1. PRODUCT AND COMPANY IDENTIFICATION

Product name: Sitagliptin / Metformin Extended Release Formulation

Manufacturer or supplier’s details
Company name of supplier: MSD
Address: Kumagaya, Saitama Prefecture, Xicheng 810 MSD Co., Ltd.
Menuma factory
Telephone: 048-588-8411
E-mail address: EHSDATASTEWARD@msd.com
Emergency telephone number: 1-908-423-6000

Recommended use of the chemical and restrictions on use
Recommended use: Pharmaceutical

2. HAZARDS IDENTIFICATION

GHS Classification
Acute toxicity (Oral): Category 4

GHS label elements
Hazard pictograms: !
Signal word: Warning
Hazard statements: H302 Harmful if swallowed.
Precautionary statements: Prevention:
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
Response:
P301 + P312 + P330 IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell. Rinse mouth.
Disposal:
P501 Dispose of contents/container to an approved waste disposal plant.

Other hazards which do not result in classification
Important symptoms and outlines of the emergency as-
Dust contact with the eyes can lead to mechanical irritation.
Contact with dust can cause mechanical irritation or drying of
SAFETY DATA SHEET

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SDS Number: 29107-00014 Date of last issue: 2019/04/24
Date of first issue: 2014/11/07

3. COMPOSITION/INFORMATION ON INGREDIENTS

Substance / Mixture: Mixture

<table>
<thead>
<tr>
<th>Components</th>
<th>Chemical name</th>
<th>CAS-No.</th>
<th>Concentration (% w/w)</th>
<th>ENCS No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin hydrochloride</td>
<td></td>
<td>1115-70-4</td>
<td>&gt;= 60 - &lt; 70</td>
<td>2-2883</td>
</tr>
<tr>
<td>Cellulose</td>
<td></td>
<td>9004-34-6</td>
<td>&gt;= 10 - &lt; 20</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td>654671-77-9</td>
<td>&gt;= 2.5 - &lt; 10</td>
<td></td>
</tr>
<tr>
<td>Kaolin</td>
<td></td>
<td>1332-58-7</td>
<td>&gt;= 1 - &lt; 10</td>
<td>1-558, 5-5225</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td></td>
<td>13463-67-7</td>
<td>&gt;= 0.1 - &lt; 1</td>
<td>1-548</td>
</tr>
<tr>
<td>Silicon dioxide</td>
<td></td>
<td>7631-86-9</td>
<td>&gt;= 0.1 - &lt; 1</td>
<td></td>
</tr>
</tbody>
</table>

4. FIRST AID MEASURES

General advice: In the case of accident or if you feel unwell, seek medical advice immediately. When symptoms persist or in all cases of doubt seek medical advice.

If inhaled: If inhaled, remove to fresh air. Get medical attention if symptoms occur.

In case of skin contact: Wash with water and soap. Get medical attention if symptoms occur.

In case of eye contact: If in eyes, rinse well with water. Get medical attention if irritation develops and persists.

If swallowed: If swallowed, DO NOT induce vomiting unless directed to do so by medical personnel. Get medical attention. Rinse mouth thoroughly with water. Never give anything by mouth to an unconscious person.

Most important symptoms and effects, both acute and delayed: Harmful if swallowed. Contact with dust can cause mechanical irritation or drying of the skin. Dust contact with the eyes can lead to mechanical irritation.

Protection of first-aiders: First Aid responders should pay attention to self-protection, and use the recommended personal protective equipment when the potential for exposure exists (see section 8).

Notes to physician: Treat symptomatically and supportively.

5. FIREFIGHTING MEASURES

Suitable extinguishing media: Water spray
Alcohol-resistant foam
Carbon dioxide (CO2)
Unsuitable extinguishing media: None known.
Specific hazards during firefighting: Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Exposure to combustion products may be a hazard to health.

Hazardous combustion products: Carbon oxides, Metal oxides, Nitrogen oxides (NOx), Silicon oxides.

Specific extinguishing methods: Use extinguishing measures that are appropriate to local circumstances and the surrounding environment. Use water spray to cool unopened containers. Remove undamaged containers from fire area if it is safe to do so. Evacuate area.

Special protective equipment for firefighters: In the event of fire, wear self-contained breathing apparatus. Use personal protective equipment.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures: Use personal protective equipment. Follow safe handling advice and personal protective equipment recommendations.

Environmental precautions: Discharge into the environment must be avoided. Prevent further leakage or spillage if safe to do so. Retain and dispose of contaminated wash water. Local authorities should be advised if significant spillages cannot be contained.

Methods and materials for containment and cleaning up: Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dispersal of dust in the air (i.e., clearing dust surfaces with compressed air). Dust deposits should not be allowed to accumulate on surfaces, as these may form an explosive mixture if they are released into the atmosphere in sufficient concentration. Local or national regulations may apply to releases and disposal of this material, as well as those materials and items employed in the cleanup of releases. You will need to determine which regulations are applicable. Sections 13 and 15 of this SDS provide information regarding certain local or national requirements.

7. HANDLING AND STORAGE

Handling: Static electricity may accumulate and ignite suspended dust
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Local/Total ventilation: Use only with adequate ventilation.

Advice on safe handling:
- Do not breathe dust.
- Do not swallow.
- Avoid contact with eyes.
- Avoid prolonged or repeated contact with skin.
- Handle in accordance with good industrial hygiene and safety practice, based on the results of the workplace exposure assessment.
- Minimize dust generation and accumulation.
- Keep container closed when not in use.
- Keep away from heat and sources of ignition.
- Take precautionary measures against static discharges.
- Take care to prevent spills, waste and minimize release to the environment.

Avoidance of contact: Oxidizing agents

Hygiene measures:
- If exposure to chemical is likely during typical use, provide eye flushing systems and safety showers close to the working place.
- When using do not eat, drink or smoke.
- Wash contaminated clothing before re-use.
- The effective operation of a facility should include review of engineering controls, proper personal protective equipment, appropriate degowning and decontamination procedures, industrial hygiene monitoring, medical surveillance and the use of administrative controls.

Storage
- Conditions for safe storage: Keep in properly labelled containers.
- Store in accordance with the particular national regulations.

Materials to avoid:
- Do not store with the following product types: Strong oxidizing agents

Packaging material: Unsuitable material: None known.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Threshold limit value and permissible exposure limits for each component in the work environment

<table>
<thead>
<tr>
<th>Components</th>
<th>CAS-No.</th>
<th>Value type (Form of exposure)</th>
<th>Control parameters / Permissible concentration</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin hydrochloride</td>
<td>1115-70-4</td>
<td>TWA</td>
<td>2 mg/m3 (OEB 1)</td>
<td>Internal</td>
</tr>
<tr>
<td>Cellulose</td>
<td>9004-34-6</td>
<td>TWA</td>
<td>10 mg/m3</td>
<td>ACGIH</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>654671-77-9</td>
<td>TWA</td>
<td>0.5 mg/m3 (OEB 2)</td>
<td>Internal</td>
</tr>
<tr>
<td>Kaolin</td>
<td>1332-58-7</td>
<td>OEL-M (Respirable dust)</td>
<td>0.5 mg/m3</td>
<td>JP OEL JSOH</td>
</tr>
</tbody>
</table>

Further information: Class 1 Dust

| OEL-M (Total | 2 mg/m3 | JP OEL |
These substance(s) are inextricably bound in the product and therefore do not contribute to a dust inhalation hazard.

Titanium dioxide

**Engineering measures**

Use feasible engineering controls to minimize exposure to compound.

All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment.

**Personal protective equipment**

**Respiratory protection**

If adequate local exhaust ventilation is not available or exposure assessment demonstrates exposures outside the recommended guidelines, use respiratory protection.

<table>
<thead>
<tr>
<th>Filter type</th>
<th>Particulates type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand protection Material</td>
<td>Chemical-resistant gloves</td>
</tr>
</tbody>
</table>

**Eye protection**

Wear safety glasses with side shields or goggles. If the work environment or activity involves dusty conditions, mists or aerosols, wear the appropriate goggles. Wear a faceshield or other full face protection if there is a potential for direct contact to the face with dusts, mists, or aerosols.

**Skin and body protection**

Work uniform or laboratory coat.

**9. PHYSICAL AND CHEMICAL PROPERTIES**

**Appearance**

powder

**Colour**

blue green

**Odour**

No data available

**Odour Threshold**

No data available

**pH**

No data available
SAFETY DATA SHEET

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Melting point/freezing point : No data available
Initial boiling point and boiling range : No data available
Flash point : Not applicable
Evaporation rate : Not applicable
Flammability (solid, gas) : May form explosive dust-air mixture during processing, handling or other means.
Flammability (liquids) : No data available
Upper explosion limit / Upper flammability limit : No data available
Lower explosion limit / Lower flammability limit : No data available
Vapour pressure : Not applicable
Relative vapour density : Not applicable
Relative density : No data available
Density : No data available
Solubility(ies)
  Water solubility : No data available
Partition coefficient: n-octanol/water : Not applicable
Auto-ignition temperature : No data available
Decomposition temperature : No data available
Viscosity
  Viscosity, kinematic : Not applicable
Explosive properties : Not explosive
Oxidizing properties : The substance or mixture is not classified as oxidizing.
Particle size : No data available

10. STABILITY AND REACTIVITY

Reactivity : Not classified as a reactivity hazard.
Chemical stability : Stable under normal conditions.
Possibility of hazardous reactions : May form explosive dust-air mixture during processing, handling or other means.
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Can react with strong oxidizing agents.

Conditions to avoid:
Heat, flames and sparks.
Avoid dust formation.

Incompatible materials:
Oxidizing agents

Hazardous decomposition products:
No hazardous decomposition products are known.

11. TOXICOLOGICAL INFORMATION

Information on likely routes of exposure:
Inhalation
Skin contact
Ingestion
Eye contact

Acute toxicity:
Harmful if swallowed.

Product:
Acute oral toxicity: Acute toxicity estimate: 1,588 mg/kg
Method: Calculation method

Components:
metformin hydrochloride:
Acute oral toxicity: LD50 (Rat): 1,000 mg/kg
LD50 (Mouse): 1,450 - 3,500 mg/kg
LD50 (Monkey): 463 mg/kg
LD50 (Rabbit): 350 mg/kg
LD50 (Guinea pig): 500 mg/kg

Cellulose:
Acute oral toxicity: LD50 (Rat): > 5,000 mg/kg

Acute inhalation toxicity:
LC50 (Rat): > 5.8 mg/l
Exposure time: 4 h
Test atmosphere: dust/mist

Acute dermal toxicity:
LD50 (Rabbit): > 2,000 mg/kg

Sitagliptin:
Acute oral toxicity:
LD50 (Rat): > 3,000 mg/kg
LD50 (Mouse): 3,000 mg/kg

Kaolin:
Acute oral toxicity:
LD50 (Rat): > 5,000 mg/kg
Remarks: Based on data from similar materials

Acute inhalation toxicity: LC50 (Rat): > 2.07 mg/l
Exposure time: 4 h
Test atmosphere: dust/mist
Assessment: The substance or mixture has no acute inhalation toxicity
Remarks: Based on data from similar materials

Acute dermal toxicity: LD50 (Rat): > 5,000 mg/kg
Assessment: The substance or mixture has no acute dermal toxicity
Remarks: Based on data from similar materials

Titanium dioxide:
Acute oral toxicity: LD50 (Rat): > 5,000 mg/kg

Acute inhalation toxicity: LC50 (Rat): > 6.82 mg/l
Exposure time: 4 h
Test atmosphere: dust/mist
Assessment: The substance or mixture has no acute inhalation toxicity

Silicon dioxide:
Acute oral toxicity: LD50 (Rat): > 5,000 mg/kg
Method: OECD Test Guideline 401

Acute inhalation toxicity: LC50 (Rat): > 2.08 mg/l
Exposure time: 4 h
Test atmosphere: dust/mist
Assessment: The substance or mixture has no acute inhalation toxicity

Acute dermal toxicity: LD50 (Rabbit): > 5,000 mg/kg

Skin corrosion/irritation
Not classified based on available information.

Components:
metformin hydrochloride:
Species: Rabbit
Result: Mild skin irritation

Sitagliptin:
Species: Rabbit
Method: Draize Test
Result: No skin irritation

Kaolin:
Species: Rabbit
Method: OECD Test Guideline 404
Result: No skin irritation
Remarks: Based on data from similar materials

Titanium dioxide:
Species: Rabbit
Result: No skin irritation

Silicon dioxide:
Species: Rabbit
Method: OECD Test Guideline 404
Result: No skin irritation

Serious eye damage/eye irritation
Not classified based on available information.

Components:

metformin hydrochloride:
Species: Rabbit
Result: Mild eye irritation

Sitagliptin:
Species: Rabbit
Result: Irritating to eyes.
Method: Draize Test

Kaolin:
Species: Rabbit
Result: No eye irritation
Remarks: Based on data from similar materials

Titanium dioxide:
Species: Rabbit
Result: No eye irritation

Silicon dioxide:
Species: Rabbit
Result: No eye irritation
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:

Sitagliptin:
Test Type : Local lymph node assay (LLNA)
Species : Mouse
Method : OECD Test Guideline 429
Result : Not a skin sensitizer.

Titanium dioxide:
Test Type : Local lymph node assay (LLNA)
Exposure routes : Skin contact
Species : Mouse
Result : negative

Germ cell mutagenicity
Not classified based on available information.

Components:

metformin hydrochloride:
Genotoxicity in vitro : Test Type: Bacterial reverse mutation assay (AMES)
Result: negative
Test Type: in vitro assay
Test system: mouse lymphoma cells
Result: negative

Test Type: Chromosomal aberration
Test system: Human lymphocytes
Result: negative

Genotoxicity in vivo : Test Type: Micronucleus test
Species: Mouse
Application Route: Oral
Result: negative

Cellulose:
Genotoxicity in vitro : Test Type: Bacterial reverse mutation assay (AMES)
Result: negative
Test Type: In vitro mammalian cell gene mutation test
Result: negative

Genotoxicity in vivo : Test Type: Mammalian erythrocyte micronucleus test (in vivo cytogenetic assay)
Species: Mouse
Application Route: Ingestion
Result: negative
Sitagliptin:  
Genotoxicity in vitro:  
  Test Type: Ames test  
  Result: negative  
  Test Type: Chromosome aberration test in vitro  
  Test system: Chinese hamster ovary cells  
  Result: negative  
  Test Type: DNA damage and repair, unscheduled DNA synthesis in mammalian cells (in vitro)  
  Test system: rat hepatocytes  
  Result: negative  

Genotoxicity in vivo:  
  Test Type: Micronucleus test  
  Species: Mouse  
  Application Route: Oral  
  Result: negative

Titanium dioxide:  
Genotoxicity in vitro:  
  Test Type: Bacterial reverse mutation assay (AMES)  
  Result: negative  

Genotoxicity in vivo:  
  Test Type: In vivo micronucleus test  
  Species: Mouse  
  Result: negative

Silicon dioxide:  
Genotoxicity in vitro:  
  Test Type: Bacterial reverse mutation assay (AMES)  
  Method: OECD Test Guideline 471  
  Result: negative  

Genotoxicity in vivo:  
  Test Type: Mutagenicity (in vivo mammalian bone-marrow cytogenetic test, chromosomal analysis)  
  Species: Rat  
  Application Route: Ingestion  
  Result: negative

Carcinogenicity  
Not classified based on available information.

Components:  

metformin hydrochloride:  
Species: Mouse  
Exposure time: 91 weeks  
Dose: 1500 mg/kg body weight  
Result: negative  

Species: Rat, male  
Application Route: Oral  
Exposure time: 104 weeks  
Dose: 900 mg/kg body weight
### Sitagliptin / Metformin Extended Release Formulation

<table>
<thead>
<tr>
<th>Result</th>
<th>negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Species</strong></td>
<td>Rat, female</td>
</tr>
<tr>
<td><strong>Application Route</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>104 weeks</td>
</tr>
<tr>
<td><strong>LOAEL</strong></td>
<td>900 mg/kg body weight</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>negative</td>
</tr>
<tr>
<td><strong>Target Organs</strong></td>
<td>Uterus (including cervix)</td>
</tr>
<tr>
<td><strong>Remarks</strong></td>
<td>The mechanism or mode of action may not be relevant in humans.</td>
</tr>
</tbody>
</table>

**Cellulose:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Route</strong></td>
<td>Ingestion</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>72 weeks</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>negative</td>
</tr>
</tbody>
</table>

**Sitagliptin:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Route</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>2 Years</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Route</strong></td>
<td>oral (drinking water)</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>2 Years</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>positive</td>
</tr>
<tr>
<td><strong>Target Organs</strong></td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Remarks</strong></td>
<td>Significant toxicity observed in testing</td>
</tr>
</tbody>
</table>

**Carcinogenicity - Assessment**

|                      | Weight of evidence does not support classification as a carcinogen |

**Titanium dioxide:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Route</strong></td>
<td>inhalation (dust/mist/fume)</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>2 Years</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>OECD Test Guideline 453</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>positive</td>
</tr>
<tr>
<td><strong>Remarks</strong></td>
<td>The mechanism or mode of action may not be relevant in humans.</td>
</tr>
</tbody>
</table>

**Carcinogenicity - Assessment**

|                      | Limited evidence of carcinogenicity in inhalation studies with animals. |

**Silicon dioxide:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Route</strong></td>
<td>Ingestion</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>103 weeks</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>negative</td>
</tr>
</tbody>
</table>
Reproductive toxicity
Not classified based on available information.

Components:

metformin hydrochloride:
Effects on fertility:
- Test Type: Fertility
- Species: Rat
- Application Route: Oral
- Fertility: NOAEL: 600 mg/kg body weight
- Result: No effects on fertility

Effects on foetal development:
- Test Type: Development
- Species: Rat
- Application Route: Oral
- Developmental Toxicity: NOAEL: 600 mg/kg body weight
- Result: No teratogenic effects

Test Type: Embryo-foetal development
- Species: Rabbit
- Application Route: Oral
- Embryo-foetal toxicity: NOAEL: 140 mg/kg body weight
- Result: No teratogenic effects

Cellulose:
Effects on fertility:
- Test Type: One-generation reproduction toxicity study
- Species: Rat
- Application Route: Ingestion
- Result: negative

Effects on foetal development:
- Test Type: Fertility/early embryonic development
- Species: Rat
- Application Route: Ingestion
- Result: negative

Sitagliptin:
Effects on fertility:
- Test Type: Fertility/early embryonic development
- Species: Rat
- Application Route: Oral
- Fertility: NOAEL Parent: 1,000 mg/kg body weight
- Result: Animal testing did not show any effects on fertility.

Effects on foetal development:
- Test Type: Embryo-foetal development
- Species: Rat
- Application Route: Oral
- Teratogenicity: LOAEL: 250 mg/kg body weight
- Result: Embryotoxic effects and adverse effects on the offspring were detected., No teratogenic effects

Test Type: Embryo-foetal development
- Species: Rabbit
- Teratogenicity: NOAEL: 125 mg/kg body weight
Result: No teratogenic effects

**Silicon dioxide:**
Effects on foetal development: Test Type: Embryo-foetal development
Species: Rat
Application Route: Ingestion
Result: negative

**STOT - single exposure**
Not classified based on available information.

**STOT - repeated exposure**
Not classified based on available information.

**Repeated dose toxicity**

**Components:**

**metformin hydrochloride:**
Species: Rat
NOAEL: 125 mg/kg
Application Route: Oral
Exposure time: 1 year
Remarks: No significant adverse effects were reported

Species: Rabbit
NOAEL: 100 mg/kg
Application Route: Oral
Exposure time: 1 Year
Remarks: No significant adverse effects were reported

Species: Dog
NOAEL: 50 mg/kg
Application Route: Subcutaneous
Exposure time: 2 year
Remarks: No significant adverse effects were reported

**Cellulose:**
Species: Rat
NOAEL: >= 9,000 mg/kg
Application Route: Ingestion
Exposure time: 90 Days

**Sitagliptin:**
Species: Mouse
NOAEL: 500 mg/kg
LOAEL: 1,000 mg/kg
Application Route: Oral
Exposure time: > 2 yr
Target Organs: Kidney
Species: Rat
### SAFETY DATA SHEET

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<table>
<thead>
<tr>
<th>Version</th>
<th>Revision Date:</th>
<th>SDS Number:</th>
<th>Date of last issue:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>09/13/2019</td>
<td>29107-00014</td>
<td>2019/04/24</td>
</tr>
</tbody>
</table>

#### NOAEL: 500 mg/kg
- **Species:** Dog
- **NOAEL:** 10 mg/kg
- **Application Route:** Oral
- **Exposure time:** 14 Weeks
- **Target Organs:** Liver, Kidney, Heart, Teeth
- **Remarks:** The mechanism or mode of action may not be relevant in humans.

#### LOAEL: 1,000 mg/kg
- **Species:** Dog
- **NOAEL:** 50 mg/kg
- **Application Route:** Oral
- **Exposure time:** 53 Weeks
- **Target Organs:** Central nervous system
- **Symptoms:** Loss of balance
- **Remarks:** The mechanism or mode of action may not be relevant in humans.

#### Species: Dog
- **NOAEL:** 2 mg/kg
- **Application Route:** Oral
- **Exposure time:** 27 Weeks
- **Target Organs:** Skeletal muscle, Central nervous system
- **Symptoms:** Loss of balance
- **Remarks:** The mechanism or mode of action may not be relevant in humans.

#### Species: Monkey
- **NOAEL:** 10 mg/kg
- **Application Route:** Oral
- **Exposure time:** 14 Weeks
- **Remarks:** No significant adverse effects were reported

#### Titanium dioxide:
- **Species:** Rat
- **NOAEL:** 24,000 mg/kg
- **Application Route:** Ingestion
- **Exposure time:** 28 Days

#### Silicon dioxide:
- **Species:** Rat
- **NOAEL:** 1.3 mg/m³
- **Application Route:** Inhalation (dust/mist/fume)
- **Exposure time:** 13 Weeks

#### Aspiration toxicity
- Not classified based on available information.
Experience with human exposure

Components:

metformin hydrochloride:

Skin contact: Remarks: May irritate skin.
Eye contact: Remarks: May irritate eyes.
Ingestion: Symptoms: Diarrhoea, Nausea, Vomiting, Gastrointestinal discomfort, flatulence, asthenia, Fatigue, Headache

Sitagliptin:

Inhalation: Symptoms: upper respiratory tract infection, pharyngitis, Headache
Ingestion: Symptoms: upper respiratory tract infection, nasopharyngitis, Headache, Nausea, Abdominal pain, Diarrhoea

12. ECOLOGICAL INFORMATION

Ecotoxicity

Components:

metformin hydrochloride:

Toxicity to algae/aquatic plants: EC50 (Pseudokirchneriella subcapitata (green algae)): > 100 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

NOEC (Pseudokirchneriella subcapitata (green algae)): 100 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201

Toxicity to fish (Chronic toxicity): NOEC (Pimephales promelas (fathead minnow)): 10 mg/l
Exposure time: 33 d
Method: OECD Test Guideline 210

Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity): NOEC (Daphnia magna (Water flea)): 40 mg/l
Exposure time: 21 d
Method: OECD Test Guideline 211

Toxicity to microorganisms: EC50: > 1,000 mg/l
Exposure time: 3 h
Test Type: Respiration inhibition
Method: OECD Test Guideline 209

Cellulose:

Toxicity to fish: LC50 (Oryzias latipes (Japanese medaka)): > 100 mg/l
Exposure time: 48 h
Remarks: Based on data from similar materials

Sitagliptin:
Toxicity to fish: LC50 (Pimephales promelas (fathead minnow)): > 100 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): 60 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

Toxicity to algae/aquatic plants: EC50 (Pseudokirchneriella subcapitata (green algae)): > 39 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 201

NOEC (Pseudokirchneriella subcapitata (green algae)): 2.2 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 201

Toxicity to fish (Chronic toxicity): NOEC (Pimephales promelas (fathead minnow)): 9.2 mg/l
Exposure time: 33 d
Method: OECD Test Guideline 210

Toxicity to daphnia and other aquatic invertebrates (Chronic toxicity): NOEC (Daphnia magna (Water flea)): 9.8 mg/l
Exposure time: 21 d
Method: OECD Test Guideline 211

Toxicity to microorganisms: EC50: > 150 mg/l
Exposure time: 3 h
Test Type: Respiration inhibition
Method: OECD Test Guideline 209

NOEC: 150 mg/l
Exposure time: 3 h
Test Type: Respiration inhibition

Kaolin:
Toxicity to fish (Chronic toxicity): NOELR (Onchorhynchus mykiss (rainbow trout)): > 100 mg/l
Exposure time: 30 d

Titanium dioxide:
Toxicity to fish: LC50 (Onchorhynchus mykiss (rainbow trout)): > 100 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): > 100 mg/l
Exposure time: 48 h

Toxicity to algae/aquatic plants: EC50 (Skeletonema costatum (marine diatom)): > 10,000 mg/l
Exposure time: 72 h

Toxicity to microorganisms: EC50: > 1,000 mg/l
Exposure time: 3 h
Silicon dioxide:
Toxicity to fish: LC50 (Danio rerio (zebra fish)): > 10,000 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates: EC50 (Daphnia magna (Water flea)): > 1,000 mg/l
Exposure time: 24 h
Method: OECD Test Guideline 202

Toxicity to algae/aquatic plants: EC50 (Desmodesmus subspicatus (green algae)): > 10,000 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201
Remarks: Based on data from similar materials

NOEC (Desmodesmus subspicatus (green algae)): 10,000 mg/l
Exposure time: 72 h
Method: OECD Test Guideline 201
Remarks: Based on data from similar materials

Persistence and degradability

Components:

metformin hydrochloride:
Biodegradability: Result: rapidly degradable
Biodegradation: 50 %
Exposure time: 2 hrs

Cellulose:
Biodegradability: Result: Readily biodegradable.

Sitagliptin:
Biodegradability: Result: not rapidly degradable
Biodegradation: 39.7 %
Exposure time: 28 d
Method: OECD Test Guideline 314

Stability in water: Hydrolysis: 50 % (401 d)
Method: OECD Test Guideline 111

Bioaccumulative potential

Components:

metformin hydrochloride:
partition coefficient: n-octanol/water: log Pow: -2
Sitagliptin / Metformin Extended Release Formulation

Sitagliptin:
Partition coefficient: n-octanol/water : log Pow: -0.03

Mobility in soil

Components:

metformin hydrochloride:
Distribution among environmental compartments : log Koc: 4.3
Method: OECD Test Guideline 106

Sitagliptin:
Distribution among environmental compartments : log Koc: 4.37

Hazardous to the ozone layer
Not applicable

Other adverse effects
No data available

13. DISPOSAL CONSIDERATIONS

Disposal methods
Waste from residues : Dispose of in accordance with local regulations.
Contaminated packaging : Empty containers should be taken to an approved waste handling site for recycling or disposal. If not otherwise specified: Dispose of as unused product.

14. TRANSPORT INFORMATION

International Regulations

UNRTDG
Not regulated as a dangerous good

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
Refer to section 15 for specific national regulation.
15. REGULATORY INFORMATION

Related Regulations

Fire Service Law
Not applicable to dangerous materials / designated flammables.

Chemical Substance Control Law
Not applicable for Specified Chemical Substance, Monitoring Chemical Substance and Priority Assessment Chemical Substance.

Industrial Safety and Health Law

Harmful Substances Prohibited from Manufacture
Not applicable

Harmful Substances Required Permission for Manufacture
Not applicable

Substances Prevented From Impairment of Health
Not applicable

Circular concerning Information on Chemicals having Mutagenicity - Annex 2: Information on Existing Chemicals having Mutagenicity
Not applicable

Circular concerning Information on Chemicals having Mutagenicity - Annex 1: Information on Notified Substances having Mutagenicity
Not applicable

Substances Subject to be Notified Names
Article 57-2 (Enforcement Order Table 9)

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Number</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium(IV) oxide</td>
<td>191</td>
<td>&gt;=0.1 - &lt;1</td>
</tr>
<tr>
<td>Crystalline silica</td>
<td>165 2</td>
<td>&gt;=0.1 - &lt;1</td>
</tr>
</tbody>
</table>

Substances Subject to be Indicated Names
Article 57 (Enforcement Order Article 18)

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalline silica</td>
<td>165 2</td>
</tr>
</tbody>
</table>

Ordinance on Prevention of Hazards Due to Specified Chemical Substances
Not applicable

Ordinance on Prevention of Lead Poisoning
Not applicable

Ordinance on Prevention of Tetraalkyl Lead Poisoning
Not applicable

Ordinance on Prevention of Organic Solvent Poisoning
Not applicable
Enforcement Order of the Industrial Safety and Health Law - Attached table 1 (Dangerous Substances)
Not applicable

Poisonous and Deleterious Substances Control Law
Not applicable

Act on Confirmation, etc. of Release Amounts of Specific Chemical Substances in the Environment and Promotion of Improvements to the Management Thereof
Not applicable

High Pressure Gas Safety Act
Not applicable

Explosive Control Law
Not applicable

Vessel Safety Law
Not applicable

Aviation Law
Not applicable

Marine Pollution and Sea Disaster Prevention etc Law
Bulk transportation : Not classified as noxious liquid substance
Pack transportation : Not classified as marine pollutant

Narcotics and Psychotropics Control Act
Narcotic or Psychotropic Raw Material (Export / Import Permission)
Not applicable

Specific Narcotic or Psychotropic Raw Material (Export / Import permission)
Not applicable

Waste Disposal and Public Cleansing Law
Industrial waste

The components of this product are reported in the following inventories:
AICS : not determined
DSL : not determined
IECSC : not determined

16. OTHER INFORMATION

Further information

Date format : yyyy/mm/dd
SAFETY DATA SHEET

Sitagliptin / Metformin Extended Release Formulation

Version: 4.2
Revision Date: 09/13/2019
SDS Number: 29107-00014
Date of first issue: 2014/11/07
Date of last issue: 2019/04/24

Date of first issue: 2014/11/07
Date of last issue: 2019/04/24

Full text of other abbreviations

ACGIH : USA. ACGIH Threshold Limit Values (TLV)

ACGIH / TWA : 8-hour, time-weighted average
JP OEL JSOH / OEL-M : Occupational Exposure Limit-Mean

AICS - Australian Inventory of Chemical Substances; ANTT - National Agency for Transport by Land of Brazil; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; 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; 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; n.o.s. - Not Otherwise Specified; Nch - Chilean Norm; NO(A)EL - No Observed (Adverse) Effect Concentration; NO(A)EC - No Observed (Adverse) Effect Concentration; NOELR - No Observable Effect Loading Rate; NOM - Official Mexican Norm; 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; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TDG - Transportation of Dangerous Goods; 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; WHMIS - Workplace Hazardous Materials Information System

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 is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and shall not be considered a warranty or quality specification of any type. The information provided relates only to the specific material identified at the top of this SDS and may not be valid when the SDS material is used in combination with any other materials or in any process, unless specified in the text. Material users should review the information and recommendations in the specific context of their intended manner of handling, use, processing and storage, including an assessment of the appropriateness of the SDS material in the user’s end product, if applicable.

JP / EN