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

The first and only FDA-approved kinase inhibitor indicated for the treatment of adult patients with newly diagnosed Ph+ ALL in combination with chemotherapy

INDICATIONS AND USAGE

ICLUSIG® (ponatinib) is indicated for the treatment of adult patients with:

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- Newly diagnosed 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).
- As monotherapy in Ph+ ALL for whom no other kinase inhibitors are indicated or T315I-positive Ph+ ALL.

Chronic Myeloid Leukemia (CML)

- Chronic phase (CP) CML with resistance or intolerance to at least two prior kinase inhibitors.
- Accelerated phase (AP) or blast phase (BP) CML for whom no other kinase inhibitors are indicated.
- T315I-positive CML (chronic phase, accelerated phase, or blast phase).

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

All manufactured NDCs displayed. Please see prescribing information for dosing instructions.
FDA, US Food and Drug Administration; NDC, National Drug Code.

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, including Boxed Warning and Important Safety Information throughout.

Takeda | ONCOLOGY

Ph+ ALL Is a Rare and Aggressive Hematologic Cancer That Occurs More Frequently in Adults Than in Children[1-5]

In 2024, an estimated 6550 adults in the US will be diagnosed with ALL, of which about 1638 cases will be Ph+ ALL. Since 2010, **the 5-year OS rate of adults with Ph+ ALL is 50%.**[6]

OS rate is based on real-world evidence. All real-world evidence has limitations. The limitations of this analysis include: a relatively small number of patients with Ph+ ALL and no data on treatment, so the analysis includes patients who did not receive any antileukemic treatment and may not reflect novel treatments. Results should be interpreted with caution.

In a Meta-Analysis, Low Deep Molecular Response Rates Contribute to Suboptimal Survival With 1G and 2G TKIs in Adults With Newly Diagnosed Ph+ ALL[7]*

Low rates of deep molecular responses

- **32%** of patients (95% CI: 25–40) achieved a complete molecular response (CMR)† with a 1G or 2G TKI

Suboptimal survival

- Patients who received a 1G or 2G TKI had a
  - 2-year OS of **58%** (95% CI: 53–63)
  - 3-year OS of **50%** (95% CI: 42–58)

CMR (also known as MRD negativity) may be an important determinant of clinical outcomes across genetic subtypes and may be the next major clinical goal after achieving a hematologic complete response[8]

This meta-analysis (25 studies; N=1644) had several limitations: it relied on study-level data with heterogeneous treatment regimens; it included studies based on targeted rather than systemic literature search; results may be limited due to changes in treatment patterns and clinical practice since data were reported; and data for analysis were limited to studies available at the time of analysis. Data should be interpreted with caution.

Resistance Mutations in BCR::ABL1 Occur Frequently in Ph+ ALL and Drive Disease Progression

At diagnosis

38% of patients with Ph+ ALL (n=12/32) had a **BCR::ABL1 resistance mutation**;

of those, 17% had a T315I mutation (n=2/12).[9‡]

In relapsed patients following their respective frontline treatments, 54%–88% of patients treated with a 1G or 2G TKI had a BCR::ABL1 kinase mutation.[10-13§] These patients are **5x more likely to experience disease relapse or death** than patients without a BCR::ABL1 mutation.[14]

T315I Is the Most Common BCR::ABL1 Resistance Mutation in Ph+ ALL and Is the Most Difficult to Treat[14,15]

T315I mutations occurred in up to

75%

of patients with Ph+ ALL.[13¶]

Unadjusted, indirect comparison for descriptive purposes only; clinical significance is not implied. Cross-trial comparisons are potentially confounded by differences in trial design and study population. Studies may have unobserved, confounding, and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Real-world analyses are often nonrandomized, observational, retrospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Outcomes should be interpreted with caution because of small sample size, limited follow-up, and heterogenous patient population.

*Based on a 2018 targeted literature review of 25 clinical studies comparing the effectiveness of frontline BCR::ABL1 TKIs in 1644 patients with newly diagnosed Ph+ ALL (median age: 46 years; age range: 8–85 years).[7]

†CMR was defined as the absence of detectable BCR::ABL1 transcripts with a sensitivity of 0.01%.[7]

‡This study was a randomized, multicenter, open-label, Phase 2 study to determine the safety and efficacy of induction therapy with imatinib in comparison with standard induction chemotherapy in adult patients aged 55 years or older with Ph+ ALL.[9]

§1G data are based on 3 studies of adult patients with relapsed Ph+ ALL (n=26, n=20, n=54) given imatinib plus chemotherapy according to protocol in respective studies.[9,14,16] 2G data are based on 4 studies of adult patients with relapsed Ph+ ALL (n=13, n=13, n=17, n=24) given dasatinib plus chemotherapy according to protocol in respective studies.[10-13]

¶This study was a Phase 2 study done in adult patients aged 55 years or older (N=71) with newly diagnosed Ph+ and/or BCR::ABL1+ ALL to evaluate the efficacy and safety of induction and consolidation therapy with dasatinib in combination with chemotherapy.[13]

1G, 1st-generation; 2G, 2nd-generation; BCR::ABL1, breakpoint cluster region-Abelson; CI, confidence interval; MRD, minimum residual disease; OS, overall survival; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor.

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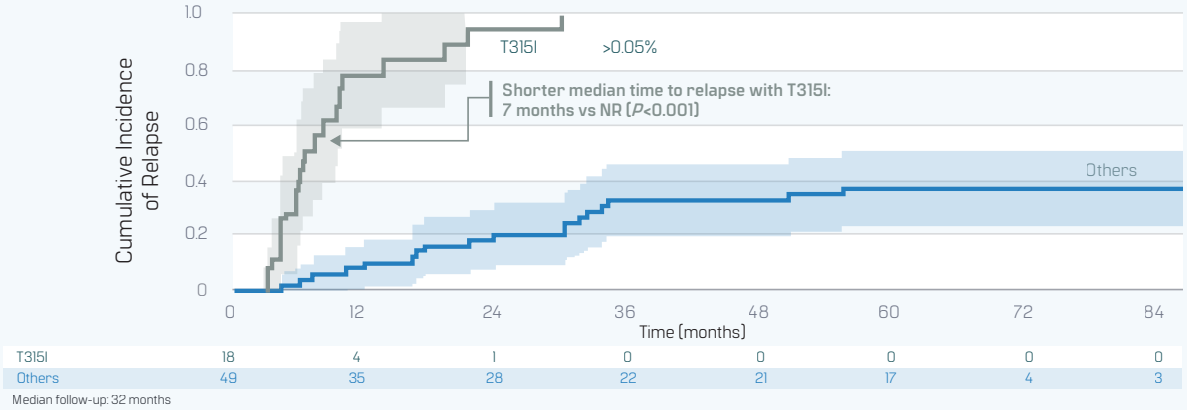
The below study was a Phase 2 study done in adult patients aged 55 years or older (N=71) with newly diagnosed Ph+ and/or BCR::ABL1+ ALL to evaluate the efficacy and safety of induction and consolidation therapy with a 2G TKI in combination with chemotherapy.[13]

Patients with a T315I mutation have a median time to relapse of 7 months vs NR in patients without T315I (P<0.0001)[9,13]

Time to relapse among patients in CR treated with a 2G TKI + low-intensity chemotherapy with or without T315I



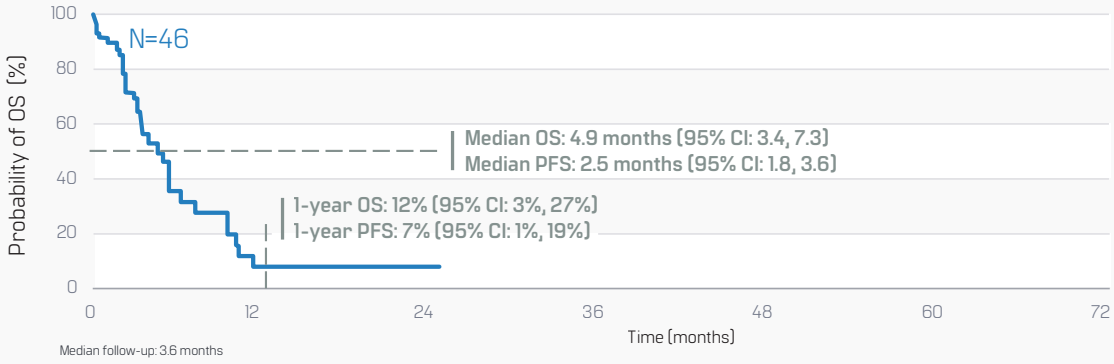
T315I	18	4	1	0	0	0	0	0
Others	49	35	28	22	21	17	4	3

Median follow-up: 32 months

The below study was an epidemiologic study on survival of adult patients aged 18 years or older (N=222) with CML or Ph+ ALL possessing the T315I mutation with a documented hematologic or cytogenic resistance to 1G or 2G TKIs.[17]

Patients with a T315I mutation have a 1-year OS of only 12%[17]

OS from first T315I mutation detection*



Median follow-up: 3.6 months

Real-world analyses are often nonrandomized, observational, retrospective studies that may have unobserved confounding and treatment selection biases as well as other limitations that should be considered when comparing results with clinical trials. Outcomes should be interpreted with caution because of small sample size, limited follow-up, and heterogenous patient population.

*Treatments after detection of T315I were reported in 216 patients (CML and Ph+ ALL grouped). Treatments included ≥1 of the following: 2G BCR::ABL1 TKI, hydroxyurea, imatinib, cytarabine, stem cell transplant, MK-0457, other investigational drug, or interferon-α.[17]

CR, complete remission; NR, not reached; PFS, progression-free survival.

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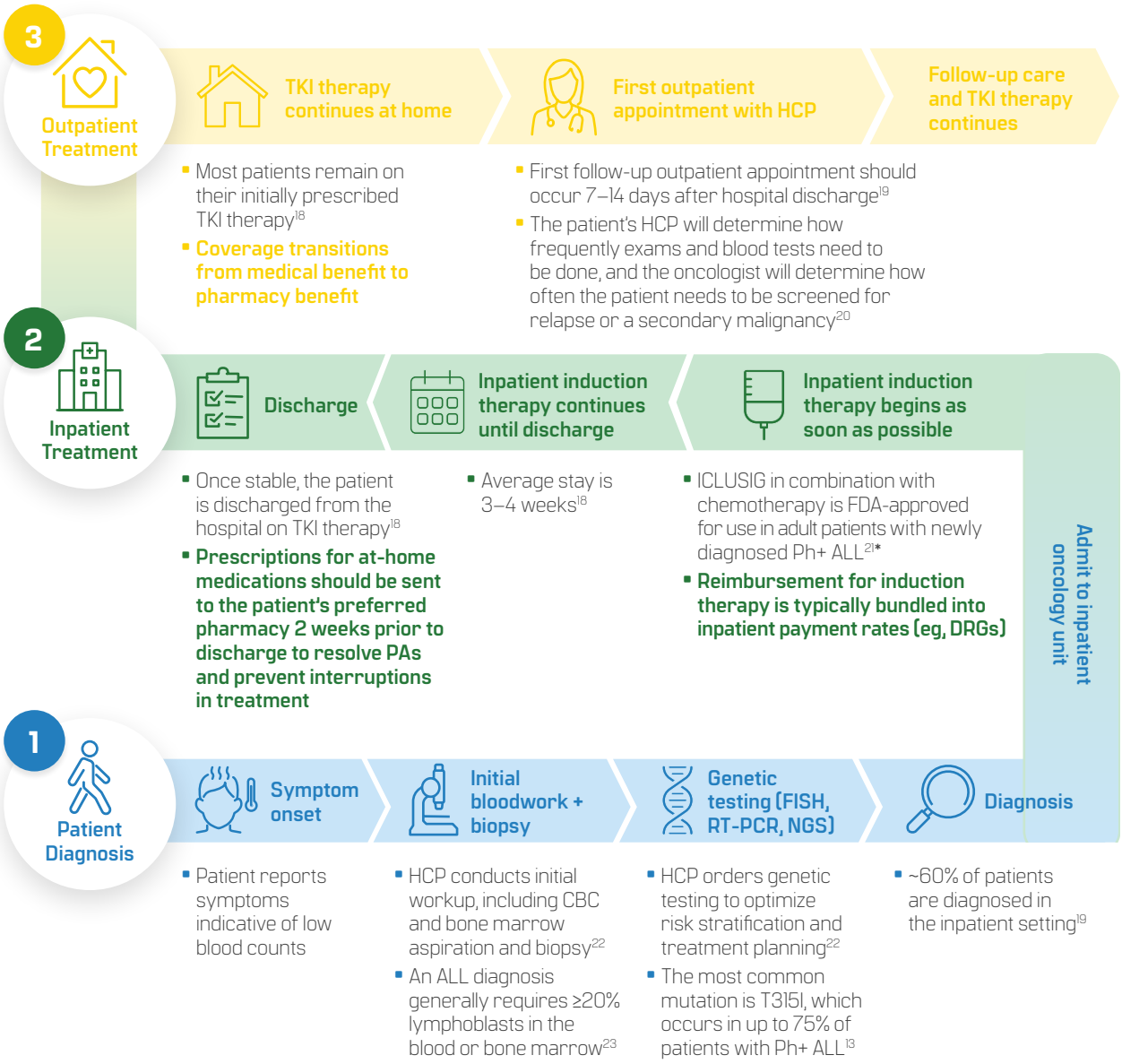
The Ph+ ALL Patient Treatment Journey Begins Immediately at Diagnosis With Inpatient Induction Treatment Transitioning to Outpatient Treatment



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

CBC, complete blood count; DRG, Diagnosis-Related Group; FISH, fluorescence in situ hybridization; HCP, health care provider; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PA, prior authorization; RT-PCR, reverse transcriptase polymerase chain reaction.

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Ponatinib Is the Only Pan-Mutational BCR::ABL1 Inhibitor and the Only Third-Generation TKI in Ph+ ALL[22,24]

Preclinical activity does not necessarily correlate with clinical outcomes.

ICLUSIG® (ponatinib) in Combination With Chemotherapy Is the First and Only FDA-Approved Frontline TKI for Adults With Newly Diagnosed Ph+ ALL[21,25-28]

PhALLCON: The First Head-to-Head Phase 3 Clinical Trial in Adult Patients With Newly Diagnosed Ph+ ALL[21]

254 global participants were randomized 2:1 to receive ICLUSIG + chemotherapy or imatinib + chemotherapy in a study with a composite primary endpoint of MRD-negative CR at the end of induction

Efficacy was based on the MRD-negative CR rate at the end of induction[21,22,29]

Term	Definition
MRD-Negative	≤0.01% BCR::ABL1/ABL or undetectable BCR::ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts as determined by central laboratory testing.
CR	Met the following criteria for at least 4 weeks: ▪ No circulating blasts and <5% blasts in the bone marrow ▪ Normal maturation of all cellular components in the bone marrow ▪ No extramedullary disease ▪ ANC >1000/mcL ▪ Platelets >100,000/mcL

ANC, absolute neutrophil count; cDNA, complementary DNA.

Primary Endpoint[21]

Efficacy Results in Patients With Ph+ ALL With Baseline BCR::ABL1 Dominant Variant of p190 or p210		
	ICLUSIG® (ponatinib) 30 mg → 15 mg With Chemotherapy (n=154)	**Imatinib 600 mg With Chemotherapy (n=78)**
MRD-negative CR* at end of induction		
Achieved at the end of induction, % (n/N)	30 (46/154)	12 (9/78)
Risk difference (95% CI)†	0.18 (0.08, 0.28)	
P-value†	0.0004	
CR‡ at End of Induction % (n/N)	79% (122/154)	63% (49/78)

ICLUSIG in combination with chemotherapy demonstrated a statistically significant higher MRD-negative CR rate at the end of induction compared with imatinib in combination with chemotherapy

ICLUSIG in Combination With Chemotherapy Safety Profile in PhALLCON[21]

Adverse Reactions

Serious adverse reactions occurred in

63%

of patients, including febrile neutropenia in 18% of patients receiving ICLUSIG in combination with chemotherapy

Permanent discontinuation of ICLUSIG occurred in

13%

of patients due to adverse reactions

Dose modifications (interruption or reduction) of ICLUSIG occurred in

71%

of patients due to adverse reactions

The most common adverse reactions with ICLUSIG in combination with chemotherapy occurring in >20% of adult patients with newly diagnosed Ph+ ALL were hepatic dysfunction, 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%) with ICLUSIG in combination with chemotherapy included decreased white blood cell count, decreased neutrophil cell count, decreased platelet count, decreased lymphocyte cell count, decreased hemoglobin, increased lipase, and increased alanine aminotransferase.

*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.

†Difference, 95% CI and two-sided *P*-value are based on Cochran-Mantel-Haenszel method stratified by the randomization stratification factor.

‡CR is defined as no circulating blasts and <5% blasts in the bone marrow with normal maturation of all cellular components; no evidence of extramedullary disease (ie, central nervous system involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass); and hematologic recovery of ANC >1.0 x 10^9/L and platelets > 100 x 10^9/L for at least 4 weeks.

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IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

Arterial Occlusive Events (AOEs): AOEs, including fatalities, have occurred in patients who received ICLUSIG in PhALLCON, OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. In PhALLCON, 6% of 163 patients experienced AOEs; 3.7% experienced Grade 3 or 4. 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 0.6% of patients in PhALLCON, 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 PhALLCON, OPTIC and PACE, AOEs were more frequent with increasing age.

In PhALLCON, patients with uncontrolled hypertension, hypertriglyceridemia, or diabetes were excluded. Patients with clinically significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revascularization procedure, venous thromboembolism, clinically significant atrial/ventricular tachyarrhythmias, unstable angina, or congestive heart failure within the 6 months prior to the first dose of ICLUSIG, were also excluded.

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.

Venous Thromboembolic Events (VTEs): Serious or severe VTEs have occurred in patients who received ICLUSIG. In PhALLCON, VTEs occurred in 12% of 163 patients, including serious or severe (Grade 3 or 4) in 3.1% of patients. One of 94 patients in OPTIC experienced a VTE (Grade 1 retinal vein occlusion). In PACE, VTEs occurred in 6% of 449 patients including serious or severe (Grade 3 or 4) VTEs in 5.8% of patients. In PhALLCON and PACE VTEs included deep venous thrombosis, embolism, pulmonary embolism, superficial vein thrombosis, thrombosis, jugular vein thrombosis, superficial thrombophlebitis, retinal vein occlusion, and retinal vein thrombosis with vision loss. The incidence of VTEs in PACE was higher in patients with Ph+ ALL (9% of 32 patients) and BP-CML (10% of 62 patients). Monitor for evidence of VTEs. Interrupt, then resume at the same or decreased dose or discontinue ICLUSIG based on recurrence/severity.

Heart Failure: Fatal, serious or severe heart failure events have occurred in patients who received ICLUSIG. In PhALLCON, heart failure occurred in 6% of 163 patients; 1.2% experienced serious or severe (Grade 3 or 4) heart failure. Heart failure occurred in 13% of 94 patients in OPTIC; 1.1% experienced serious or severe (Grade 3 or 4). In PACE, heart failure occurred in 9% of 449 patients; 7% experienced serious or severe (Grade 3 or higher). In PhALLCON the most frequently reported heart failure event (>1 patient) was increased brain natriuretic peptide (BNP) (2.5%). In OPTIC, the most frequently reported heart failure events (>1 patient each) were left ventricular hypertrophy (3.2%) and BNP increased (3.2%). 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%). 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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (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 treated with monotherapy. Hepatotoxicity occurred in 66% of 163 patients in PhALLCON, in 28% of 94 patients in OPTIC and in 32% of 449 patients in PACE. Grade 3 or 4 hepatotoxicity occurred in PhALLCON (30% of 163 patients), in OPTIC (6% of 94 patients), and in 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.

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.

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 2-3 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.

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.

Neuropathy: Peripheral and cranial neuropathy occurred in patients in PhALLCON, OPTIC and PACE. Some of these events in PhALLCON and 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.

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 PhALLCON, 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.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (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 PhALLCON, OPTIC and PACE. In PACE, the incidence of serious bleeding events was higher in patients with AP-CML, BP-CML, and Ph+ ALL. Intracranial hemorrhage, 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. In PhALLCON serious fluid retention included pericardial effusion. The most frequent occurrences of fluid retention in patients who received ICLUSIG were peripheral edema and pleural effusion. 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, atrial arrhythmias, tachycardia, syncope, atrial fibrillation and supraventricular tachycardia occurred in patients in PhALLCON, 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.

Myelosuppression: Grade 3 or 4 events of neutropenia, thrombocytopenia, and anemia occurred in patients in PhALLCON, OPTIC and PACE. In PACE, the incidence of myelosuppression was greater in patients with AP-CML, BP-CML, and Ph+ ALL treated with monotherapy 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 PhALLCON, 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.

IMPORTANT SAFETY INFORMATION (CONT'D)

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, 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.
- ICLUSIG in combination with chemotherapy: hepatic dysfunction, 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.

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 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. For patients with newly diagnosed Ph+ ALL, no dosage adjustment is recommended.

Please see accompanying full Prescribing Information, including Boxed Warning.

To learn more about ICLUSIG, please visit www.iclusig.com/hcp.

Pricing of ICLUSIG® (ponatinib)

Drug	WAC Pricing[30]
ICLUSIG® (ponatinib)	45 mg (30 tablets): $20,831.00
	30 mg (30 tablets): $20,831.00
	15 mg (30 tablets): $20,831.00
	10 mg (30 tablets): $20,831.00

Please see PI for appropriate dosing of ICLUSIG for adult patients with newly diagnosed Ph+ ALL in combination with chemotherapy and all other indications.

Billing Information for ICLUSIG

ICLUSIG is expected to be bundled into inpatient payment rates (ie, MS-DRGs) when used in the hospital

MS-DRG[31]	Description
ALL	
834	Acute leukemia without major OR procedures with MCC
835	Acute leukemia without major OR procedures with CC
836	Acute leukemia without major OR procedures without CC/MCC

Outlier Payments[32]

Outlier payments may be available if the costs of care for a very complex patient exceed the payment for the appropriate MS-DRG. To qualify as an outlier, a claim must have costs greater than the sum of all prospective payments plus the fixed-loss threshold. Refer to your CMS- and plan-specific billing documentation and procedures should application for an outlier payment be necessary. Refer to your revenue cycle management team for outlier payment billing and qualifications.

Note: There is no New Technology Add-on Payment (NTAP) for ICLUSIG or other TKIs indicated for the treatment of Ph+ ALL. Hospital billers should use their institution's billing guides and procedures.

Click **here** to learn more about CMS Outlier Payments, including threshold amounts.

For information, please see the Hospital Billing and Coding Guide.
For additional information regarding ICLUSIG, please contact your Takeda representative.

CC; complication or comorbidity; CMS, Centers for Medicare and Medicaid Services; MCC; major complication or comorbidity; MS-DRG, Medicare Severity Diagnosis-Related Group; OR, operating room; WAC, wholesale acquisition cost.

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