APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Carole Jones

3. acting in the capacity of Division Director, Office of Drug Security, Integrity & Response

4. bears the seal/stamp of U.S. Department of Health and Human Services

Certified

5. at Washington, D.C.

6. the ninth of June, 2023

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 23035256-46

9. Seal/Stamp:

10. Signature:

Patrick O. Hatchett

United States Food and Drug Administration

Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America

CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Foreign Manufacturer

rtificate Number: **ANPH-7NGR** Certificate Issued Date: **March 01, 2023** Certificate Expiration Date: **March 01, 2025**

porting Country: **CHILE** Exporting Country: **UNITED STATES of AMERICA**

Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: **ICLUSIG ® (PONATINIB), Tablet**

Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): **ponatinib 15 MG**

Is this product authorized by the certifying authority to be marketed in the certifying country or within the jurisdiction of the certifying regional authority? **Yes**

Is this product actually on the market in the certifying country or within the jurisdiction of the certifying regional authority? **Yes**

.1 Are there restrictions of sale, distribution or administration of the product specified in the marketing authorization? **No**

.1 Number of marketing authorization & date of issuance: **203469 12/14/2012**

.2 Marketing authorization holder (name and address): **Takeda Pharmaceuticals U.S.A., Inc., 95 Hayden Avenue, Lexington, MA 02421 United States of America**

.3 Status of marketing authorization holder: **Neither**

.4 Is a summary basis for approval appended? **No**

.5 Is the attached product information, complete and consistent with the marketing authorization? **Yes**

.6 Applicant name & address for certificate (if different than the marketing authorization holder): **ICON/PRA (behalf of Takeda), 3 Parkway North Center, 2nd Floor, Deerfield, IL 60015 United States of America**

.7 Center weblinks to marketing authorization: Orangebook for approved drug products and Purplebook for CDER-regulated Biologics License Applications

marks: **Shelf life: 36 months; Packager & Release site: Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 Canada.**

Manufacturer name & address: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADA**

2 Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? **Yes**

3 Periodicity of routine inspections (years): **Pursuant to section 510(h)(3) of the Federal Food, Drug & Cosmetic Act, Inspections will occur in accordance with a risk-based schedule**

4 Has the manufacture of this type of dosage form been inspected? **Yes**

5 Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): **Yes, at time of inspection, site complies with FDA cGMP**

5 Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? **Yes**

Carole Jones, Division Director

Exports Compliance Branch

Division of Global Drug Distribution and Policy

Office of Drug Security, Integrity & Response

Carole Jones

f the information on this certificate, you may scan the QR code or visit www.access.fda.gov/fecv/searchCderCertificate to view a copy of the certificate as issued by FDA.
format recommended by the World Health Organization format revised March 25, 2021. Website: www.who.int

FOR A CDER - REGULATED HUMAN DRUG

icate Number: **ANPH-7NGR**

ting Country: **CHILE**

ct Name: **ICLUSIG ® (PONATINIB), Tablet**

Certificate Issued Date: **March 01, 2023**

Certificate Expiration Date: **March 01, 2025**

Exporting Country: **UNITED STATES of AMERICA**

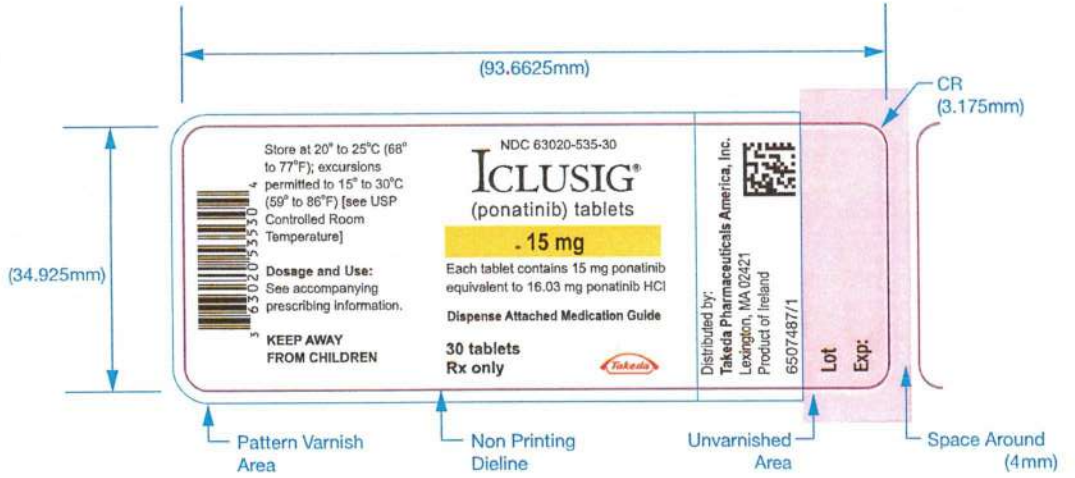
ADDITIONAL MANUFACTURER INFORMATION

achment is to attest that the establishments listed below may manufacture, prepare, market, and legally export the products associated with the human drug identified in th mber listed above as of the date of this certificate issuance date. The facilities listed below are subject to the jurisdiction of FDA and are subject to periodic inspections. Tl pection at each facility showed substantial compliance with Current Good Manufacturing Practice (CGMP) regulations as required by the Federal Food, Drug, and Cosmet e list of facilities may not include all sites that may manufacture, prepare, market, and legally export the product identified above, but are sites that the applicant of this included on this certificate request to review by CDER. Any facility associated with the manufacture, preparation, or marketing of the drug that is the subject of the ted CPP that did not achieve substantial compliance with CGMPs is not listed on this declaration.

f Manufacturing Site	Address	Activity
evens LLC	**18655 Krause Street, Riverview, MI 48193**	**API Manufacturer**

ADDITIONAL INFORMATION

ks: Shelf life: 36 months; Packager & Release site: Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 Canada.; This FDA certification pertains to the produ ed in the United States of America.



Takeda

TAKEDA IRELAND LIMITED
BRAY BUSINESS PARK
KILRUDDERY
CO. WICKLOW
IRELAND

esmark finch limited
DIGITAL INNOVATION

OWNER	TAKEDA IRELAND LTD
ITEM	6507487
DESCRIPTION	LA BTL: ICLUSIG 15MG 30TBS USA
REVISION	REV 1
VERSION	VERSION 2
DIMENSIONS	93.6 x 34.9mm
OPERATOR	BARTOSZ DZIADOS
SOFTWARE	ILLUSTRATOR CC
TECHNICAL	
DRAWING REF NO.	n/a
PHARMA CODE	n/a
WINDING DIRECTION	n/a

COLOURS USED

- BLACK
- PANTONE 185
- PANTONE 116
- KEYLINE
- VARNISH FREE
- GUIDES

THIS PROOF SHOULD BE VIEWED WITH OVERPRINT PREVIEW Preferences > Page Display > Page and Content Information > Overprint Preview ON (Always)

NDC 63020-535-30

ICLUSIG®
(ponatinib) tablets

15 mg

lm-coated tablets

ach tablet contains 15 mg
natinib equivalent to 16.03 mg
natinib HCl

) tablets
x only

Takeda

istributed by:
akeda Pharmaceuticals America, Inc.
exington, MA 02421
roduct of Ireland

NDC 63020-535-30

ICLUSIG®
(ponatinib) tablets

15 mg

Swallow the tablets whole. Do not cut, crush or dissolve the tablets.

30 tablets
Rx only

Takeda

Dispense Attached Medication Guide

3 63020 53530 4

GTIN 00363020535304

SN
Exp:
Lot

6507490/1

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Dosage and Use:
See accompanying prescribing information.

KEEP AWAY FROM CHILDREN

Rx only
film-coated tablets
15 mg
ICLUSIG®
(ponatinib) tablets

Takeda

TAKEDA IRELAND LIMITED
BRAY BUSINESS PARK
KILRUDDERY
CO. WICKLOW
IRELAND

OWNER	TAKEDA IRELAND LTD
ITEM	6507490
DESCRIPTION	CN: ICLUSIG 15MG 30TBS USA
REVISION	REV 1
VERSION	VERSION 2
DIMENSIONS	206.17mm x 196.25mm
OPERATOR	BARTOSZ DZIADOS
SOFTWARE	ILLUSTRATOR CC
TECHNICAL	
DRAWING REF NO.	n/a
PHARMA CODE	n/a
WINDING DIRECTION	n/a

COLOURS USED

BLACK
PANTONE 185
PANTONE 116
KEYLINE
VARNISH FREE
GUIDES

til resolution, then resume

or 1 (less than 1.5 times
er dose.

e resolution of
of lipase elevation Grade 0 or
dose.

t least 1.5 x 10⁹/L and platelet
me at same dose.

ig until resolution, then resume

ed, then resume at same dose.

e 0 or 1, then resume at same

sig until Grade 0 or 1, then

de 0 or 1, then resume at next

urrence.

absolute neutrophil count

r Patients with AP-CML,
, and Ph+ ALL

lly once daily

lly once daily

ntly discontinue Iclusig in patients
tolerate 15 mg orally once daily.

be avoided, reduce the dosage of Iclusig

was tolerated prior to initiating the strong

g Dosage
Inhibitor

e daily

e daily

e daily

th a strong CYP3A inhibitor

g hepatic impairment (Child-Pugh A, B, or C)

Serious or severe hypertension, including hyp...

Of the 94 patients who received a starting dose of 45 mg in OPTIC, hypertension events were reported in 32% of patients; 12% experienced ... hypertension. Based on vital sign data, Grade 1 blood pressure elevation occurred in 8 out of 18 (44%) patients with normal initial blood pressure, Grade 2 occurred in 28 out of 81 (35%) patients with initial blood pressure of less than Grade 2, and Grade 3 occurred in 18 out of 92 (20%) patients with initial blood pressure of less than Grade 3. Three patients (3.2%) experienced hypertensive crisis.

In PACE, hypertension events were reported in 32% of 449 patients; 13% experienced serious or severe hypertension. Any post-baseline elevation of systolic or diastolic BP of Grade 2 or higher in patients with normal baseline blood pressure occurred in 44% of 449 patients. Grade 1 BP elevation occurred in 26%, Grade 2 in 45%, and Grade 3 in 26%. Two patients (<1%) experienced Grade 4 hypertension (hypertensive crisis).

Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.2)]*. For significant worsening, labile or treatment-resistant hypertension, interrupt Iclusig and consider evaluating for renal artery stenosis.

5.6 Pancreatitis

Serious or severe pancreatitis has occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, pancreatitis occurred in 23% of patients; 15% experienced serious or severe (Grade 3 or 4) pancreatitis. Pancreatitis resulted in discontinuation in 1.1% of patients and interruption and/or dose [redacted] in 20% of patients. The [redacted] to onset of pancreatitis was 23 days (range: 3 days to 5.6 months). In two patients with clinical pancreatitis th[redacted]se modification or treatme[redacted]inuation pancreatitis resolved within 2 weeks. Laboratory abnormalities of amylase elevation occurred in 11%[redacted], while lipase elevation oc[redacted]34% of patients.

In PACE, pancreatitis occurred in 26% of 449 patients; 17% experienced serious or severe (Grade 3 [redacted]atitis. Pancreatitis resulte[redacted]tinuation 0.4% of patients and interruption and/or dose reduction in 17% of patients. The median time to onset [redacted]titis was 29 days (range: [redacted]ears). Nineteen of the 28 cases of clinical pancreatitis that led to dose modification or treatment discontinua[redacted]ed within 2 weeks. Labor[redacted]malities of amylase elevations occurred in 18% of patients, while lipase elevations occurred in 39% of patients.

Monitor serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically [redacted]. Consider additional serum[redacted]onitoring in patients with a history of pancreatitis or alcohol abuse. Interrupt, then resume at the same or reduced [redacted]continue Iclusig based on [redacted]ee Dosage *and Administration (2.2)]*. Evaluate for pancreatitis when lipase elevation is accompanied by abdomi[redacted]ms.

5.7 Increased Toxicity in Newly Diagnosed Chronic Phase CML

In a prospective randomized clinical trial in the first line treatment of newly diagnosed patients with [redacted] 45 mg [redacted] increased the risk of serious adverse reactions 2-fold compared to single agent imatinib 400 mg once daily. The me[redacted]s less [redacted]ths. 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.

5.8 Neuropathy

Of the 94 patients who received a starting dose of 45 mg in OPTIC, neuropathy occurred in 9% of patients. Peripheral neuropathy occurred in 6% of patients. The most frequently reported peripheral neuropathies were hypoesthesia (2.1%), muscular weakness (2.1%), and paresthesia (2.1%). Cranial neuropathy developed in 2 patients. The median time to onset of peripheral neuropathy and cranial neuropathy was 7.7 months (range: 1.5 months to 1.4 years) and 2.1 years (range: Day 1 to 4.2 years), respectively.

In PACE, neuropathy occurred in 22% of patients; 2.4% experienced Grade 3 or 4 neurop[redacted] patients, 1.8% experienced Grade 3 or 4 peripheral neuropathy. The most frequent peripheral neuropathies wer[redacted]sia (5%), neuropa[redacted]ral (4.5%), and hypoesthesia (3.6%). Cranial neuropathy developed in 3% of patients; 0.7% were Grade 3 or 4. The [redacted]e to onset of perip[redacted]opathy and cranial neuropathy was 5.3 months (range: 1 day to 4.6 years) and 1.2 years (range: 18 days to 4 years), resp[redacted]

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, disco[redacted]rning sensation, [redacted]s. Interrupt, then resume at the same or reduced dose or discontinue Iclusig based on recurrence/severity [redacted]*ge and Administ*[redacted]

5.9 Ocular Toxicity

Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patien[redacted]

Of the 94 patients who received a starting dose of 45 mg in OPTIC, ocular toxicities occurred in 11%[redacted]; 1.1% experienc[redacted]s or severe ocular toxicity. The most frequent ocular toxicities were blurred vision and eye pain. Retinal toxicities, inclu[redacted]elated macular de[redacted] occlusion, occurred in 2.1% of patients.

In PACE, ocular toxicities occurred in 30% of 449 patients; 3.6% experienced a serious or severe ocular toxicity. The most frequent ocular toxicities were dry eye, blurred vision, and eye pain. Retinal toxicities occurred in 3.6% of patients. The most frequent retinal toxicities were macular edema, retinal vein occlusion, retinal hemorrhage, and vitreous floaters (0.7% each).

Conduct comprehensive eye exams at baseline and periodically during treatment.

5.10 Hemorrhage

Fatal and serious hemorrhage events have occurred in patients who received Iclusig.

Of the 94 patients who received a starting dose of 45 mg in OPTIC, hemorrhage occurred in 12% of patients; 1 patient experienced a serious subdural hematoma.

In PACE, hemorrhage occurred in 28% of 449 patients; 6% experienced a serious hemorrhage and 1.3% experienced a fatal hemorrhage. 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, each occurring in 0.9% of patients. Most hemorrhages occurred in patients with Grade 4 thrombocytopenia *[see Warnings and Precautions (5.13)]*.

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 *[see Dosage and Administration (2.2)]*.

5.11 Fluid Retention

Fatal and serious fluid retention events have occurred in patients who received Iclusig.

- Impaired wound ...

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be c... with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions identified in the Highlights of the Prescribing Information are from a pooled safety population of 543 pati... or Ph+ ALL who received Iclusig at a starting dose of 45 mg orally once daily. In this pooled safety population, the most common (>20%) adve... were rash and related conditions, arthralgia, abdominal pain, headache, constipation, dry skin, hypertension, fatigue, fluid retention and edema, ... pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction, and AOEs. The most common Grade 3 or 4 laboratory abnormalities (>... count decreased, neutrophil cell count decreased, and white blood cell decreased.

Previously Treated CP-CML
The safety of Iclusig was evaluated in OPTIC *[see Clinical Studies (14)]*. Patients received one of three starting doses of Iclusig: 45 mg orall... (n=94), 30 mg orally once daily (n=94) or 15 mg orally once daily (n=94). Patients with uncontrolled hypertension or diabetes and patients wit... significant, uncontrolled, or active cardiovascular disease, including any history of myocardial infarction, peripheral vascular infarction, revasc... procedure, congestive heart failure, venous thromboembolism, or clinically significant atrial/ventricular arrhythmias, were excluded. Only the s... for the recomm[redacted]ting d[redacted]low. Patients who received a starting dose of Iclusig 45 mg orally once daily had a [redacted]R-ABL1[IS]. Of these patients, 76% were exposed for 1 year or longer and 38% wer... reduction to 1[redacted] daily [redacted]d dose reduction to 15 mg was 6.4 months (range 3.1 months to 1.8 years). greater than [redacted]The me[redacted]

[redacted]erious adv[redacted]ns occur[redacted] of patients who received Iclusig at a starting dose of 45 mg. Serious adverse reactions in >2% of pat... AOEs (9%;[redacted]2.1% wer[redacted]eath), cardiac arrhythmias (6%), thrombocytopenia (5%), pyrexia (4.3%), anemia (3.2%), abdominal ... [redacted]rillation [redacted]ancreatitis[redacted]ation (2.1%), neutropenia (2.1%), and hypertension (2.1%). Fatal adverse reactions occurred in 2 pati... which w[redacted]n death.

[redacted]nuation of I[redacted]ction occurred in 19% of patients who received Iclusig at a starting dose of 45 mg. A... [redacted]ermanent d[redacted]on in >2% of patients included AOEs, thrombocytopenia, hypertension, and sudden death.

[redacted]ns (dose inter[redacted]eductions) of Iclusig due to an adverse reaction occurred in 71% of patients who received Iclusig at a ... [redacted]reactions which[redacted]dose interruptions or reductions in >5% of patients included thrombocytopenia, pancreatitis/lipase ele... [redacted]patic dysfunctio[redacted] related conditions, and anemia.

[redacted]mon (>20%) adv[redacted]elated conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pa... lipase elevation, and abdominal [redacted](>20%) Grade 3 or 4 laboratory abnormalities were platelet count decreased and neutr... decreased.

Table 4 summarizes the adverse reactions in OPTIC for patients who received Iclusig at a starting dose of 45 mg.

Table 4: Adverse Reactions (≥10%) In Patients with CP-CML Who Received Iclusig at Starting Dose of 45 mg Followed by Reductio... Achievement of ≤1% BCR-ABL1[IS] In OPTIC

Adverse Reaction	Iclusig 45 mg → 15 mg (N = 94) All Grades (%)	Gr...
[redacted] Tissue Disorders		
[redacted]onditions	51	
D[redacted]	12	
Vas[redacted]		
[redacted]	32	
[redacted]	14	
[redacted]al occ[redacted]ts	12	
[redacted]morrhage		
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[a]	30	
Metabolism and Nutrition Disorders		
Hyperlipidemia[b]	28	
Gastrointestinal Disorders		
Abdominal Pain[c]	25	
Pancreatitis/lipase elevation	23	
Constipation	11	
Hepatobiliary Disorders		
Hepatotoxicity	28	
Nervous System Disorders		
Headache	17	

... liver problems, including liver failure, which can be severe

floaters, blurred vision, dry,
healthcare provider will mo...

	249 (56%)
	128 (29%)
	159 (35%)
	57 (13%)
	100 (22%)
	67 (15%)

L kinase domain mutations detected at entry, 37 unique mutations were detected.

and Table 13.

tients with Resistant or Intolerant CP-CML in PACE

	Overall (N = 267)	Cohort	
		R/I Cohort (N = 203)	T315I Cohort (N = 64)
	55% (49%, 62%)	51% (44%, 58%)	70% (58%, 81%)
	46% (40%, 52%)	40% (33%, 47%)	66% (53%, 77%)
	40% (35%, 47%)	35% (28%, 42%)	58% (45%, 70%)

orts was MCyR by 12 months, which combines both complete (no d Ph+ cells) and partial (1% + cells
tic responses.
ohorts was MMR (proportion of patients who met the criteria for M ition c atment)
ned as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (i.e., ≤0.1% BCR-ABL[IS]; patients
anscript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

d MCyR or MMR, the median time to response was 3 months (range: 1.8 to 12.3 months) and 6 months (range: 2 to
imum follow-up of 60 months, the median durations of MCyR (range: 1 day to 70.1 months) and MMR (range: 1 day to
1.

tients with Resistant or Intolerant Advanced Disease (includes R/I and T315I Cohorts) in PACE

	AP-CML Overall (N = 83)	BP-CML Overall (N = 62)	Ph+ ALL erall = 32)
	57% (45%, 68%)	31% (20%, 44%)	41% (24%, 59%
	51% (39%, 62%)	21% (12%, 33%)	34% (19%, 53%

ients with AP-CML, BP-CML, and Ph+ ALL was MaHR by 6 which combine te
nd no evidence of leukemia.
al ULN, ANC ≥1000/mm³, platelets ≥100,000/mm³, no blasts elocytes in peri ood, bone
% myelocytes plus metamyelocytes in peripheral blood, basophi n peripheral blo
no hepatomegaly or splenomegaly).

. in patients with AP-CML, BP-CML, and Ph+ ALL was 0.8 months (range: 0.4 to 6.3 months), 1.0 month
nd 0.7 months (range: 0.4 to 6 months), respectively. The median duration of MaHR for patients with
Ph+ ALL was 14 months (range: 1.3 to 74.3 months), 6.5 months (range: 1.9 to 64.7 months), and 3.5 months
s), respectively.

STORAGE AND HANDLING

the following configurations.

Description	Presentation
yal, white to off-white, biconvex -coated tablets with debossed n one side and plain on the	30 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with a desiccant canister and induction sealed child resistant closure.
vex film-coated	30 tablets in a wide-mouth white high density polyethylene (HDPE) bottle with a desiccant canister and induction sealed child resistant closure.

provider. Iclusig may be taken with or without food. Iclusig

Patients should not take two doses at the same time to make up for a missed dose.

Advise patients not to drink grapefruit juice or eat grapefruit as it may increase the amount of Iclusig in their blood and therefore increase their risk of adverse reactions.

Lactose
Inform patients that Iclusig tablets contain lactose monohydrate.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Lexington, MA 02421

348 R9

MEDICATION GUIDE
ICLUSIG® (eye-CLUE-sig)
(ponatinib)
tablets

t most in ant information I should know about Iclusig?

cause se side effects, including:

B ts or bloc d vessels (arteries and veins). Blood clots or blockage in your blood vessels may lead to heart attack, stroke, or death. A blood clot or blockage in your blood vessels can prevent proper blood flow to your heart, brain, bowels (intestines), legs, eyes, and other parts of your body. You may need emergency surgery or treatment in a hospital. Get medical help right away if you get any of the following symptoms:

- chest pain or pressure
- ain in arm
- of breath
- ss or weakness side of
- trouble talking
- headache
- dizziness
- severe stomach area pain
- decreased vision or loss of vision

clots o age in yo d vessels can happen in people with or without risk factors for heart and blood vessel disease, including people 50 years of age or younger. The most common risk factors for these problems are a history of high blood pressure (hypertension), high cholesterol, and heart disease. Blood clots or blockages in your blood vessels happen more often in people as they get older, and in people with a history of decreased blood flow, high blood pressure, diabetes, or high cholesterol.

Heart problems. Iclusig can cause heart problems, including heart failure which can be serious and may lead to death. Heart failure means your heart does not pump blood well enough. Iclusig can also cause irregular, slow, or fast heartbeats and heart attack. Your healthcare provider will check you for heart problems during your treatment with Iclusig. Get medical help right away if you get any of the following symptoms: shortness of breath, chest pain, fast or irregular heartbeats, dizziness, or feel faint.

Liver problems. Iclusig can cause liver problems, including liver failure, which can be severe

- Iclusig may affec this is a concern
- are breastfeeding or plan to milk. **Do not** breastfeed du

Tell your healthcare provider al medicines and over-the-counter m medicines may affect each other

Know the medicines you take. K pharmacist when you get a new

How should I take Iclusig?

- Take Iclusig exactly as yo
- Do not change your dose
- Swallow Iclusig tablets wh
- Take Iclusig with or witho
- Do not eat grapefruit or dr
- If you miss a dose of Iclus next day. Do not take 2 do
- If you take too much Iclusi emergency room right away

What are the possible effec
Iclusig may cause serious side e

- See **"What is the most imp**
- **High blood pressure (hyp** pressure. Your blood pressu should be treated during tre if you get confusion, headac
- **Inflammation of the panc** if you get any of the follow nausea, and vomiting. Your pancreatitis during treatmer
- **Neuropathy.** Iclusig may c or feet (neuropathy). Tell yo symptoms during treatment
  - muscle weakness, tingli and feet
  - double vision and other of part of the face, sagg
- **Eye problems.** Serious eye happen with Iclusig. Tell yo following symptoms: bleed floaters, blurred vision, dry healthcare provider will mo

Description	Component	Percent (w/w)	Function		Quality Standard	
			15 mg	45 mg		
Core Tablet	Ponatinib free base (added as ponatinib HCl)[a]	15.0	15.0	45.0	Active Ingredient	In-house (see 3.2.S.4.1 Specification)
	Lactose monohydrate[b]	40.15	40.15	120.45	Filler	NF, Ph. Eur., JP
	Microcrystalline cellulose	40.15	40.15	120.45	Filler/Binder	NF, Ph. Eur., JP
	Sodium starch glycolate	4.0	4.0	12.0	Disintegrant	NF, Ph. Eur., JP
	Colloidal silicon dioxide	0.2	0.2	0.6	Glidant	NF, Ph. Eur., JP
	Magnesium stearate	0.5	0.5	1.5	Lubricant	NF, Ph. Eur., JP
	Total	**100%**	**100 mg**	**300 mg**		--
	Components of Opadry White II (Tablet Coating)					
Film Coat	Opadry II White film coating[c]	--	2.5	7.5	Coating Agent	In-house (see 3.2.P.4.1 Specifications – Non-compendial- Patheon)
	Talc		*0.37*	*1.11*	*glidant*	*USP/FCC, Ph. Eur., JP*
	Polyethylene glycol		*0.505*	*1.515*	*solvent*	*NF/FCC, Ph. Eur., JP*
	Polyvinyl alcohol		*1*	*3*	*adhesive*	*USP/FCC, Ph. Eur., JP*
	Titanium Dioxide		*0.625*	*1.875*	*colorant*	*USP/FCC, Ph. Eur., JP*
	Purified Water		*q.s.*[e]	*q.s.*[e]	*solvent*	*USP/NF, Ph. Eur., JP*
	Total Tablet Weight (mg)		**102.5**	**307.5**		

a Target quantities of ponatinib free base shown in table are provided as ponatinib HCl. The amount of ponatinib HCl used for manufacturing is adjusted based on the free base content of each drug substance batch (per the certificate of analysis).

b Amount of lactose monohydrate is adjusted downward from values shown in table to accommodate the quantity of ponatinib HCl used and to maintain target total core tablet weights as shown.

c Contains: talc (USP, Ph. Eur., JP), polyethylene glycol (NF, Ph. Eur., JP), polyvinyl alcohol (USP, Ph. Eur., JP), and titanium dioxide (USP, Ph. Eur., JP)

d Removed during processing

e Purified water quantity is based on 15% solids content.