SECTION 1. IDENTIFICATION

Product name : Sitagliptin / Simvastatin Formulation
Other means of identification : No data available

Manufacturer or supplier’s details
Company name of supplier : Merck & Co., Inc
Address : 2000 Galloping Hill Road
Kenilworth - New Jersey - U.S.A. 07033
Telephone : 908-740-4000
Telefax : 908-735-1496
Emergency telephone : 1-908-423-6000
E-mail address : EHSDATASTEWARD@merck.com

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

SECTION 2. HAZARDS IDENTIFICATION

GHS classification in accordance with the Hazardous Products Regulations
Eye irritation : Category 2A
Skin sensitization : Category 1
Carcinogenicity (Inhalation) : Category 2
Specific target organ toxicity - repeated exposure : Category 1 (Liver, muscle, optic nerve, Eye)

GHS label elements
Hazard pictograms : ![Icon]
Signal Word : Danger
Hazard Statements : H317 May cause an allergic skin reaction.
H319 Causes serious eye irritation.
H351 Suspected of causing cancer if inhaled.
H372 Causes damage to organs (Liver, muscle, optic nerve, Eye) through prolonged or repeated exposure.

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/ vapors/ spray.
P264 Wash skin thoroughly after handling.
P270 Do not eat, drink or smoke when using this product.
P272 Contaminated work clothing should not be allowed out of the workplace.
P280 Wear protective gloves/ protective clothing/ 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.
P308 + P313 IF exposed or concerned: Get medical advice/ attention.
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.

Storage:
P405 Store locked up.

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

Other hazards
May form explosive dust-air mixture during processing, handling or other means.

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>Substance / Mixture</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Mixture</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>Sitagliptin</td>
<td>654671-77-9</td>
<td>&gt;= 10 - &lt; 30</td>
</tr>
<tr>
<td>Cellulose</td>
<td>9004-34-6</td>
<td>&gt;= 5 - &lt; 10</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>79902-63-9</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
<tr>
<td>Starch</td>
<td>9005-25-8</td>
<td>&gt;= 1 - &lt; 5</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>13463-67-7</td>
<td>&gt;= 0.1 - &lt; 1</td>
</tr>
</tbody>
</table>

Actual concentration or concentration range is withheld as a trade secret

SECTION 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.
- Suspected of causing cancer if inhaled.
- Causes 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.

SECTION 5. FIRE-FIGHTING MEASURES

Suitable extinguishing media:
- Water spray
- Alcohol-resistant foam
- Carbon dioxide (CO2)
- Dry chemical

Unsuitable extinguishing media:
- None known.

Specific hazards during fire fighting:
- 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 fire-fighters:
- In the event of fire, wear self-contained breathing apparatus. Use personal protective equipment.

SECTION 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.

SECTION 7. HANDLING AND STORAGE

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.
- 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.

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

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

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Ingredients with workplace control parameters

<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>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>CA AB OEL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TWA (Total)</td>
<td>10 mg/m³</td>
<td>CA BC OEL</td>
</tr>
</tbody>
</table>
Simvastatin

TWA (respirable dust fraction) 3 mg/m³ CA BC OEL
TWA (Total dust) 10 mg/m³ CA QC OEL
TWA 10 mg/m³ ACGIH

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

Starch
TWA 10 mg/m³ CA AB OEL
TWA (Total dust) 10 mg/m³ CA QC OEL
TWA (respirable dust fraction) 3 mg/m³ CA BC OEL
TWA 10 mg/m³ ACGIH

Titanium dioxide
TWA 10 mg/m³ CA AB OEL
TWA (Total dust) 10 mg/m³ CA QC OEL
TWA (respirable dust fraction) 3 mg/m³ CA BC OEL
TWA 10 mg/m³ (Titanium dioxide) ACGIH

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.

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.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance: powder
Color: pink
Odor: No data available
Odor Threshold: No data available
pH: No data available
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
Vapor pressure: Not applicable
Relative vapor density: Not applicable
Relative density: No data available
Density: No data available
Solubility(ies): No data available
  Water solubility: No data available
Partition coefficient: n-octanol/water: Not applicable
Autoignition temperature: No data available
Decomposition temperature: No data available
Viscosity: Not applicable
  Viscosity, kinematic: Not applicable
Explosive properties: Not explosive
Oxidizing properties: The substance or mixture is not classified as oxidizing.
Particle size: No data available

SECTION 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.

SECTION 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

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

### Starch:
- **Acute oral toxicity**: LD50 (Mouse): > 5,000 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

Simvastatin:
Species: Rabbit
Remarks: slight irritation

Titanium dioxide:
Species: Rabbit
Result: No eye irritation

Respiratory or skin sensitization

Skin sensitization
May cause an allergic skin reaction.

Respiratory sensitization
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.

Simvastatin:
Assessment: Probability or evidence of skin sensitization in humans
Result: positive

Titanium dioxide:
Test Type: Local lymph node assay (LLNA)
Routes of exposure: 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
<table>
<thead>
<tr>
<th>Substance</th>
<th>Genotoxicity in vitro</th>
<th>Genotoxicity in vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sitagliptin</strong></td>
<td>Result: negative</td>
<td>Test Type: Micronucleus test</td>
</tr>
<tr>
<td></td>
<td>Test Type: DNA damage and repair, unscheduled DNA synthesis in mammalian cells (in vitro)</td>
<td>Species: Mouse</td>
</tr>
<tr>
<td></td>
<td>Test system: rat hepatocytes</td>
<td>Application Route: Oral</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td><strong>Cellulose</strong></td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
<td>Test Type: Mammalian erythrocyte micronucleus test (in vivo cytogenetic assay)</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Species: Mouse</td>
</tr>
<tr>
<td></td>
<td>Test Type: In vitro mammalian cell gene mutation test</td>
<td>Application Route: Ingestion</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td></td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
<td>Test Type: Micronucleus test</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Species: Mouse</td>
</tr>
<tr>
<td></td>
<td>Test Type: Alkaline elution assay</td>
<td>Application Route: Oral</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td></td>
<td>Test Type: Chromosomal aberration</td>
<td>Test Type: In vitro mammalian cell gene mutation test</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
<td>Test Type: Micronucleus test</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Species: Mouse</td>
</tr>
<tr>
<td></td>
<td>Test Type: Alkaline elution assay</td>
<td>Application Route: Oral</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td></td>
<td>Test Type: Chromosomal aberration</td>
<td>Test Type: In vitro mammalian cell gene mutation test</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td></td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
<td>Test Type: Mammalian erythrocyte micronucleus test (in vivo cytogenetic assay)</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Species: Mouse</td>
</tr>
<tr>
<td></td>
<td>Test Type: Micronucleus test</td>
<td>Application Route: Oral</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
<tr>
<td><strong>Titanium dioxide</strong></td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
<td>Germ cell mutagenicity - Assessment</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Weight of evidence does not support classification as a germ cell mutagen.</td>
</tr>
<tr>
<td></td>
<td>Test Type: In vitro mammalian cell gene mutation test</td>
<td>Test Type: Bacterial reverse mutation assay (AMES)</td>
</tr>
<tr>
<td></td>
<td>Result: negative</td>
<td>Result: negative</td>
</tr>
</tbody>
</table>

**Notes:**
- Result: negative
- Test Type: DNA damage and repair, unscheduled DNA synthesis in mammalian cells (in vitro)
- Test system: rat hepatocytes
- Result: negative
- Test Type: Micronucleus test
- Species: Mouse
- Application Route: Oral
- Result: negative
- Test Type: Bacterial reverse mutation assay (AMES)
- Species: Mouse
- Application Route: Oral
- Result: negative
- Test Type: In vitro mammalian cell gene mutation test
- Result: negative
- Test Type: Mammalian erythrocyte micronucleus test (in vivo cytogenetic assay)
- Species: Mouse
- Application Route: Ingestion
- Result: negative
- Germ cell mutagenicity - Assessment: Weight of evidence does not support classification as a germ cell mutagen.
**Carcinogenicity**

Suspected of causing cancer if inhaled.

**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

**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:** Weight of evidence does not support classification as a carcinogen
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 fetal development: Test Type: Embryo-fetal 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-fetal 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 fetal development: Test Type: Fertility/early embryonic development  
Species: Rat  
Application Route: Ingestion  
Result: negative

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

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

Test Type: Embryo-fetal development  
Species: Rabbit  
Application Route: Oral  
Embryo-fetal toxicity.: NOAEL: 10 mg/kg body weight
Result: No teratogenic effects., No adverse effects.

Test Type: Embryo-fetal development
Species: Rat
Application Route: Oral
Embryo-fetal 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
Causes 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 y
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

Species : Dog
NOAEL : 10 mg/kg
LOAEL : 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
LOAEL : 10 mg/kg
<table>
<thead>
<tr>
<th>Application Route</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<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>

| Species | Monkey |
| NOAEL   | 100 mg/kg |
| Application Route | Oral |
| Exposure time | 14 Weeks |
| Remarks | No significant adverse effects were reported |

| Cellulose: |
| Species | Rat |
| NOAEL   | $\geq 9,000$ mg/kg |
| Application Route | Ingestion |
| Exposure time | 90 Days |

| Simvastatin: |
| Species | Rat |
| NOAEL   | 5 mg/kg |
| LOAEL   | 30 mg/kg |
| Application Route | Oral |
| Exposure time | 14 - 104 Weeks |
| Target Organs | Liver, Testis, Musculo-skeletal system, Eye |
| Species | Dog |
| LOAEL   | 10 mg/kg |
| Application Route | Oral |
| Exposure time | 14 - 104 Weeks |
| Target Organs | Liver, Testis, Eye |
| 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 |
| Species | Rat |
| NOAEL   | $10$ mg/m³ |
| Application Route | inhalation (dust/mist/fume) |
| Exposure time | 2 y |

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, Diarrhea

**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

**SECTION 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 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

**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
Test Type: Respiration inhibition
Method: OECD Test Guideline 209

NOEC: 21 mg/l
Exposure time: 3 h
Test Type: Respiration inhibition
Method: OECD Test Guideline 209

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

Mobility in soil

**Components:**

**Sitagliptin:**
Distribution among environmental compartments: log Koc: 4.37

Other adverse effects

No data available

SECTION 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.
SECTION 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.

Domestic regulation

TDG
Not regulated as a dangerous good

SECTION 15. REGULATORY INFORMATION

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

AICS : not determined

DSL : not determined

IECSC : not determined

SECTION 16. OTHER INFORMATION

Full text of other abbreviations

ACGIH : USA. ACGIH Threshold Limit Values (TLV)


CA BC OEL : Canada. British Columbia OEL

CA QC OEL : Québec. Regulation respecting occupational health and safety, Schedule 1, Part 1: Permissible exposure values for airborne contaminants

ACGIH / TWA : 8-hour, time-weighted average

CA AB OEL / TWA : 8-hour Occupational exposure limit

CA BC OEL / TWA : 8-hour time weighted average

CA QC OEL / TWAEV : Time-weighted average exposure value

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