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

Material Name: Diclofenac and Misoprostol Tablets

Trade Name: ARTHROTEC(R)

Chemical Family: Mixture

Intended Use: Pharmaceutical product used as non-steroidal, anti-inflammatory drug (nsaid)

2. COMPOSITION/INFORMATION ON INGREDIENTS

### Hazardous

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS Number</th>
<th>EU EINECS List</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>15307-79-6</td>
<td>239-346-4</td>
<td>11-15</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>59122-46-2</td>
<td>Not listed</td>
<td>0.04</td>
</tr>
<tr>
<td>Talc (non-asbestiform)</td>
<td>14807-96-6</td>
<td>238-877-9</td>
<td>*</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>9005-25-8</td>
<td>232-679-6</td>
<td>*</td>
</tr>
<tr>
<td>Silicon dioxide, colloidal NF</td>
<td>7631-86-9</td>
<td>231-545-4</td>
<td>*</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>557-04-0</td>
<td>209-150-3</td>
<td>*</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>9004-34-6</td>
<td>232-674-9</td>
<td>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS Number</th>
<th>EU EINECS List</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypromellose</td>
<td>9004-65-3</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Povidone</td>
<td>9003-39-8</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>9003-39-8</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>64044-51-5</td>
<td>Not listed</td>
<td>*</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>77-93-0</td>
<td>201-070-7</td>
<td>*</td>
</tr>
<tr>
<td>Hydrogenated castor oil</td>
<td>8001-78-3</td>
<td>232-292-2</td>
<td>*</td>
</tr>
<tr>
<td>Methacrylic Acid Copolymer, Type C</td>
<td>Not Assigned</td>
<td>Not listed</td>
<td>*</td>
</tr>
</tbody>
</table>

Additional Information: * Proprietary

Ingredient(s) indicated as hazardous have been assessed under standards for workplace safety.

3. HAZARDS IDENTIFICATION

Appearance: White tablet

Signal Word: WARNING
Statement of Hazard:  
Causes eye irritation. 
Causes skin irritation. 
Harmful if swallowed. 
May cause damage to: blood and blood forming organs, liver, heart, gastrointestinal system through prolonged or repeated exposure. 
Suspected of damaging the unborn child. 
May cause allergic reaction in aspirin-sensitive individuals.

Additional Hazard Information:  
Short Term:  
May cause eye irritation, May cause skin irritation. (based on components).

Long Term:  
Repeat-dose studies in animals have shown a potential to cause adverse effects on blood, spleen, reproductive system, gastrointestinal system. Animal studies indicate that this material may cause adverse effects on the developing fetus.

Known Clinical Effects:  
Clinical use has caused effects on the gastrointestinal system, including abdominal pain, nausea, vomiting, diarrhea, constipation, peptic ulcer, acid reflux, and gastrointestinal bleeding. 
Clinical use has resulted in liver effects. Symptoms may include jaundice, liver function test abnormalities, and hepatitis. Clinical use has caused effects on the nervous system, including drowsiness, anxiety, dizziness, visual disturbances. Serious allergic reactions, including anaphylaxis, have been reported. Clinical use of this drug has caused decreased red blood cell count (anemia), effects on blood forming organs. Drugs of this class may cause menstrual irregularities, cramps, pain, postmenopausal menstrual bleeding, miscarriage, uterine rupture, bleeding and death. Miscarriages have been seen in pregnant women taking this drug. Clinical use has caused effects on the cardiovascular system, including heart attack (myocardial infarction), stroke.

EU Indication of danger:  
Harmful.

EU Hazard Symbols:  

EU Risk Phrases:  
R22 - Harmful if swallowed. 
R61 - May cause harm to the unborn child.

Note:  
This document has been prepared in accordance with standards for workplace safety, which require the inclusion of all known hazards of the active substance or its intermediates regardless of the potential risk. The precautionary statements and warnings included may not apply in all cases. Your needs may vary depending upon the potential for exposure in your workplace.

4. FIRST AID MEASURES

Eye Contact:  
Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. If irritation occurs or persists, get medical attention.

Skin Contact:  
Wash exposed area with soap and water, remove contaminated clothing and obtain medical assistance if irritation occurs.

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: Toxic or corrosive gases including oxides of carbon and nitrogen together with chlorine and hydrogen chloride are expected in fires involving this material.

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. Avoid generating airborne dust.

Storage Conditions: Store as directed by product packaging.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Misoprostol
Pfizer OEL TWA-8 Hr: 0.7 ug/m³

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

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

Silicon dioxide, colloidal NF
OSHA - Final PELs - Table Z-3 Mineral D: (80)/(% SiO₂) mg/m³ TWA
= 20 mppcf TWA
Australia TWA = 2 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
Microcrystalline cellulose

OSHA - Final PELS - TWAs:

= 15 mg/m³ TWA total
= 5 mg/m³ TWA

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.

The purpose of the Occupational Exposure Band (OEB) classification system is to separate substances into different Hazard categories when the available data are sufficient to do so, but inadequate to establish an Occupational Exposure Limit (OEL). The OEB given is based upon an analysis of all currently available data; as such, this value may be subject to revision when new information becomes available.

Diclofenac Sodium

Pfizer Occupational Exposure Band (OEB):

OEB2 (control exposure to the range of >100ug/m³ to < 1000ug/m³)

Analytical Method:

Analytical method available for misoprostol. Contact Pfizer Inc for further information.

Engineering Controls:

Engineering controls should be used as the primary means to control exposures. Use process containment, local exhaust ventilation, or other engineering controls to maintain airborne levels within the OEB range.

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 airborne exposures are within or exceed the Occupational Exposure Band (OEB) range, wear an appropriate respirator with a protection factor sufficient to control exposures to the bottom of the OEB range.

9. PHYSICAL AND CHEMICAL PROPERTIES:

<table>
<thead>
<tr>
<th>Physical State:</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula:</td>
<td>Mixture</td>
</tr>
<tr>
<td>Color:</td>
<td>White</td>
</tr>
<tr>
<td>Molecular Weight:</td>
<td>Mixture</td>
</tr>
</tbody>
</table>

10. STABILITY AND REACTIVITY

Stability: Stable at normal conditions

Conditions to Avoid: None known

Incompatible Materials: As a precautionary measure, keep away from strong oxidizers.

11. TOXICOLOGICAL INFORMATION

General Information: The information included in this section describes the potential hazards of the individual ingredients.

Acute Toxicity: (Species, Route, End Point, Dose)
<table>
<thead>
<tr>
<th>Material Name</th>
<th>Route</th>
<th>LOAEL/LOEL</th>
<th>Duration</th>
<th>Species</th>
<th>LOAEL/LOEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Oral</td>
<td>LD 50</td>
<td>53-77 mg/kg</td>
<td>Rat</td>
<td>None identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Oral</td>
<td>LD 50</td>
<td>81 mg/kg</td>
<td>Rat</td>
<td>&gt; 1.43 mg/L</td>
</tr>
<tr>
<td></td>
<td>Inhalation</td>
<td>LC 50</td>
<td>&gt; 1.43 mg/L</td>
<td>Mouse</td>
<td>27 mg/kg</td>
</tr>
<tr>
<td>Talc (non-asbestiform)</td>
<td>Oral</td>
<td>LD50</td>
<td>&gt; 1600 mg/kg</td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>Oral</td>
<td>LD 50</td>
<td>29700 mg/kg</td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Oral</td>
<td>LD50</td>
<td>&gt; 2000 mg/kg</td>
<td>Rat</td>
<td>&gt; 2000 mg/m²</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Oral</td>
<td>LD50</td>
<td>&gt; 5000 mg/kg</td>
<td>Rabbit</td>
<td>&gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Dermal</td>
<td>LD50</td>
<td>&gt; 2000 mg/kg</td>
<td>Rabbit</td>
<td></td>
</tr>
<tr>
<td>Hypermellose</td>
<td>Oral</td>
<td>LD50</td>
<td>&gt; 10,000 mg/kg</td>
<td>Rat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Toxicity Comments:</td>
<td>A greater than symbol (&gt;) indicates that the toxicity endpoint being tested was not achievable at the highest dose used in the test.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Material Name</th>
<th>Route</th>
<th>LOAEL/LOEL</th>
<th>Duration</th>
<th>Species</th>
<th>LOAEL/LOEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Skin Irritation</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye Irritation</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Skin Irritation</td>
<td>Rabbit</td>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Skin Irritation</td>
<td>Rabbit</td>
<td>Non-irritating</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eye Irritation</td>
<td>Rabbit</td>
<td>Non-irritating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Material Name</th>
<th>Route</th>
<th>LOAEL/LOEL</th>
<th>Duration</th>
<th>Species</th>
<th>LOAEL/LOEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Oral</td>
<td>14 mg/kg</td>
<td>30 Day(s)</td>
<td>Rat</td>
<td>LOAEL *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None identified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Intravenous</td>
<td>10 µg/kg/day</td>
<td>4 Week(s)</td>
<td>Dog</td>
<td>LOEL *</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>120 µg/kg/day</td>
<td>13 Week(s)</td>
<td>Rat</td>
<td>LOEL *</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>30 µg/kg/day</td>
<td>13 Week(s)</td>
<td>Dog</td>
<td>LOEL *</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>160 µg/kg/day</td>
<td>1 Year(s)</td>
<td>Rat</td>
<td>LOEL *</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>30 µg/kg/day</td>
<td>1 Year(s)</td>
<td>Dog</td>
<td>LOEL *</td>
</tr>
</tbody>
</table>
Reproduction & Developmental Toxicity: (Study Type, Species, Route, Dose, End Point, Effect(s))

Diclofenac Sodium
- Embryo / Fetal Development: Rat (Oral 24 mg/kg) LOAEL Maternal toxicity, Fetotoxicity
- Embryo / Fetal Development: Rat (1 mg/kg) LOAEL Developmental toxicity
- Embryo / Fetal Development: Rat (No route specified 20 mg/kg/day) NOEL Not Teratogenic
- Embryo / Fetal Development: Rabbit (No route specified 10 mg/kg/day) NOEL Not Teratogenic

Misoprostol
- Reproductive & Fertility: Rat (Oral 10 mg/kg/day) LOAEL Fertility
- Embryo / Fetal Development: Rabbit (Oral 1 mg/kg/day) LOAEL Embryotoxicity
- Embryo / Fetal Development: Mouse (Oral 30 mg/kg) LOAEL Embryotoxicity
- Embryo / Fetal Development: Rabbit (Oral 1 mg/kg/day) NOAEL Not Teratogenic
- Embryo / Fetal Development: Rabbit (Oral 10 mg/kg/day) NOAEL Not Teratogenic

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

Diclofenac Sodium
- Bacterial Mutagenicity (Ames) Salmonella Negative

Misoprostol
- Bacterial Mutagenicity (Ames) Salmonella Negative
- In Vitro Mouse Lymphoma Negative
- Sister Chromatid Exchange Negative

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

Diclofenac Sodium
- Not specified: Rat (Oral 2 mg/kg/day) NOEL Not carcinogenic

Misoprostol
- 21 Month(s): Mouse (Oral 16 mg/kg/day) NOAEL Not carcinogenic
- 24 Month(s): Rat (Oral 2.4 mg/kg/day) NOAEL Not carcinogenic

Carcinogen Status: None of the components of this formulation are listed as a carcinogen by IARC, NTP or OSHA. See below

Povidone
- IARC: Group 3

Crospovidone
- IARC: Group 3

Talc (non-asbestiform)
- IARC: Group 3

Silicon dioxide, colloidal NF
- IARC: Group 3

12. ECOLOGICAL INFORMATION
Environmental Overview: May have harmful effects on the aquatic environment. Releases to the environment should be avoided. This formulation has not been tested as a whole, the following apply to component substance(s):

Aquatic Toxicity: (Species, Method, End Point, Duration, Result)

**Diclofenac Sodium**
- Rainbow Trout EC-50 96 Hours 130.6 mg/L
- Daphnia EC-50 48 Hours 103.5 mg/L
- Skeletonema Algae EC-50 48 Hours 42 mg/L
- Skeletonema Algae EC-50 72 Hours 100 mg/L

**Misoprostol**
- Daphnia LC-50 48 Hours > 932.5 mg/L
- Rainbow Trout LC-50 72 Hours > 26.4 mg/L
- Skeletonema Algae EC-50 72 Hours > 104 mg/L
- Skeletonema Algae NOEC 26.5 mg/L

Aquatic Toxicity Comments: A greater than (>) symbol indicates that acute ecotoxicity was not observed at the maximum solubility. Since the substance is insoluble in aqueous solutions above this concentration, an acute ecotoxicity value (i.e. LC/EC50) is not achievable.

**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:** T
- **EU Indication of danger:** Harmful
  - Toxic to Reproduction: Category 2
- **EU Risk Phrases:**
  - R22 - Harmful if swallowed.
  - R61 - May cause harm to the unborn child.
- **EU Safety Phrases:**
  - S53 - Avoid exposure - obtain special instructions before use.

**OSHA Label:**
WARNING
Causes eye irritation.
Causes skin irritation.
Harmful if swallowed.
May cause damage to: blood and blood forming organs, liver, heart, gastrointestinal system through prolonged or repeated exposure.
Suspected of damaging the unborn child.
May cause allergic reaction in aspirin-sensitive individuals

**Canada - WHMIS: Classifications**

**WHMIS hazard class:**
Class D, Division 1, Subdivision B
Class D, Division 2, Subdivision A

**Diclofenac Sodium**
Australia (AICS): Present
EU EINECS List 239-346-4

**Misoprostol**
California Proposition 65 developmental toxicity, initial date 4/1/90
Standard for the Uniform Scheduling for Drugs and Poisons: Schedule 4

**Talc (non-asbestiform)**
Inventory - United States TSCA - Sect. 8(b) Present
Australia (AICS): Present
EU EINECS List 238-877-9

**Hypromellose**
Inventory - United States TSCA - Sect. 8(b) XU
Australia (AICS): Present
EU EINECS List 232-679-6

**Povidone**
Inventory - United States TSCA - Sect. 8(b) XU
Australia (AICS): Present

**Corn Starch**
Inventory - United States TSCA - Sect. 8(b) XU
Australia (AICS): Present
EU EINECS List 232-679-6

**Crospovidone**
Inventory - United States TSCA - Sect. 8(b) XU
Australia (AICS): Present

**Lactose Monohydrate**
Australia (AICS): Present

**Triethyl Citrate**
Inventory - United States TSCA - Sect. 8(b) Present
Australia (AICS): Present
EU EINECS List 201-070-7

Hydrogenated castor oil
- Inventory - United States TSCA - Sect. 8(b): Present
- Australia (AICS): Present
- EU EINECS List 232-292-2

Silicon dioxide, colloidal NF
- Inventory - United States TSCA - Sect. 8(b): Present
- Australia (AICS): Present
- EU EINECS List 232-674-9

Magnesium stearate
- Inventory - United States TSCA - Sect. 8(b): Present
- Australia (AICS): Present
- EU EINECS List 209-150-3

Microcrystalline cellulose
- Inventory - United States TSCA - Sect. 8(b): XU
- Australia (AICS): Present
- EU EINECS List 232-674-9

16. OTHER INFORMATION

Reasons for Revision: Updated Section 3 - Hazard Identification. Updated Section 11 - Toxicology Information.

Prepared by: Corporate Occupational Toxicology & Hazard Assessment

Pfizer Inc believes that the information contained in this Material Safety Data Sheet is accurate, and while it is provided in good faith, it is without warranty of any kind, expressed or implied.

End of Safety Data Sheet