1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: DEPO-ESTRADIOL® Sterile Solution
USE: Human drug used in the treatment of various symptoms associated with menopause or female hypogonadism.
MANUFACTURER/SUPPLIER:
THE UPJOHN COMPANY
7171 PORTAGE RD.
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS:
(616) 323-5122 (24 Hours)
(616) 323-7555 (8:00 AM – 4:30 PM)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: Cottonseed Oil.
% BY WEIGHT: 98% (approximately)
CAS NUMBER: 8001-29-4
EXPOSURE LIMIT(S): Not established.

INGREDIENT 2
COMMON NAME: Chlorobutanol.
% BY WEIGHT: <1%
CAS NUMBER: 57-15-8
EXPOSURE LIMIT(S): Not established.

INGREDIENT 3
COMMON NAME: Estradiol Cypionate.
CHEMICAL NAME: Estra-1,-3,5(10)-triene-3,17-diol (17β)-, 17-cyclopentanepropanoate
% BY WEIGHT: <1%
CAS NUMBER: 313-06-4
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 0.05 $\mu g/m^3$
UPJOHN EXPOSURE LIMIT-STEL: 0.15 $\mu g/m^3$

EXPOSURE LIMIT(S) FOR THE MATERIAL: Not established.

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation.
EFFECTS OF OVEREXPOSURE: The active ingredient, estradiol cypionate, is an oil soluble ester of estradiol. Estradiol is a naturally occurring hormone secreted principally by the ovaries, adrenals, corpus luteum, placenta and testes. It is the most potent of the naturally occurring estrogens. Estrogens are essential hormones responsible for the normal growth and development of the female sex organs and for maintenance of secondary sex characteristics. Extremely small amounts of this material are physiologically active and enough material can be absorbed through the skin or by the respiratory tract to produce effects. Females may experience irregular vaginal bleeding, breast changes including tenderness, enlargement and secretion. In males, manifestations of overexposure include breast enlargement, loss of libido and testicular shrinking. Adverse effects may also include dizziness, nausea, vomiting, abdominal cramps, anorexia, migraine headaches, mental depression, diarrhea, changes in libido, hypertension and skin hyperpigmentation (particularly face and

3. HAZARDS IDENTIFICATION, Con't

nipples). Ocular curvature changes may cause discomfort to those who wear contact lenses. High estrogen dosages have been shown to increase the risk of thromboembolic disorders, liver tumors and gallbladder disease with predisposition to gallstone formation. Estrogens have a weak anabolic effect and may cause sodium retention with associated fluid retention (bloating) and edema. Estrogens affect bone by increasing calcium deposition and concentration in the blood. Symptoms are generally reversible after cessation of exposure. The primary ingredient, cottonseed oil, may be harmful when inhaled, ingested or in contact with skin and by causing eye or skin irritation.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Estradiol cypionate is contraindicated in persons with serious liver, kidney or heart diseases, undiagnosed abnormal genital bleeding, existing thromboembolic disease, mammary or uterine carcinoma or a strong family history of the same (or abnormal mammographic findings), and known or suspected pregnancy.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.
SKIN: Wash with soap and water. Remove contaminated clothing.
INHALATION: Remove from exposure.
INGESTION: Contact a physician or poison control center.

5. FIRE FIGHTING MEASURES

FLASH POINT: Nonflammable.
LOWER EXPLOSION LIMIT (LEL): Not applicable.
UPPER EXPLOSION LIMIT (UEL): Not applicable.
EXTINGUISHING MEDIA: Water, carbon dioxide dry chemical, or polymer foam.
FIRE FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full-body protective equipment.
UNUSUAL FIRE OR EXPLOSION HAZARDS: None.
HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide. Carbon dioxide.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Provide ventilation and respiratory, skin and eye protection to prevent overexposure. Keep the product out of drains; prevent entry to surface water, groundwater and soil. Small spills should be absorbed with paper towels or other appropriate media. Large spills can be vacuumed or scooped and placed in a suitable container. As treatment with bleach substantially reduces the estrogenic potency, wash the spill site with bleach when material pickup is complete.

7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: Avoid contact with skin, eyes and clothing. Wash thoroughly after handling. Launder contaminated clothes before reuse. Store in a cool, dry place and protect from light. Keep out of the reach of children.

8. EXPOSURE CONTROLS/ PERSONAL PROTECTION

RESPIRATORY PROTECTION: Not required.
VENTILATION: Local exhaust.
PROTECTIVE GLOVES: Rubber.
EYE PROTECTION: Safety glasses with side shields.
OTHER PROTECTIVE EQUIPMENT: Protective covering for exposed areas of skin.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: Pale-yellow clear liquid in 5- or 10-mL vials.
MOLECULAR WEIGHT: Mixture.
SOLUBILITY IN WATER: No information found.

10. STABILITY AND REACTIVITY

STABILITY: Stable.
PHYSICAL CONDITIONS TO AVOID: Sensitive to light, strong oxidizing agents, and heat (cottonseed oil).
INCOMPATIBILITY WITH OTHER MATERIALS: None.
HAZARDOUS DECOMPOSITION PRODUCTS: None.
HAZARDOUS POLYMERIZATION: Does not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:

ACUTE TOXICITY: Lowest dose to induce toxic effect—rat, subcutaneous: 25 µg/kg; rat, intramuscular: 1.2 mg/kg; mouse, subcutaneous: 40 µg/kg; rabbit, oral: 300 µg/kg; rabbit, subcutaneous: 50 µg/kg; rabbit, intramuscular: 12.5 µg/kg; pig, intramuscular: 33 µg/kg; hamster, oral: 24 mg/kg; hamster, subcutaneous: 200 µg/kg.

INTRAPERITONEAL LD50 (MOUSE): >1 g/kg (estradiol cypionate).

SUBCUTANEOUS LD50 (MOUSE): >1 g/kg (estradiol cypionate).

OTHER STUDIES: Oral or intramuscular treatment of female dogs with estradiol cypionate (treatment levels of 44 µg/kg) caused an increase in the incidence of pyometra (uterine infection) and a tendency for the development of aplastic anemia.

GENOTOXICITY: Mutagenicity: estradiol was negative in the DNA damage/alkaline elution assay and induced no mutation in Chinese hamster V79 cells, no chromosome anomalies in mouse bone marrow cells *in vivo* or in human lymphocytes *in vitro*.

TERATOGENICITY: Pregnant women should avoid exposure to estrogens, particularly during the first trimester when the fetal reproductive tract is developing and may be affected by external estrogens. Several reports suggest an association between intrauterine exposure to estrogens and birth defects. Estradiol has been shown to cause birth defects in animal models. An association has been reported between *in utero* exposure of the female fetus to diethylstilbesterol and increased risk of the postpubertal development of an ordinarily extremely rare form of vaginal or cervical cancer. Although similar data is not available on the use of other estrogens, it cannot be presumed they would not induce similar changes.

CARCINOGENICITY: Long-term estrogen treatment increases the frequency of certain benign or malignant tumors such as those of the breast, uterus, cervix, vagina, ovary, liver and pituitary in certain animal species. Studies in postmenopausal women indicate that continuous estrogen monotherapy may lead, depending on the dose and duration, to an increased risk of uterine cancer. Estrogens have been reported to be associated with mammary cancer in the male, and so, exposed males should have regular breast examinations. Estradiol, a structurally related analog, is listed by IARC as a Group 2B carcinogen (sufficient evidence for carcinogenicity to animals). Information on the toxicity of cottonseed oil pertains to concentration much higher than those normally found in therapeutic compounds.

12. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

13. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

14. OTHER INFORMATION

REVIEWED BY: Health and Safety Regulatory Affairs.
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15. LABELING

This drug is subject to FDA labeling requirements; therefore, it is exempt from the labeling requirements of the OSHA Hazard Communication Standard.

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