ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

ICLUSIG Dosing Guide

Utilize a response-based dosing strategy in CP-CML[1]

INDICATIONS AND USAGE

ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.

Limitations of Use: ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

IMPORTANT SAFETY INFORMATION

WARNING: ARTERIAL OCCLUSIVE EVENTS, VENOUS THROMBOEMBOLIC EVENTS, HEART FAILURE, and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Arterial occlusive events (AOEs), including fatalities, have occurred in ICLUSIG-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue ICLUSIG based on severity. Consider benefit-risk to guide a decision to restart ICLUSIG.**
- **Venous thromboembolic events (VTEs) have occurred in ICLUSIG-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue ICLUSIG based on severity.**
- **Heart failure, including fatalities, occurred in ICLUSIG-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or discontinue ICLUSIG for new or worsening heart failure.**
- **Hepatotoxicity, liver failure and death have occurred in ICLUSIG-treated patients. Monitor liver function tests. Interrupt or discontinue ICLUSIG based on severity.**

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

Optimal response-based dosing strategy in CP-CML[1,2]

45 mg → 15 mg
for patients who achieve ≤1% BCR-ABL1[IS]

1 Induce at 45 mg

Initiate treatment at 45 mg orally, once daily[1]

- Start at 30 mg once daily in patients taking strong CYP3A inhibitors and in patients with pre-existing hepatic impairment (Child-Pugh A, B, or C)
- Consider discontinuing ICLUSIG® (ponatinib) if hematologic response has not occurred by 3 months

2 Reduce to 15 mg

Reduce the dose to 15 mg once daily after ≤1% BCR-ABL1[IS] is achieved[1]

- Of the 93 patients in the OPTIC trial who received ICLUSIG 45 mg→15 mg, 52 achieved ≤1% BCR-ABL1 at any time[2,a]

3 Maintain at 15 mg

Patients who lose response can have their dose re-escalated to a previously tolerated dosage of 30 mg or 45 mg once daily[1]

- Of the 52 patients who achieved ≤1% BCR-ABL1 at any time, 13 lost response and had their dose re-escalated[2]
  - 62% of these patients (n=8/13) regained response following dose re-escalation
- Patients taking 15 mg orally once daily who experience an adverse reaction can have their dose reduced to 10 mg orally once daily once the adverse reaction resolves[1]

AP- and BP-CML[1]

The recommended starting dosage of ICLUSIG is 45 mg orally once daily. Consider reducing the dose of ICLUSIG for patients with AP-CML who have achieved a major cytogenetic response. Continue treatment with ICLUSIG until loss of response or unacceptable toxicity

Consider discontinuing ICLUSIG if response has not occurred by 3 months

The optimal dose of ICLUSIG has not been identified

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

Important dosing considerations[1]

- ICLUSIG is an oral, once-daily TKI
  - Tablets should be swallowed whole. Do not crush, break, cut, or chew tablets
  - ICLUSIG can be taken with or without food
  - If a dose is missed, take the next dose at the regularly scheduled time the next day
- ICLUSIG is available in 45-, 30-, 15-, and 10-mg tablet strengths
- There are recommended dosage modifications for ARs including: AOEs, VTEs, heart failure, hepatotoxicity, pancreatitis and elevated lipase, myelosuppression, and non-hematologic adverse reactions (hypertension, neuropathy, hemorrhage, fluid retention, and cardiac arrhythmias)
  - Table 1 of the full Prescribing Information contains the complete ICLUSIG dosage modifications for ARs depending on severity
  - These dosage modifications can be found within this guide, starting on page 6
- Consider the efficacy and safety of ICLUSIG in relation to the dose for your patients:
  - In PACE, the dose intensity-safety relationship indicated that there are significant increases in Grade ≥3 adverse reactions (hypertension, thrombocytopenia, pancreatitis, neutropenia, rash, ALT increase, AST increase, lipase increase, myelosuppression) over the dose range of 15 mg to 45 mg. In addition to dose, increased age and history of ischemia, hypertension, diabetes, or hypercholesterolemia were also contributory factors to a higher incidence of AOEs
  - In OPTIC, an exposure-response relationship between ponatinib exposure and molecular response rate at 12 months was observed. A relationship between higher ponatinib exposures and higher incidence of adverse reactions, including thrombocytopenia (Grade ≥3) and AOEs, was observed

ALT=alanine aminotransferase; AOE=arterial occlusive event; AP-CML=accelerated phase chronic myeloid leukemia; AR=adverse reaction; AST=aspartate aminotransferase; BCR-ABL1[IS]=BCR-ABL1 International Scale; BP-CML=blast phase chronic myeloid leukemia; CP-CML=chronic phase chronic myeloid leukemia; TKI=tyrosine kinase inhibitor.

[a]The primary endpoint for OPTIC was ≤1% BCR-ABL1[IS] at 12 months.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOEs in OPTIC (45 mg→15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOEs was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOEs occurred in 2.1% of patients in OPTIC, and in 2% of patients in PACE. Some patients in PACE experienced recurrent or multisite vascular occlusion. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. The most common risk factors observed with these events in PACE were history of hypertension, hypercholesterolemia, and non-ischemic cardiac disease. In OPTIC and PACE, AOEs were more frequent with increasing age.

In OPTIC, patients with uncontrolled hypertension or diabetes and patients with clinically significant, uncontrolled, or active cardiovascular disease were excluded. In PACE, patients with uncontrolled hypertriglyceridemia and patients with clinically significant or active cardiovascular disease within the 3 months prior to the first dose of ICLUSIG were excluded. Consider whether the benefits of ICLUSIG are expected to exceed the risks.

Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk to guide a decision to restart ICLUSIG

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

ICLUSIG® (ponatinib) achieved and maintained a clinically meaningful depth of response[1,3]

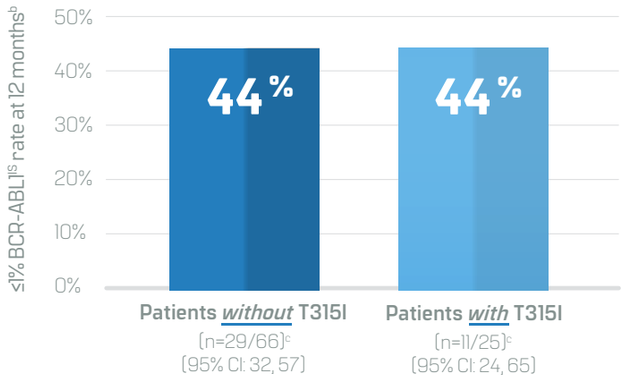
Rates of response and maintenance for the 45 mg→15 mg dosing strategy

TKI-resistant population

- **98%** of patients had developed resistance to their prior line of therapy before receiving ICLUSIG[1]
- Only **2%** of patients achieved ≤1% BCR-ABL1 or better on their last prior therapy[3]

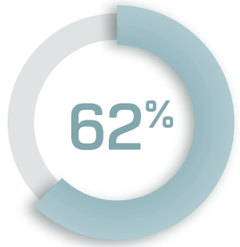
Efficacy regardless of mutation status

Overall, 44% of patients achieved ≤1% BCR-ABL1^{IS} at 12 months (n=41/93)[1,a,b]



- Median duration of follow-up in the 45 mg→15 mg arm was 27.0 months[1]

Response maintained



of patients (n=28/45)[d] maintained their response at a reduced dose of 15 mg[1]

- 100% of the patients (n=28/28)[d] who maintained ≤1% BCR-ABL1 at 15 mg did so for ≥90 days[1]

*OPTIC (NCT02467270) is an ongoing, dose-optimization trial evaluating 3 starting doses (45 mg/day, 30 mg/day, and 15 mg/day) of ICLUSIG in 282 adult patients with CP-CML whose disease was considered to be resistant or resistant/intolerant to at least two prior TKI therapies or who have the T315I mutation. Patients were randomized 1:1:1 to 3 cohorts, 45 mg/day, 30 mg/day, or 15 mg/day orally once daily.[1,3]

Please see Table 9 in the full Prescribing Information for full demographics including age, disease history, and comorbidities.

[a]ITT population (N=93) defined as patients who had b2a2/b3a2 BCR-ABL1 transcripts.

[b]Primary endpoint was ≤1% BCR-ABL1^{IS} rate at 12 months. Defined as a ≤1% ratio of BCR-ABL1 to ABL transcripts on the International Scale (IS) (ie, ≤1% BCR-ABL1^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

[c]Of the 93 patients, 2 patients did not have a baseline mutation assessment and were excluded from the response by mutation analysis.

[d]Patients who achieved ≤1% BCR-ABL1 at any time.

CP-CML=chronic phase chronic myeloid leukemia.

IMPORTANT SAFETY INFORMATION (cont'd)

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. VTEs included deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

OPTIC safety profile 45 mg→15 mg[1]

Serious adverse reactions

Serious adverse reactions occurred in 34% of patients who received ICLUSIG at a starting dose of 45 mg. Serious adverse reactions in >2% of patients included

- AOEs (9%; of which 2.1% were sudden death)
- cardiac arrhythmias (6%)
- thrombocytopenia (5%)
- pyrexia (4.3%)
- anemia (3.2%)
- abdominal pain (3.2%)
- atrial fibrillation (2.1%)
- pancreatitis/lipase elevation (2.1%)
- neutropenia (2.1%)
- hypertension (2.1%)

Fatal adverse reactions occurred in 2 patients (2.1%), both of which were sudden death.

Most common adverse reactions

The most common (>20%) adverse reactions were

- rash and related conditions
- hypertension
- arthralgia
- hyperlipidemia
- hepatic dysfunction
- pancreatitis/lipase elevation
- abdominal pain

The most common (>20%) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutrophil cell count decreased.

Discontinuations

Permanent discontinuation of ICLUSIG due to an adverse reaction occurred in 19% of patients who received ICLUSIG at a starting dose of 45 mg. Adverse reactions which resulted in permanent discontinuation in >2% of patients included AOEs, thrombocytopenia, hypertension, and sudden death.

IMPORTANT SAFETY INFORMATION (cont'd)

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, the most frequently reported heart failure events (≥2%) were congestive cardiac failure (3.1%), decreased ejection fraction (2.9%), and cardiac failure (2%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG for new or worsening heart failure.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Dosage modifications for adverse reactions[1]

Recommended dosage modifications of ICLUSIG® (ponatinib) for adverse reactions are provided in Table 1 of the Prescribing Information and recommended dosage reductions of ICLUSIG for adverse reactions are presented in Table 2.

Recommended dosage modifications for AOEs and VTEs[1]

Adverse Reaction	Severity	ICLUSIG Dosage Modifications
AOE: cardiovascular or cerebrovascular	Grade 1	Interrupt ICLUSIG until resolved, then resume at same dose.
	Grade 2	Interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 3 or 4	Discontinue ICLUSIG.
AOE: peripheral vascular and other **or** **VTE**	Grade 1	Interrupt ICLUSIG until resolved, then resume at same dose.
	Grade 2	Interrupt ICLUSIG until Grade 0 or 1, then resume at same dose. If recurrence, interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose.
	Grade 3	Interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
	Grade 4	Discontinue ICLUSIG.

Monitor for evidence of AOEs or VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity. For AOEs, consider benefit-risk to guide a decision to restart ICLUSIG

AOE=arterial occlusive event; VTE=venous thromboembolic event.

IMPORTANT SAFETY INFORMATION (cont'd)

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in 3 patients, with hepatic failure occurring within 1 week of starting ICLUSIG in one of these patients. These fatal cases occurred in patients with BP-CML or Ph+ ALL. Hepatotoxicity occurred in 28% of 94 patients in OPTIC and 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in OPTIC (6% of 94 patients) and PACE (13% of 449 patients). The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, then resume at a reduced dose or discontinue ICLUSIG based on recurrence/severity.

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

Additional dosage modifications

Recommended dosage modifications for heart failure[1]

Severity	ICLUSIG Dosage Modifications
Grade 2 or 3	Interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.
Grade 4	Discontinue ICLUSIG.

Monitor patients for signs or symptoms consistent with heart failure and manage heart failure as clinically indicated. Interrupt, then resume at reduced dose or discontinue ICLUSIG for new or worsening heart failure

Recommended dosage modifications for hepatotoxicity[1]

Severity	ICLUSIG Dosage Modifications
AST or ALT greater than 3 times ULN	Interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose.
AST or ALT at least 3 times ULN concurrent with bilirubin greater than 2 times ULN and alkaline phosphatase less than 2 times ULN	Discontinue ICLUSIG.

Liver function tests: Recommended at baseline, then at least monthly or as clinically indicated[1]

Recommended dosage modifications for myelosuppression[1]

Severity	ICLUSIG Dosage Modifications
ANC less than 1 x 10^9/L or platelets less than 50 x 10^9/L	Interrupt ICLUSIG until ANC at least 1.5 x 10^9/L and platelet at least 75 x 10^9/L, then resume at same dose. If recurrence, interrupt ICLUSIG until resolution, then resume at next lower dose.

Complete blood count monitoring: Recommended every 2 weeks for the first 3 months and then monthly or as clinically indicated[1]

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (cont'd)

Hypertension: Serious or severe hypertension, including hypertensive crisis, has occurred in patients who received ICLUSIG. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath. Monitor blood pressure at baseline and as clinically indicated and manage hypertension as clinically indicated. Interrupt, dose reduce, or stop ICLUSIG if hypertension is not medically controlled. For significant worsening, labile or treatment-resistant hypertension, interrupt ICLUSIG and consider evaluating for renal artery stenosis.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Additional dosage modifications[1]

Recommended dosage modifications for pancreatitis and elevated lipase

Severity	ICLUSIG Dosage Modifications
Serum lipase greater than 1 to 1.5 times ULN	Consider interrupting ICLUSIG® (ponatinib) until resolution, then resume at same dose.
Serum lipase greater than 1.5 to 2 times ULN, 2 to 5 times ULN and asymptomatic, or asymptomatic radiologic pancreatitis	Interrupt ICLUSIG until Grade 0 or 1 (<1.5 times ULN), then resume at next lower dose.
Serum lipase greater than 2 to 5 times ULN and symptomatic, symptomatic Grade 3 pancreatitis, or serum lipase greater than 5 times ULN and asymptomatic	Interrupt ICLUSIG until complete resolution of symptoms and after recovery of lipase elevation Grade 0 or 1, then resume at next lower dose.
Symptomatic pancreatitis and serum lipase greater than 5 times ULN	Discontinue ICLUSIG.

Monitor serum lipase: Recommended every 2 weeks for the first 2 months and then monthly or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse.[1] Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms

IMPORTANT SAFETY INFORMATION (cont'd)

Pancreatitis: Serious or severe pancreatitis has occurred in patients who received ICLUSIG. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2 weeks. Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on severity. Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

Additional dosage modifications[1]

Recommended dosage modifications for other non-hematologic adverse reactions (hypertension, neuropathy, hemorrhage, fluid retention, and cardiac arrhythmias)

Severity	ICLUSIG Dosage Modifications
Grade 1	Interrupt ICLUSIG until resolved, then resume at same dose.
Grade 2	Interrupt ICLUSIG until Grade 0 or 1, then resume at same dose. If recurrence, interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose.
Grade 3 or 4	Interrupt ICLUSIG until Grade 0 or 1, then resume at next lower dose. Discontinue ICLUSIG if recurrence.

Monitor patients for evidence or symptoms of hypertension, neuropathy, hemorrhage, fluid retention, and cardiac arrhythmias while on ICLUSIG. Manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity. Refer to Section 5 (5.5, 5.8, 5.10, 5.11, 5.12) of the full Prescribing Information for the monitoring recommendations for these specific warnings

Dose reductions

Recommended dose reductions for adverse reactions

Dose Reduction	Dosage for Patients with CP-CML	Dosage for Patients with AP-CML, BP-CML, and Ph+ ALL
First	30 mg orally once daily	30 mg orally once daily.
Second	15 mg orally once daily	15 mg orally once daily.
Third	10 mg orally once daily	Permanently discontinue ICLUSIG in patients unable to tolerate 15 mg orally once daily.
Subsequent Reduction	Permanently discontinue ICLUSIG in patients unable to tolerate 10 mg orally once daily.	

IMPORTANT SAFETY INFORMATION (cont'd)

Increased Toxicity in Newly Diagnosed Chronic Phase CML: In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with CP-CML, single agent ICLUSIG 45 mg once daily increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The median exposure to treatment was less than 6 months. The trial was halted for safety. Arterial and venous thrombosis and occlusions occurred at least twice as frequently in the ICLUSIG arm compared to the imatinib arm. Compared to imatinib-treated patients, ICLUSIG-treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Considerations for strong CYP3A inhibitors and inducers[1]

Strong CYP3A inhibitors

Avoid coadministration of strong CYP3A inhibitors during treatment with ICLUSIG® (ponatinib)

Coadministration increases ponatinib plasma concentrations, which may increase the risk of ICLUSIG adverse reactions

If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the ICLUSIG once-daily dose from:

- **45 mg→30 mg**
- **30 mg→15 mg**
- **15 mg→10 mg**

If the patient's dose has already been reduced to 10 mg orally, once daily, avoid coadministration of ICLUSIG with a strong CYP3A inhibitor

After the strong CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the ICLUSIG dosage that was tolerated prior to initiating the strong CYP3A inhibitor

Strong CYP3A inducers

Avoid coadministration with a strong CYP3A inducer unless benefit outweighs the risk of decreased ponatinib exposure. Monitor patients for reduced efficacy. Selecting concomitant medication with no or minimal CYP3A induction potential is recommended.

IMPORTANT SAFETY INFORMATION (cont'd)

Neuropathy: Peripheral and cranial neuropathy occurred in patients in OPTIC and PACE. Some of these events in PACE were Grade 3 or 4. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

Recommendations for specific populations[1]

Pregnancy

Based on findings in animals and its mechanism of action, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Lactation

Because of the potential for serious adverse reactions in the breastfed child from ICLUSIG, advise women not to breastfeed during treatment with ICLUSIG and for 6 days following the last dose.

Females and males of reproductive potential

ICLUSIG can cause fetal harm when administered to pregnant women. Verify the pregnancy status of females of reproductive potential prior to initiating ICLUSIG. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Patients aged 65 years or older are more likely to experience adverse reactions including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic impairment

Patients with hepatic impairment are more likely to experience adverse reactions compared to patients with normal hepatic function. Reduce the starting dose of ICLUSIG for patients with preexisting hepatic impairment (Child-Pugh A, B, or C). The safety of multiple doses, or doses higher than 30 mg, has not been studied in patients with hepatic impairment.

IMPORTANT SAFETY INFORMATION (cont'd)

Ocular Toxicity: Serious or severe ocular toxicity leading to blindness or blurred vision have occurred in ICLUSIG-treated patients. The most frequent ocular toxicities occurring in OPTIC and PACE were dry eye, blurred vision, and eye pain. Retinal toxicities included age-related macular degeneration, macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Available doses of ICLUSIG® (ponatinib)[1]

Strength	NDC number	Description	Presentation
10 mg	63020-536-30	Oval, white to off-white, biconvex film-coated tablets with debossed "NZ" on one side and plain on the other side	30 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with a desiccant canister and induction-sealed, child-resistant closure.
15 mg	63020-535-30	Round, white, biconvex film-coated tablets with debossed "A5" on one side and plain on the other side	30 tablets in a wide-mouth white HDPE bottle with a desiccant canister and induction-sealed, child-resistant closure.
	63020-535-60		60 tablets in a wide-mouth white HDPE bottle with a desiccant canister and induction-sealed, child-resistant closure.
30 mg	63020-533-30	Round, white, biconvex film-coated tablets with debossed "C7" on one side and plain on the other side	30 tablets in a wide-mouth white HDPE bottle with a desiccant canister and induction-sealed, child-resistant closure.
45 mg	63020-534-30	Round, white, biconvex film-coated tablets with debossed "AP4" on one side and plain on the other side	30 tablets in a wide-mouth white HDPE bottle with a desiccant canister and induction-sealed, child-resistant closure.

All tablet strengths of ICLUSIG are taken orally, once daily, with or without food[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Hemorrhage: Fatal and serious hemorrhage events have occurred in patients who received ICLUSIG. Fatal hemorrhages occurred in PACE and serious hemorrhages occurred in OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Gastrointestinal hemorrhage and subdural hematoma were the most frequently reported serious hemorrhages. Events often occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Fluid Retention: Fatal and serious fluid retention events have occurred in patients who received ICLUSIG. In PACE, one instance of brain edema was fatal and serious events included pleural effusion, pericardial effusion, and angioedema. Monitor for fluid retention and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, occurred in patients in OPTIC and PACE. For some patients, events were serious or severe (Grade 3 or 4) and led to hospitalization. Monitor for signs and symptoms suggestive of slow heart rate (fainting, dizziness) or rapid heart rate (chest pain, palpitations or dizziness) and manage patients as clinically indicated. Interrupt, then resume at the same or reduced dose or discontinue ICLUSIG based on recurrence/severity.

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

IMPORTANT SAFETY INFORMATION (cont'd)

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in OPTIC and PACE. The incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. If ANC less than 1 x 10^9/L or platelets less than 50 x 10^9/L, interrupt ICLUSIG until ANC at least 1.5 x 10^9/L and platelets at least 75 x 10^9/L, then resume at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS was reported in ICLUSIG-treated patients in OPTIC and PACE. Ensure adequate hydration and treat high uric acid levels prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS (also known as Posterior Reversible Encephalopathy Syndrome) has been reported in patients who received ICLUSIG. Patients may present with neurological signs and symptoms, visual disturbances, and hypertension. Diagnosis is made with supportive findings on magnetic resonance imaging (MRI) of the brain. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG in patients upon resolution of RPLS is unknown.

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of ICLUSIG after resolution of wound healing complications has not been established. Gastrointestinal perforation or fistula occurred in patients receiving ICLUSIG. Permanently discontinue in patients with gastrointestinal perforation.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, ICLUSIG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common (>20%) adverse reactions are rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, pyrexia, nausea, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-817-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Strong CYP3A Inhibitors: Avoid coadministration or reduce ICLUSIG dose if coadministration cannot be avoided.

Strong CYP3A Inducers: Avoid coadministration.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during treatment with ICLUSIG and for 6 days following last dose.

Females and Males of Reproductive Potential: Verify pregnancy status of females of reproductive potential prior to initiating ICLUSIG. Ponatinib may impair fertility in females, and it is not known if these effects are reversible.

Pre-existing Hepatic Impairment: Reduce the starting dose of ICLUSIG to 30mg orally once daily for patients with pre-existing hepatic impairment as these patients are more likely to experience adverse reactions compared to patients with normal hepatic function.

References:

1. ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc. 02/2022.
2. Cortes J, Apperley J, Lomaia E, et al. [supplemental appendix]. *Blood*. 2021;138(21):2042-2050. Accessed February 17, 2022. https://ashpublications.org/blood/article/138/21/2042/476603/Ponatinib-dose-ranging-study-in-chronic-phase
3. Cortes J, Apperley J, Lomaia E, et al. *Blood*. 2021;138(21):2042-2050.

ICLUSIG® (ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Notes

Notes

Please see full Prescribing Information and additional Important Safety Information throughout this brochure.

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

ICLUSIG®
(ponatinib) tablets
45mg / 30mg / 15mg / 10mg

Visit ICLUSIG.com/hcp for more information on ICLUSIG.

Takeda | ONCOLOGY