Takeda Pharmaceutical Company Limited

Safety Data Sheet

Section 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier

Product name	Brigatinib Drug Product Synonyms: AP26113, ML00954084-001-E
EC No.	None
REACH registration No.	None
CAS No.	Mixture

1.2 Relevant identified uses of the substance or mixture and uses advised against

Relevant identified uses	Active pharmaceutical product
Uses advised against	No information available
Reason why uses advised against	No information available

1.3 Details of the supplier of the Safety Data Sheet

Company	Takeda Pharmaceuticals International Co. 40 Landsdowne Street Cambridge, MA 02139

1.4 Emergency telephone number

For Chemical Emergency
Spill, Leak, Fire, Exposure, or Accident
Call CHEMTREC Day or Night
Within USA and Canada: 1-800-424-9300
Outside USA and Canada: +1 703-527-3887 (collect calls accepted)

Section 2: Hazards identification

2.1 Classification of the substance or mixture

2.1.1 Classification according to Regulation (EC) No 1272/2008 [CLP]

Physical	Health	Environment
Not Hazardous	Acute Oral Toxicity Category 4 (H302) Reproductive Toxicity Category 2 (H361) Specific Target Organ Toxicity Repeat Dose Category 1 (H372)	Not Hazardous

2.2 Label elements

Labelling according to Regulation (EC) No 1272/2008 [CLP]

Signal Word: DANGER

Pictograms:

Hazard Statements:
H302 Harmful if swallowed.

H361 Suspected of damaging fertility or the unborn child.
H372 Causes damage to blood, gastrointestinal tract, immune system and vision through prolonged or repeated exposure.

Precautionary Statements:
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P260 Do not breathe dust
P264 Wash exposed skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P280 Wear protective clothing, protective gloves and eye protection.
P301 + P312 IF SWALLOWED: Call **a POISON CENTER or doctor** if you feel unwell.
P330 Rinse mouth.
P308 + P313 IF exposed or concerned: Get medical advice/attention.
P405 Store locked up.
P501 Dispose of contents and container in accordance with local and national regulations

Supplemental hazard information (EU) Not applicable

2.3 Other hazards

Not applicable

Section 3: Composition/ information on ingredients

3.2 Mixture

Ingredients:

Identifier number (CAS No, EC No, Index No in CLP annex VI)	REACH Registration No	% (weight)	Name	Classification according to Regulation (EC) No 1272/2008 (CLP)
1197953-54-0	-	<=30	Brigatinib	Acute Oral Toxicity 3 (H301) Reproductive Toxicity 2 (H361) Specific Target Organ Toxicity Repeat Exposure 1 (H372)
9004-34-6 232-674-9	-	Proprietary	Microcrystalline Cellulose	Not Hazardous
557-04-0 209-150-3	-	Proprietary	Magnesium Stearate	Not Hazardous
7631-86-9	-	Proprietary	Colloidal silica	Not Hazardous
Mixture	-	>=70%	Other Non-hazardous Excipients	Not Hazardous

Section 4: First-aid measures

4.1 Description of first aid measures

After inhalation	Move victim to fresh air. If victim not breathing, give artificial respiration. Notify physician.
In case of skin contact	Wash exposed area with soap and water and remove contaminated clothing. Notify physician.
After eye contact	Immediately flush eyes with a large quantity of water for at least 15 minutes. If worn and easy to do, remove contact lenses and continue washing. Notify physician.
If swallowed	Notify physician immediately. Rinse the mouth; do not induce vomiting or give anything to drink unless directed by medical personnel.
Self-protection of the first-aider	Use personal protective equipment (see Section 8).

4.2 Most important symptoms and effects, both acute and delayed

Effects of exposure	Harmful if swallowed in amounts above therapeutic doses. May cause adverse effects on reproduction, blood, gastrointestinal tract, immune system and vision based on animal studies.

4.3 Indication of any immediate medical attention and special treatment needed

Seek immediate medical attention if swallowed or inhaled. If skin or eye irritation develop, seek medical attention.

Section 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media	For Small fire: Dry chemical, CO_2 or water spray. For Large fire: Dry chemical, CO_2, foam or water spray.
Unsuitable extinguishing media	Do not use straight streams of water.

5.2 Specific hazards arising from the substance or mixture

Tablets are not a fire hazard but may burn under fire conditions. Combustion will generate carbon oxides, phosphorus oxides, nitrogen oxides.

5.3 Advice for firefighters

Cool containers with water spray. Move containers from fire area if you can do it without risk.

Wear self-contained breathing apparatus and appropriate protective clothing (with thermal and chemical protection).

Section 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedure

For non-emergency personnel and emergency responders	Wear suitable protective equipment (see Section 8) to prevent any contamination of skin/eye and inhalation. Do not touch the spilled material. If dust is present, eliminate all ignition sources. Keep unauthorized personnel away.

6.2 Environmental precautions

Discharge into the environment must be avoided. Prevent entry into waterways or sewers.

6.3 Methods and materials for containment and cleaning up

Carefully collect in a manner to minimize damage to tablets (carefully scoop up). If capsules are damaged, avoid the generation of airborne dusts. Collect by scooping up intact capsules. Carefully wipe up with a damp cloth. Place in a suitable, closed container for disposal. Clean the spill area thoroughly. Decontaminate the area twice. Dispose of as pharmaceutical waste.

6.4 Reference to other sections For the indication about waste treatment, see section 13.

Section 7: Handling and storage

7.1 Precautions for safe handling

Protective measures: Brigatinib is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents. Prevent contact with the eyes, skin and clothing. Do not generate airborne dust. Wear suitable personal protective clothing.

Advice on general occupational hygiene: Wash hands and face after use. Remove contaminated clothing and protective equipment before entering eating areas.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions: Store below 30ºC. Store in a secure area. Protect from light.

7.3 Specific end use(s)

Apart from the uses mentioned in section 1.2, no other specific uses are stipulated.

Section 8: Exposure controls/personal protection

8.1 Control parameters Refer to local regulations for countries not listed below

Chemical Name	Exposure Limit/Source
Brigatinib	30 ug/m3 TWA Takeda OEL (draft)
Microcrystalline Cellulose	10 mg/m3 (inhalable) TWA Belgium, Ireland, Spain, France, UK 4 mg/m3 (respirable) TWA UK
Magnesium Stearate (as stearates)	10 mg/m3 TWA Belgium, Ireland, Spain 5 mg/m3 TWA Sweden
Colloidal silica	4 mg/m3 (inhalable) Austria, Germany 6 mg/m3 TWA, 2.4 mg/m3 (respirable) Ireland, UK 10 mg/m3 TWA Belgium, Ireland, Spain 2 mg/m3 (inhalable) Denmark

8.2 Exposure controls

Appropriate engineering controls: Engineering controls should be used as the primary means to control exposures. Use local exhaust ventilation, lab hoods or other engineering controls to minimize exposures.

Personal protective equipment: Respiratory protection: In case of insufficient ventilation, especially in handling large amount, suitable respiratory

	protective equipment can be effectively used. Hand protection: Wear chemical-resistant gloves. Follow European Standard (EN 374) Skin protection: Select and wear appropriate gloves, boots, coat, suit, and the like, if necessary. Eye/face protection: Wear safety glasses, goggles or face shield as described by European standard (EN166).
Environmental exposure controls	Do not empty into drains.

Section 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

Appearance (physical state, colour)	White tablet
Odour	None
Odour threshold	Not applicable
pH	Not applicable
Melting point/freezing point	No data
Initial boiling point and boiling range	No data
Flash point	Not applicable
Flammability (solid, gas)	No testing has been performed; when it is in a powder form; it has potential explosive properties similar to any other organic dust.
Upper/lower flammability or explosive limits	No data
Vapour pressure	Not applicable
Vapour density	Not applicable
Relative density	No data
Solubility(ies)	No data
Partition coefficient: n-octanol/water	No data
Auto-ignition temperature	No data
Decomposition temperature	No data
Viscosity	No data
Explosive properties	No data
Oxidizing properties	No data

9.2 Other information

No information available

Section 10: Stability and reactivity

10.1 Reactivity

No data.

10.2 Chemical stability

Stable at the controlled temperature.

10.3 Possibility of hazardous reactions

It is considered to be stable under storage and handling conditions in accordance with relevant regulations.

10.4 Condition to avoid

No data.

10.5 Incompatible materials

Strong oxidizing agents.

10.6 Hazardous decomposition products

No information available

Section 11: Toxicological information

11.1 Information on toxicological effects

Acute effects of occupational exposure:

Inhalation: Inhalation of dusts or aerosols may be hazardous. Inhalation data not identified. Dust from damaged tablets may cause irritation.

Ingestion: Harmful if swallowed. Based on animal studies and human experience hematological effects, immune system, vision and gastrointestinal effects would be expected from ingestion.

Skin contact: Dust from damaged tablets may cause skin irritation.

Eye contact: Dust from damaged tablets may cause eye irritation.

Chronic effects of occupational exposure: May cause adverse effects on reproduction, blood, gastrointestinal tract, immune system and vision based on animal studies.

Known clinical effects: The most commonly reported adverse events from clinical use were asthenic conditions (including fatigue, malaise, and weakness), nausea, diarrhea, constipation, vomiting, anemia, visual disturbances, bradycardia, headache, dyspnea, hypertension and rash.

Acute toxicity: Brigatinib: The acute oral LD50 in rats is 174 mg/kg; in mice 149 mg/kg. The calculated acute toxicity estimate (ATE) for the tablet is 588 mg/kg

Skin corrosion/irritation: No data.

Serious eye damage/irritation: No data.

Respiratory or skin sensitization: No data.

Germ cell mutagenicity: Brigatinib was not mutagenic in an in vitro bacterial mutagenesis assay (Ames test) and was not clastogenic in an in vitro chromosome aberration assay in cultured human lymphocytes. In an in vivo rat bone marrow micronucleus assay, brigatinib increased induction of chromosomal damage at the maximum tolerated dose of 125 mg/kg/day.

Carcinogenicity: Carcinogenicity studies have not been conducted.

Reproductive toxicity	Brigatinib may impair male fertility. Dedicated animal fertility studies were not conducted with brigatinib. Male reproductive toxicity was observed in repeat-dose animal studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period. In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis; dose-related embryofetal toxicity was observed were observed at doses as low as 12.5 mg/kg/day. Findings included embryo-lethality, reduced fetal growth, and skeletal variations.
STOT-single exposure*	Single-dose oral toxicity studies in mice and rats identified adverse effects such as body weight loss, decreased activity, spasms, and mortality. The no observed adverse effect level (NOAEL) doses in the single-dose oral toxicity studies in mice and rats were 75 and 125 mg/kg,
STOT-repeated exposure*	In a rat, 6-month oral study the severely toxic dose level was 7.5 mg/kg/day. In a monkey 6 month oral study the HNSTD was 10 mg/kg/day. A NOAEL was not identified in either study. The key toxicities identified in general toxicology studies occurred in the lung, immune system, gastrointestinal system, hematopoietic system, liver, kidney, bone, testes/epididymes, heart, pancreas, and eyes. These organ toxicities were generally reversible except for effects in the eyes and testes/epididymes.
Aspiration hazard	Solid form precludes classification.
(* STOT: specific target organ toxicity)	

Section 12: Ecological information

12.1 Toxicity

No data

12.2 Persistence and degradability

No data

12.3 Bioaccumulative potential

No data

12.4 Mobility in soil

No data

12.5 Results of PBT and vPvB assessment

Does not meet the criteria for PBT or vPvB.

12.6 Other adverse effects

No information available

12.7 Additional information

No information available

Section 13: Disposal Considerations

13.1 Waste treatment methods

Waste material must be disposed of in accordance with the Directive 2008/98/EC on waste as well as other national and local regulations. Leave product in original containers. No mixing with other waste. Handle unclean container like the product itself.

Section 14: Transport information

14.1 UN number

Non regulated

14.2 UN proper shipping name

Non regulated

14.3 Transport hazard class(es)

Non regulated

14.4 Packing group

Non regulated

14.5 Environmental hazards

No data

14.6 Special precautions for user

Do not damage packaging materials.

14.7 Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Not applicable

Section 15: Regulatory information

15.1 Safety, health and environmental regulations/legislations specific for the substance or mixture

This product is classified and labeled in accordance with EC CLP. This Safety Data Sheet complies with the requirements of Regulation (EC) No 1907/2006 (REACH)

15.2 Chemical safety assessment

No Chemical Safety Assessment has been carried out for this mixture by the supplier.

Section 16: Other information

(i) Information on revision of the SDS

Date of revision	October 2, 2017
Replacing version dated	New REACH SDS
Changes in this version	New REACH SDS

(ii) Abbreviations and acronyms

Used abbreviations and acronyms can be looked up at www.wikipedia.org.

(iii) Relevant CLP hazard phrases (referred to under section 3)

H301 Toxic if swallowed.

H361 Suspected of damaging fertility or the unborn child.

H372 Causes damage to blood, gastrointestinal tract, immune system and vision through prolonged or repeated exposure

(iv) Training advice

Provide adequate information, instruction and training for operators.

Disclaimer

The information in this document is based on the present state of our knowledge but does not purport to be all inclusive and does not guarantee of the properties of the product. When the product is used under the conditions which we are unfamiliar with, the users must make their own determination of the effects, properties and protections which pertain to their particular conditions.

End of SDS