Product Information as approved by the CHMP on 23 October 2014, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Iclusig 15 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

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 Assessment of cardiovascular status prior to start of therapy and 4.4 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.

Consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).

The risk of vascular occlusive events is likely to be dose-related. There is insufficient data available to make formal recommendations on dose reduction (in the absence of an adverse event) in patients with chronic phase (CP) CML patients who have achieved Major Cytogenetic Response. If a dose reduction is considered, the following factors should be to taken into account in the individual benefit-risk 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 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: • 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	

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 sections 4.4 and 4.8) 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
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	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	

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 severe hepatic impairment (see section 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

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

4.3 Contraindications

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

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 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. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

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

In the phase 2 trial, arterial and venous occlusive adverse reactions have occurred in 23% 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 9.6%, 7.3%, and 6.9% of Iclusig-treated patients, respectively. Venous occlusive reactions (treatment-emergent frequencies) occurred in 5.0% of patients.

In the phase 2 trial, serious arterial and venous occlusive adverse reactions occurred in 18% of patients (treatment-emergent frequencies). Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 6.7%, 5.6%, and 5.1% of Iclusig treated patients, respectively. Serious venous occlusive reactions (treatment-emergent frequencies) occurred in 4.5% of patients (see section 4.8).

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 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 (see sections 4.2 and 4.8).

Hypertension may contribute to risk of arterial thrombotic events. 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).

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.

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. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of ponatinib 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.

Liver function abnormality
Iclusig may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated.

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 3/4 thrombocytopenia. Interrupt Iclusig for serious or severe haemorrhage and evaluate.

<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.

Special populations

Hepatic impairment
Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with severe hepatic impairment (see section 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
There are no adequate data from the use of Iclusig in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. 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.

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
The effect of Iclusig on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Iclusig has a 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. At the time of reporting, all ongoing patients had a minimum follow-up of 27 months. The median duration of treatment with Iclusig was 866 days in CP-CML patients, 590 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 36 mg or, 80% of the expected 45 mg dose.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were pancreatitis (5.6%), pyrexia (4.2%), abdominal pain (4.0%), myocardial infarction (3.6%), atrial fibrillation (3.3%), anaemia, (3.3%), platelet count decreased (3.1%), febrile neutropenia (2.9%), cardiac failure (2.0%), lipase increased (1.8%), dyspnea (1.6%), diarrhoea (1.6%), neutrophil count decreased (1.3%), pancytopenia (1.3%), and pericardial effusion (1.3%).

Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 6.7%, 5.6%, and 5.1% of Iclusig treated patients, respectively. Serious venous occlusive reactions (treatment-emergent frequencies) occurred in 4.5% of patients.

Overall, the most common adverse reactions (≥20%) were platelet count decreased, rash, dry skin, and abdominal pain.

Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 9.6%, 7.3%, and 6.9% of Iclusig-treated patients, respectively. Venous occlusive reactions (treatment-emergent frequencies) occurred in 5.0% of patients. Overall arterial and venous occlusive adverse reactions have occurred in 23% of Iclusig-treated patients from the phase 2 trial, with serious adverse reactions occurring in 18% of patients. Some patients experienced more than one type of event.

The rates of treatment-related adverse events resulting in discontinuation were 14% in CP-CML, 7% in AP-CML and 4% in BP-CML/Ph+ ALL.

Tabulated list of adverse reactions

Adverse reactions reported in all CML and Ph+ ALL patients are presented in Table 3. 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 3 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
	Uncommon	myocardial ischemia, acute coronary syndrome, cardiac discomfort, ischemic cardiomyopathy, arteriospasm coronary, left ventricular dysfunction, atrial flutter,
Vascular Disorders	Very common	hypertension

System organ class	Frequency	Adverse reactions
	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 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

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. Vascular occlusive adverse events were more frequent with increasing age and in patients with prior 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 4). 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 4.5%, neutropenia and anaemia <1% each).

Table 4 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)	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	13	12	13	14
Phosphorus decreased	9	9	12	9
Glucose increased	7	7	12	1
ALT increased	6	4	8	7
Sodium decreased	5	5	6	2
AST increased	4	3	6	3
Potassium increased	2	2	1	3
Alkaline phosphatase increased	2	1	4	2
Bilirubin	1	<1	2	1
Potassium decreased	2	<1	5	2
Amylase increased	3	3	2	3
Calcium decreased	1	<1	2	1

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

Reporting 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 agent, protein kinase inhibitor, ATC code: L01XE24

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 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.

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 5 below.

Table 5 Demographics and disease characteristics

Patient characteristics at entry	Total safety population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)
Resistant to Prior TKI Therapy*, n (%)	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 (%)	
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 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 6, Table 7, and Table 8.

Table 6 Efficacy of Iclusig in resistant or intolerant chronic phase CML patients

	Overall (N=267)	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response			
Major (MCyR) [a]			
%	54%	49%	70%
(95% CI)	(48-60)	(42-56)	(58-81)
Complete (CCyR)			
%	44%	37%	66%
(95% CI)	(38-50)	(31-44)	(53-77)
Major Molecular Response [b]			
%	30%	23%	50%
(95% CI)	(24-36)	(18-30)	(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% (65/105), 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 updated reporting with minimum follow-up for all ongoing patients of 27 months, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 87% (95% CI: [78%–92%]) of CP-CML (median duration of treatment: 866 days) patients who achieved a MCyR and 66% (95% CI: [55%- 75%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 24 months.

Table 7 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)	58% (47-69)	60% (47-72)	50% (26 - 74)	31% (20 – 44)	32% (18 – 49)	29% (13 – 51)
Complete[b] (CHR) % (95% CI)	47% (36-58)	46% (34-49)	50% (26-74)	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 ≥1000/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.

Table 8 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% (12-73)	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 ≥1000/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.

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 21 days (range: 12 to 176 days), 29 days (range: 12 to 113 days), and 20 days (range: 11 to 168 days), respectively. At the time

of updated reporting with minimum follow-up for all ongoing patients of 27 months, the median duration of MaHR for AP-CML (median duration of treatment: 590 days) BP-CML (median duration of treatment: 89 days), and Ph+ ALL (median duration of treatment: 81 days) patients was estimated as 13.1 months (range: 1.2 to 35.8+ months), 6.1 months (range: 1.8 to 31.8+ months), and 3.3 months (range: 1.8 to 13.0 months), 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) 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 15mg 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.

Safety
In the phase 2 trial, 87 CP-CML patients achieved MCyR at a dose of 45mg, 45 CP-CML patients achieved MCyR after a dose reduction to 30mg, mostly for adverse events.
Vascular occlusive events occurred in 44 of these 132 patients. Most of these events occurred at the dose at which the patient achieved MCyR; fewer events occurred after dose reduction.

Table 9 Vascular Occlusive First Adverse Events in CP-CML Patients who Achieved MCyR at 45 mg or 30mg (data extraction 7 April 2014)

	Most Recent Dose at Onset of First Vascular Occlusive Event		
	45mg	**30mg**	**15mg**
Achieved MCyR at 45mg (N=87)	19	6	0
Achieved MCyR at 30mg (N=45)	1	13	5

Efficacy
Preliminary 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 10 shows these data for patients who achieved MCyR and MMR at 45mg; similar data are available for patients who achieved MCyR and MMR at 30mg.
The majority of patients who underwent dose reduction maintained response (MCyR and MMR) for the duration of currently available follow-up. Most patients who ultimately reduced dose to 15mg initially had their dose reduced to 30mg for a period. A proportion of patients did not undergo any dose reduction, based on an individual benefit-risk assessment.
Further data on maintenance of response are required in order to make a formal recommendation for dose modifications in the absence of an adverse event as a risk minimisation strategy (see sections 4.2 and 4.4).

Table 10 Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45mg dose (data extraction 7 April 2014)

	Achieved MCyR at 45 mg (N=87)		Achieved MMR at 45mg (N=63)	
	Number of Patients	**Maintained MCyR**	**Number of Patients**	**Maintained MMR**
No Dose Reduction	23	18 (78%)	18	11 (61%)
Dose reduction to 30 mg only	25	24 (96%)	13	11 (85%)
≥ 90 day reduction at 30 mg	21	20 (95%)	8	9 (89%)
≥ 180 day reduction at 30 mg	11	10 (89%)	5	4 (80%)
≥ 360 day reduction at 30 mg	5	4 (80%)	2	1 (50%)
Any dose reduction to 15 mg	39	39 (100%)	32	30 (94%)
≥ 90 day reduction at 15 mg	32	32 (100%)	27	26 (96%)
≥ 180 day reduction at 15 mg	10	10 (100%)	6	6 (100%)
≥ 360 day reduction at 15 mg	6	6 (100%)	3	3 (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 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).

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Iclusig in children from birth to less than 1 year in CML and Ph+ ALL. The European Medicines Agency has deferred the obligation to submit the results of studies with Iclusig in paediatric patients from 1 year to less than 18 years in CML and Ph+ ALL (see section 4.2 for information on paediatric use).

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.

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).

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, and phototoxicity 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Colloidal anhydrous silica
Magnesium stearate

Tablet coating
Talc
Macrogol 4000
Poly(vinyl alcohol)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original container in order to protect from light.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with screw-top closures, containing either 60 or 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

ARIAD Pharma Ltd.
Riverbridge House
Guildford Road
Leatherhead
Surrey KT22 9AD
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/839/001

EU/1/13/839/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Iclusig 45 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Iclusig is indicated 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 Assessment of cardiovascular status prior to start of therapy and 4.4 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.

Consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).

The risk of vascular occlusive events is likely to be dose-related. There is insufficient data available to make formal recommendations on dose reduction (in the absence of an adverse event) in patients with chronic phase (CP) CML patients who have achieved Major Cytogenetic Response. If a dose reduction is considered, the following factors should be to taken into account in the individual benefit-risk 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 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: • 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	

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 sections 4.4 and 4.8) 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
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	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	

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 severe hepatic impairment (see section 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

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

4.3 Contraindications

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

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 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. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

The risk of vascular occlusive events is likely to be dose-related (see sections 4.2 and 5.1).
In the phase 2 trial, arterial and venous occlusive adverse reactions have occurred in 23% 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 9.6%, 7.3%, and 6.9% of Iclusig-treated patients, respectively. Venous occlusive reactions (treatment-emergent frequencies) occurred in 5.0% of patients.

In the phase 2 trial, serious arterial and venous occlusive adverse reactions occurred in 18% of patients (treatment-emergent frequencies). Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 6.7%, 5.6%, and 5.1% of Iclusig treated patients, respectively. Serious venous occlusive reactions (treatment-emergent frequencies) occurred in 4.5% of patients (see section 4.8).

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 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 (see sections 4.2 and 4.8).

Hypertension may contribute to risk of arterial thrombotic events. 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).

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.

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. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of ponatinib 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.

Liver function abnormality
Iclusig may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated.

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 3/4 thrombocytopenia. Interrupt Iclusig for serious or severe haemorrhage and evaluate.

<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.

Special populations

Hepatic impairment
Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with severe hepatic impairment (see section 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
There are no adequate data from the use of Iclusig in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. 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.

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
The effect of Iclusig on male and female fertility is unknown.

4.7 *Effects on ability to drive and use machines*

Iclusig has a 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. At the time of reporting, all ongoing patients had a minimum follow-up of 27 months. The median duration of treatment with Iclusig was 866 days in CP-CML patients, 590 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 36 mg or, 80% of the expected 45 mg dose.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were pancreatitis (5.6%), pyrexia (4.2%), abdominal pain (4.0%), myocardial infarction (3.6%), atrial fibrillation (3.3%), anaemia, (3.3%), platelet count decreased (3.1%), febrile neutropenia (2.9%), cardiac failure (2.0%), lipase increased (1.8%), dyspnea (1.6%), diarrhoea (1.6%), neutrophil count decreased (1.3%), pancytopenia (1.3%), and pericardial effusion (1.3%).

Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 6.7%, 5.6%, and 5.1% of Iclusig treated patients, respectively. Serious venous occlusive reactions (treatment-emergent frequencies) occurred in 4.5% of patients.

Overall, the most common adverse reactions (≥20%) were platelet count decreased, rash, dry skin, and abdominal pain.

Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 9.6%, 7.3%, and 6.9% of Iclusig-treated patients, respectively. Venous occlusive reactions (treatment-emergent frequencies) occurred in 5.0% of patients. Overall arterial and venous occlusive adverse reactions have occurred in 23% of Iclusig-treated patients from the phase 2 trial, with serious adverse reactions occurring in 18% of patients. Some patients experienced more than one type of event.

The rates of treatment-related adverse events resulting in discontinuation were 14% in CP-CML, 7% in AP-CML and 4% in BP-CML/Ph+ ALL.

Tabulated list of adverse reactions

Adverse reactions reported in all CML and Ph+ ALL patients are presented in Table 3. 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 3 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
	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

System organ class	Frequency	Adverse reactions
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 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

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. Vascular occlusive adverse events were more frequent with increasing age and in patients with prior 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 4). 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 4.5%, neutropenia and anaemia <1% each).

Table 4 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)	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	13	12	13	14
Phosphorus decreased	9	9	12	9
Glucose increased	7	7	12	1
ALT increased	6	4	8	7
Sodium decreased	5	5	6	2
AST increased	4	3	6	3
Potassium increased	2	2	1	3
Alkaline phosphatase increased	2	1	4	2
Bilirubin	1	<1	2	1
Potassium decreased	2	<1	5	2
Amylase increased	3	3	2	3
Calcium decreased	1	<1	2	1

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

Reporting 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 agent, protein kinase inhibitor, ATC code: L01XE24

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 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.

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 5 below.

Table 5 Demographics and disease characteristics

Patient characteristics at entry	Total safety population N=449
Age	
Median, years (range)	59 (18 - 94)
Gender, n (%)	
Male	238 (53%)
Race, n (%)	
Asian	59 (13%)
Black/African American	25 (6%)
White	352 (78%)
Other	13 (3%)
ECOG Performance Status, n (%)	
ECOG=0 or 1	414 (92%)
Disease History	
Median time from diagnosis to first dose, years (range)	6.09 (0.33 - 28.47)
Resistant to Prior TKI Therapy*, n (%)	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 (%)	
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 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 6, Table 7, and Table 8.

Table 6 Efficacy of Iclusig in resistant or intolerant chronic phase CML patients

	Overall (N=267)	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response			
Major (MCyR) [a]			
%	54%	49%	70%
(95% CI)	(48-60)	(42-56)	(58-81)
Complete (CCyR)			
%	44%	37%	66%
(95% CI)	(38-50)	(31-44)	(53-77)
Major Molecular Response [b]			
%	30%	23%	50%
(95% CI)	(24-36)	(18-30)	(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% (65/105), 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 updated reporting with minimum follow-up for all ongoing patients of 27 months, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 87% (95% CI: [78%–92%]) of CP-CML patients (median duration of treatment: 866 days) who achieved a MCyR and 66% (95% CI: [55%- 75%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 24 months.

Table 7 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)	58% (47-69)	60% (47-72)	50% (26 - 74)	31% (20 – 44)	32% (18 – 49)	29% (13 – 51)
Complete[b] (CHR) % (95% CI)	47% (36-58)	46% (34-49)	50% (26-74)	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 ≥1000/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.

Table 8 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% (12-73)	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 ≥1000/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.

The median time to MaHR in patients with AP-CML, BP-CML, and Ph+ ALL was 21 days (range: 12 to 176 days), 29 days (range: 12 to 113 days), and 20 days (range: 11 to 168 days), respectively. At the time

of updated reporting with minimum follow-up for all ongoing patients of 27 months, the median duration of MaHR for AP-CML (median duration of treatment: 590 days), BP-CML (median duration of treatment: 89 days), and Ph+ ALL (median duration of treatment: 81 days) patients was estimated as 13.1 months (range: 1.2 to 35.8+ months), 6.1 months (range: 1.8 to 31.8+ months), and 3.3 months (range: 1.8 to 13.0 months), 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) 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 15mg 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.

Safety
In the phase 2 trial, 87 CP-CML patients achieved MCyR at a dose of 45mg, 45 CP-CML patients achieved MCyR after a dose reduction to 30mg, mostly for adverse events.
Vascular occlusive events occurred in 44 of these 132 patients. Most of these events occurred at the dose at which the patient achieved MCyR; fewer events occurred after dose reduction.

Table 9 Vascular Occlusive First Adverse Events in CP-CML Patients who Achieved MCyR at 45 mg or 30mg (data extraction 7 April 2014)

	Most Recent Dose at Onset of First Vascular Occlusive Event		
	45mg	**30mg**	**15mg**
Achieved MCyR at 45mg (N=87)	19	6	0
Achieved MCyR at 30mg (N=45)	1	13	5

Efficacy
Preliminary 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 10 shows these data for patients who achieved MCyR and MMR at 45mg; similar data are available for patients who achieved MCyR and MMR at 30mg.
The majority of patients who underwent dose reduction maintained response (MCyR and MMR) for the duration of currently available follow-up. Most patients who ultimately reduced dose to 15mg initially had their dose reduced to 30mg for a period. A proportion of patients did not undergo any dose reduction, based on an individual benefit-risk assessment.
Further data on maintenance of response are required in order to make a formal recommendation for dose modifications in the absence of an adverse event as a risk minimisation strategy (see sections 4.2 and 4.4).

Table 10 Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45mg dose (data extraction 7 April 2014)

	Achieved MCyR at 45 mg (N=87)		Achieved MMR at 45mg (N=63)	
	Number of Patients	**Maintained MCyR**	**Number of Patients**	**Maintained MMR**
No Dose Reduction	23	18 (78%)	18	11 (61%)
Dose reduction to 30 mg only	25	24 (96%)	13	11 (85%)
≥ 90 day reduction at 30 mg	21	20 (95%)	8	9 (89%)
≥ 180 day reduction at 30 mg	11	10 (89%)	5	4 (80%)
≥ 360 day reduction at 30 mg	5	4 (80%)	2	1 (50%)
Any dose reduction to 15 mg	39	39 (100%)	32	30 (94%)
≥ 90 day reduction at 15 mg	32	32 (100%)	27	26 (96%)
≥ 180 day reduction at 15 mg	10	10 (100%)	6	6 (100%)
≥ 360 day reduction at 15 mg	6	6 (100%)	3	3 (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 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).

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Iclusig in children from birth to less than 1 year in CML and Ph+ ALL. The European Medicines Agency has deferred the obligation to submit the results of studies with Iclusig in paediatric patients from 1 year to less than 18 years in CML and Ph+ ALL (see section 4.2 for information on paediatric use).

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 transporters 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.

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).

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, and phototoxicity 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Colloidal anhydrous silica
Magnesium stearate

Tablet coating
Talc
Macrogol 4000
Poly(vinyl alcohol)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original container in order to protect from light.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with screw-top closures, containing either 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

ARIAD Pharma Ltd.
Riverbridge House
Guildford Road
Leatherhead
Surrey KT22 9AD
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/839/003
EU/1/13/839/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Haupt Pharma - AMAREG GmbH
Donaustaufer Strasse 378
D-93055 Regensburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted by 24 November 2014.

- **Additional risk minimisation measures**

In each Member State, the Marketing Authorisation Holder shall agree the format and content of the educational programme, including communication media, distribution modalities, and any other aspects of the programme with the National Competent Authority.

The educational programme is aimed at providing information that helps identify patients eligible for therapy, understand how ponatinib should be used safely, the risks for patients and the important adverse reactions for which monitoring and dose adjustment are recommended.

The Marketing Authorisation Holder shall ensure that in each Member State where ICLUSIG is marketed all physicians who are expected to prescribe ICLUSIG are provided with the Healthcare Professional Brochure.

Key elements of the Healthcare Professional Brochure:

• Importance of assessing the risks before starting treatment with ponatinib.

• Available data on the relationship between dose and risk of vascular occlusive events. Factors to take into account if considering dose reduction in CP-CML patients who have achieved a MCyR in the absence of an adverse event. Recommendation for close monitoring of response if a dose reduction is undertaken.

• Recommendation to consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).

• Information on important adverse reactions for which monitoring and/or dose adjustment are recommended as outlined in the SmPC: pancreatitis, increased amylase and lipase levels, myelosuppression, liver function test abnormalities, haemorrhage, cardiac failure/left ventricular dysfunction, vascular occlusive events and hypertension.

• Instructions on management of adverse events based on monitoring and dose modifications or treatment withdrawal.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to determine the optimal starting dose of Iclusig and characterise the safety and efficacy of Iclusig following dose reductions after achieving MCyR in patients with CP-CML, the MAH should conduct and submit the results of a dose-ranging study.	June 2019

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Iclusig 15 mg film-coated tablets
Ponatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ARIAD Pharma Ltd.
Riverbridge House
Guildford Road
Leatherhead
Surrey KT22 9AD
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/839/001 60 film-coated tablets
EU/1/13/839/002 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
Iclusig 15 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Iclusig 45 mg film-coated tablets
Ponatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ARIAD Pharma Ltd.
Riverbridge House
Guildford Road
Leatherhead
Surrey KT22 9AD
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/839/003 30 film-coated tablets
EU/1/13/839/004 90 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer Carton:
Iclusig 45 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Iclusig 15 mg film-coated tablets
Iclusig 45 mg film-coated tablets
Ponatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Iclusig is and what it is used for

Iclusig is **used to treat** adults with the following **leukaemia** types who are no longer benefiting from treatment with other medicines, or have a certain genetic difference known as a T315I mutation:
- chronic myeloid leukaemia (CML): a blood cancer involving too many abnormal white blood cells in the blood and the bone marrow (where blood cells are formed).
- Philadelphia-chromosome positive acute lymphoblastic leukaemia (Ph+ ALL): a type of leukaemia involving too many immature white blood cells in the blood and blood forming bone marrow. In this kind of leukaemia, some of the DNA (genetic material) has become rearranged to form an abnormal chromosome, the Philadelphia chromosome.

Iclusig belongs to a group of medicines called tyrosine kinase inhibitors. In patients with CML and Ph+ ALL, changes in the DNA trigger a signal that tells the body to produce abnormal white blood cells. Iclusig blocks this signal, thereby stopping the production of these cells.

2. What you need to know before you take Iclusig

Do not take Iclusig
- if you are **allergic** to ponatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Iclusig if you have:

- a liver or pancreas disorder or reduced kidney function. Your doctor may want to take additional precautions.
- a history of alcohol abuse
- had a prior heart attack or stroke
- a history of blood clots in your blood vessels
- heart problems, including heart failure, irregular heartbeats, and QT prolongation
- high blood pressure
- a history of bleeding issues

Your doctor will perform:
- evaluations of your heart function and the condition of your arteries and veins
- a complete blood count
  This will be repeated every 2 weeks for the first 3 months after starting the therapy. Afterwards it is performed monthly or as indicated by the doctor.
- checks of the serum protein known as lipase
  A serum protein called lipase will be checked every 2 weeks for the first 2 months, then periodically. A break in treatment or a decrease in dose may be required when lipase is increased.
- liver tests
  Liver function tests will be performed periodically, as indicated by your doctor.

Children and adolescents

Do not give this medicine to children under 18 years because no data are available in children.

Other medicines and Iclusig

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
The following medicines can affect or be affected by Iclusig:
- **ketoconazole, itraconazole, voriconazole:** medicines to treat fungal infections.
- **indinavir, nelfinavir, ritonavir, saquinavir:** medicines to treat HIV infection.
- **clarithromycin, telithromycin, troleandomycin:** medicines to treat bacterial infections.
- **nefazodone**: a medicine to treat depression.
- **St. John's wort**: a herbal product used to treat depression.
- **carbamazepine:** a medicine to treat epilepsy, euphoric/depressive stages and certain pain conditions.
- **phenobarbital, phenytoin**: medicines to treat epilepsy.
- **rifabutin, rifampicin:** medicines to treat tuberculosis or certain other infections.
- **digoxin**: a medicine to treat heart weakness.
- **dabigatran**: a medicine to prevent the formation of blood clots.
- **colchicine**: a medicine to treat gout attacks.
- **pravastatin**, **rosuvastatin**: medicines to lower elevated cholesterol levels.
- **methotrexate**: a medicine to treat severe joint inflammation (rheumatoid arthritis), cancer and the skin disease psoriasis.
- **sulfasalazine**: a medicine to treat severe bowel and rheumatic joint inflammation.

Iclusig with food and drink
Avoid grapefruit products such as grapefruit juice.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **Contraceptive advice for men and women**

Women of childbearing age being treated with Iclusig should avoid becoming pregnant. **Men** receiving treatment with Iclusig are advised not to father a child during treatment. Effective contraception must be used during treatment.
Only use Iclusig during pregnancy **if your doctor tells you it is absolutely necessary**, as potential risks exist for the unborn child.

- **Breast-feeding**
  Stop breast-feeding during treatment with Iclusig. It is not known if Iclusig passes into breast milk.

Driving and using machines

You should take special care when driving and using machines as patients taking Iclusig may experience visual disturbance, dizziness, sleepiness, and tiredness.

Iclusig contains lactose

If you have been told by your doctor that you have an intolerance to milk sugar (lactose) contact your doctor before taking this medicine.

3. How to take Iclusig

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Iclusig therapy should be prescribed by a doctor experienced in leukaemia treatment.

Iclusig is available as:
- a 45 mg film-coated tablet for the recommended dose.
- a 15 mg film-coated tablet to allow for dose adjustments.

The recommended starting dose is one 45 mg film-coated tablet once daily.

Your doctor may reduce your dose or tell you to temporarily stop taking Iclusig if:
- the number of white blood cells called neutrophils is reduced.
- the number of blood platelets is reduced.
- a severe side effect occurs, not affecting the blood
  - pancreas inflammation.
  - increased levels of the serum proteins lipase or amylase.
- you develop heart or blood vessel problems.

Iclusig use may be resumed at the same, or a reduced dose, after the event is resolved or controlled. Your doctor may evaluate your response to the treatment at regular intervals.

Method of use

Swallow the tablets whole, with a glass of water. The tablets can be taken with or without food. Do not crush or dissolve the tablets.

Duration of use

Make sure you take Iclusig daily for as long as it is prescribed. This is a long-term treatment.

If you take more Iclusig than you should

Talk to your doctor immediately if this occurs.

If you forget to take Iclusig

Do not take a double dose to make up for a forgotten dose. Take your next dose at your regular time.

If you stop taking Iclusig

Do not stop taking Iclusig without your doctor's permission.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Patients aged 65 and over are more likely to be affected by side effects.

Seek medical attention immediately if you experience any of the **following serious** side effects.

If abnormal results from blood tests are received, a doctor should be contacted immediately.

Serious side effects (**common:** affects 1 to 10 users in 100):
- pancreas inflammation. Inform your doctor immediately if pancreas inflammation occurs. Symptoms are severe pain in the stomach and back.
- fever, often with other signs of infection due to decreased number of white blood cells
- heart attack
- changes in blood levels:
  - decreased number of red blood cells (symptoms include: weakness, dizziness, fatigue)
  - decreased number of blood platelets (symptoms include: increased tendency to bleed or bruise)
  - decreased number of white blood cells called neutrophilis (symptoms include: increase tendency of infection)
  - increased level of the serum protein known as lipase
- a heart rhythm disorder, abnormal pulse
- heart failure (symptoms include: weakness, fatigue, swollen legs)
- breathing difficulties
- diarrhoea
- blood clot in a deep vein, sudden vein obstruction, blood clot in a blood vessel of the lung (symptoms include: hot flush, flushing, redness of the face, breathing difficulty)
- stroke (symptoms include: difficulty to speak or move, sleepiness, migraine, abnormal sensations)
- blood circulation problems (symptoms include: pain in the legs or arms, coldness of the extremities of the limbs)
- increased tendency to bleed or bruise

Other possible side effects that may occur with the following frequencies are:

Very common side effects (affects more than 1 per 10 users):
- upper airway infection
- decreased appetite
- insomnia
- headache, dizziness
- high blood pressure
- cough

- diarrhoea, vomiting, constipation, nausea
- increased blood levels of several liver enzymes called:
  - alanine aminotransferase
  - aspartate aminotransferase
- rash, dry skin
- pain in bones, joints, back, arms or legs, muscle spasms
- fatigue, accumulation of fluid in arms and/or legs, fever, pain

Common side effects (affects 1 to 10 users in 100):
- lung infection, blood infection, inflammation of hair follicles
- fluid retention
- dehydration
- low calcium, phosphate or potassium levels in the blood
- increased blood sugar or uric acid levels in the blood, high blood fat values of triglycerides
- weight loss
- mini stroke, cerebral infarction
- nerve disorder in the arms and/or legs (often causes numbness and pain in the hands and feet)
- lethargy, migraine
- increased or reduced sense of touch or sensation, abnormal sensation such as prickling, tingling and itchiness
- blurred vision, dry eye
- tissue swelling in eyelid or around the eyes, caused by excess fluid
- uncomfortable pressure, fullness, squeezing or pain in the centre of the chest (Angina pectoris)
- palpitation
- pain in one or both legs when walking or exercising, which disappears after some minutes of rest
- hot flush, flushing
- fluid in the thorax (may cause breathing difficulty), nosebleed, difficulty producing voice sounds, hypertension in the lungs
- increased blood levels of liver and pancreatic enzymes:
  - amylase
  - alkaline phosphatase
  - gamma-glutamyltransferase
- heartburn caused by reflux of stomach juices, inflammation in the mouth, abdominal swelling or discomfort or indigestion, dry mouth
- increased blood level of bilirubin - the yellow breakdown substance of the blood pigment
- pain in muscles, skeletal system, neck or chest
- skin rash, itching, peeling of the skin, redness, bruising, skin pain, hair loss
- tissue swelling in face caused by excess fluid
- night sweats, increased sweating
- chest pain not in connection with the heart
- inability to develop or maintain an erection
- chills, flu-like illness

Uncommon side effects (affects 1 to 10 users in 1,000):
- metabolic disorders caused by the break-down products of dying cancer cells
- narrowing of the arteries in the brain
- obstruction of the blood vessels in the eye, visual disturbance
- heart problems, problems of the blood vessels in the heart muscle, left sided chest pain, dysfunction of the left heart chamber
- narrowing of the blood vessels, poor blood circulation
- circulatory problems in the spleen
- stomach bleeding (symptoms include: stomach pain, vomiting blood)
- liver damage, jaundice (symptoms include: yellowing of the skin and eyes)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Iclusig

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

Store in the original container in order to protect from light.

6. Contents of the pack and other information

What Iclusig contains

- The active substance is ponatinib.
  Each 15 mg film-coated tablet contains 15 mg ponatinib (as ponatinib hydrochloride).
  Each 45 mg film-coated tablet contains 45 mg ponatinib (as ponatinib hydrochloride).
- The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, silica (colloidal anhydrous), magnesium stearate, talc, macrogol 3000, polyvinyl alcohol, titanium dioxide (E171).

What Iclusig looks like and contents of the pack

Iclusig film-coated tablets are white, round and rounded on the upper and lower side.
Iclusig 15 mg film-coated tablets are approximately 6 mm in diameter with "A5" on one side.
Iclusig 45 mg film-coated tablets are approximately 9 mm in diameter with "AP4" on one side.

Iclusig is available in plastic bottles within a cardboard box.
Bottles of Iclusig 15 mg contain either 60 or 180 film-coated tablets.
Bottles of Iclusig 45 mg contain either 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

ARIAD Pharma Ltd.
Riverbridge House
Guildford Road
Leatherhead
Surrey KT22 9AD, United Kingdom

Manufacturer

Haupt Pharma Amareg GmbH
Donaustaufer Str. 378
93055 Regensburg, Germany

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu