Ponatinib

INDICATION:

- 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
    - 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.

Limitations of use:

- Ponatinib is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML

Prior to a course of treatment

- Cardiovascular status of the patient should be assessed, including history and physical examination, and cardiovascular risk factors should be actively managed.
- Consider reducing the dose of Ponatinib to 30 mg daily in patietnts with concurrent use of strong CYP3A inhibitors such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.
- Co administration of strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort with ponatinib should be avoided, and alternatives medications should be sought, unless the benefit outweighs the possible risk of ponatinib underexposure.
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss (low) risk of infertility - offer semen cryopreservation to male patients
- Written consent for course

Prior to each dose

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- For first 2 months: every 2 weeks before each prescription: FBC, U&Es, LFTs, serum lipase to look for pancreatitis
- It is recommended to monitor FBC every 2 weeks for first 3 months to monior myelosupression
- Subsequently – every 4 weeks before each prescription: FBC, U&Es, LFTs, serum lipase
- BCR-ABL transcript monitoring every 3 months

Ponatinib	45 mg daily

Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity

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

Prophylaxis for acute emesis	None
Prophylaxis for delayed emesis	None
Other medications	**None**

Dose modifications for myelosuppression

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

Vascular occlusion

Ponatinib should be immediately interrupted in a patient suspected of developing an arterial or venous occlusive event.

A benefit-risk consideration should guide a decision to restart Ponatinib therapy after the event is resolved.

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

Dose modifications for 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 and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 30 mg: • Withhold Ponatinib and resume at 15 mg after recovery to ≤ Grade 1 (< 1.5 x IULN) Recurrence at 15 mg: • Consider discontinuing Ponatinib
Grade 3 pancreatitis	Occurrence at 45 mg: • Withhold Ponatinib and resume at 30 mg after recovery to < Grade 2 Recurrence at 30 mg: • Withhold Ponatinib and resume at 15 mg after recovery to < Grade 2 Recurrence at 15 mg: • Consider discontinuing Ponatinib
Grade 4 pancreatitis	Discontinue Ponatinib

*IULN = institution upper limit of normal

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**

Toxicities

Myelosupression
Vascular occlusion
Hepatotoxicity
Pancreatitis

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