Iclusig ® ▼(ponatinib)

15mg, 30mg and 45mg film-coated tablets*

Important Safety Information

for Healthcare Professionals

This document contains important safety information that you need to be aware of when treating patients with Iclusig (ponatinib).
Please read the information inside, in addition to the Summary of Product Characteristics.

This brochure only addresses selected side effects and does not replace the overall information included in the Summary of Product Characteristics.
* Not all strengths may be marketed.

▼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 of the Summary of Product Characteristics for how to report adverse reactions.

Table of contents

1. What is the purpose of this brochure?

This information brochure provides important safety information and advice to healthcare professionals who are involved in the treatment of patients taking Iclusig (ponatinib).

This document will help you to:

- identify patients eligible for therapy and understand how ponatinib should be used in patients beginning or undergoing treatment.
- understand the individual medical risks for which monitoring and dose adjustment are recommended, including:
    - pancreatitis
    - increased amylase and lipase levels
    - myelosuppression (thrombocytopenia, neutropenia, anaemia)
    - hepatotoxicity
    - haemorrhage
    - cardiac failure/left ventricular dysfunction
    - arterial occlusion and venous thromboembolism events
    - hypertension
- explain the possible individual medical risks to patients

This information does not replace the Summary of Product Characteristics (SmPC) which contains full prescribing information.

2. What is Iclusig?

It 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.

Indication

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.

Contraindications

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

3. What should I consider before prescribing Iclusig?

The patient's prior medical history and individual risk factors must be considered before prescribing Iclusig.

The following must be considered:

- Pre-existing myelosuppression (thrombocytopenia, neutropenia, anaemia)
- Pre-existing arterial occlusion and venous thromboembolism
- History of hypertension, ischaemia, diabetes mellitus or hyperlipidaemia
- History of myocardial infarction, prior revascularisation or stroke
- Pre-existing congestive heart failure / left ventricular dysfunction
- History of pancreatitis, increase of amylase and lipase or alcohol abuse
- Hepatotoxicity
- Prior haemorrhage

Recommendations for each of the above potential individual risk factors are presented in this brochure.

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

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

For a full list of patient risk factors for consideration prior to treatment, please see the Summary of Product Characteristics.

4. What is the starting dose, what dose modifications may be required during treatment and what monitoring is required?

Starting Dose

Treatment with this medicinal product should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

The recommended starting dose is 45 mg administered orally once daily.

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

Dose modifications

Dose modification is recommended to reduce the risks of a number of the adverse events addressed in this brochure.

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

There are specific dose modification recommendations in cases of neutropenia and thrombocytopenia unrelated to leukaemia (see section 5), pancreatitis and elevation of serum lipase/amylase (see section 9) and hepatotoxicity (see section 10).

In the case of severe adverse reactions, treatment should be withheld.

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

Treatment discontinuation for lack of response

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

5. Is there a risk of myelosuppression in patients treated with Iclusig and how can it be managed?

Background

Myelosuppression was commonly (≥ 1/100 to < 1/10) reported in all patient populations.
The frequency of Grade 3 or 4 thrombocytopenia, neutropenia, and anaemia (National Cancer Institute Common Terminology Criteria) was higher in patients with accelerated phase CML (AP-CML) and blast phase CML (BP-CML)/Ph+ ALL than in chronic phase CML (CP-CML).
Myelosuppression was reported in patients with normal baseline laboratory values, as well as in patients with pre-existing laboratory abnormalities.
Most of the patients with grade 3 or 4 platelet count decreased, anaemia or neutropenia, developed it within the first 3 months of treatment.
Myelosuppression was generally reversible and usually managed by withholding Iclusig temporarily or reducing the dose.

Recommendations

Monitoring
A complete blood count should be performed every 2 weeks for the first 3 months and thereafter monthly or as clinically indicated.

Dose modifications
Dose modifications for neutropenia (ANC* < 1.0 x 10^9/L) and thrombocytopenia (platelet < 50 x 10^9/L), unrelated to leukaemia, are summarised in Table 1

Table 1: Dose modifications for neutropenia and thrombocytopenia unrelated to leukaemia

ANC* < 1.0 x 10^9/L or platelet < 50 x 10^9/L	First occurrence: • Withhold ponatinib and resume same dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Recurrence at 45 mg: • Withhold ponatinib and resume at 30 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
	Recurrence at 30mg: • Withhold ponatinib and resume at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L
*ANC = absolute neutrophil count	

6. Is there a risk of arterial occlusion in patients treated with Iclusig and how can it be managed?

Background

Serious arterial occlusion has occurred in patients, including cardiovascular, cerebrovascular and peripheral vascular events.

Arterial occlusions, including fatal myocardial infarction, stroke, retinal arterial occlusions associated in some cases with permanent visual impairment or vision loss, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, renal artery stenosis (associated with worsening, labile or treatment-resistant hypertension), and the need for urgent revascularization procedures have also occurred in Iclusig-treated patients.

Patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced these events. Arterial occlusive adverse events were more frequent with increasing age and in patients with history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

Serious arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 9%, 7%, and 7% of patients treated with ponatinib in the pivotal clinical trial, respectively.
Arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 13%, 9%, and 9% of Iclusig-treated patients, respectively.

Overall arterial occlusive adverse reactions have occurred in 23% of Iclusig-treated patients from the phase 2 trial, with serious adverse reactions occurring in 19% of patients.

The median time to onset of the first cardiovascular, cerebrovascular, and peripheral vascular arterial occlusive events was 329, 537, and 481 days, respectively.

Some patients experienced more than one type of event.

Recommendations

- Ponatinib should not be used in patients with a history of myocardial infarction, prior re-vascularization or stroke, unless the potential benefit of treatment outweighs potential risk. In these patients, alternative treatment options should also be considered before starting treatment with ponatinib.

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

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

- If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed.

- Hypertension may contribute to the risk of arterial thrombotic events, including renal artery stenosis.

- During treatment, blood pressure should be monitored and managed at each clinic visit and hypertension should be treated to normal.

- Treatment should be temporarily interrupted if hypertension is not medically controlled.

- In the event of significant worsening, labile or treatment-resistant hypertension, interrupt treatment and consider evaluating for renal artery stenosis.

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

- In a patient suspected of developing an arterial occlusive event, Iclusig should be immediately interrupted.

- A benefit–risk consideration should guide a decision to restart ponatinib therapy once the event has been resolved.

Dose considerations:

A reduction in dose is expected to reduce the risk of vascular occlusive events, however, there may be a 'carry over' effect of higher doses such that it might take up to several months before a dose reduction manifests in risk reduction.

Dose reduction in CP-CML patients

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

Table 2 Vascular Occlusive First Adverse Events in CP-CML Patients who Achieved MCyR at 45 mg or 30 mg (data extraction 7 April 2014)

	Most Recent Dose at Onset of First Vascular Occlusive Event		
	45mg	**30mg**	**15mg**
Achieved MCyR at 45mg (N=86)	19	6	0
Achieved MCyR at 30mg (N=45)	1	13	5

When adjusted for exposure, the incidence of first arterial occlusive events was greatest in the first two years of follow-up and declined with decreasing daily dose intensity (following recommendation for prospective dose reduction). Factors other than dose may also contribute to this risk of arterial occlusion.

Efficacy

The majority of patients who underwent dose reduction maintained response (MCyR and MMR) for the duration of currently available follow-up. A proportion of patients did not undergo any dose reduction, based on an individual benefit-risk assessment.

Table 3 Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45 mg dose (data extraction 03 August 2015)

	Achieved MCyR at 45 mg (N=86)		Achieved MMR at 45 mg (N=63)	
	Number of Patients	Maintained MCyR	Number of Patients	Maintained MMR
No Dose Reduction	19	13 (68%)	18	11 (61%)
Dose reduction to 30 mg only	14	13 (93%)	5	3 (60%)
≥ 3 months reduction at 30 mg	11	10 (91%)	3	2 (67%)
≥ 6 months reduction at 30 mg	10	9 (90%)	3	2 (67%)
≥ 12 months reduction at 30 mg	8	7 (88%)	3	2 (67%)
≥ 18 month reduction at 30 mg	7	6 (86%)	2	2 (100%)
≥ 24 month reduction at 30 mg	1	1 (100%)	--	--
≥ 36 month reduction at 30 mg	1	1 (100%)	--	--
Any dose reduction to 15 mg	53	52 (98%)	40	36 (90%)
≥ 3 months reduction at 15 mg	50	50 (100%)	39	36 (92%)
≥ 6 months reduction at 15 mg	47	47 (100%)	37	35 (95%)
≥ 12 months reduction at 15 mg	42	42 (100%)	32	31 (97%)
≥ 18 month day reduction at 15 mg	35	35 (100%)	26	26 (100%)
≥ 24 month reduction at 15 mg	5	5 (100%)	3	3 (100%)
≥ 36 month reduction at 15 mg	2	2 (100%)	--	--

7. Is there a risk of venous thromboembolism in patients treated with Iclusig and how can it be managed?

Background

Serious venous thromboembolic adverse reactions occurred in 5% of patients (treatment-emergent frequencies) in the pivotal clinical trial. Venous thromboembolic adverse reactions have occurred in 6% of patients (treatment-emergent frequencies).

Retinal venous occlusions associated in some cases with permanent visual impairment or vision loss have occurred in Iclusig-treated patients.

The incidence of thromboembolic events is higher in patients with Ph+ ALL or BP-CML than those with AP-CML or CP-CML. No venous occlusive events were fatal.

Recommendations

- Monitor for evidence of thromboembolism.
- If decreased vision or blurred vision occurs, an ophthalmic examination (including fundoscopy) should be performed.
- In a patient suspected of developing thromboembolism, ponatinib should be immediately interrupted.
- A benefit–risk consideration should guide a decision to restart ponatinib therapy once the event has been resolved.

8. Is there a risk of heart failure in patients treated with Iclusig and how can it be managed?

Background

In patients treated in the pivotal clinical trial cardiac failure was reported as common (≥1/100 to < 1/10) and left ventricular dysfunction as uncommon (≥ 1/1000 to < 1/100).

Fatal and serious heart failure or left ventricular dysfunction may occur in Iclusig-treated patients, including events related to prior vascular occlusive events.

Recommendations

- Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig.
- Consider discontinuation of treatment in patients who develop serious heart failure

9. Is there a risk of pancreatic adverse reactions in patients treated with Iclusig and how can it be managed?

Background

Pancreatitis has been reported commonly (≥ 1/100 to < 1/10) in patients treated with ponatinib in the pivotal clinical trial.

Patients may experience pancreatitis and elevation of serum lipase/amylase. The frequency of pancreatitis is greater in the first two months of use.

Hypertriglyceridaemia is a risk factor of pancreatitis.

Recommendations

- Caution is recommended in patients with a history of pancreatitis or alcohol abuse.
- Patients with severe or very severe hypertriglyceridaemia should be appropriately managed to reduce the risk of pancreatitis.

Monitoring

- Check serum lipase every two weeks for the first two months and then periodically thereafter – dose interruption or reduction may be required (see below).
- If lipase elevations are accompanied by abdominal symptoms, ponatinib should be withheld and patients evaluated for evidence of pancreatitis.

Dose modifications

Recommended dose modifications for pancreatitis and elevation of lipase/amylase are detailed in Table 4.

Table 4: Dose modifications in case of pancreatitis and elevation of lipase/amylase

Grade 2 pancreatitis and/or asymptomatic elevation of lipase/amylase	Continue ponatinib at the same dose
Grade 3 or 4 asymptomatic elevation of lipase/amylase (> 2.0 x IULN*) only	Occurrence at 45 mg: • Withhold ponatinib treatment and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Occurrence at 30 mg: • Withhold ponatinib treatment and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Occurrence at 15 mg: • Consider discontinuing ponatinib treatment
Grade 3 pancreatitis	Occurrence at 45 mg: • Withhold ponatinib treatment and resume at 30 mg after recovery to < Grade 2 Occurrence at 30 mg: • Withhold ponatinib treatment and resume at 15 mg after recovery to < Grade 2 Occurrence at 15 mg: • Consider discontinuing ponatinib treatment
Grade 4 pancreatitis	Discontinue ponatinib treatment
*IULN = institution upper limit of normal	

10. Is there a risk of hepatotoxicity in patients treated with Iclusig and how can it be managed?

Background

Treatment with ponatinib may result in elevation in ALT, AST, bilirubin, and alkaline phosphatase. Hepatic failure (including fatal outcome) has been observed.
Most patients who had an event of hepatotoxicity had their first event during the first year of treatment.
Liver dysfunction has been reported in patients treated with ponatinib in the pivotal clinical trial with the following frequencies:

- Alanine aminotransferase and aspartate aminotransferase increase was very common (≥ 1/10).
- Blood bilirubin, blood alkaline phosphatase and gamma glutamyltransferase increase were common (≥ 1/100 to < 1/10).
- Hepatotoxicity, hepatic failure and jaundice were uncommon (≥ 1/1000 to < 1/100).

Recommendations

Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated.

Dose modifications
Dose interruption or discontinuation may be required as described in Table 5.

Table 5 Recommended dose modifications for hepatic toxicity

Elevation of liver transaminase >3× ULN* Persistent grade 2 (longer than 7 days) Grade 3 or higher	Occurrence at 45 mg: • Interrupt ponatinib and monitor hepatic function • Resume ponatinib at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN), or has returned to pre-treatment grade Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1, or has returned to pre-treatment grade Occurrence at 15 mg: • Discontinue ponatinib
Elevation of AST or ALT ≥3× ULN concurrent with an elevation of bilirubin >2× ULN and alkaline phosphatase <2× ULN	Discontinue ponatinib

*ULN = Upper Limit of Normal for the lab

Patients with hepatic impairment may receive the recommended starting dose. Caution is recommended when administering Iclusig to patients with hepatic impairment.

11. Is there a risk of haemorrhage in patients treated with Iclusig and how can it be managed?

Background

Decreased platelet count has been reported very commonly in patients treated with ponatinib in clinical trials.

Severe haemorrhage, including fatalities, occurred in ponatinib-treated patients.

The incidence of severe bleeding events was higher in patients with AP-CML, BP-CML and Ph+ ALL.
Gastrointestinal haemorrhage and subdural hematoma were the most commonly reported grade 3/4 bleeding events.
Most haemorrhagic events occurred in patients with grade 3/4 thrombocytopenia.

Recommendations

Interrupt Iclusig for serious or severe haemorrhage events and evaluate.
Concomitant use of ponatinib with anti-clotting agents should be approached with caution in patients who may be at risk of bleeding events. Formal studies of ponatinib with anti-clotting medicinal products have not been conducted.

12. How do I report adverse reactions?

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form available online at http://www.medicinesauthority.gov.mt/adrportal and sent to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN or sent by email to: postlicensing.medicinesauthority@gov.mt.

13. Where can I obtain further information?

To learn more about Iclusig, please refer to the Summary of Product Characteristics (SmPC).
The SmPC is available from www.ema.europa.eu

If you have further questions or require additional information, please contact:

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Where to find further information
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