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

Pfizer Inc
Pfizer Pharmaceuticals Group
235 East 42nd Street
New York, New York 10017
1-212-573-2222

Pfizer Ltd
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom
+00 44 (0)1304 616161

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

Material Name: Estrostep® - 1/20, 1/30, and 1/35 Tablets (Norethindrone Acetate and Ethinyl Estradiol Tablets, USP)

Trade Name: Estrostep(R)
Chemical Family: Mixture
Intended Use: Pharmaceutical product used as oral contraceptive

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>Norethindrone Acetate</td>
<td>51-98-9</td>
<td>200-132-0</td>
<td>1.43</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>57-63-6</td>
<td>200-342-2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Calcium stearate</td>
<td>1592-23-0</td>
<td>216-472-8</td>
<td>*</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>9005-25-8</td>
<td>232-679-6</td>
<td>*</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>9004-34-6</td>
<td>232-674-9</td>
<td>*</td>
</tr>
<tr>
<td>Lactose NF, monohydrate</td>
<td>64044-51-5</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 triangular tablets - 1/20  White square tablets - 1/30  White round tablets - 1/35
Signal Word: CAUTION

Statement of Hazard: Carcinogen
May cause reproductive system effects
May cause harm to the unborn child.

Additional Hazard Information:
Short Term: Dust may be absorbed through the skin and cause systemic effects. Accidental ingestion may cause effects similar to those seen in clinical use.

Long Term: Occupational exposure to components of this mixture has resulted in menstrual irregularities in women and breast changes (enlargement, mammary secretions), loss of libido, and changes in sex hormone levels in men.
Known Clinical Effects: The use of oral contraceptives is associated with increased risks of myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease. The most common adverse effects seen during clinical use of oral contraceptives are menstrual irregularities.

EU Indication of danger: Carcinogenic: Category 1
Toxic to reproduction: Category 1

EU Hazard Symbols:

EU Risk Phrases:
R45 - May cause cancer.
R60 - May impair fertility.
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 product or its ingredients 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: 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. If irritation occurs or persists, get medical attention.

Ingestion: Get medical attention. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

Inhalation: Remove to fresh air. If not breathing, give artificial respiration. Get medical attention.

5. FIRE FIGHTING MEASURES

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

Hazardous Combustion Products: No data available

Fire Fighting Procedures: Wear approved positive pressure, self-contained breathing apparatus and full protective turn out gear.

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. Minimize dust generation and accumulation. Use only in a well-ventilated area.

Storage Conditions: Store in a cool, dry, well-ventilated area.

Storage Temperature: Store below 30°C

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Norethindrone Acetate
Pfizer OEL TWA-8 Hr: 0.8 ug/m³, Skin

Ethinyl Estradiol
Pfizer OEL TWA-8 Hr: 40 ng/m³, Skin

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

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

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.


Engineering Controls: Engineering controls should be used as the primary means to control exposures. Keep airborne contamination levels below the exposure limits listed above in this section.

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: Tablet
Molecular Formula: Mixture
Color: White
Molecular Weight: Mixture

10. STABILITY AND REACTIVITY

Stability: Stable under normal conditions of use.
Conditions to Avoid: None known
Incompatible Materials: None known
Hazardous Decomposition Products: None known

11. TOXICOLOGICAL INFORMATION

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

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

Norethindrone Acetate
Rat Oral LD50 > 5010 mg/kg
Mouse Oral LD50 > 5010 mg/kg

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

Ethyl Estradiol
Mouse Oral LD50 1737 mg/kg
Rat Oral LD50 1200 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
Eye Irritation / Sensitization No data available
Skin Irritation / Sensitization No data available
Chronic Effects/Carcinogenicity

The combination of ethinyl estradiol and norethindrone acetate was tested for carcinogenicity in mice, rats, and monkeys. Mice exhibited pituitary tumors. Rats developed mammary and benign liver-cell tumors along with endometrial carcinomas, hyperplastic nodules of the liver, and hepatocellular carcinoma. Monkeys treated for 10 years did not develop malignant tumors. There is significant evidence that combined oral contraceptives cause benign and malignant liver tumors in humans.

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

Norethindrone Acetate

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo / Fetal Development</td>
<td>Rat</td>
<td>No route specified</td>
<td>1 mg/kg/day</td>
<td>LOEL Teratogenic</td>
</tr>
<tr>
<td>Embryo / Fetal Development</td>
<td>Mouse</td>
<td>No route specified</td>
<td>0.5 mg/kg/day</td>
<td>LOEL Teratogenic</td>
</tr>
<tr>
<td>Embryo / Fetal Development</td>
<td>Rat</td>
<td>No route specified</td>
<td>3.5 mg/kg/day</td>
<td>NOAEL Not Teratogenic</td>
</tr>
</tbody>
</table>

Ethinyl Estradiol

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo / Fetal Development</td>
<td>Mouse</td>
<td>No route specified</td>
<td>0.02 mg/kg/day</td>
<td>LOEL Embryotoxicity Not teratogenic</td>
</tr>
</tbody>
</table>

Reproductive Effects

This product is an oral contraceptive and as such, may adversely effect fertility. Reproductive toxicity has been reported in male animals exposed to estradiol. Effects included a decrease in testicular size and a reduction in testosterone levels. Norethindrone acetate has been shown to effectively inhibit ovulation in rats.

Teratogenicity

Rhesus monkeys given norethindrone acetate and ethinyl estradiol in combination exhibited embryo lethality and virilization of female offspring. There are conflicting reports concerning the ability of oral contraceptives to cause genital anomalies in exposed human fetuses.

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

Norethindrone Acetate

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Organism</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Mutagenicity (Ames)</td>
<td>Salmonella</td>
<td>Negative</td>
</tr>
<tr>
<td>In Vitro Chromosome Aberration</td>
<td>Human Lymphocytes</td>
<td>Positive</td>
</tr>
<tr>
<td>In Vitro Sister Chromatid Exchange</td>
<td>Human Lymphocytes</td>
<td>Negative</td>
</tr>
<tr>
<td>In Vivo Unscheduled DNA Synthesis</td>
<td>Rat Hepatocyte</td>
<td>Positive</td>
</tr>
<tr>
<td>In Vivo Direct DNA Damage</td>
<td>Mouse Bone Marrow</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Ethinyl Estradiol

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Organism</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Mutagenicity (Ames)</td>
<td>Salmonella</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromosome Aberration</td>
<td>Human Lymphocytes</td>
<td>Positive</td>
</tr>
<tr>
<td>Sister Chromatid Exchange</td>
<td>Human Lymphocytes</td>
<td>Positive</td>
</tr>
<tr>
<td>Chromosome Aberration</td>
<td>Chinese Hamster Ovary (CHO) cells</td>
<td>Positive</td>
</tr>
<tr>
<td>In Vivo Micronucleus</td>
<td>Mouse Bone Marrow</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Mutagenicity

Genotoxicity testing results indicate that EE and NA do not directly interact with DNA but that they may produce non-specific chromosome damage.

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

Norethindrone Acetate

<table>
<thead>
<tr>
<th>Duration</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Year(s)</td>
<td>Male Rat</td>
<td>Oral</td>
<td>3-4 mg/kg/day</td>
<td>LOEL Malignant tumors, Liver</td>
</tr>
<tr>
<td>2 Year(s)</td>
<td>Female Rat</td>
<td>Oral</td>
<td>3-4 mg/kg/day</td>
<td>LOEL Tumors, Female reproductive system</td>
</tr>
<tr>
<td>104 Week(s)</td>
<td>Male Rat</td>
<td>Intramuscular</td>
<td>10 mg/kg/day</td>
<td>LOEL Malignant tumors, Mammary gland, Liver, Endocrine system</td>
</tr>
<tr>
<td>104 Week(s)</td>
<td>Female Rat</td>
<td>Intramuscular</td>
<td>10 mg/kg/day</td>
<td>LOEL Malignant tumors, Liver, Mammary gland</td>
</tr>
</tbody>
</table>

Ethinyl Estradiol

<table>
<thead>
<tr>
<th>Duration</th>
<th>Species</th>
<th>Route</th>
<th>Dose</th>
<th>Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 Week(s)</td>
<td>Mouse</td>
<td>Oral, in feed</td>
<td>0.07 mg/kg/day</td>
<td>LOEL Tumors, Pituitary gland</td>
</tr>
<tr>
<td>104 Week(s)</td>
<td>Rat</td>
<td>No route specified</td>
<td>0.07 mg/kg/day</td>
<td>LOEL Malignant tumors, Liver</td>
</tr>
<tr>
<td>105 Week(s)</td>
<td>Rat</td>
<td>Oral, in feed</td>
<td>0.053 mg/kg/day</td>
<td>NOEL Not carcinogenic</td>
</tr>
</tbody>
</table>
Carcinogen Status: See below

Norethindrone Acetate
- **IARC:** Group 2B
- **NTP:** Listed
- **OSHA:** Present

Ethinyl Estradiol
- **IARC:** Group 1
- **NTP:** Listed
- **OSHA:** Present

At increase risk from exposure: Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use.

Additional Information: Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk.

### 12. ECOLOGICAL INFORMATION

Environmental Overview: The environmental characteristics of this material have not been fully evaluated. 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:** T
**EU Indication of danger:**
- Carcinogenic: Category 1
- Toxic to reproduction: Category 1

**EU Risk Phrases:**
- R45 - May cause cancer.
- R60 - May impair fertility.
- R61 - May cause harm to the unborn child.

**EU Safety Phrases:**
S22 - Do not breathe dust.  
S36/37 - Wear suitable protective clothing and gloves.  
S53 - Avoid exposure - obtain special instructions before use.

**OSHA Label:**
CAUTION  
Carcinogen  
May cause reproductive system effects  
May cause harm to the unborn child.

**Canada - WHMIS: Classifications**

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

**Norethindrone Acetate**
- California Proposition 65: developmental toxicity, initial date 10/1/91  
- Australia (AICS): Present  
- EU EINECS List: 200-132-0

**Ethinyl Estradiol**
- California Proposition 65: carcinogen, initial date 1/1/88  
  developmental toxicity, initial date 4/1/90 (when mixed with Norethisterone)  
- Inventory - United States TSCA - Sect. 8(b): Present  
- Australia (AICS): Present  
- Standard for the Uniform Scheduling for Drugs and Poisons: Schedule 4  
- EU EINECS List: 200-342-2

**Calcium stearate**
- Inventory - United States TSCA - Sect. 8(b): Present  
- Australia (AICS): Present  
- EU EINECS List: 216-472-8

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

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

**Lactose NF, monohydrate**
- Australia (AICS): Present
16. OTHER INFORMATION

Reasons for Revision: 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. Updated Section 15 - Regulatory Information.

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

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End of Safety Data Sheet