

## When you see resistance to a second TKI in adults with CP-CML, robust clinical evidence supports considering ICLUSIG<sup>1-4</sup>

### PACE TRIAL

#### 5-year results

from the ICLUSIG pivotal study that included patients with highly resistant CP-CML (n=270)<sup>1,2,4</sup>

### OPTIC TRIAL

#### Dose optimization

study in patients with highly resistant CP-CML who were resistant or intolerant to ≥2 prior TKIs +/- T315I mutations (N=282)<sup>1</sup>

### THE APPROACH

PACE evaluated efficacy and safety in adult patients with CP-CML receiving ICLUSIG 45 mg orally once-daily with<sup>1,4</sup>:

- Resistance or intolerance to prior TKI therapy
- +/- T315I mutations
- Additional cohorts included patients with AP-CML (n=85), BP-CML (n=62), and Ph+ ALL (n=32)

OPTIC explored the effect of response-based dosing on safety and efficacy of ICLUSIG using<sup>1,3</sup>:

- Three cohorts with starting doses of 45 mg, 30 mg, and 15 mg (n=94 each)
- Doses of 45 mg and 30 mg were reduced to 15 mg upon achieving ≤1% BCR::ABL1<sup>1S</sup>

▶ **80%** of patients were resistant to their prior TKIs<sup>4</sup>

▶ **49%** had at least one BCR::ABL1 mutation<sup>4</sup>

▶ **98%** of patients were resistant to prior TKI therapy<sup>1</sup>

▶ **44%** had at least one BCR::ABL1 mutation<sup>1</sup>

### THE IMPACT

PACE provided **long-term efficacy and safety data** for ICLUSIG in patients with CP-CML **with or without the T315I mutation**<sup>1,4</sup>

OPTIC established a **response-based dosing strategy** for ICLUSIG in patients with CP-CML to help **mitigate risk and maximize benefit**<sup>3</sup>

[SEE NEXT PAGE FOR MORE RESULTS >](#)

Explore more data: [PACE efficacy](#) > [PACE safety](#) > [OPTIC efficacy](#) > [OPTIC safety](#) >

BCR::ABL1<sup>1S</sup>=BCR::ABL1 international scale; CP-CML=chronic-phase chronic myeloid leukemia; TKI=tyrosine kinase inhibitor.

### INDICATIONS AND USAGE

ICLUSIG<sup>®</sup> (ponatinib) 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.

Please see full [Prescribing Information](#) and additional Important Safety Information on pages 3 and 4.

### 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.

For adults with CP-CML resistant to  $\geq 2$  prior TKIs **ICLUSIG offers long-term proven results with optimized benefit:risk<sup>1-4</sup>**

## PACE TRIAL

## OPTIC TRIAL

### THE OUTCOME

#### Deep and durable responses at 5 years<sup>1,4</sup>

**55%** of patients (n=148/267) achieved MCyR by 12 months\*

**40%** of patients (n=105/267) achieved MMR at any time\*

**73%** estimated 5-year OS [95% CI: 66, 79]\*

#### 69% of patients experienced serious adverse reactions overall.

Serious adverse reactions in  $>2\%$  of patients included AOE, pneumonia, cardiac arrhythmias, pancreatitis/lipase elevation, abdominal pain, cardiac failure, hemorrhage, sepsis, VTEs, fluid retention and edema, pyrexia, secondary malignancies, anemia, hypertension, thrombocytopenia, febrile neutropenia, cellulitis, and arthralgia. Fatal adverse reactions occurred in 9% of patients.

**Permanent discontinuation** due to an adverse reaction occurred in 21% of CP-CML patients.

**The most common ( $>20\%$ ) non-hematologic adverse reactions** were rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, AOE, diarrhea, vomiting, and myalgia.

**Optimal benefit:risk ratio** was seen in the patient cohort receiving **45 mg  $\rightarrow$  15 mg<sup>1,3</sup>**

**44%** of patients (n=41/93) achieved  $\leq 1\%$  BCR:ABL1 at 12 months†

**62%** of patients (n=28/45) maintained a durable response at the lower 15 mg dose‡

#### 34% of patients experienced serious adverse reactions overall.

Serious adverse reactions in  $>2\%$  of patients included AOE, cardiac arrhythmias, thrombocytopenia, pyrexia, anemia, abdominal pain, atrial fibrillation, pancreatitis/lipase elevation, neutropenia, and hypertension. Sudden death occurred in 2 patients.

**Permanent discontinuation** due to an adverse reaction occurred in 19% of patients who received a starting dose of 45 mg.

**The most common ( $>20\%$ ) adverse reactions** were rash and related conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pancreatitis/lipase elevation, and abdominal pain. The most common ( $>20\%$ ) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutrophil cell count decreased.

**The PACE and OPTIC studies both support choosing ICLUSIG for adults with CP-CML resistant to  $\geq 2$  prior TKIs<sup>1</sup>**

**Explore more data:** [PACE efficacy](#)> [PACE safety](#)> [OPTIC efficacy](#)> [OPTIC safety](#)>

\*The major efficacy outcome measure (primary endpoint) for patients with CP-CML was MCyR by 12 months, which included CCyR and PCyR. Median duration of treatment for CP-CML patients was 35 months<sup>1,2</sup>.

†The primary endpoint was  $\leq 1\%$  BCR:ABL1<sup>IS</sup> rate at 12 months. Defined as a  $\leq 1\%$  ratio of BCR:ABL1 to ABL transcripts on the International Scale (ie,  $\leq 1\%$  BCR:ABL1IS); patients must have the b2a2/b3a2 (p210) transcript, in peripheral blood measured by qRT-PCR.<sup>1</sup>

‡Median duration of follow-up in the 45 mg  $\rightarrow$  15 mg arm was 27.0 months.<sup>1</sup>

AOEs=arterial occlusive events; BCR:ABL1<sup>IS</sup>=BCR:ABL1 international scale; CCyR=complete cytogenetic response; CP-CML=chronic-phase chronic myeloid leukemia; MCyR=major cytogenetic response; MMR=major molecular response; OS=overall survival; PCyR=partial cytogenetic response; TKI=tyrosine kinase inhibitor.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS

**Arterial Occlusive Events (AOEs):** AOE, including fatalities, have occurred in patients who received ICLUSIG in OPTIC and PACE. These included cardiovascular, cerebrovascular, and peripheral vascular events. The incidence of AOE in OPTIC (45 mg  $\rightarrow$  15 mg) was 14% of 94 patients; 6% experienced Grade 3 or 4. In PACE, the incidence of AOE was 26% of 449 patients; 14% experienced Grade 3 or 4. Fatal AOE 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, AOE 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 AOE. 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.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS

**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.

**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 ( $\geq 2\%$ ) 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.

**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.

**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 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 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.

**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.

**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.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS

**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  $1 \times 10^9/L$  or platelets less than  $50 \times 10^9/L$ , interrupt ICLUSIG until ANC at least  $1.5 \times 10^9/L$  and platelets at least  $75 \times 10^9/L$ , 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 AOE. 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](http://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.

Please see full [Prescribing Information](#) including Boxed Warning.

**References:** 1. ICLUSIG. Prescribing information. Takeda Pharmaceuticals; 2/2022. 2. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. *N Engl J Med*. 2013;369(19):1783-1796. 3. Cortes J, Apperley J, Lomaia E, et al. *Blood*. 2021;138(21):2042-2050. 4. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. *Blood*. 2018;132(4):393-404.



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