68%)	18	11 (61%)
Dose reduction to 30 mg only	15	13 (87%)	5	3 (60%)
≥ 3 month reduction at 30 mg	12	10 (83%)	3	2 (67%)
≥ 6 month reduction at 30 mg	11	9 (82%)	3	2 (67%)
≥ 12 month reduction at 30 mg	8	7 (88%)	3	2 (67%)
≥ 18 month reduction at 30 mg	7	6 (86%)	2	2 (100%)
≥ 24 month reduction at 30 mg	6	6 (100%)	2	2 (100%)
≥ 36 month reduction at 30 mg	1	1 (100%)	--	--
Any dose reduction to 15 mg	52	51 (98%)	40	36 (90%)
≥ 3 month reduction at 15 mg	49	49 (100%)	39	36 (92%)
≥ 6 month reduction at 15 mg	47	47 (100%)	37	35 (95%)
≥ 12 month reduction at 15 mg	44	44 (100%)	34	33 (97%)
≥ 18 month day reduction at 15 mg	38	38 (100%)	29	29 (100%)
≥ 24 month reduction at 15 mg	32	32 (100%)	23	23 (100%)
≥ 36 month reduction at 15 mg	8	8 (100%)	4	4 (100%)

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 completed. Of 43 CP-CML patients, 31 CP-CML patients achieved a MCyR with a median duration of follow-up of 55.5months (range: 1.7 to 91.4months). At the time of reporting, 25 CP-CML patients were in MCyR (median duration of MCyR had not been reached).

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.

5.2 Pharmacokinetic properties

Absorption
Peak concentrations of ponatinib are observed approximately 4 hours after oral administration. Within the range of clinically relevant doses evaluated in patients (15 mg to 60 mg), ponatinib exhibited dose proportional increases in both C_{max} and AUC. The geometric mean (CV%) C_{max} and $AUC_{(0-\tau)}$ exposures achieved for ponatinib 45 mg daily at steady state were 77 ng/mL (50%) and 1296 ng•hr/mL (48%), respectively. 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. Co-administration of Iclusig with a potent inhibitor of gastric acid secretion resulted in a minor reduction in ponatinib C_{max} without a reduction in $AUC_{0-\infty}$.

Distribution
Ponatinib is highly bound (> 99%) to plasma proteins *in vitro*. The blood/plasma ratio of ponatinib is 0.96. Ponatinib is not displaced by concomitant administration of ibuprofen, nifedipine, propranolol, salicylic acid, or warfarin. At daily doses of 45 mg, the geometric mean (CV%) apparent steady state volume of distribution is 1101 L (94%) suggesting that ponatinib is extensively distributed in the extravascular space. *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.

Biotransformation
Ponatinib is metabolized to an inactive carboxylic acid by esterases and/or amidases, and metabolized by CYP3A4 to an N-desmethyl metabolite that is 4 times less active than ponatinib. The carboxylic acid and the N-desmethyl metabolite comprise 58% and 2% of the circulating levels of ponatinib, respectively.

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. *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.

Elimination
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. Although plasma ponatinib exposures increased to steady-state levels with continuous dosing, a population pharmacokinetic analysis predicts a limited increase in apparent oral clearance within the first two weeks of continuous dosing, which is not considered clinically relevant. 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. Although renal excretion is not a major route of ponatinib elimination, the potential for moderate or severe renal impairment to affect hepatic elimination has not been determined (see section 4.2).

Hepatic impairment
A single dose of 30 mg ponatinib was administered to patients with mild, moderate, or severe hepatic impairment and to healthy volunteers with normal hepatic function. Ponatinib C_{max} was comparable in patients with mild hepatic impairment and healthy volunteers with normal hepatic function. In patients with moderate or severe hepatic impairment, ponatinib C_{max} and $AUC_{0-\infty}$ were lower and ponatinib plasma elimination half-life was longer in patients with mild, moderate, and severe hepatic impairment but not clinically significantly different than in healthy volunteers with normal hepatic function.

In vitro data showed no difference in plasma protein binding in plasma samples of healthy subjects and hepatically impaired (mild, moderate and severe) subjects. Compared to healthy volunteers with normal liver function, no major differences in ponatinib PK were observed in patients with varying degrees of hepatic impairment. A reduction of the starting dose of Iclusig in patients with hepatic impairment is not necessary (see sections 4.2 and 4.4).

Caution is recommended when administering Iclusig to patients with hepatic impairment (see sections 4.2 and 4.4).

Iclusig has not been studied at doses above 30 mg in patients with hepatic impairment (Childs-Pugh Classes A, B & C).

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.

5.3 Preclinical safety data

Iclusig has been evaluated in safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive toxicity, phototoxicity and carcinogenicity studies.

Ponatinib did not exhibit genotoxic properties when evaluated in the standard *in vitro* and *in vivo* systems.

Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use are described below.

Depletion of lymphoid organs was observed in repeat-dose toxicity studies in rats and cynomolgus monkeys. The effects were shown to be reversible after withdrawal of the treatment.

Hyper-/hypoplastic changes of the chondrocytes in the physis were noted in repeat-dose toxicity studies in rats.

In rats, inflammatory changes accompanied by increases in neutrophils, monocytes, eosinophils, and fibrinogen levels were found in the preputial and clitoral glands following chronic dosing.

Skin changes in the form of crusts, hyperkeratosis, or erythema were observed in toxicity studies in cynomolgus monkeys. Dry flaky skin was observed in toxicity studies in rats.

In a study in rats, diffuse corneal edema with neutrophilic cell infiltration, and hyperplastic changes in the lenticular epithelium suggestive of a mild phototoxic reaction were observed in animals treated with 5 and 10 mg/kg ponatinib.

In cynomolgus monkeys, systolic heart murmurs with no macroscopic or microscopic correlates were noted in individual animals treated with 5 and 45 mg/kg in the single dose toxicity study and at 1, 2.5

and 5 mg/kg in the 4-week repeat-dose toxicity study. The clinical relevance of this finding is unknown.

In cynomolgus monkeys, thyroid gland follicular atrophy mostly accompanied by a reduction in T3 levels and a tendency toward increased TSH levels were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys.

Ponatinib-related microscopic findings in the ovaries (increased follicular atresia) and testes (minimal germ cell degeneration) in animals treated with 5 mg/kg ponatinib were noted in repeat-dose toxicity studies in cynomolgus monkeys.

Ponatinib at doses of 3, 10, and 30 mg/kg produced increases in urine output and electrolyte excretions and caused a decrease in gastric emptying in safety pharmacology studies in rats.

In rats, embryo-foetal toxicity in the form of post-implantation loss, reduced foetal body weight, and multiple soft tissue and skeletal alterations were observed at maternal toxic dosages. Multiple foetal soft tissue and skeletal alterations were also observed at maternal nontoxic dosages.

In a fertility study in male and female rats, female fertility parameters were reduced at dose levels corresponding to human clinical exposures. Evidence for pre- and post-implantation loss of embryos was reported in female rats and ponatinib may therefore impair female fertility. There were no effects on male rat fertility parameters. The clinical relevance of these findings on human fertility is unknown.

In juvenile rats, mortality related to inflammatory effects was observed in animals treated with 3 mg/kg/day, and reductions in body weight gain were observed at doses of 0.75, 1.5 and 3 mg/kg/day during the pre-weaning and early post-weaning treatment phases. Ponatinib did not adversely affect important developmental parameters in the juvenile toxicity study.

In a two-year carcinogenicity study in male and female rats, oral administration of ponatinib at 0.05, 0.1 and 0.2 mg/kg/day in males and at 0.2 and 0.4 mg/kg/day in females did not result in any tumorigenic effects. The 0.8 mg/kg/day dose in females resulted in a plasma exposure level generally lower or equivalent to the human exposure at the range of dose from 15 mg to 45 mg daily. A statistically significant increased incidence of squamous cell carcinoma of the clitoral gland was observed at that dose. The clinical relevance of this finding for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Colloidal silicone dioxide
Magnesium stearate

Tablet coating
Talc
Polyethylene glycol
Polyvinyl alcohol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: use within 60 days.

6.4 Special precautions for storage

Store in the original container in order to protect from light at a temperature below 25 °C.
The bottle contains one sealed canister containing molecular sieve desiccant. Keep the canister in the bottle.

6.5 Nature and contents of container

Iclusig 15 mg film-coated tablets
High density polyethylene (HDPE) bottles with screw-top closures, containing either 30 film-coated tablets, together with one plastic canister containing a molecular sieve desiccant.

Iclusig 30 mg film-coated tablets
High density polyethylene (HDPE) bottles with screw-top closures, containing 30 film-coated tablets, together with one plastic canister containing a molecular sieve desiccant.

Iclusig 45 mg film-coated tablets
High density polyethylene (HDPE) bottles with screw-top closures, containing either 30 film-coated tablets, together with one plastic canister containing a molecular sieve desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal

No special requirements for disposal.

7. MANUFACTURER

Incyte Biosciences Distribution B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

8. LICENSE HOLDER

Medison Pharma Ltd.
Hashiloah 10, POB 7090
Petach-Tikva.

9. REGISTRATION NUMBERS

Iclusig 15 mg -coated tablets
153-53-34243
Iclusig 30 mg coated tablets

159-07-35088

Iclusig 45 mg -coated tablets
153-54-34244

Revised in June 2026 according to MOHs guidelines.

Iclusig -SPC-0626- V1