1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND THE COMPANY/UNDERTAKING

Material Name: Tramadol Hydrochloride Modified Release Tablets

Trade Name: Nobligan Retard
Chemical Family: Mixture
Intended Use: Pharmaceutical product used as analgesic

2. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS Number</th>
<th>EU EINECS List</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol Hydrochloride</td>
<td>73806-49-2</td>
<td>Not listed</td>
<td>100-200 mg***</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>9004-34-6</td>
<td>232-674-9</td>
<td>*</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>557-04-0</td>
<td>209-150-3</td>
<td>*</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>7631-86-9</td>
<td>231-545-4</td>
<td>*</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>57-55-6</td>
<td>200-338-0</td>
<td>*</td>
</tr>
<tr>
<td>Talc (non-asbestiform)</td>
<td>14807-96-6</td>
<td>238-877-9</td>
<td>*</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>13463-67-7</td>
<td>236-675-5</td>
<td>*</td>
</tr>
<tr>
<td>Hypromellose</td>
<td>9004-65-3</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Lactose NF, monohydrate</td>
<td>64044-51-5</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Macrogol 6000</td>
<td>Not assigned</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Red iron oxide</td>
<td>Not assigned</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Brown iron oxide</td>
<td>Not assigned</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Quinoline yellow lake (E104)</td>
<td>Not assigned</td>
<td>Not listed</td>
<td>*</td>
</tr>
</tbody>
</table>

Additional Information: * Proprietary
*** per tablet/capsule/lozenge/suppository
Ingredient(s) indicated as hazardous have been assessed under standards for workplace safety.

3. HAZARDS IDENTIFICATION

Appearance: Tablets
Signal Word: WARNING

Statement of Hazard: Harmful if swallowed.
May cause central nervous system effects

Emergency telephone number: CHEMTREC (24 hours): 1-800-424-9300
Emergency telephone number: ChemSafe (24 hours): +44 (0)208 762 8322
4. FIRST AID MEASURES

Eye Contact: Immediately flush eyes with water for at least 15 minutes. If irritation occurs or persists, get medical attention.

Skin Contact: Remove clothing and wash affected skin with soap and water. This material may not be completely removed by conventional laundering. Consult professional laundry service. Do not home launder. If irritation occurs or persists, get medical attention.

Ingestion: Never give anything by mouth to an unconscious person. Wash out mouth with water. Do not induce vomiting unless directed by medical personnel. Seek medical attention immediately.

Inhalation: Remove to fresh air and keep patient at rest. Seek medical attention immediately.

5. FIRE FIGHTING MEASURES

Extinguishing Media: Use carbon dioxide, dry chemical, or water spray.

Hazardous Combustion Products: Formation of toxic gases is possible during heating or fire.

Fire Fighting Procedures: During all fire fighting activities, wear appropriate protective equipment, including self-contained breathing apparatus.

Fire / Explosion Hazards: Not applicable

6. ACCIDENTAL RELEASE MEASURES

Health and Safety Precautions: Personnel involved in clean-up should wear appropriate personal protective equipment (see Section 8). Minimize exposure.
Measures for Cleaning / Collecting: Contain the source of spill if it is safe to do so. Collect spilled material by a method that controls dust generation. A damp cloth or a filtered vacuum should be used to clean spills of dry solids. Clean spill area thoroughly.

Measures for Environmental Protections: Place waste in an appropriately labeled, sealed container for disposal. Care should be taken to avoid environmental release.

Additional Consideration for Large Spills: Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean up operations should only be undertaken by trained personnel.

7. HANDLING AND STORAGE

General Handling: If tablets or capsules are crushed and/or broken, avoid breathing dust and avoid contact with eyes, skin, and clothing.

Storage Conditions: Store at room temperature in properly labeled containers. Keep away from heat, sparks and flames.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Microcrystalline cellulose
OSHA - Final PELs - TWAs: 15 mg/m³ TWA total
ACGIH Threshold Limit Value (TWA) 5 mg/m³ TWA
Australia TWA 10 mg/m³ TWA

Magnesium stearate
ACGIH Threshold Limit Value (TWA) 10 mg/m³ TWA except stearates of toxic metals
Australia TWA 10 mg/m³ TWA

Colloidal silicon dioxide
OSHA - Final PELs - Table Z-3 Mineral D: 20 mppcf TWA
Australia TWA 2 mg/m³ TWA

Propylene glycol
Australia TWA 10 mg/m³ TWA
150 ppm TWA
474 mg/m³ TWA

Talc (non-asbestiform)
OSHA - Final PELs - Table Z-3 Mineral D: 20 mppcf TWA
ACGIH Threshold Limit Value (TWA) 2 mg/m³ TWA
Australia TWA 2.5 mg/m³ TWA containing no asbestos fibers

Titanium dioxide
OSHA - Final PELs - TWAs: 15 mg/m³ TWA total
ACGIH Threshold Limit Value (TWA) 10 mg/m³ TWA
Australia TWA 10 mg/m³ TWA
The exposure limit(s) listed for solid components are only relevant if dust may be generated.

Engineering Controls: Engineering controls should be used as the primary means to control exposures.

Personal Protective Equipment:
Hands: Not required for the normal use of this product. Wear protective gloves when working with large quantities.

Eyes: Not required under normal conditions of use. Wear safety glasses or goggles if eye contact is possible.

Skin: Not required for the normal use of this product. Wear protective clothing when working with large quantities.

Respiratory protection: Not required for the normal use of this product. If the applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.

9. PHYSICAL AND CHEMICAL PROPERTIES:

Physical State: Tablets  
Color: No data available.
Molecular Formula: Mixture  
Molecular Weight: Mixture

10. STABILITY AND REACTIVITY

Stability: Stable under normal conditions of use.
Conditions to Avoid: None known
Incompatible Materials: As a precautionary measure, keep away from strong oxidizers.

11. TOXICOLOGICAL INFORMATION

General Information: There are no data for this formulation. The information included in this section describes the potential hazards of the individual ingredients.

Acute Toxicity: (Species, Route, End Point, Dose)

Hypromellose  
Rat Oral LD50 > 10,000 mg/kg

Microcrystalline cellulose  
Rat Oral LD50 > 5000 mg/kg  
Rabbit Dermal LD50 > 2000 mg/kg

Magnesium stearate  
Rat Oral LD50 > 2000 mg/kg  
Rat Inhalation LC50 > 2000 mg/m³

Talc (non-asbestiform)  
Rat Oral LD50 > 1600 mg/kg

Titanium dioxide  
Rat Oral LD50 > 7500 mg/kg  
Rat Subcutaneous LD 50 50 mg/kg

Tramadol Hydrochloride  
Rat Oral LD50 228 mg/kg  
Rat Intravenous LD50 57.6 mg/kg  
Rat Subcutaneous LD50 286 mg/kg  
Mouse Oral LD50 270 mg/kg
**Propylene glycol**
Mouse Oral LD50 22,000 mg/kg
Rat Oral LD50 20,000 mg/kg
Rabbit Dermal LD50 20,800 mg/kg

**Acute Toxicity Comments:** A greater than symbol (>) indicates that the toxicity endpoint being tested was not achievable at the highest dose used in the test.

**Irritation / Sensitization: (Study Type, Species, Severity)**

- **Microcrystalline cellulose**
  - Skin Irritation Rabbit Non-irritating
  - Eye Irritation Rabbit Non-irritating

- **Propylene glycol**
  - Skin Irritation Rabbit Mild
  - Eye Irritation Rabbit Mild

**Repeated Dose Toxicity: (Duration, Species, Route, Dose, End Point, Target Organ)**

**Tramadol Hydrochloride**
- 6 Week(s) Rat Oral 20 mg/kg/day NOAEL
- 26 Week(s) Dog Oral 10 mg/kg/day NOAEL

**Reproduction & Developmental Toxicity: (Study Type, Species, Route, Dose, End Point, Effect(s))**

- **Tramadol Hydrochloride**
  - Reproductive & Fertility Rat Oral 50-75 mg/kg NOAEL Fertility
  - Embryo / Fetal Development Rat Oral 25 mg/kg LOAEL Maternal Toxicity, Fetotoxicity
  - Embryo / Fetal Development Rabbit Oral 75 mg/kg LOAEL Maternal Toxicity, Fetotoxicity
  - Embryo / Fetal Development Mouse Oral 120 mg/kg LOAEL Maternal Toxicity, Fetotoxicity
  - Peri-/Postnatal Development Rat Oral 50 mg/kg LOAEL Maternal Toxicity, Fetotoxicity

**Genetic Toxicity: (Study Type, Cell Type/Organism, Result)**

- **Tramadol Hydrochloride**
  - Bacterial Mutagenicity (Ames) *Salmonella*, *E. coli* Negative
  - *In Vivo* Chromosome Aberration Chinese Hamster Ovary (CHO) cells Negative
  - *In Vivo* Micronucleus Mouse Bone Marrow Negative
  - *In Vitro* Micronucleus Rat Positive
  - *In Vitro* Mammalian Cell Mutagenicity Mouse Lymphoma Positive

**Carcinogenicity: (Duration, Species, Route, Dose, End Point, Effect(s))**

- **Tramadol Hydrochloride**
  - 2 Year(s) Mouse Oral 30 mg/kg/day LOAEL Liver, Lungs, Tumors
  - 2 Year(s) Rat Oral 30 mg/kg/day NOAEL Not carcinogenic

**Carcinogen Status:** See below

**Talc (non-asbestiform)**

- **IARC:** Group 3

**Titanium dioxide**
12. ECOLOGICAL INFORMATION

Environmental Overview: Environmental properties have not been thoroughly investigated. Releases to the environment should be avoided.

13. DISPOSAL CONSIDERATIONS

Disposal Procedures: Dispose of waste in accordance with all applicable laws and regulations.

14. TRANSPORT INFORMATION

Not regulated for transport under USDOT, EUADR, IATA, or IMDG regulations.

15. REGULATORY INFORMATION

EU Symbol: Xn
EU Indication of danger: Harmful
EU Risk Phrases: R22 - Harmful if swallowed.
EU Safety Phrases: S22 - Do not breathe dust.

OSHA Label:
WARNING
Harmful if swallowed.
May cause central nervous system effects

Canada - WHMIS: Classifications

WHMIS hazard class: Class D, Division 1, Subdivision B
16. OTHER INFORMATION

Reasons for Revision: Updated Section 2 - Composition / Information on Ingredients. Updated Section 3 - Hazard Identification. Updated Section 5 - Fire Fighting Measures. Updated Section 6 - Accidental Release Measures. Updated Section 8 - Exposure Controls / Personal Protection. Updated Section 10 - Stability and Reactivity. Updated Section 11 - Toxicology Information. Updated Section 13 - Disposal Considerations.

Prepared by: Toxicology and Hazard Communication
Pfizer Global Environment, Health, and Safety

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End of Safety Data Sheet