1L Ph+ ALL

DOSING GUIDE

ICLUSIG is the first and only FDA-approved TKI for adults with newly diagnosed Ph+ ALL, in combination with chemotherapy[1]*

INDICATION

ICLUSIG is a kinase inhibitor indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy.

This indication is approved under accelerated approval based on minimal residual disease (MRD)-negative complete remission (CR) at the end of induction. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s).

*Approved under accelerated approval. Please see full Indications and Usage.
1L=first line; FDA=Food and Drug Administration; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI=tyrosine kinase inhibitor.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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.

Optimized dosing with ICLUSIG + chemotherapy for adults with newly diagnosed Ph+ ALL[1,2]

A starting dose of ICLUSIG 30 mg can be reduced to 15 mg once a patient achieves a meaningful response

For maximized disease control, follow the 3 Rs:

Respond with 30 mg

Start at 30 mg to establish efficacy

Reduce to 15 mg to manage tolerability

The dose can be reduced to 15 mg once daily for patients who achieve an MRD-negative CR at the end of induction

Remain on 15 mg for as long as response is maintained

Continue ICLUSIG in combination with chemotherapy for up to 20 cycles until loss of response or unacceptable toxicity*

ICLUSIG | One pill | Once a day | With or without food

See Table 1 of the PI for the complete recommended dosage modifications for ARs depending on severity.

ICLUSIG is a single tablet taken orally once daily[1]

- Can be taken with or without food. Tablets should be swallowed whole. Do not crush, break, cut, or chew tablets[1]
- If a dose is missed, take the next dose at the regularly scheduled time the next day[1]
- Store ICLUSIG tablets at 20°C to 25°C (68°F to 77°F)[1]
  - Excursions permitted to 15°C to 30°C (59°F to 86°F)
- See Section 16 of the PI for more information about storage and handling[1]

*One cycle is 28 days.[1]

AR=adverse reaction; CR=complete remission/response; MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; PI=Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG. These included cardiovascular, cerebrovascular, and peripheral vascular events, and occurred in patients with and without cardiovascular risk factors. Monitor for evidence of AOEs. Interrupt, then resume at the same or decreased dose, or discontinue ICLUSIG based on recurrence/severity. Consider benefit-risk before restarting ICLUSIG.

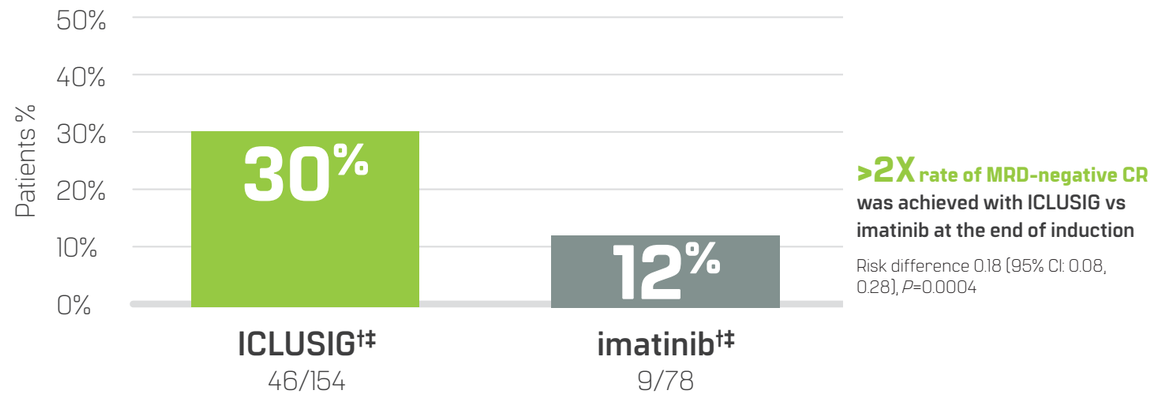
Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG, including events such as deep vein thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose, or discontinue ICLUSIG based on recurrence/severity.

DOSING GUIDE

Primary endpoint: MRD-negative CR

Significantly superior rate of MRD-negative CR with ICLUSIG vs imatinib at the end of induction[1]

In PhALLCON, ICLUSIG delivered more than double the rate of MRD-negative CR at the end of the 3-month induction phase[1†]



- MRD-negative CR is defined as ≤0.01% BCR::ABL1/ABL1 or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts, and meeting criteria for CR.[§]

†Of the 245 randomized patients, 244 were treated. Efficacy population included patients with baseline BCR::ABL1 dominant variant p190 and p210; 13/245 patients had atypical, missing, or unevaluable BCR::ABL1 assessment and were not included in the efficacy analysis.[1,3,4]

‡Treatments were used in combination with chemotherapy.[1]

§BCR::ABL1/ABL1 levels were reported as an absolute (raw) ratio for the p190 variant test and on the International Scale (BCR::ABL1[IS]) for the p210 variant test. Patients were considered to achieve CR if they maintained/had no circulating blasts and <5% blasts and normal maturation of all cellular components in the bone marrow, no extramedullary disease, ANC ≥1000/mcL, and platelets ≥100,000/mcL for at least 4 weeks. Patients who met both criteria were considered to have achieved MRD-negative CR.

ANC=absolute neutrophil count; cDNA=complementary DNA; CI=confidence interval; CRi=complete remission incomplete; EFS=event-free survival.

PhALLCON Trial[1,4]

245 global participants were randomized 2:1 to receive ICLUSIG 30 mg or imatinib 600 mg in combination with 20 cycles of the chemotherapy regimen. The major efficacy outcome was MRD-negative CR at the end of induction. Secondary endpoints included EFS, molecular response rates (MRD negativity [MR4] and MR4.5), and duration of CR and MRD negativity. The ICLUSIG dose was reduced from 30 mg once daily to 15 mg once daily after completion of the induction phase and achievement of MRD-negative CR. If a patient lost MRD negativity at any time after dose reduction to 15 mg, re-escalation to 30 mg once daily was allowed. Only patients who achieved CR or CR with incomplete hematologic recovery (CRi) with MRD-negativity at the end of induction could continue study treatment at the investigator's discretion.

Patients with uncontrolled hypertension, hypertriglyceridemia, or diabetes were excluded, as were patients with clinically significant, uncontrolled, or active cardiovascular disease. (See Section 6.1 of the PI for additional details).

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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

Rates of discontinuation and dose modification due to TEAEs in PhALLCON[5]

Characteristic	ICLUSIG arm % (n=163)	Imatinib arm % (n=81)
Discontinuation	**10%** (n=17)	**9%** (n=7)
Reduction	**20%** (n=33)	**22%** (n=18)
Interruption	**68%** (n=111)	**40%** (n=32)

- Certain patients may have received both a dose reduction and interruption

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Heart Failure: Fatal, serious, or severe heart failure events have occurred, including increased brain natriuretic peptide (BNP), left ventricular hypertrophy, left ventricular dysfunction, congestive cardiac failure, cardiac failure, left atrial dilatation, and decreased ejection fraction. Monitor for signs or symptoms of heart failure and manage as clinically indicated. Interrupt, then resume at reduced dose, or discontinue ICLUSIG for new or worsening heart failure.

Hepatotoxicity: ICLUSIG can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death has occurred. The most frequent hepatotoxic events were elevations of ALT, AST, GGT, bilirubin, and alkaline phosphatase, and decreased albumin and blood fibrinogen. 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.

Rates of discontinuation and dose modification due to TEAEs in PhALLCON[1,3,4] (cont'd)

- Clinically relevant adverse reactions in ≤10% of patients receiving ICLUSIG with chemotherapy: urinary tract infection (10%), arterial occlusive events (6%), cardiac failure (6%), and acute kidney injury (4.3%)[1]
- Serious adverse reactions occurred in 63% of patients receiving ICLUSIG in combination with chemotherapy and 57% of the patients receiving imatinib in combination with chemotherapy. Serious adverse reactions in >2% of ICLUSIG patients included febrile neutropenia (18%), pyrexia (6%), thrombocytopenia (4.3%), sepsis (3.7%), septic shock (3.7%), anemia (2.5%), hemorrhage (2.5%), neutropenia (2.5%), pancreatitis (2.5%), peripheral neuropathy (2.5%), pneumonia (2.5%), and acute kidney injury (2.5%). Fatal adverse reactions occurred in 6% of patients in both arms (ICLUSIG: 9 patients; imatinib: 5 patients). These events included sepsis in 6 (3.7%) ICLUSIG patients and 2 (2.4%) imatinib patients, sudden death, pneumonitis, and respiratory failure in 1 (0.6%) ICLUSIG patient each, and pulmonary sepsis, depressed level of consciousness, and pseudomembranous colitis in 1 (1.2%) imatinib patient each. One fatal TEAE was considered treatment-related in the imatinib arm (depressed level of consciousness)[1,3,5]
- Permanent discontinuation of ICLUSIG due to adverse reactions occurred in 13% of patients. Adverse reactions resulting in permanent discontinuation of ICLUSIG in >2% of patients included arterial occlusive events and sepsis[1]
- Dosage modifications (dose interruption or reduction) of ICLUSIG due to adverse reactions occurred in 71% of patients. Adverse reactions leading to dose interruption or reduction of ICLUSIG in >5% of patients included increased ALT, neutropenia, increased lipase, thrombocytopenia, increased AST, febrile neutropenia, and abdominal pain[1]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; TEAE=treatment-emergent adverse event.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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

Recommended dosage modifications for ICLUSIG for adverse reactions[1]

Recommended dosage modifications of ICLUSIG for adverse reactions are provided in Table 1 of the accompanying Prescribing Information, and recommended dose 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. Consider benefit-risk to guide a decision to restart ICLUSIG.

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 to monitor at baseline, then at least monthly or as clinically indicated.

Based on CTCAE v5.0: Grade 1 mild, Grade 2 moderate, Grade 3 severe, Grade 4 life-threatening.[1]

ALT=alanine aminotransferase; ANC=absolute neutrophil count; AOE=arterial occlusive event; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; ULN=upper limit of normal; VTE=venous thromboembolic event.

Recommended dosage modifications for ICLUSIG for adverse reactions[1] (cont'd)

Recommended dosage modifications of ICLUSIG for adverse reactions are provided in Table 1 of the accompanying Prescribing Information, and recommended dose reductions of ICLUSIG for adverse reactions are presented in Table 2.

Recommended dosage modifications for Pancreatitis and Elevated Lipase[1]

Severity	ICLUSIG Dosage Modifications
Serum lipase greater than 1 to 1.5 times ULN	Consider interrupting ICLUSIG 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 (less than 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. 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.

Recommended dosage modifications for Myelosuppression[1]

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.

Recommended dosage modifications for Other Non-Hematologic Adverse Reactions (hypertension, neuropathy, hemorrhage, fluid retention, and cardiac arrhythmias)[1]

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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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

Recommended dosage modifications for ICLUSIG for adverse reactions[1] (cont'd)

Recommended dosage modifications of ICLUSIG for adverse reactions are provided in Table 1 of the accompanying Prescribing Information, and recommended dose reductions of ICLUSIG for adverse reactions are presented in Table 2.

Dose Reduction	Dosage for Patients With Newly Diagnosed Ph+ ALL
First	15 mg orally once daily
Second	10 mg orally once daily
Third	Permanently discontinue ICLUSIG in patients unable to tolerate 10 mg orally once daily
Subsequent Reduction	

ICLUSIG is available in 45 mg, 30 mg, 15 mg, and 10 mg tablets[1]

Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Pancreatitis: Serious or severe pancreatitis has occurred. Elevations of lipase and amylase also occurred. In the majority of cases that led to dose modification or treatment discontinuation, pancreatitis resolved within 2-3 weeks. Monitor serum lipase 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. 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.

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 increased the risk of serious adverse reactions. The trial was halted for safety. ICLUSIG is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

Neuropathy: Peripheral and cranial neuropathy occurred in ICLUSIG-treated patients, including Grade 3 or 4 events. Monitor for symptoms 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.

Dosage modification for coadministration of strong CYP3A inhibitors[1]

Avoid coadministration of ICLUSIG with strong CYP3A inhibitors. If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the dosage of ICLUSIG as recommended below or in Table 3 of the Prescribing Information.[1]

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. See Sections 7 and 12 of the Prescribing Information for information about Drug Interactions or Clinical Pharmacology, respectively.[1]

ICLUSIG Dosage	Recommended ICLUSIG Dosage With a Strong CYP3A Inhibitor
30 mg orally once daily	15 mg orally once daily
15 mg orally once daily	10 mg orally once daily
10 mg orally once daily	Avoid coadministration of ICLUSIG with a strong CYP3A inhibitor

Strong CYP3A Inhibitors
Coadministration of ICLUSIG with a strong CYP3A inhibitor increases ponatinib plasma concentrations *[see prescribing information; Clinical Pharmacology (12.3)]*, which may increase the risk of ICLUSIG adverse reactions. Avoid coadministration of ICLUSIG with strong CYP3A inhibitors. If coadministration of ICLUSIG with strong CYP3A inhibitors cannot be avoided, reduce the ICLUSIG dosage *[see prescribing information; Dosage and Administration (2.3)]*.[1]

Strong CYP3A Inducers
Coadministration of ICLUSIG with a strong CYP3A inducer decreases ponatinib plasma concentrations *[see prescribing information; Clinical Pharmacology (12.3)]*. Avoid coadministration of ICLUSIG with strong CYP3A inducers unless the benefit outweighs the risk of decreased ponatinib exposure. Monitor patients for reduced efficacy. Selection of concomitant medication with no or minimal CYP3A induction potential is recommended.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Ocular Toxicity: Serious or severe ocular toxicities leading to blindness and blurred vision have occurred. The most frequent ocular toxicities were dry eye, blurred vision, and eye pain. Retinal toxicities included retinal vein occlusion, retinal hemorrhage, age-related macular degeneration, arteriosclerotic retinopathy, retinal vascular disorder, macular edema, and vitreous floaters. Conduct comprehensive eye exams at baseline and periodically during treatment.

Hemorrhage: Fatal and serious hemorrhages have occurred. Intracranial hemorrhage, gastrointestinal hemorrhage, and subdural hematoma were the most frequently reported serious hemorrhages. Most hemorrhages occurred in patients with Grade 4 thrombocytopenia. Monitor for hemorrhage and manage as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

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

In adults with newly diagnosed Ph+ ALL

ICLUSIG + chemotherapy had a comparable safety profile to imatinib + chemotherapy by utilizing optimized dosing[1]

Most common ARs[a] ≥20% in the PhALLCON study[1]

Adverse reaction	ICLUSIG (n=163)		imatinib (n=81)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hepatobiliary disorders				
Hepatotoxicity	66	30	57	14
Musculoskeletal and connective tissue disorders				
Arthralgia[b]	47	4	35	1
Nervous system disorders				
Headache	45	2	43	1
Neuropathy peripheral	33	1	24	1
Paresthesia	22	0	10	0
Skin and subcutaneous tissue disorders				
Rash and related conditions	47	1	33	1
Gastrointestinal disorders				
Abdominal pain[c]	43	5	28	0
Constipation	41	1	21	1
Nausea	37	3	52	7
Oral mucositis	35	5	30	10
Pancreatitis/lipase elevation	34	15	37	20
Vomiting	24	1	40	3
Diarrhea	20	0	35	3

[a]Graded using CTCAE v5.0.

[b]Includes arthralgia, arthritis, back pain, flank pain, intervertebral disc degeneration, joint swelling, osteoarthritis, neck pain, pain, pain in extremity, pain of skin, sciatica, spinal pain, tendonitis, and tenosynovitis.

[c]Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, chronic gastritis, colitis, enteritis, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gastrointestinal pain, gastroesophageal reflux disease, and helicobacter gastritis.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Fluid Retention: Fatal and serious events, including one instance of fatal brain edema and serious events of pleural effusion, pericardial effusion, and angioedema have occurred. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema, pleural effusion, hydrothorax, pericardial effusion, and peripheral swelling. Monitor for fluid retention and manage as clinically indicated. Interrupt, then resume at the same or reduced dose, or discontinue ICLUSIG based on recurrence/severity.

In adults with newly diagnosed Ph+ ALL

ICLUSIG + chemotherapy had a comparable safety profile to imatinib + chemotherapy by utilizing optimized dosing[1] (cont'd)

Most common ARs[a] ≥20% in the PhALLCON study[1]

Adverse reaction	ICLUSIG (n=163)		imatinib (n=81)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
General disorders				
Pyrexia	44	4	26	3
Fatigue or asthenia	40	3	38	4
Fluid retention and edema	24	1	48	4
Vascular disorders				
Hypertension	34	14	15	7
Hemorrhage	31	2	30	7
Blood and lymphatic system disorders				
Febrile neutropenia	28	25	22	20
Metabolism and nutrition disorders				
Impaired glucose tolerance	20	5	20	9
Cardiac disorders				
Cardiac arrhythmias	22	3	17	6

AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Cardiac Arrhythmias: Cardiac arrhythmias, including ventricular and atrial arrhythmias, tachycardia, bradycardia, cardio-respiratory arrest, syncope, atrial fibrillation, and supraventricular tachycardia, have occurred, including some patients with serious or severe (Grade 3 or 4) events leading 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.

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

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 1 week after 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. Advise females of reproductive potential of the potential for reduced fertility from ICLUSIG.

Pediatric use

Safety and effectiveness of ICLUSIG 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)

WARNINGS AND PRECAUTIONS (cont'd)

Myelosuppression: Grade 3 or 4 neutropenia, thrombocytopenia, and anemia have occurred. Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated. Interrupt ICLUSIG if ANC <1 × 10^9/L or platelets <50 × 10^9/L, and resume when ANC ≥1.5 × 10^9/L and platelets ≥75 × 10^9/L, at same or reduced dose.

Tumor Lysis Syndrome (TLS): Serious TLS has occurred. Ensure adequate hydration and treat elevated uric acid prior to initiating ICLUSIG.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has been reported. Patients can present with hypertension, seizure, headache, decreased alertness, altered mental functioning, vision loss, and other visual and neurological disturbances. MRI is necessary to confirm diagnosis. Interrupt ICLUSIG until resolution. The safety of resumption of ICLUSIG upon resolution of RPLS is unknown.

Select laboratory abnormalities (≥20%) that worsened from baseline in adults with newly diagnosed Ph+ ALL in PhALLCON[1]

Summary of laboratory abnormalities in PhALLCON for patients who received ICLUSIG or imatinib in combination with chemotherapy[1]

Laboratory Abnormality	ICLUSIG 30 mg → 15 mg With Chemotherapy (n = 163)		Imatinib 600 mg With Chemotherapy (n = 81)	
	All Grades[a] (%)	Grade 3 or 4[a] (%)	All Grades[a] (%)	Grade 3 or 4[a] (%)
Hematologic Laboratory Tests				
White blood cell decreased	79	71	78	70
Lymphocyte cell count decreased	77	61	94	89
Neutrophil cell count decreased	66	63	57	53
Platelet count decreased	65	62	64	53
Hemoglobin decreased	53	38	59	49
Liver Function Tests				
ALT increased	69	21	62	7
AST increased	53	7	48	6
Alkaline phosphatase increased	44	1	24	0
Total bilirubin increased	25	1	24	0
Direct bilirubin increased	24	4	24	1
Pancreatic Enzymes				
Lipase increased	60	24	78	38
Amylase increased	25	6	35	7
Chemistry				
Calcium decreased	67	3	69	5
Phosphate decreased	58	16	85	36
Potassium decreased	44	10	74	25
Albumin decreased	42	2	56	0
Glucose increased	34	3	38	3
Creatinine increased	34	4	48	5
Sodium decreased	32	3	35	4
Potassium increased	31	4	12	0
Magnesium decreased	15	1	31	3

[a]Graded using CTCAE v5.0.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Impaired Wound Healing and Gastrointestinal Perforation: Impaired wound healing occurred in patients receiving ICLUSIG. Withhold ICLUSIG for at least 1 week before elective surgery and for at least 2 weeks after major surgery until adequate wound healing. Gastrointestinal perforation or fistula have occurred. Permanently discontinue ICLUSIG in patients with gastrointestinal perforation.

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

Takeda Oncology Here2Assist®

Committed to supporting your patients

Takeda Oncology Here2Assist® is a comprehensive support program committed to helping your patients navigate coverage requirements, identify available financial assistance, and connect with helpful resources throughout their Takeda Oncology treatment.

- Works with your patients' insurance company to help get your patient started on their medication
- Identifies available financial assistance that may be right for your patients
- Identifies specialty pharmacies to help fill and ship your patients' prescriptions appropriately
- Conducts regular follow-up calls to patients

Visit us at www.here2assist.com/hcp/home to learn more

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Embryo-Fetal Toxicity: ICLUSIG can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to the fetus. Females of reproductive potential should use effective contraception during treatment with ICLUSIG and for 3 weeks after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (occurring in >20% of patients) are:

- ICLUSIG as a single agent: rash and related conditions, arthralgia, abdominal pain, fatigue, headache, constipation, hypertension, dry skin, hepatotoxicity, fluid retention and edema, pyrexia, pancreatitis/lipase elevation, nausea, hemorrhage, anemia, AOEs, and cardiac arrythmias. The most common Grade 3 or 4 laboratory abnormalities (>20%) are platelet count decreased, neutrophil cell count decreased, and white blood cell decreased.
- ICLUSIG in combination with chemotherapy: hepatotoxicity, arthralgia, rash and related conditions, headache, pyrexia, abdominal pain, constipation, fatigue, nausea, oral mucositis, hypertension, pancreatitis/lipase elevation, neuropathy peripheral, hemorrhage, febrile neutropenia, fluid retention and edema, vomiting, paresthesia, and cardiac arrhythmias. The most common Grade 3 or 4 laboratory abnormalities (>20%) are decreased white blood cell count, decreased neutrophil cell count, decreased platelet count, decreased lymphocyte cell count, decreased hemoglobin, increased lipase, and increased alanine aminotransferase.

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.

Notes

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

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

DOSING GUIDE

Optimized dosing with ICLUSIG + chemotherapy for adults with newly diagnosed Ph+ ALL[1,2]

A starting dose of ICLUSIG 30 mg can be reduced to 15 mg once a patient achieves a meaningful response

For maximized disease control, follow the 3 Rs:

Respond with 30 mg

Start at 30 mg to establish efficacy

Reduce to 15 mg to manage tolerability

The dose can be reduced to 15 mg once daily for patients who achieve an MRD-negative CR at the end of induction

Remain on 15 mg for as long as response is maintained

Continue ICLUSIG in combination with chemotherapy for up to 20 cycles until loss of response or unacceptable toxicity*

ICLUSIG | **One pill** | **Once a day** | **With or without food**

See Table 1 of the PI for the complete recommended dosage modifications for ARs depending on severity.

*One cycle is 28 days.[1]

AR=adverse reactions; CR=complete remission/response; MRD=minimal residual disease; Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia; PI=Prescribing Information.

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 1 week 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: For patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL receiving monotherapy, reduce the starting dose of ICLUSIG to 30 mg orally once daily for patients with pre-existing hepatic impairment. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended when administering ICLUSIG to patients with mild hepatic impairment.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

Visit ICLUSIG.com/hcp

References: 1. ICLUSIG (ponatinib) [prescribing information]. Cambridge, MA: Takeda Pharmaceuticals U.S.A., Inc. 10/2025. **2.** Cortes J, Apperley J, Lomaia E. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. *Blood* 2021;138(21):2050. doi:10.1182/blood.2021200128 **3.** Data on file. Takeda Pharmaceutical Company Limited, Inc. **4.** Jabbour E, Kantarjian HM, Aldoss I, et al. Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2024;331(21):1814-1823. doi:10.1001/jama.2024.4783 **5.** Jabbour E, Kantarjian HM, Aldoss I, et al. Supplement to: Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2024;331(21):1814-1823. doi:10.1001/jama.2024.4783

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