



SAFETY DATA SHEET

1. Identification

Product identifier	Brigatinib tablets
Other means of identification	
Product code	Alunbrig tablets (30mg, 90mg, 180mg), Brigatinib drug product, AP26113
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

SDS Information

US Office	40 Landsdowne Street, Cambridge, MA, 02139, USA
CH Office	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
	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, long-term hazard	Category 2
OSHA defined hazards	Not classified.	
Label elements		



Signal word	Danger
Hazard statement	Harmful if swallowed. 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.

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: Call a poison center/doctor. 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	%
Microcrystalline cellulose	9004-34-6	Proprietary
Lactose monohydrate	64044-51-5	Proprietary
Brigatinib	1197953-54-0	Proprietary
Sodium starch glycolate	9063-38-1	Proprietary
Polyvinyl alcohol	9002-89-5	Proprietary
Magnesium stearate	557-04-0	Proprietary
Hydrophobic colloidal silica	68611-44-9	Proprietary
Titanium dioxide	13463-67-7	Proprietary
Polyethylene oxide	25322-68-3	Proprietary
Talc	14807-96-6	Proprietary

Composition comments	The manufacturer has claimed the exact percentage as trade secret under the OSHA Hazard Communication Standard.
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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	Direct contact with eyes may cause temporary irritation. 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. 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
Hydrophobic colloidal silica (CAS 68611-44-9)	TWA	0.8 mg/m3
		20 mppcf

US. ACGIH Threshold Limit Values

Components	Type	Value	Form
Magnesium stearate (CAS 557-04-0)	TWA	3 mg/m3	Respirable fraction.
		10 mg/m3	Inhalable fraction.
		10 mg/m3	
Microcrystalline cellulose (CAS 9004-34-6)	TWA	10 mg/m3	
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
Biological limit values	No biological exposure limits noted for the ingredient(s).		
Exposure guidelines	Brigatinib (CAS 1197953-54-0): OEL - 25 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. Impervious oil/water/chemical-resistant gloves (nitrile, etc.). Gloves meeting EN374, ASTM F1001 or international equivalent standard are recommended.		
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 tablets.
Color	White to off-white.
Odor	No data available.
Odor threshold	Property has not been measured.
pH	Not pH extreme.
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)	Capable of catching on fire.
Upper/lower flammability or explosive limits	
Explosive limit - lower (%)	Not applicable, material is a solid.
Explosive 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)	Property has not been measured.
Solubility (water)	
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	May cause damage to organs by inhalation. Dust may irritate respiratory system.
Skin contact	Dust or powder may irritate the skin.
Eye contact	Dust may irritate the eyes.
Ingestion	Harmful if swallowed.

Symptoms related to the physical, chemical and toxicological characteristics	Direct contact with eyes may cause temporary irritation. Prolonged exposure may cause chronic effects.
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Information on toxicological effects

Acute toxicity	Harmful if swallowed.
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Components	Species	Test Results
Brigatinib (CAS 1197953-54-0)		
<u>Acute</u>		
Oral		
LD50	Mouse	149 mg/kg
	Rat	174 mg/kg

Titanium dioxide (CAS 13463-67-7)

Acute

Oral

LD50	Rat	> 5000 mg/kg
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Skin corrosion/irritation	Prolonged skin contact may cause temporary irritation.
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Serious eye damage/eye irritation	Direct contact with eyes may cause temporary irritation.
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Respiratory or skin sensitization

Respiratory sensitization	Not classifiable.
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Skin sensitization	Not classifiable.
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Germ cell mutagenicity

Not classified.

Brigatinib: Brigatinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) or the mammalian cell chromosomal aberration assays.

In a rat micronucleus study brigatinib was administered by oral gavage for 2 days at doses of 10, 25, 50, 125 mg/kg/day. At the dose of 125 mg/kg/day, the micronuclei induction was >2-fold compared to vehicle control, and was considered toxicologically relevant. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity) and not a clastogenic effect on chromosomes. The projected exposure at 125 mg/kg/day in rats is approximately 5x the Geomean steady state human AUC(0-24) at the maximum clinical dose of 180 mg/day. Therefore, the genotoxicity risk is considered low based on the limited clinical exposure.

Carcinogenicity	Not classifiable. Due to the physical form of the product inhalation of airborne titanium dioxide dust is not relevant.
Brigatinib (CAS 1197953-54-0)	Result: Carcinogenicity studies have not been performed with brigatinib.
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. Brigatinib: In an embryo-fetal development study in rats (5, 12.5, and 25 mg/kg/day on days 6 to 17 pc), lower maternal body weights, an increase in the number of resorptions, post implantation losses, lower number of fetuses, lower fetal weights, embryoletality, decreased fetal growth, and teratogenicity were observed. NOAELs for embryofetal and maternal toxicity were 5 and 12.5 mg/kg/day, respectively. Brigatinib may impair male fertility. Testicular toxicity was observed in repeat-dose animal studies. No apparent adverse effects on female reproductive organs were observed in general toxicology studies in rats and monkeys.
Specific target organ toxicity - single exposure	Causes damage to organs.
Brigatinib (CAS 1197953-54-0)	Result: Clinical signs of toxicity following single oral doses of 125-250 mg/kg brigatinib consisted of decreased activity, prostration, and spasm in mice, and decreased activity, lethargy, ruffled fur, eye squint, and body weight loss in rats.
Specific target organ toxicity - repeated exposure	Causes damage to organs through prolonged or repeated exposure. Brigatinib: In a 6-month rat study (7.5, 15, and 25 mg/kg/day), oral administration, reversible changes in hematological parameters, serum chemistry, and urinalysis. Some clinical signs were noted at all doses (typically noted in animals that progressed towards death or moribund euthanasia) and persisted during a recovery period at 25 mg/kg/day. Decreased organ weights and corresponding microscopic effects were seen at all doses (partially reversible in the kidney and liver). Irreversible testicular toxicity and eye effects occurred at 15 mg/kg/day. NOAEL was not identified (the overall oral LOAEL was 7.5 mg/kg/day). In a 6-month monkey study (5, 10, and 15 mg/kg/day), oral administration resulted in moribund euthanasia at 15 mg/kg/day. was associated with reversible changes in serum chemistry, decreased organ weights and associated microscopic effects at all doses. Based on these data, a NOAEL was not identified (the overall oral LOAEL was 5 mg/kg/day).
Aspiration hazard	Not relevant, due to the form of the product.
Chronic effects	Causes damage to organs through prolonged or repeated exposure.
Further information	None known.

12. Ecological information

Ecotoxicity Toxic to aquatic life with long lasting effects.

Components		Species	Test Results
Brigatinib (CAS 1197953-54-0)			
Aquatic			
<i>Acute</i>			
Algae	ErC50	Algae	8.83 mg/l, 72 hours (OECD 201)
<i>Chronic</i>			
Algae	NOEC	Algae	0.041 mg/l (OECD 201)
Crustacea	NOEC	Crustacea	0.915 mg/l (OECD 211)
Fish	NOEC	Fish	0.256 mg/l (OECD 210)
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. Brigatinib: Not readily biodegradable. (OECD 301F).
Bioaccumulative potential	No data available.
Partition coefficient n-octanol / water (log Kow) Brigatinib (CAS 1197953-54-0)	1.62 Log Pow, (OECD TG 107)
Mobility in soil	No data available.
Other adverse effects	None.

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. (Brigatinib)
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. (Brigatinib)
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. (Brigatinib)
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

No (Exempt)

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)

Titanium dioxide (CAS 13463-67-7)

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

Microcrystalline cellulose (CAS 9004-34-6)

Titanium dioxide (CAS 13463-67-7)

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

Microcrystalline cellulose (CAS 9004-34-6)

Titanium dioxide (CAS 13463-67-7)

US. Rhode Island RTK

Microcrystalline cellulose (CAS 9004-34-6)

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

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))

Titanium dioxide (CAS 13463-67-7)

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

Issue date 18-October-2021

Revision date -

Version # 01

List of abbreviations EC50: Effective Concentration 50%.
ErC50: EC50 in terms of reduction of growth rate.
LD50: Lethal Dose 50%.
LL50: Lethal level, 50%.
NOAEL: No observed adverse effect level.
NOEC: No observed effect concentration.
OEL: Occupational Exposure Limit.
PEL: Permissible Exposure Limit.
TWA: Time Weighted Average.

References HSDB® - Hazardous Substances Data Bank
IARC Monographs. Overall Evaluation of Carcinogenicity
In-house data

Disclaimer 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.