SECTION 1. IDENTIFICATION

Product name : Giotrif® Tablets (finished product)

Synonyms : Active ingredient: Afatinib
Giotrif® 20 mg film-coated tablets, Giotrif® 30 mg film-coated tablets, Giotrif® 40 mg film-coated tablets and Giotrif® 50 mg film-coated tablets

Manufacturer or supplier's details

Company name of supplier : Boehringer Ing. Pharma GmbH & Co.KG
Address : Binger Str. 173
Ingelheim am Rhein 07 55216
Telephone : +498007790900

Prepared by : EHS-Services@Boehringer-Ingelheim.com

Emergency telephone number : Int. Emergency Telephone number: +1 703-527-3887
Chemtrec 24-hours

Recommended use of the chemical and restrictions on use

Recommended use : Pharmaceutical
Restrictions on use : Safety Data Sheet only for the professional user.

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with 29 CFR 1910.1200

Eye irritation : Category 2A
Reproductive toxicity : Category 2

Effects on or via lactation

Specific target organ toxicity - repeated exposure : Category 1 (Skin, Gastro-intestinal system)

GHS label elements

Hazard pictograms : 

Signal word : Danger

Hazard statements : H319 Causes serious eye irritation.
H361 Suspected of damaging fertility or the unborn child.
Precautionary statements :

Prevention:
P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P260 Do not breathe dust/ fume/ gas/ mist/ vapours/ spray.
P263 Avoid contact during pregnancy/ while nursing.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P280 Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response:
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308 + P313 IF exposed or concerned: Get medical advice/ attention.
P337 + P313 If eye irritation persists: Get medical advice/ attention.

Storage:
P405 Store locked up.

Disposal:
P501 Dispose of contents/ container to an approved waste disposal plant.

Other hazards
The pharmacological effect of the medicament has to be considered (see package leaflet).
This drug is not subject to the labelling requirements under the Globally Harmonized System (GHS)

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>Substance / Mixture</th>
<th>Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical nature</td>
<td>organic</td>
</tr>
<tr>
<td>Substance name</td>
<td>Active ingredient: Afatinib</td>
</tr>
<tr>
<td>Hazardous components</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>CAS-No.</th>
<th>Concentration (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib dimaleate</td>
<td>850140-73-7</td>
<td>&gt;= 10 - &lt; 20</td>
</tr>
</tbody>
</table>

SECTION 4. FIRST AID MEASURES

General advice : In the case of accident or if you feel unwell, seek medical ad-
If inhaled: Move to fresh air.

In case of skin contact: Wash off immediately with plenty of water.

In case of eye contact: Rinse immediately with plenty of water for at least 15 minutes. Keep eye wide open while rinsing.

If swallowed: Rinse mouth. Drink plenty of water.

Most important symptoms and effects, both acute and delayed: No information available. Causes serious eye irritation. Suspected of damaging fertility or the unborn child. May cause harm to breast-fed children. Causes damage to organs through prolonged or repeated exposure.

Notes to physician: Observe the summary of product characteristics of proprietary medicinal products. Symptomatic treatment (decontamination, vital functions).

SECTION 5. FIREFIGHTING MEASURES

Suitable extinguishing media: Use extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Water
Dry chemical
Foam
Carbon dioxide (CO2)

Specific hazards during firefighting: In case of fire and/or explosion do not breathe fumes. Can be released in case of fire:

Carbon oxides
Nitrogen oxides (NOx)
Hydrogen chloride gas
Hydrogen fluoride

Further information: Collect contaminated fire extinguishing water separately. This must not be discharged into drains. Fire residues and contaminated fire extinguishing water must be disposed of in accordance with local regulations.

Special protective equipment for firefighters: In the event of fire, wear self-contained breathing apparatus. Complete suit protecting against chemicals.

SECTION 6. ACCIDENTAL RELEASE MEASURES
**SAFETY DATA SHEET**

**Giotrif® Tablets (finished product)**

<table>
<thead>
<tr>
<th>Version</th>
<th>Revision Date:</th>
<th>SDS Number:</th>
<th>Date of last issue:</th>
<th>Date of first issue:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>06/21/2017</td>
<td>000000031715</td>
<td>-</td>
<td>06/21/2017</td>
</tr>
</tbody>
</table>

- **Personal precautions, protective equipment and emergency procedures:**
  - Wear personal protective equipment.
  - Ensure adequate ventilation.
- **Environmental precautions:**
  - Do not flush into surface water or sanitary sewer system.
- **Methods and materials for containment and cleaning up:**
  - Pick up and transfer to properly labelled containers.

---

**SECTION 7. HANDLING AND STORAGE**

- **Advice on protection against fire and explosion:** No special protective measures against fire required.
- **Advice on safe handling:**
  - Provide sufficient air exchange and/or exhaust in work rooms.
- **Conditions for safe storage:** No special storage conditions required.
- **Materials to avoid:**
  - Keep away from food, drink and animal feedingstuffs.
  - Advice on Segregation

---

**SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION**

**Components with workplace control parameters**

<table>
<thead>
<tr>
<th>Components</th>
<th>Basis</th>
<th>Category</th>
<th>Values</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib dimaleate 850140-73-7</td>
<td>BIEL</td>
<td>3A</td>
<td>15 µg/m³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BIPC</td>
<td>1b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:**
- **BIEL:** Boehringer Ingelheim Exposure Limit (internal value)
- **BI-STEL:** Boehringer Ingelheim Short-Term Exposure Limit (Excursion limit)
- **BIPC:** Boehringer Ingelheim Pregnancy Category
- **BIPC 1b:** No risk of harm to the unborn is to be expected, when the exposure does not exceed the BIEL value. There is evidence in animals and/or humans that this material has the potential to cause harm to the unborn at exposure levels exceeding the BIEL value.

Contains no substances with occupational exposure limit values.

**Hazardous components without workplace control parameters**

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib dimaleate</td>
<td>Afatinib dimaleate</td>
<td></td>
</tr>
</tbody>
</table>

**Engineering measures:** Local exhaust

**Personal protective equipment**

- **Respiratory protection:** Use NIOSH approved respiratory protection.
Hand protection
- Material: Nitrile rubber
- Break through time: 480 min
- Glove thickness: 0.43 mm
- Directive: Protective gloves against chemicals and micro-organisms
- Protective index: Class 6

Eye protection: Safety glasses with side-shields

Skin and body protection: Laboratory: laboratory coat; factory: disposable Overall.

Protective measures: Handle in accordance with good industrial hygiene and safety practice.
- Do not breathe dust.
- Avoid contact with skin, eyes and clothing.
- Only use protective equipment in accordance with national/international regulations. Follow the national regulations about wearing personal protective equipment and the warranty given by the manufacturer for the safe function.

Hygiene measures: General industrial hygiene practice.
- Wash hands and face before breaks and immediately after handling the product.
- Keep working clothes separately.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

- Appearance: solid
- Colour: No data available
- Odour: No data available
- Odour Threshold: No data available
- pH: No data available
- Melting point/range: Not applicable
- Boiling point/boiling range: Not applicable
- Flash point: Not applicable
- Evaporation rate: Not applicable
- Flammability (solid, gas): No data available
- Self-ignition: No data available
- Upper explosion limit: No data available
Section 10. Stability and Reactivity

Reactivity: No dangerous reaction known under conditions of normal use.
Chemical stability: No decomposition if stored and applied as directed.
Possibility of hazardous reactions: No dangerous reaction known under conditions of normal use.
Conditions to avoid: Extremes of temperature and direct sunlight.
Incompatible materials: No data available
Hazardous decomposition products: No data available

Section 11. Toxicological Information

Acute toxicity
Not classified based on available information.

Product:
Acute oral toxicity: Acute toxicity estimate: 3,125 mg/kg
Method: Calculation method
Components:

Afatinib dimaleate:

Acute oral toxicity:
LD50 (Rat): > 300 - < 600 mg/kg
LD50 (Mouse): > 1,200 mg/kg

Acute inhalation toxicity:
Remarks: No data available

Acute dermal toxicity:
Remarks: No data available

Skin corrosion/irritation
Not classified based on available information.

Components:

Afatinib dimaleate:
Species: Rabbit
Result: No skin irritation

Serious eye damage/eye irritation
Causes serious eye irritation.

Components:

Afatinib dimaleate:
Species: Rabbit
Result: Irritating to eyes.
Method: OECD Test Guideline 405

Respiratory or skin sensitisation

Skin sensitisation
Not classified based on available information.

Respiratory sensitisation
Not classified based on available information.

Components:

Afatinib dimaleate:
Method: DEREK
Result: Alert for skin sensitization

Germ cell mutagenicity
Not classified based on available information.

Components:

Afatinib dimaleate:
Genotoxicity in vitro:
Test Type: Ames test
Species: Salmonella typhimurium
Result: positive
SAFETY DATA SHEET

Giotrif® Tablets (finished product)

Version 1.0  Revision Date: 06/21/2017  SDS Number: 000000031715  Date of last issue: -

Date of first issue: 06/21/2017

Genotoxicity in vivo:
- Test Type: Chromosomal aberration test
  Species: Human lymphocytes
  Result: negative

- Test Type: Micronucleus test
  Species: Rat
  Result: negative

- Test Type: Micronucleus test
  Species: Mouse
  Result: negative

- Test Type: Comet assay
  Species: Rat
  Result: negative

Carcinogenicity:
Not classified based on available information.

Components:
Afatinib dimaleate:
Remarks: No data available

IARC:
No component of this product present at levels greater than or equal to 0.1% is identified as probable, possible or confirmed human carcinogen by IARC.

OSHA:
No component of this product present at levels greater than or equal to 0.1% is identified as a carcinogen or potential carcinogen by OSHA.

NTP:
No component of this product present at levels greater than or equal to 0.1% is identified as a known or anticipated carcinogen by NTP.

Reproductive toxicity:
Suspected of damaging fertility or the unborn child.
May cause harm to breast-fed children.

Components:
Afatinib dimaleate:
Effects on fertility:
- Test Type: Fertility/early embryonic development
  Species: Rat
  Application Route: Oral
  Dose: 4, 6, 8 milligram per kilogram
  Early Embryonic Development: NOAEL: 8 mg/kg body weight

- Test Type: Pre-/postnatal development
  Species: Rat
  Application Route: Oral
  Dose: 4, 6, 8 milligram per kilogram
  General Toxicity - Parent: NOAEL: = 8 mg/kg body weight
Fertility: NOAEL: = 8 mg/kg body weight

Effects on foetal development:
- Test Type: Embryo-foetal development
- Species: Rat
- Application Route: Oral
- Dose: 4, 8, 16 milligram per kilogram
- General Toxicity Maternal: NOAEL: = 8 mg/kg body weight
- Embryo-foetal toxicity: NOAEL: = 8 mg/kg body weight
- Test Type: Embryo-foetal development
- Species: Rabbit
- Application Route: Oral
- Dose: 2.5, 5, 10 milligram per kilogram
- General Toxicity Maternal: NOAEL: = 2.5 mg/kg body weight
- Embryo-foetal toxicity: NOAEL: = 2.5 mg/kg body weight

Reproductive toxicity - Assessment:
- Effects on or via lactation, Suspected of damaging the unborn child.
- Some evidence of adverse effects on development, based on animal experiments.

STOT - single exposure
Not classified based on available information.

Components:
- Afatinib dimaleate:
  Remarks: No data available

STOT - repeated exposure
Causes damage to organs (Skin, Gastro-intestinal system) through prolonged or repeated exposure.

Components:
- Afatinib dimaleate:
  Target Organs: Skin, Gastro-intestinal system
  Assessment: The substance or mixture is classified as specific target organ toxicant, repeated exposure, category 1.

Repeated dose toxicity

Components:
- Afatinib dimaleate:
  Species: Rat
  NOAEL: 4 mg/kg
  Exposure time: 28-day

Species: Rat
NOAEL: 1.5 mg/kg
Exposure time: 26 weeks

Species: miniature swine
NOAEL: 0.5 mg/kg
Exposure time: 13 weeks

Species: miniature swine
NOAEL: 0.5 mg/kg
Exposure time: 52 weeks

Species: Mouse
NOAEL: 9 mg/kg
Exposure time: 13 weeks

**Aspiration toxicity**
Not classified based on available information.

**Components:**

**Afatinib dimaleate:**
No data available

**Further information**

**Components:**

**Afatinib dimaleate:**
Remarks: May (possibly) cause phototoxic reactions.

---

**SECTION 12. ECOLOGICAL INFORMATION**

**Ecotoxicity**

**Components:**

**Afatinib dimaleate:**

Toxicity to fish: Remarks: No data available

Toxicity to daphnia and other aquatic invertebrates: Remarks: No data available

Toxicity to algae:

- EC50 (Pseudokirchneriella subcapitata (green algae)): = 33 mg/l
  - End point: Growth rate
  - Test Type: static test
  - Method: OECD Test Guideline 201

- EC50 (Pseudokirchneriella subcapitata (green algae)): = 8.6 mg/l
  - End point: Biomass
  - Test Type: static test
  - Method: OECD Test Guideline 201

- NOEC (Pseudokirchneriella subcapitata (green algae)): = 1.2 mg/l
  - Test Type: static test
Method: OECD Test Guideline 201

Toxicity to fish (Chronic toxicity)  NOEC (Brachydanio rerio (zebrafish)): = 0.032 mg/l
Exposure time: 35 d
Test Type: flow-through test
Method: OECD Test Guideline 210

Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity)  NOEC (Daphnia (water flea)): = 2.7 mg/l
Exposure time: 21 d
Test Type: semi-static test
Method: OECD Test Guideline 211
EC50 (Daphnia (water flea)): = 5.2 mg/l
Exposure time: 21 d
Test Type: semi-static test
Method: OECD Test Guideline 211
NOEC (Chironomus riparius (harlequin fly)): = 80 mg/l
Exposure time: 27 d

M-Factor (Chronic aquatic toxicity): 1

Toxicity to microorganisms  EC50 (activated sludge): = 143 mg/l
Exposure time: 3 h
Method: OECD Test Guideline 209
NOEC (activated sludge): = 9 mg/l
Exposure time: 3 h
Method: OECD Test Guideline 209

Persistence and degradability

Components:

Afatinib dimaleate:
Biodegradability: Result: Not readily biodegradable.
Biodegradation: 0 %
Exposure time: 28 d
Method: OECD Test Guideline 301B

Bioaccumulative potential

Components:

Afatinib dimaleate:
Bioaccumulation: Remarks: An appreciable bioaccumulation potential is to be expected (log P(o/w) > 3).
Partition coefficient: n-octanol/water: log Pow: 3.68
pH: 7

Mobility in soil
No data available
Other adverse effects

**Product:**

Ozone-Depletion Potential: Regulation: 40 CFR Protection of Environment; Part 82 Protection of Stratospheric Ozone - CAA Section 602 Class I Substances

Remarks: This product neither contains, nor was manufactured with a Class I or Class II ODS as defined by the U.S. Clean Air Act Section 602 (40 CFR 82, Subpt. A, App.A + B).

SECTION 13. DISPOSAL CONSIDERATIONS

**Disposal methods**

- **Waste from residues:** Dispose of in accordance with local regulations.
- **Contaminated packaging:** Packs that cannot be cleaned should be disposed of in the same manner as the contents. Uncontaminated packaging can be recycled.

SECTION 14. TRANSPORT INFORMATION

**International Regulations**

- **IATA-DGR:** Not regulated as a dangerous good
- **IMDG-Code:** Not regulated as a dangerous good
- **Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code:** Not applicable for product as supplied.

**National Regulations**

- **49 CFR:** Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

**EPCRA - Emergency Planning and Community Right-to-Know Act**

**CERCLA Reportable Quantity**

This material does not contain any components with a CERCLA RQ.

**SARA 304 Extremely Hazardous Substances Reportable Quantity**

This material does not contain any components with a section 304 EHS RQ.

**SARA 302 Extremely Hazardous Substances Threshold Planning Quantity**

This material does not contain any components with a section 302 EHS TPQ.

**SARA 311/312 Hazards**

- Acute Health Hazard
- Chronic Health Hazard
SARA 313

This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.

Clean Air Act

This product neither contains, nor was manufactured with a Class I or Class II ODS as defined by the U.S. Clean Air Act Section 602 (40 CFR 82, Subpt. A, App.A + B).

This product does not contain any hazardous air pollutants (HAP), as defined by the U.S. Clean Air Act Section 112 (40 CFR 61).

This product does not contain any chemicals listed under the U.S. Clean Air Act Section 112(r) for Accidental Release Prevention (40 CFR 68.130, Subpart F).

This product does not contain any chemicals listed under the U.S. Clean Air Act Section 111 SOCM Intermediate or Final VOC's (40 CFR 60.489).

Clean Water Act

This product does not contain any Hazardous Substances listed under the U.S. CleanWater Act, Section 311, Table 116.4A.

This product does not contain any Hazardous Chemicals listed under the U.S. CleanWater Act, Section 311, Table 117.3.

This product does not contain any toxic pollutants listed under the U.S. Clean Water Act Section 307

US State Regulations

Massachusetts Right To Know

Lactose Monohydrate

D-Glucose, 4-O-\(\beta\)-D-galactopyranosyl- monohydrate

Pennsylvania Right To Know

Lactose Monohydrate

D-Glucose, 4-O-\(\beta\)-D-galactopyranosyl- monohydrate

Non-hazardous galenic excipients

Aftatinib dimaleate

Not Assigned

The components of this product are reported in the following inventories:

REACH : Not in compliance with the inventory

DSL : This product contains the following components that are not on the Canadian DSL nor NDSL.

Afatinib dimaleate

Non-hazardous galenic excipients

AICS : Not in compliance with the inventory

NZIoC : Not in compliance with the inventory

ENCS : Not in compliance with the inventory

ISHL : Not in compliance with the inventory
KECI: Not in compliance with the inventory
PICCS: Not in compliance with the inventory
IECSC: Not in compliance with the inventory
TCSI: Not in compliance with the inventory
TSCA: Not On TSCA Inventory

**TSCA list**

No substances are subject to a Significant New Use Rule.

No substances are subject to TSCA 12(b) export notification requirements.

**SECTION 16. OTHER INFORMATION**

**Full text of other abbreviations**

AICS - Australian Inventory of Chemical Substances; ASTM - American Society for the Testing of Materials; bw - Body weight; CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DOT - Department of Transportation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; EHS - Extremely Hazardous Substance; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; ERG - Emergency Response Guide; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; HMIS - Hazardous Materials Identification System; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50% of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; MSHA - Mine Safety and Health Administration; n.o.s. - Not Otherwise Specified; NFPA - National Fire Protection Association; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NTP - National Toxicology Program; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; RCRA - Resource Conservation and Recovery Act; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RQ - Reportable Quantity; SADT - Self-Accelerating Decomposition Temperature; SAR - Superfund Amendments and Reauthorization Act; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative
Further information

NFPA:

| Flammability | 1 | 4 |
| Health       | 1 | 0 | Special hazard.
| Instability  | 4 | 0 |

HMIS® IV:

| HEALTH     | * |
| PHYSICAL HAZARD | 0 |
| FLAMMABILITY | 4 |

HMIS® ratings are based on a 0-4 rating scale, with 0 representing minimal hazards or risks, and 4 representing significant hazards or risks. The "*" represents a chronic hazard, while the "/" represents the absence of a chronic hazard.

Vertical lines in the left hand margin indicate an amendment from the previous version.

Refer to NFPA 654, Standard for the Prevention of Fire and Dust Explosions from the Manufacturing, Processing, and Handling of Combustible Particulate Solids, for safe handling.

Sources of key data used to compile the Safety Data Sheet:
The specifications are based on own tests and/or literature data.

Revision Date: 06/21/2017

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

US / EN