SAFETY DATA SHEET
Sitagliptin / Simvastatin Formulation

Version 7.1  Revision Date: 2021/08/27  SDS Number: 24504-00017  Date of last issue: 2021/04/09  Date of first issue: 2014/10/21

1. PRODUCT AND COMPANY IDENTIFICATION

Chemical product name : Sitagliptin / Simvastatin Formulation

Supplier’s company name, address and phone number
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 of chemical product
Serious eye damage/eye irritation : Category 2A
Skin sensitisation : Category 1
Specific target organ toxicity - repeated exposure : Category 2 (Liver, muscle, optic nerve, Eye)
Short-term (acute) aquatic hazard : Category 3
Long-term (chronic) aquatic hazard : Category 3

GHS label elements
Hazard pictograms :
Signal word : Warning
Hazard statements : H317 May cause an allergic skin reaction.
H319 Causes serious eye irritation.
H373 May cause damage to organs (Liver, muscle, optic nerve, Eye) through prolonged or repeated exposure.
H412 Harmful to aquatic life with long lasting effects.

Precautionary statements : Prevention:
P260 Do not breathe dust.
P264 Wash skin thoroughly after handling.
P272 Contaminated work clothing should not be allowed out of the workplace.
P273 Avoid release to the environment.
P280 Wear protective gloves/ eye protection/ face protection.

Response:
P302 + P352 IF ON SKIN: Wash with plenty of water.
P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P314 Get medical advice/ attention if you feel unwell.
P333 + P313 If skin irritation or rash occurs: Get medical advice/ attention.
P337 + P313 If eye irritation persists: Get medical advice/ attention.
P362 + P364 Take off contaminated clothing and wash it before reuse.

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 assumed: May form explosive dust-air mixture during processing, handling or other means.

3. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>Substance / Mixture</th>
<th>Mixture</th>
</tr>
</thead>
</table>

<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>Sitagliptin</td>
<td>654671-77-9</td>
<td>&gt;= 10 - &lt; 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose</td>
<td>9004-34-6</td>
<td>&gt;= 1 - &lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 1 - &lt; 10</td>
<td>8-98</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>79902-63-9</td>
<td>&gt;= 2.5 - &lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>13463-67-7</td>
<td>&gt;= 0.1 - &lt; 1</td>
<td>1-558, 5-5225</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.

In case of skin contact: In case of contact, immediately flush skin with plenty of water.
Remove contaminated clothing and shoes. Get medical attention. Wash clothing before reuse. Thoroughly clean shoes before reuse.

**In case of eye contact**: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If easy to do, remove contact lens, if worn. Get medical attention.

**If swallowed**: If swallowed, DO NOT induce vomiting. Get medical attention if symptoms occur. Rinse mouth thoroughly with water.

**Most important symptoms and effects, both acute and delayed**: May cause an allergic skin reaction. Causes serious eye irritation. May cause damage to organs through prolonged or repeated exposure.

**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)
- Dry chemical

**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
- Oxides of phosphorus

**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 (see section 7) and personal protective equipment recommendations (see section 8).

**Environmental precautions**: Avoid release to the environment. 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

Technical measures:
- Static electricity may accumulate and ignite suspended dust causing an explosion.
- Provide adequate precautions, such as electrical grounding and bonding, or inert atmospheres.

Local/Total ventilation:
- Use only with adequate ventilation.

Advice on safe handling:
- Do not get on skin or clothing.
- Do not breathe dust.
- Do not swallow.
- Do not get in eyes.
- Wash skin thoroughly after handling.
- 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.
- Do not eat, drink or smoke when using this product.
- Take care to prevent spills, waste and minimize release to the environment.

Avoidance of contact

Hygiene measures:
- Oxidizing agents
- 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.
- Contaminated work clothing should not be allowed out of the workplace.
- 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.
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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 / Reference concentration / Permissible concentration</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>654671-77-9</td>
<td>TWA</td>
<td>0.5 mg/m³ (OEL 2)</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>Simvastatin</td>
<td>79902-63-9</td>
<td>TWA</td>
<td>25 µg/m³ (OEL 3)</td>
<td>Internal</td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>TWA</td>
<td>10 mg/m³</td>
<td>ACGIH</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>13463-67-7</td>
<td>OEL-M (Respirable dust)</td>
<td>1 mg/m³ (Titanium)</td>
<td>JP OEL JSOH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OEL-M (Total dust)</td>
<td>4 mg/m³ (Titanium)</td>
<td>JP OEL JSOH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TWA</td>
<td>10 mg/m³ (Titanium dioxide)</td>
<td>ACGIH</td>
</tr>
</tbody>
</table>

**Further information**: Wipe limit 250 µg/100 cm² Internal

**Engineering measures**: All engineering controls should be implemented by facility design and operated in accordance with GMP principles to protect products, workers, and the environment.
Containment technologies suitable for controlling compounds are required to control at source and to prevent migration of the compound to uncontrolled areas (e.g., open-face containment devices).
Minimize open handling.

**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.

- **Filter type**: Particulates type
- **Hand protection**: Chemical-resistant gloves
- **Remarks**: Consider double gloving.
- **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. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces. Use appropriate degowning techniques to remove potentially contaminated clothing.

9. PHYSICAL AND CHEMICAL PROPERTIES

<table>
<thead>
<tr>
<th>Physical state</th>
<th>powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>pink</td>
</tr>
<tr>
<td>Odour</td>
<td>No data available</td>
</tr>
<tr>
<td>Odour Threshold</td>
<td>No data available</td>
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<tr>
<td>Melting point/freezing point</td>
<td>No data available</td>
</tr>
<tr>
<td>Boiling point, initial boiling point and boiling range</td>
<td>No data available</td>
</tr>
<tr>
<td>Flammability (solid, gas)</td>
<td>May form explosive dust-air mixture during processing, handling or other means.</td>
</tr>
<tr>
<td>Flammability (liquids)</td>
<td>No data available</td>
</tr>
<tr>
<td>Lower explosion limit and upper explosion limit / flammability limit</td>
<td>No data available</td>
</tr>
<tr>
<td>Upper explosion limit / Upper flammability limit</td>
<td>No data available</td>
</tr>
<tr>
<td>Lower explosion limit / Lower flammability limit</td>
<td>No data available</td>
</tr>
<tr>
<td>Flash point</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Decomposition temperature</td>
<td>No data available</td>
</tr>
<tr>
<td>pH</td>
<td>No data available</td>
</tr>
<tr>
<td>Evaporation rate</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Auto-ignition temperature</td>
<td>No data available</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Viscosity, kinematic</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Solubility(ies)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Water solubility</td>
<td>No data available</td>
</tr>
<tr>
<td>Partition coefficient: n-</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
octanol/water

Vapour pressure : Not applicable

Density and / or relative density
Relative density : No data available

Density : No data available

Relative vapour density : Not applicable

Explosive properties : Not explosive

Oxidizing properties : The substance or mixture is not classified as oxidizing.

Particle characteristics
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.
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
Not classified based on available information.

Components:

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

LD50 (Mouse): 3,000 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

**Starch:**
Acute oral toxicity : LD50 (Rat): > 5,000 mg/kg
Acute dermal toxicity : LD50 (Rabbit): > 2,000 mg/kg

**Simvastatin:**
Acute oral toxicity : LD50 (Rat): 5,000 mg/kg
   LD50 (Mouse): 3,800 mg/kg

**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

**Skin corrosion/irritation**
Not classified based on available information.

**Components:**

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

**Simvastatin:**
Species : Rabbit
Remarks : Moderate skin irritation

**Titanium dioxide:**
Species : Rabbit
Result : No skin irritation

**Serious eye damage/eye irritation**
Causes serious eye irritation.

**Components:**

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

**Starch:**
- Species: Rabbit
- Result: No eye irritation

**Simvastatin:**
- Species: Rabbit
- Remarks: slight irritation

**Titanium dioxide:**
- Species: Rabbit
- Result: No eye irritation

**Respiratory or skin sensitisation**

**Skin sensitisation**
May cause an allergic skin reaction.

**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.

**Starch:**
- Test Type: Maximisation Test
- Exposure routes: Skin contact
- Species: Guinea pig
- Result: negative

**Simvastatin:**
- Assessment: Probability or evidence of skin sensitisation in humans
- Result: positive

**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:

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

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

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

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

Test Type: Alkaline elution assay
Result: negative

Test Type: Chromosomal aberration
Result: negative

Test Type: In vitro mammalian cell gene mutation test
Result: negative

Genotoxicity in vivo : Test Type: Micronucleus test
Species: Mouse
Application Route: Oral
Germ cell mutagenicity - Assessment: Weight of evidence does not support classification as a germ cell mutagen.

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

Carcinogenicity
Not classified based on available information.

Components:

Sitagliptin:
Species: Mouse
Application Route: Oral
Exposure time: 2 Years
Result: negative
Species: Rat
Application Route: oral (drinking water)
Exposure time: 2 Years
Result: positive
Target Organs: Liver
Remarks: Significant toxicity observed in testing
Carcinogenicity - Assessment: Weight of evidence does not support classification as a carcinogen

Cellulose:
Species: Rat
Application Route: Ingestion
Exposure time: 72 weeks
Result: negative

Simvastatin:
Species: Mouse
Application Route: Oral
Exposure time: < 92 weeks
Target Organs: Harderian gland
Tumor Type: Liver, Lungs
Remarks: The significance of these findings for humans is not certain.
Species: Rat
Application Route: Oral
Exposure time: 2 Years
Tumor Type: Liver, Thyroid
Remarks: The significance of these findings for humans is not certain.

Titanium dioxide:
Species: Rat
Application Route: inhalation (dust/mist/fume)
Exposure time: 2 Years
Method: OECD Test Guideline 453
Result: positive
Remarks: The mechanism or mode of action may not be relevant in humans.

Carcinogenicity - Assessment: Limited evidence of carcinogenicity in inhalation studies with animals.

Reproductive toxicity
Not classified based on available information.

Components:
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

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

Simvastatin:
Effects on fertility: Test Type: Fertility
Species: Rat, male
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Application Route: Oral
Fertility: LOAEL: 25 mg/kg body weight

Effects on foetal development:
- Test Type: Embryo-foetal development
  - Species: Rat
  - Application Route: Oral
  - Embryo-foetal toxicity: NOAEL: 25 mg/kg body weight
  - Result: No teratogenic effects, No adverse effects

- Test Type: Embryo-foetal development
  - Species: Rabbit
  - Application Route: Oral
  - Embryo-foetal toxicity: NOAEL: 25 mg/kg body weight
  - Result: No teratogenic effects, No adverse effects

- Test Type: Embryo-foetal development
  - Species: Rat
  - Application Route: Oral
  - Embryo-foetal toxicity: LOAEL: 60 mg/kg body weight
  - Result: Teratogenic potential
  - Remarks: Based on data from similar materials

STOT - single exposure
Not classified based on available information.

STOT - repeated exposure
May cause damage to organs (Liver, muscle, optic nerve, Eye) through prolonged or repeated exposure.

Components:

Simvastatin:
- Target Organs: Liver, muscle, optic nerve, Eye
- Assessment: Causes damage to organs through prolonged or repeated exposure.

Repeated dose toxicity

Components:

Sitagliptin:
- Species: Mouse
  - NOAEL: 500 mg/kg
  - LOAEL: 1,000 mg/kg
- Application Route: Oral
- Exposure time: > 2 yr
- Target Organs: Kidney

- Species: Rat
  - NOAEL: 500 mg/kg
  - LOAEL: 1,000 mg/kg
- Application Route: Oral
- Exposure time: 14 Weeks
- Target Organs: Liver, Kidney, Heart, Teeth
<table>
<thead>
<tr>
<th>Species</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>LOAEL</td>
<td>50 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>53 Weeks</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Loss of balance</td>
</tr>
<tr>
<td>Remarks</td>
<td>The mechanism or mode of action may not be relevant in humans.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>LOAEL</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>27 Weeks</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Skeletal muscle, Central nervous system</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Loss of balance</td>
</tr>
<tr>
<td>Remarks</td>
<td>The mechanism or mode of action may not be relevant in humans.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Monkey</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>14 Weeks</td>
</tr>
<tr>
<td>Remarks</td>
<td>No significant adverse effects were reported</td>
</tr>
</tbody>
</table>

**Cellulose:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>&gt;= 9,000 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Ingestion</td>
</tr>
<tr>
<td>Exposure time</td>
<td>90 Days</td>
</tr>
</tbody>
</table>

**Starch:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>&gt;= 2,000 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Skin contact</td>
</tr>
<tr>
<td>Exposure time</td>
<td>28 Days</td>
</tr>
</tbody>
</table>

| Method      | OECD Test Guideline 410 |

**Simvastatin:**

<table>
<thead>
<tr>
<th>Species</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>LOAEL</td>
<td>30 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>14 - 104 Weeks</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Liver, Testis, Musculo-skeletal system, Eye</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOAEL</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>Application Route</td>
<td>Oral</td>
</tr>
<tr>
<td>Exposure time</td>
<td>14 - 104 Weeks</td>
</tr>
<tr>
<td>Target Organs</td>
<td>Liver, Testis, Eye</td>
</tr>
</tbody>
</table>
Species: Rabbit
NOAEL: 30 mg/kg
LOAEL: 50 mg/kg
Application Route: Oral
Target Organs: Liver, Kidney

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

Aspiration toxicity
Not classified based on available information.

Experience with human exposure

Components:

Sitagliptin:
Inhalation: Symptoms: upper respiratory tract infection, pharyngitis, Headache

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

Simvastatin:
Skin contact: Remarks: May produce an allergic reaction.
Ingestion: Target Organs: Liver
Symptoms: upper respiratory tract infection, Headache, Abdominal pain, constipation, Nausea
Target Organs: Musculo-skeletal system

12. ECOLOGICAL INFORMATION

Ecotoxicity
Components:

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: EC50 (Daphnia magna (Water flea)): 60 mg/l
aquatic invertebrates

Toxicity to algae/aquatic plants:
EC50 (Pseudokirchneriella subcapitata (green algae)): > 39 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

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

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

Simvastatin:
Toxicity to fish:
LC50 (Pimephales promelas (fathead minnow)): 2.91 mg/l
Exposure time: 96 h
Method: OECD Test Guideline 203

Toxicity to daphnia and other aquatic invertebrates:
EC50 (Daphnia magna (Water flea)): 3.5 mg/l
Exposure time: 48 h
Method: OECD Test Guideline 202

Toxicity to algae/aquatic plants:
EC50 (Pseudokirchneriella subcapitata (green algae)): > 25 mg/l
Exposure time: 96 h

NOEC (Pseudokirchneriella subcapitata (green algae)): 25 mg/l
Exposure time: 96 h

Toxicity to microorganisms:
EC50: > 30 mg/l
Exposure time: 3 h
Titanium dioxide:

Toxicity to fish: LC50 (Oncorhynchus 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
Method: OECD Test Guideline 209

Persistence and degradability

Components:

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

Cellulose:
Biodegradability: Result: Readily biodegradable.

Simvastatin:
Biodegradability: Result: rapidly degradable

Stability in water: Hydrolysis: 50 % (3.2 d)

Bioaccumulative potential

Components:

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

Simvastatin:
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Date of first issue: 2014/10/21

Partition coefficient: n-octanol/water
log Pow: > 4.07

Mobility in soil

Components:

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
UN number: Not applicable
Proper shipping name: Not applicable
Class: Not applicable
Subsidiary risk: Not applicable
Packing group: Not applicable
Labels: Not applicable

IATA-DGR
UN/ID No.: Not applicable
Proper shipping name: Not applicable
Class: Not applicable
Subsidiary risk: Not applicable
Packing group: Not applicable
Labels: Not applicable
Packing instruction (cargo aircraft): Not applicable
Packing instruction (passenger aircraft): Not applicable

IMDG-Code
UN number: Not applicable
Proper shipping name: Not applicable
Class: Not applicable
Subsidiary risk: Not applicable
Packing group: Not applicable
Labels: Not applicable
EmS Code : Not applicable
Marine pollutant : Not applicable

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.

Special precautions for user
Not applicable

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>
</tbody>
</table>

Substances Subject to be Indicated Names
Not applicable

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 regulated as a dangerous good

Aviation Law  
Not regulated as a dangerous good

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
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Date of first issue: 2014/10/21

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

AIIIC - Australian Inventory of Industrial Chemicals; 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; IECS - 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; KECl - 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)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; 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; TECI - Thailand Existing Chemicals 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; 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