



SAFETY DATA SHEET

1. Identification

Product identifier	Ponatinib tablets
Other means of identification	
Product code	Ponatinib tablets 10 mg, Ponatinib tablets 15 mg, Ponatinib tablets 30 mg, Ponatinib tablets 45 mg
Synonyms	Iclusig tablets, Ponatinib hydrochloride tablets, Ponatinib drug product, AP24534 (HCl) tablets
Recommended use	Pharmaceutical product.

This safety data sheet is written to provide health, safety and environmental information for people handling this formulated product in the workplace. It is not intended to provide information relevant to medicinal use of the product. In this instance patients should consult prescribing information/package insert/product label or consult their pharmacist or physician. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate safety data sheet for each ingredient.

Recommended restrictions	All other uses.
Manufacturer/Importer/Supplier/Distributor information	
Main Office	Takeda Pharmaceutical Company Limited 1-1, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8668, Japan
US contact:	40 Landsdowne Street, Cambridge, MA, 02139, USA
Phone Number	1-617-679-7000
CH contact:	Takeda Pharmaceuticals International AG Thurgauerstrasse 130, 8152 Glattpark-Opfikon (Zurich), Switzerland
E-mail	Takeda-SDS@takeda.com
Emergency phone number	Call CHEMTREC Day or Night Within USA and Canada: 1-800-424-9300 Outside USA and Canada: +1 703-741-5970 (collect calls accepted) From anywhere in the world: +1 703-527-3887

2. Hazard(s) identification

Physical hazards	Not classified.	
Health hazards	Acute toxicity, oral	Category 4
	Carcinogenicity	Category 2
	Reproductive toxicity	Category 2
	Specific target organ toxicity, single exposure	Category 1
	Specific target organ toxicity, repeated exposure	Category 1
Environmental hazards	Hazardous to the aquatic environment, acute hazard	Category 2
	Hazardous to the aquatic environment, long-term hazard	Category 1
OSHA defined hazards	Not classified.	
Label elements		



Signal word Danger

Hazard statement	Harmful if swallowed. Suspected of causing cancer. Suspected of damaging fertility or the unborn child. Causes damage to organs. Causes damage to organs through prolonged or repeated exposure. Toxic to aquatic life. Very toxic to aquatic life with long lasting effects.
Precautionary statement	
Prevention	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Do not breathe dust. Do not eat, drink or smoke when using this product. Wear protective gloves/protective clothing/eye protection/face protection. Wash thoroughly after handling. Avoid release to the environment.
Response	If swallowed: Call a poison center/doctor if you feel unwell. Rinse mouth. If exposed or concerned: Get medical advice/attention. Collect spillage.
Storage	Store locked up.
Disposal	Dispose of contents/container in accordance with local/regional/national/international regulations.
Hazard(s) not otherwise classified (HNOC)	None known.
Supplemental information	In finished form: Exempt from labeling - product regulated as a medicinal product.

3. Composition/information on ingredients

Mixtures

Chemical name	CAS number	%
Colloidal silicon dioxide	7631-86-9	Proprietary
Lactose monohydrate	10039-26-6	Proprietary
Magnesium stearate	557-04-0	Proprietary
Microcrystalline cellulose	9004-34-6	Proprietary
Polyethylene oxide	25322-68-3	Proprietary
Polyvinyl alcohol	9002-89-5	Proprietary
Ponatinib hydrochloride	1114544-31-8	Proprietary
Sodium starch glycolate	9063-38-1	Proprietary
Talc	14807-96-6	Proprietary
Titanium dioxide	13463-67-7	Proprietary

Composition comments	The manufacturer has claimed the exact percentage as trade secret under the OSHA Hazard Communication Standard.
-----------------------------	---

4. First-aid measures

Inhalation	Dust: Move to fresh air. Call a physician if symptoms develop or persist.
Skin contact	Wash off with soap and water. Get medical attention if irritation develops and persists.
Eye contact	Rinse with water. Get medical attention if irritation develops and persists.
Ingestion	Rinse mouth. If vomiting occurs, keep head low so that stomach content doesn't get into the lungs. Get medical advice/attention if you feel unwell.
Most important symptoms/effects, acute and delayed	Prolonged exposure may cause chronic effects.
Indication of immediate medical attention and special treatment needed	Provide general supportive measures and treat symptomatically. Keep victim warm. Keep victim under observation. Symptoms may be delayed.
General information	The exposure risk via inhalation/skin contact/eye contact will be negligible unless the tablets/capsules are broken into crumbs or powder. IF exposed or concerned: Get medical advice/attention. If you feel unwell, seek medical advice (show the label where possible). Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves. Show this safety data sheet to the doctor in attendance.

5. Fire-fighting measures

Suitable extinguishing media	Water fog. Foam. Dry chemical powder. Carbon dioxide (CO2).
Unsuitable extinguishing media	Do not use water jet as an extinguisher, as this will spread the fire.
Specific hazards arising from the chemical	During fire, gases hazardous to health may be formed.

Special protective equipment and precautions for firefighters	Self-contained breathing apparatus and full protective clothing must be worn in case of fire.
Fire fighting equipment/instructions	Use water spray to cool unopened containers.
Specific methods	Use standard firefighting procedures and consider the hazards of other involved materials.
General fire hazards	No unusual fire or explosion hazards noted.

6. Accidental release measures

Personal precautions, protective equipment and emergency procedures	Keep unnecessary personnel away. Keep people away from and upwind of spill/leak. Wear appropriate protective equipment and clothing during clean-up. Ensure adequate ventilation. Local authorities should be advised if significant spillages cannot be contained. For personal protection, see section 8 of the SDS.
Methods and materials for containment and cleaning up	Prevent product from entering drains. Large Spills: Stop the flow of material, if this is without risk. Following product recovery, flush area with water. Small Spills: Clean surface thoroughly to remove residual contamination. Never return spills to original containers for re-use. Put material in suitable, covered, labeled containers. For waste disposal, see section 13 of the SDS.
Environmental precautions	Avoid release to the environment. Inform appropriate managerial or supervisory personnel of all environmental releases. Prevent further leakage or spillage if safe to do so. Avoid discharge into drains, water courses or onto the ground.

7. Handling and storage

Precautions for safe handling	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Do not breathe dust. Do not taste or swallow. Avoid prolonged exposure. When using, do not eat, drink or smoke. Pregnant or breastfeeding women must not handle this product. Should be handled in closed systems, if possible. Provide adequate ventilation. Wear appropriate personal protective equipment. Wash hands thoroughly after handling. Avoid release to the environment. Observe good industrial hygiene practices.
Conditions for safe storage, including any incompatibilities	Store locked up. Store in tightly closed original container in a dry, cool and well-ventilated place. Store away from incompatible materials (see Section 10 of the SDS).

8. Exposure controls/personal protection

Occupational exposure limits

US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)

Components	Type	Value	Form
Microcrystalline cellulose (CAS 9004-34-6)	PEL	5 mg/m3	Respirable fraction.
		15 mg/m3	Total dust.
Titanium dioxide (CAS 13463-67-7)	PEL	15 mg/m3	Total dust.

US. OSHA Table Z-3 (29 CFR 1910.1000)

Components	Type	Value	Form
Talc (CAS 14807-96-6)	TWA	0.1 mg/m3	Respirable.
		20 mppcf	
		2.4 mppcf	Respirable.

US. ACGIH Threshold Limit Values

Components	Type	Value	Form
Microcrystalline cellulose (CAS 9004-34-6)	TWA	10 mg/m3	
Talc (CAS 14807-96-6)	TWA	2 mg/m3	Respirable fraction.
Titanium dioxide (CAS 13463-67-7)	TWA	10 mg/m3	

US. NIOSH: Pocket Guide to Chemical Hazards

Components	Type	Value	Form
Microcrystalline cellulose (CAS 9004-34-6)	TWA	5 mg/m3	Respirable.
		10 mg/m3	Total
Talc (CAS 14807-96-6)	TWA	2 mg/m3	Respirable.

US. Workplace Environmental Exposure Level (WEEL) Guides

Components	Type	Value	Form
Polyethylene oxide (CAS 25322-68-3)	TWA	10 mg/m3	Particulate.

Biological limit values	No biological exposure limits noted for the ingredient(s).
Exposure guidelines	Ponatinib hydrochloride (CAS 1114544-31-8): OEL - 9 µg/m3 (Takeda internal value).
Appropriate engineering controls	Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.
Individual protection measures, such as personal protective equipment	
Eye/face protection	If contact is likely, safety glasses with side shields are recommended.
Skin protection	
Hand protection	Wear appropriate chemical resistant gloves.
Skin protection	
Other	Use of an impervious apron is recommended.
Respiratory protection	In case of insufficient ventilation, wear suitable respiratory equipment.
Thermal hazards	Wear appropriate thermal protective clothing, when necessary.
General hygiene considerations	Observe any medical surveillance requirements. Keep away from food and drink. Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove contaminants.

9. Physical and chemical properties**Appearance**

Physical state	Solid.
Form	Film-coated tablet.
Color	No data available.
Odor	No data available.
Odor threshold	Property has not been measured.
pH	Property has not been measured.
Melting point/freezing point	Property has not been measured.
Initial boiling point and boiling range	Property has not been measured.
Flash point	Property has not been measured.
Evaporation rate	Not applicable, material is a solid.
Flammability (solid, gas)	Will burn if involved in a fire.
Upper/lower flammability or explosive limits	
Flammability limit - lower (%)	Not applicable, material is a solid.
Flammability limit - upper (%)	Not applicable, material is a solid.
Vapor pressure	Not applicable, material is a solid.
Vapor density	Not applicable, material is a solid.
Relative density	Property has not been measured.
Solubility(ies)	
Solubility (water)	Property has not been measured.

Partition coefficient (n-octanol/water)	Not applicable, product is a mixture.
Auto-ignition temperature	Not applicable, material is a solid.
Decomposition temperature	Property has not been measured.
Viscosity	Not applicable, material is a solid.
Other information	
Density	Property has not been measured.
Explosive properties	Not explosive.
Kinematic viscosity	Not applicable, material is a solid.
Oxidizing properties	Not oxidizing.
Particle size	Property has not been measured.

10. Stability and reactivity

Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport.
Chemical stability	Material is stable under normal conditions.
Possibility of hazardous reactions	No dangerous reaction known under conditions of normal use.
Conditions to avoid	Contact with incompatible materials.
Incompatible materials	Strong acids, alkalis and oxidizing agents.
Hazardous decomposition products	No hazardous decomposition products are known.

11. Toxicological information

Information on likely routes of exposure

Inhalation	Prolonged inhalation of dust may be harmful.
Skin contact	Prolonged skin contact may cause temporary irritation.
Eye contact	Direct contact with eyes may cause temporary irritation.
Ingestion	Harmful if swallowed.

Symptoms related to the physical, chemical and toxicological characteristics Prolonged exposure may cause chronic effects.

Information on toxicological effects

Acute toxicity Harmful if swallowed.

Components	Species	Test Results
Polyethylene oxide (CAS 25322-68-3)		
<u>Acute</u>		
Dermal		
LD50	Rabbit	> 20000 mg/kg
Inhalation		
LC50	Rat	> 1008 mg/m ³ , 4 Hours
Oral		
LD50	Mouse	6400 mg/kg
	Rat	17300 mg/kg
Ponatinib hydrochloride (CAS 1114544-31-8)		
<u>Acute</u>		
Oral		
LD50	Rat	55 mg/kg Estimate
Talc (CAS 14807-96-6)		
<u>Acute</u>		
Oral		
LD50	Rat	> 5000 mg/kg

Components	Species	Test Results
Titanium dioxide (CAS 13463-67-7)		
<u>Acute</u>		
Oral		
LD50	Rat	> 5000 mg/kg
Skin corrosion/irritation	No data available.	
Serious eye damage/eye irritation	No data available.	
Respiratory or skin sensitization		
Respiratory sensitization	No data available.	
Skin sensitization	No data available.	
Germ cell mutagenicity	Not classified.	
Germ cell mutagenicity: Ames test		
Ponatinib hydrochloride (CAS 1114544-31-8)	Bacterial mutagenesis (Ames) assay. Result: Negative.	
Germ cell mutagenicity: Chromosome Aberration		
Ponatinib hydrochloride (CAS 1114544-31-8)	In vitro Chromosome aberration assay in human lymphocytes. Result: Negative.	
Germ cell mutagenicity: Micronucleus		
Ponatinib hydrochloride (CAS 1114544-31-8)	In vivo Micronucleus assay in mouse. Result: Negative.	
Carcinogenicity	Suspected of causing cancer.	
Ponatinib hydrochloride (CAS 1114544-31-8)	Result: Ponatinib was not found to be carcinogenic in male rats. Species: Male Rat Two year oral carcinogenicity study in rat. Result: Squamous cell carcinoma of the clitoral gland was observed at 0.8 mg/kg/day and an increased incidence of sex cord stromal hyperplasia and mixed sex cord stromal benign tumors in the ovaries were noted at 0.4 and 0.8 mg/kg/day. Species: Female Rat	
IARC Monographs. Overall Evaluation of Carcinogenicity		
Titanium dioxide (CAS 13463-67-7)	2B Possibly carcinogenic to humans.	
NTP Report on Carcinogens		
Not listed.		
OSHA Specifically Regulated Substances (29 CFR 1910.1001-1053)		
Not listed.		
Reproductive toxicity	Suspected of damaging fertility or the unborn child.	
Reproductivity		
Ponatinib hydrochloride (CAS 1114544-31-8)	Oral embryo-fetal developmental study in rat. Result: Embryo-fetal toxicity manifested as post-implantation loss and reduced fetal body weights at 3 mg/kg/day and fetal alterations (soft tissue and skeletal malformations and variations) at 1 and 3 mg/kg/day. Oral embryo-fetal developmental study in rat. Result: The NOAEL for embryo-fetal development impairment was 0.3 mg/kg/day. Oral fertility and early embryonic development study. Result: The NOAEL for reproductive performance and fertility was 0.75 mg/kg/day in females. Ponatinib decreased female fertility parameters as indicated by increased pre- and post-implantation embryo-fetal lethality in the rats dosed with 1.50 mg/kg/day ponatinib Species: Female Rat Oral fertility and early embryonic development study. Result: The NOAEL for reproductive performance and fertility was 1.50 mg/kg/day in males. Ponatinib had no effect on male fertility parameters. Species: Male Rat	
Specific target organ toxicity - single exposure	Causes damage to organs.	

Specific target organ toxicity - single exposure

Ponatinib hydrochloride (CAS 1114544-31-8)

Result: Lymphoid depletion was noted consistent with bacterial sepsis, skin findings, and hematologic findings.

Species: Rat

Result: Monkeys presented with follicular atrophy of the thyroid gland and hyperkeratosis. LOAEL estimated <100 mg/kg.

Species: Monkey

Result: Ponatinib was tolerated up to 450 mg/kg.

Species: Mouse

Specific target organ toxicity - repeated exposure

Ponatinib hydrochloride (CAS 1114544-31-8)

Result: In a monkey, 6-month oral study the NOAEL was <0.25 mg/kg/day.

Result: In a rat, 6-month oral study the NOAEL was 0.25 mg/kg/day.

Result: Toxicology studies in rats and monkeys indicated the following key target organs of ponatinib toxicity: pancreas, lymphoid organs, bone, skin, thyroid gland, testes, and ovaries.

Aspiration hazard

Not relevant, due to the form of the product.

Chronic effects

Prolonged inhalation may be harmful. Causes damage to organs through prolonged or repeated exposure.

Further information

None known.

12. Ecological information

Ecotoxicity

Toxic to aquatic life. Very toxic to aquatic life with long lasting effects.

Components		Species	Test Results
Ponatinib hydrochloride (CAS 1114544-31-8)			
Aquatic			
<i>Acute</i>			
Algae	EC50	Pseudokirchneriella subcapitata	0.677 mg/l, 72 hours
	NOEC	Pseudokirchneriella subcapitata	0.14 mg/l, 72 hours
<i>Chronic</i>			
Crustacea	NOEC	Water flea (Daphnia magna)	0.04 mg/l
Fish	NOEC	Zebrafish (Danio rerio)	0.0012 mg/l
Titanium dioxide (CAS 13463-67-7)			
Aquatic			
<i>Acute</i>			
Crustacea	EC50	Daphnia magna	> 100 mg/l, 48 Hours
Fish	LL50	Oryzias latipes	> 100 mg/l, 96 Hours

Persistence and degradability

No data is available on the degradability of this product.
Ponatinib hydrochloride: Not readily biodegradable.

Bioaccumulative potential

No data available.

Partition coefficient n-octanol / water (log Kow)

Ponatinib hydrochloride (CAS 1114544-31-8)

4.5 log Pow @ pH 7 (OECD TG 123)

Mobility in soil

No data available.

Other adverse effects

No other adverse environmental effects (e.g. ozone depletion, photochemical ozone creation potential, endocrine disruption, global warming potential) are expected from this component.

13. Disposal considerations

Disposal instructions

Collect and reclaim or dispose in sealed containers at licensed waste disposal site. Do not allow this material to drain into sewers/water supplies. Do not contaminate ponds, waterways or ditches with chemical or used container. Dispose of contents/container in accordance with local/regional/national/international regulations.

Local disposal regulations

Dispose in accordance with all applicable regulations.

Hazardous waste code

The waste code should be assigned in discussion between the user, the producer and the waste disposal company.

Waste from residues / unused products	Dispose in accordance with local regulations. Empty containers or liners may retain some product residues. This material and its container must be disposed of in a safe manner.
Contaminated packaging	Since emptied containers may retain product residue, follow label warnings even after container is emptied. Empty containers should be taken to an approved waste handling site for recycling or disposal.

14. Transport information

DOT	
UN number	UN3077
UN proper shipping name	Environmentally hazardous substances, solid, n.o.s. (Ponatinib hydrochloride)
Transport hazard class(es)	
Class	9
Subsidiary risk	-
Label(s)	9
Packing group	III
Environmental hazards	
Marine pollutant	Yes.
Special precautions for user	Read safety instructions, SDS and emergency procedures before handling.
Special provisions	8, 146, 335, A112, B54, IB8, IP3, N20, T1, TP33
Packaging exceptions	155
Packaging non bulk	213
Packaging bulk	240
IATA	
UN number	UN3077
UN proper shipping name	Environmentally hazardous substance, solid, n.o.s. (Ponatinib hydrochloride)
Transport hazard class(es)	
Class	9
Subsidiary risk	-
Label(s)	9
Packing group	III
Environmental hazards	Yes.
ERG Code	9L
Special precautions for user	Read safety instructions, SDS and emergency procedures before handling.
IMDG	
UN number	UN3077
UN proper shipping name	ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Ponatinib hydrochloride)
Transport hazard class(es)	
Class	9
Subsidiary risk	-
Label(s)	9
Packing group	III
Environmental hazards	
Marine pollutant	Yes.
EmS	F-A, S-F
Special precautions for user	Read safety instructions, SDS and emergency procedures before handling.
Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code	Not applicable.

General information Can be shipped as a limited quantity when packed in inner or single packs ≤ 5 kg. When packed in inner or single packs ≤ 5 kg, Special Provision 375 of 2013 UN Model Regulations for the transportation of dangerous goods (IATA Special Provision A197) exempts this product from the labelling and documentation provisions of Dangerous Goods Regulations.

15. Regulatory information

US federal regulations This product is a "Hazardous Chemical" as defined by the OSHA Hazard Communication Standard, 29 CFR 1910.1200.
All components are listed on or exempt from the U.S. EPA TSCA Inventory List.
This product may only be used for TSCA Exempt purposes such as R&D or Food, Drug or Cosmetic use.

TSCA Section 12(b) Export Notification (40 CFR 707, Subpt. D)

Not regulated.

CERCLA Hazardous Substance List (40 CFR 302.4)

Not listed.

SARA 304 Emergency release notification

Not regulated.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1053)

Not listed.

Toxic Substances Control Act (TSCA)

All components are either listed on the TSCA 8(b) inventory and designated "active" or exempt from listing.

Superfund Amendments and Reauthorization Act of 1986 (SARA)**SARA 302 Extremely hazardous substance**

Not listed.

SARA 311/312 Hazardous chemical

Yes

Classified hazard categories

Acute toxicity (any route of exposure)
Carcinogenicity
Reproductive toxicity
Specific target organ toxicity (single or repeated exposure)

SARA 313 (TRI reporting)

Not regulated.

Other federal regulations**Clean Air Act (CAA) Section 112 Hazardous Air Pollutants (HAPs) List**

Not regulated.

Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130)

Not regulated.

Safe Drinking Water Act (SDWA)

Not regulated.

US state regulations**US. Massachusetts RTK - Substance List**

Microcrystalline cellulose (CAS 9004-34-6)
Talc (CAS 14807-96-6)
Titanium dioxide (CAS 13463-67-7)

US. New Jersey Worker and Community Right-to-Know Act

Microcrystalline cellulose (CAS 9004-34-6)
Talc (CAS 14807-96-6)
Titanium dioxide (CAS 13463-67-7)

US. Pennsylvania Worker and Community Right-to-Know Law

Microcrystalline cellulose (CAS 9004-34-6)
Talc (CAS 14807-96-6)
Titanium dioxide (CAS 13463-67-7)

US. Rhode Island RTK

Microcrystalline cellulose (CAS 9004-34-6)
Talc (CAS 14807-96-6)
Titanium dioxide (CAS 13463-67-7)

California Proposition 65

WARNING: This product can expose you to Titanium dioxide, which is known to the State of California to cause cancer. For more information go to www.P65Warnings.ca.gov.

California Proposition 65 - CRT: Listed date/Carcinogenic substance

Talc (CAS 14807-96-6)	Listed: April 1, 1990
Titanium dioxide (CAS 13463-67-7)	Listed: September 2, 2011

US. California. Candidate Chemicals List. Safer Consumer Products Regulations (Cal. Code Regs, tit. 22, 69502.3, subd. (a))

Talc (CAS 14807-96-6)
Titanium dioxide (CAS 13463-67-7)

16. Other information, including date of preparation or last revision

Issue date 02-October-2020

Revision date 18-February-2021

Version #	02
List of abbreviations	<p>EC50: Effective Concentration 50%.</p> <p>LD50: Lethal Dose 50%.</p> <p>LOAEL: Lowest observed adverse effect level.</p> <p>NOEC: No observed effect concentration.</p> <p>PEL: Permissible Exposure Limit.</p> <p>TWA: Time Weighted Average.</p>
References	<p>HSDB® - Hazardous Substances Data Bank</p> <p>IARC Monographs. Overall Evaluation of Carcinogenicity</p> <p>In-house data</p>
Disclaimer	<p>Takeda Pharmaceutical Company Limited cannot anticipate all conditions under which this information and its product, or the products of other manufacturers in combination with its product, may be used. It is the user's responsibility to ensure safe conditions for handling, storage and disposal of the product, and to assume liability for loss, injury, damage or expense due to improper use. The information in the sheet was written based on the best knowledge and experience currently available.</p>