

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.

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 and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy 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.

Dose adjustments or modifications

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

Myelosuppression

Dose modifications for neutropenia (ANC* < 1.0 x 10⁹/L) and thrombocytopenia (platelet < 50 x 10⁹/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: <ul style="list-style-type: none"> Withhold Iclusig and resume initial 45 mg dose after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| | Second occurrence: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| | Third occurrence: <ul style="list-style-type: none"> Withhold Iclusig and resume at 15 mg after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| *ANC = absolute neutrophil count | |

Non-haematological adverse reactions

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

Vascular occlusion

In a patient suspected of developing an arterial or venous occlusive event, Iclusig should be immediately interrupted. A benefit-risk consideration should guide a decision to restart Iclusig therapy (see 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

| | |
|--|--|
| Asymptomatic Grade 2 pancreatitis and/or elevation of lipase/amylase | Continue Iclusig at the same dose |
| Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x IULN*) only | Occurrence at 45 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) |
| | Recurrence at 30 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) |
| | Recurrence at 15 mg: <ul style="list-style-type: none"> Consider discontinuing Iclusig |
| Grade 3 pancreatitis | Occurrence at 45 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to < Grade 2 |
| | Recurrence at 30 mg: |

| | |
|---|---|
| | <ul style="list-style-type: none"> • Withhold Iclusig and resume at 15 mg after recovery to < Grade 2 Recurrence at 15 mg: <ul style="list-style-type: none"> • Consider discontinuing Iclusig |
| Grade 4 pancreatitis | Discontinue Iclusig |
| *IULN = institution upper limit of normal | |

For patients whose adverse reactions are resolved, escalation of the dose back to 45 mg once daily should be considered, if clinically appropriate.

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

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for Iclusig, the presence of moderate to severe hepatic impairment may result in increased plasma concentrations. Caution is recommended when administering Iclusig to patients with varying degrees of hepatic impairment (see section 4.4).

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.

Iclusig should not be used in patients with a history of myocardial infarction or stroke, unless the potential benefit of treatment outweighs the potential risk (see sections 4.2 and 4.8). Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with 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 elevations should be monitored and managed and hypertension should be treated to normal. Iclusig treatment should be temporarily interrupted if hypertension is not medically controlled (see section 4.2).

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 periodically, as clinically indicated.

Medicinal product interactions

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).

Elevated gastric pH

Caution should be exercised with concurrent use of Iclusig and medicinal products that elevate the gastric pH (such as proton pump inhibitors, H₂ blockers, or antacids) as these may decrease the solubility of ponatinib and subsequently reduce its bioavailability.

QT prolongation

The QT interval prolongation potential of Iclusig was assessed in 39 leukaemia patients and no clinically significant QT prolongation was observed (see section 5.1). However, a thorough QT study has not been performed; therefore a clinically significant effect on QT cannot be excluded.

Special populations

Hepatic impairment

Caution is recommended when administering Iclusig to patients with varying degrees of hepatic impairment (see section 4.2).

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-∞} and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone.

Caution should be exercised with concurrent use of Iclusig and moderate or strong CYP3A inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.

Substances that may decrease ponatinib serum concentrations

CYP3A inducers

The effect of CYP3A inducers on ponatinib pharmacokinetics has not been studied. Based on the role of CYP3A in the metabolism of ponatinib, it is anticipated that strong inducers will decrease ponatinib systemic exposures; however, the magnitude of decrease is unknown. Caution should be exercised with concurrent use of Iclusig and strong CYP3A inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort.

Elevated gastric pH

The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Medicinal products that elevate the gastric pH (such as proton pump inhibitors, H₂ blockers, or antacids) may decrease the solubility of ponatinib and subsequently reduce its bioavailability. However, no clinical studies have been conducted.

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.

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, the median duration of treatment with Iclusig was 281 days in CP-CML patients, 286 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 37 mg or, 83% of the expected 45 mg dose.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were pancreatitis (5.1%), abdominal pain (3.6%), pyrexia (3.3%), anaemia, (2.9%), febrile neutropenia (2.9%), platelet count decreased (2.9%), myocardial infarction (2.9%), diarrhoea (1.6%), lipase increased (1.3%), neutrophil count decreased (1.3%), and pancytopenia (1.3%). Overall, the most common adverse reactions (≥20%) were platelet count decreased, rash, dry skin, and abdominal pain. The rates of treatment-related adverse events resulting in discontinuation were 10% in CP-CML, 7% in AP-CML and 3% 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 | Common | pneumonia, sepsis, upper respiratory tract infection, 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 |

| System organ class | Frequency | Adverse reactions |
|---|-------------|--|
| | Uncommon | tumour lysis syndrome |
| Psychiatric disorders | Common | insomnia |
| Nervous system disorders | Very common | headache |
| | Common | cerebrovascular accident, neuropathy peripheral, lethargy, dizziness, migraine, hyperaesthesia, hypoaesthesia, paraesthesia |
| | Uncommon | cerebral infarction, cerebral artery stenosis |
| Eye disorders | Common | vision blurred, dry eye |
| | Uncommon | retinal vein thrombosis, retinal vein occlusion, visual impairment, eyelid oedema |
| 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, Prinzmetal Angina, left ventricular dysfunction, atrial flutter, |
| Vascular Disorders | Very common | hypertension |
| | Common | peripheral arterial occlusive disease, peripheral ischaemia, intermittent claudication, deep vein thrombosis, hot flush, flushing, |
| | Uncommon | peripheral artery stenosis, 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 |
| Gastrointestinal disorders | Very common | abdominal pain, diarrhea, vomiting, constipation, nausea, lipase increased |
| | Common | pancreatitis, blood amylase increased, gastroesophageal reflux disease, stomatitis, dyspepsia, abdominal distension, abdominal discomfort, dry mouth |
| | Uncommon | gastric hemorrhage |
| Hepatobiliary disorders | Very common | alanine aminotransferase increased |
| | Common | blood bilirubin increased, aspartate aminotransferase 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, periorbital oedema |
| | Uncommon | dermatitis exfoliative |
| Musculoskeletal and connective tissue disorders | Very common | bone pain, arthralgia, myalgia, pain in extremity, back pain |
| | Common | musculoskeletal pain, neck pain, musculoskeletal chest pain, muscle spasms |
| Reproductive system and breast disorders | Common | erectile dysfunction |
| General disorders and | Very common | fatigue, asthenia, oedema peripheral, pyrexia |

| System organ class | Frequency | Adverse reactions |
|--------------------------------|------------------|---|
| administrative site conditions | Common | chills, influenza like illness, non-cardiac chest pain, 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 3.6%, 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) | 39 | 34 | 47 | 45 |
| Neutropenia (ANC decreased) | 33 | 23 | 47 | 52 |
| Leukopenia (WBC decreased) | 25 | 12 | 33 | 53 |
| Anaemia (Hgb decreased) | 20 | 9 | 26 | 48 |
| Lymphopenia | 15 | 9 | 24 | 28 |
| Biochemistry | | | | |
| Lipase increased | 10 | 11 | 9 | 5 |
| Phosphorus decreased | 7 | 6 | 8 | 9 |
| Glucose increased | 5 | 6 | 7 | 0 |
| ALT increased | 8 | 6 | 8 | 12 |
| Sodium decreased | 4 | 4 | 6 | 2 |
| AST increased | 3 | 3 | 2 | 3 |
| Potassium increased | 2 | 2 | 1 | 3 |
| Alkaline phosphatase increased | 2 | 1 | 1 | 4 |
| Bilirubin | 1 | <1 | 4 | 1 |
| Potassium decreased | 2 | <1 | 4 | 2 |
| Amylase decreased | <1 | 0 | 0 | 2 |
| ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, Hgb=hemoglobin, 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 IC₅₀ 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 IC₅₀ 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. At the time of analysis, patients had a minimum follow-up of 6 months (median follow-up: 10 months). Baseline demographic characteristics are described in Table 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.

At the time of analysis, median duration of Iclusig treatment was 281 days in CP-CML patients, 286 days in AP-CML patients, 89 days in BP-CML patients, and 81 days in patients with Ph+ ALL. 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 % (95% CI) | 54% (48-60) | 49% (42-56) | 70% (58-81) |
| Complete (CCyR) % (95% CI) | 44% (38-50) | 37% (31-44) | 66% (53-77) |
| Major Molecular Response ^b % (95% CI) | 30% (24-36) | 23% (18-30) | 50% (37-63) |
| ^a Primary endpoint for CP-CML Cohorts was MCyR, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses. | | | |

^b Measured in peripheral blood. Defined as a $\leq 0.1\%$ ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (ie, $\leq 0.1\%$ 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 reporting, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 91% (95% CI: [85%–95%]) of CP-CML (median duration of treatment: 421 days) patients who achieved a MCyR and 81% (95% CI: [70%–88%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 12 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. The median duration of MaHR for AP-CML (median duration of treatment: 446 days) BP-CML (median duration of treatment: 89 days), and Ph+ ALL (median duration of treatment: 81 days) patients was

estimated as 11.8 months (range: 1.2 to 21.5+ months), 4.7 months (range: 1 to 19.6+ months), and 3.2 months (range: 1.8 to 13.8+ months), respectively.

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-t) 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.

Distribution

Ponatinib is highly bound (>99%) to plasma proteins *in vitro*. The blood/plasma ratio of ponatinib is 0.96. 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. Ponatinib is mainly eliminated via feces. Following a single oral dose of [¹⁴C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and <1% of the administered dose in feces 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

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations (see section 4.2).

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.

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 3000
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.
Brooklands Business Park
Wellington Way
Weybridge, KT13 0TT
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.

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 and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy 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.

Dose adjustments or modifications

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

Myelosuppression

Dose modifications for neutropenia (ANC* < 1.0 x 10⁹/L) and thrombocytopenia (platelet < 50 x 10⁹/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: <ul style="list-style-type: none"> Withhold Iclusig and resume initial 45 mg dose after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| | Second occurrence: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| | Third occurrence: <ul style="list-style-type: none"> Withhold Iclusig and resume at 15 mg after recovery to ANC ≥ 1.5 x 10⁹/L and platelet ≥ 75 x 10⁹/L |
| *ANC = absolute neutrophil count | |

Non-haematological adverse reactions

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

Vascular occlusion

In a patient suspected of developing an arterial or venous occlusive event, Iclusig should be immediately interrupted. A benefit-risk consideration should guide a decision to restart Iclusig therapy (see 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

| | |
|--|--|
| Asymptomatic Grade 2 pancreatitis and/or elevation of lipase/amylase | Continue Iclusig at the same dose |
| Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x IULN*) only | Occurrence at 45 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 30 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 15 mg: <ul style="list-style-type: none"> Consider discontinuing Iclusig |
| Grade 3 pancreatitis | Occurrence at 45 mg: <ul style="list-style-type: none"> Withhold Iclusig and resume at 30 mg after recovery to < Grade 2 |

| | |
|---|--|
| | Recurrence at 30 mg: <ul style="list-style-type: none"> • Withhold Iclusig and resume at 15 mg after recovery to < Grade 2 Recurrence at 15 mg: <ul style="list-style-type: none"> • Consider discontinuing Iclusig |
| Grade 4 pancreatitis | Discontinue Iclusig |
| *IULN = institution upper limit of normal | |

For patients whose adverse reactions are resolved, escalation of the dose back to 45 mg once daily should be considered, if clinically appropriate.

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

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for Iclusig, the presence of moderate to severe hepatic impairment may result in increased plasma concentrations. Caution is recommended when administering Iclusig to patients with varying degrees of hepatic impairment (see section 4.4).

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.

Iclusig should not be used in patients with a history of myocardial infarction or stroke, unless the potential benefit of treatment outweighs the potential risk (see sections 4.2 and 4.8). Before starting treatment with ponatinib, the cardiovascular status of the patient should be assessed and cardiovascular risk factors should be actively managed. Cardiovascular status should continue to be monitored and therapy optimised during treatment with 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 elevations should be monitored and managed and hypertension should be treated to normal. Iclusig treatment should be temporarily interrupted if hypertension is not medically controlled (see section 4.2).

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 periodically, as clinically indicated.

Medicinal product interactions

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).

Elevated gastric pH

Caution should be exercised with concurrent use of Iclusig and medicinal products that elevate the gastric pH (such as proton pump inhibitors, H₂ blockers, or antacids) as these may decrease the solubility of ponatinib and subsequently reduce its bioavailability.

QT prolongation

The QT interval prolongation potential of Iclusig was assessed in 39 leukaemia patients and no clinically significant QT prolongation was observed (see section 5.1). However, a thorough QT study has not been performed; therefore a clinically significant effect on QT cannot be excluded.

Special populations

Hepatic impairment

Caution is recommended when administering Iclusig to patients with varying degrees of hepatic impairment (see section 4.2).

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-∞} and C_{max} values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone.

Caution should be exercised with concurrent use of Iclusig and moderate or strong CYP3A inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.

Substances that may decrease ponatinib serum concentrations

CYP3A inducers

The effect of CYP3A inducers on ponatinib pharmacokinetics has not been studied. Based on the role of CYP3A in the metabolism of ponatinib, it is anticipated that strong inducers will decrease ponatinib systemic exposures; however, the magnitude of decrease is unknown. Caution should be exercised with concurrent use of Iclusig and strong CYP3A inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort.

Elevated gastric pH

The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Medicinal products that elevate the gastric pH (such as proton pump inhibitors, H₂ blockers, or antacids) may decrease the solubility of ponatinib and subsequently reduce its bioavailability. However, no clinical studies have been conducted.

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.

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, the median duration of treatment with Iclusig was 281 days in CP-CML patients, 286 days in AP-CML patients, and 86 days in BP-CML/Ph+ ALL patients. The median dose intensity was 37 mg or, 83% of the expected 45 mg dose.

The most common serious adverse reactions >1% (treatment-emergent frequencies) were pancreatitis (5.1%), abdominal pain (3.6%), pyrexia (3.3%), anaemia, (2.9%), febrile neutropenia (2.9%), platelet count decreased (2.9%), myocardial infarction (2.9%), diarrhoea (1.6%), lipase increased (1.3%), neutrophil count decreased (1.3%), and pancytopenia (1.3%). Overall, the most common adverse reactions (≥20%) were platelet count decreased, rash, dry skin, and abdominal pain. The rates of treatment-related adverse events resulting in discontinuation were 10% in CP-CML, 7% in AP-CML and 3% 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 | Common | pneumonia, sepsis, upper respiratory tract infection, 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 |

| System organ class | Frequency | Adverse reactions |
|---|------------------|--|
| | Uncommon | tumour lysis syndrome |
| Psychiatric disorders | Common | insomnia |
| Nervous system disorders | Very common | headache |
| | Common | cerebrovascular accident, neuropathy peripheral, lethargy, dizziness, migraine, hyperaesthesia, hypoaesthesia, paraesthesia |
| | Uncommon | cerebral infarction, cerebral artery stenosis |
| Eye disorders | Common | vision blurred, dry eye |
| | Uncommon | retinal vein thrombosis, retinal vein occlusion, visual impairment, eyelid oedema, |
| 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, Prinzmetal Angina, left ventricular dysfunction, atrial flutter |
| Vascular Disorders | Very common | hypertension |
| | Common | peripheral arterial occlusive disease, peripheral ischaemia, intermittent claudication, deep vein thrombosis, hot flush, flushing |
| | Uncommon | peripheral artery stenosis, 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 |
| 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 hemorrhage |
| Hepatobiliary disorders | Very common | alanine aminotransferase increased |
| | Common | blood bilirubin increased, aspartate aminotransferase 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, periorbital oedema |
| | Uncommon | dermatitis exfoliative |
| Musculoskeletal and connective tissue disorders | Very common | bone pain, arthralgia, myalgia, pain in extremity, back pain |
| | Common | musculoskeletal pain, neck pain, musculoskeletal chest pain, muscle spasms |
| Reproductive system and breast disorders | Common | erectile dysfunction |

| System organ class | Frequency | Adverse reactions |
|--|-------------|---|
| General disorders and administrative site conditions | Very common | fatigue, asthenia, oedema peripheral, pyrexia |
| | Common | chills, influenza like illness, non-cardiac chest pain, 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 3.6%, 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) | 39 | 34 | 47 | 45 |
| Neutropenia (ANC decreased) | 33 | 23 | 47 | 52 |
| Leukopenia (WBC decreased) | 25 | 12 | 33 | 53 |
| Anaemia (Hgb decreased) | 20 | 9 | 26 | 48 |
| Lymphopenia | 15 | 9 | 24 | 28 |
| Biochemistry | | | | |
| Lipase increased | 10 | 11 | 9 | 5 |
| Phosphorus decreased | 7 | 6 | 8 | 9 |
| Glucose increased | 5 | 6 | 7 | 0 |
| ALT increased | 8 | 6 | 8 | 12 |
| Sodium decreased | 4 | 4 | 6 | 2 |
| AST increased | 3 | 3 | 2 | 3 |
| Potassium increased | 2 | 2 | 1 | 3 |
| Alkaline phosphatase increased | 2 | 1 | 1 | 4 |
| Bilirubin | 1 | <1 | 4 | 1 |
| Potassium decreased | 2 | <1 | 4 | 2 |
| Amylase decreased | <1 | 0 | 0 | 2 |
| ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, Hgb=hemoglobin, 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 IC₅₀ 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 IC₅₀ 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. At the time of analysis, patients had a minimum follow-up of 6 months (median follow-up: 10 months). Baseline demographic characteristics are described in Table 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.

At the time of analysis, median duration of Iclusig treatment was 281 days in CP-CML patients, 286 days in AP-CML patients, 89 days in BP-CML patients, and 81 days in patients with Ph+ ALL. 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 % (95% CI) | 54% (48-60) | 49% (42-56) | 70% (58-81) |
| Complete (CCyR) % (95% CI) | 44% (38-50) | 37% (31-44) | 66% (53-77) |
| Major Molecular Response^b % (95% CI) | 30% (24-36) | 23% (18-30) | 50% (37-63) |
| ^a Primary endpoint for CP-CML Cohorts was MCyR, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses. | | | |
| ^b Measured in peripheral blood. Defined as a $\leq 0.1\%$ ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (ie, $\leq 0.1\%$ 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 reporting, the median durations of MCyR and MMR had not yet been reached. Based on the Kaplan-Meier estimates, 91% (95% CI: [85%–95%]) of CP-CML patients (median duration of treatment: 421 days) who achieved a MCyR and 81% (95% CI: [70%– 88%]) of CP-CML patients who achieved a MMR are projected to maintain that response at 12 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. The median duration of MaHR for AP-CML (median duration of treatment: 446 days) BP-CML (median duration of treatment: 89 days), and Ph+ ALL (median duration of treatment: 81 days) patients was

estimated as 11.8 months (range: 1.2 to 21.5+ months), 4.7 months (range: 1 to 19.6+ months), and 3.2 months (range: 1.8 to 13.8+ months), respectively.

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-t) 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.

Distribution

Ponatinib is highly bound (>99%) to plasma proteins *in vitro*. The blood/plasma ratio of ponatinib is 0.96. 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. Ponatinib is mainly eliminated via feces. Following a single oral dose of [¹⁴C]-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. Unchanged ponatinib accounted for 24% and <1% of the administered dose in feces 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

Iclusig has not been studied in patients with hepatic impairment. As hepatic elimination is a major route of excretion for ponatinib, hepatic impairment may result in increased plasma ponatinib concentrations (see section 4.2).

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.

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 3000
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.
Brooklands Business Park
Wellington Way
Weybridge, KT13 0TT
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
Donaustauer 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 within 30 days of the granting of the Marketing Authorisation.

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.
Brooklands Business Park
Wellington Way
Weybridge, KT13 0TT
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.
Brooklands Business Park
Wellington Way
Weybridge, KT13 0TT
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
2. What you need to know before you take Iclusig
3. How to take Iclusig
4. Possible side effects
5. How to store Iclusig
6. Contents of the pack and other information

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

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:

- **ketocoazole, itraconazole, voriconazole:** medicines to treat fungal infections.
- **atazanavir, 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.
- **medicines which decrease stomach acid** such as omeprazole, pantopranzole, ranitidine, cimetidine, famotidine, aluminium and magnesium hydroxides.
- **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 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.

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.

Inform your doctor immediately if you experience any of the side effects.

Very common serious side effects (affects more than 1 per 10 users):

- abdominal pain
- changes in blood levels:
 - decreased number of red blood cells
 - decreased number of blood platelets
 - decreased number of white blood cells called neutrophils
 - increased level of the serum protein known as lipase

Common serious side effects (affects 1 to 10 users in 100):

- lung infection
- blood poisoning from harmful bacteria, fungi and their toxins
- decreased number of white blood cells
- fever, often with other signs of infection, decreased number of white blood cells called neutrophils
- heart failure with tissue swelling caused by excess fluid
- disease of the heart arteries, chest pain due to narrowed heart blood vessels, dysfunction of the left heart chamber
- abnormal accumulation of fluid around the heart
- a heart rhythm disorder which causes very rapid activity in the upper heart chambers
- blood clot in a deep vein, sudden vein obstruction, blood clot in a blood vessel of the lung
- heart failure (weakness), heart attack
- fluid in the thorax
- pancreas inflammation. Inform your doctor immediately if pancreas inflammation occurs. Symptoms are severe pain in the stomach and back.
- stroke
- blood circulation problems

Uncommon serious side effects (affects 1 to 10 users in 1,000):

- metabolic disorders caused by the break-down products of dying cancer cells
- bleeding in the brain
- a type of stroke called cerebral infarction, narrowing artery in the brain
- obstruction of veins in the eye
- abnormal heart beat
- stomach bleeding
- liver damage

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

Very common side effects (affects more than 1 per 10 users):

- headache
- constipation

- nausea
- rash, dry skin
- joint or muscle pain
- fatigue
- high blood pressure
- breathing difficulties
- cough
- diarrhoea, vomiting
- pain in bones, muscles, skeletal system, back, neck, chest, arms or legs
- accumulation of fluid in arms and/or legs
- increased blood levels of several proteins:
 - alanine aminotransferase

Common side effects (affects 1 to 10 users in 100):

- inflammation of hair follicles, hair loss
- upper airway infection
- decreased appetite, dehydration
- fluid retention
- low calcium, phosphate or potassium levels in the blood
- high blood fat values of triglycerides
- increased blood sugar or uric acid levels in the blood
- sleeplessness, dizziness, lethargy
- migraine
- increased or reduced sense of touch or sensation, abnormal sensation such as prickling, tingling and itchiness
- nerve disorder in the arms and/or legs (often causes numbness and pain in the hands and feet)
- dry eye, blurred vision
- hot flush, flushing
- nosebleed
- difficulty producing voice sounds
- abdominal distension or discomfort or indigestion
- dry mouth
- inflammation in the mouth
- disease caused by reflux of stomach juices
- skin rash, itching, peeling of the skin
- night sweats, increased sweating
- bruising
- skin pain
- muscle spasms
- inability to develop or maintain an erection
- weakness
- fever, chills, flu-like illness
- tissue swelling in the face, eyelid or around the eyes, caused by excess fluid
- abnormal swelling
- increased blood levels of several proteins:
 - aspartate aminotransferase
 - amylase
 - alkaline phosphatase
 - gamma-glutamyltransferase
- decreased number of white blood cells
- weight loss
- decrease in performance of the heart
- uncomfortable pressure, fullness, squeezing or pain in the center of the chest (Angina pectoris)
- increased blood level of bilirubin - the yellow breakdown substance of the blood pigment
- pain in one or both legs when walking or exercising, which disappears after some minutes of rest

Uncommon side effects (affects 1 to 10 users in 1,000):

- jaundice
- scaly skin inflammation
- heart problems, problems of the blood vessels in the heart muscle
- chest pain which happens at rest (Prinzmetal's angina), left sided chest pain
- narrowing of the blood vessels, poor blood circulation
- palpitations
- visual disturbance

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.
Brooklands Business Park
Wellington Way
Weybridge, KT13 0TT, United Kingdom

Manufacturer

Haupt Pharma Amareg GmbH
Donaustauer Str. 378
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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>