FLUTAMIDE BULK PRODUCT FORMULATION

MERCK

Revised: 12/27/2011

MSDS | **Material Safety Data Sheet**

MSD is a tradename of Merck & Co., Inc., with headquarters in Whitehouse Station, N.J., U.S.A.

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MATERIAL SAFETY DATA SHEET

Merck urges each user or recipient of this MSDS to read the entire data sheet to become aware of the hazards associated with this material.

SECTION1. IDENTIFICATION OF SUBSTANCE AND CONTACT INFORMATION

MSDS NAME: **Flutamide Bulk Product Formulation**

SYNONYM(S):
Flutamide Bulk Product Formulation
Eulexin Capsules
Eulexin Tablets
Drogenil Tablets
Drogenil Tabletas
Eulexin Capsulas
Eulexin Compresse
Eulexin Comprimidos
Eulexin Tabletas
Eulexin Tabletten
Eulexine Comprimes
Euflex Tablets
Flucinom Tablets
Flucinom Tabletten
Fugerel Tablets
Fugerel Tabletten
Odyne

MSDS NUMBER: SP000244

EMERGENCY NUMBER(S): Schering-Plough Security Control Center (908) 820-6921 (24 Hours)

Transportation Emergencies - SETIQ:
01 800 00 214 00 (Toll free in Mexico City)
55 59 15 88 (Toll outside of Mexico City)

INFORMATION: +52 (55) 57 28 44 44 (Xochimico Mexico)

MERCK SDS HELPLINE: +1 (908) 473-3371 (Worldwide)
Monday to Friday, 9am to 5pm (US Eastern Time)

SECTION 2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Color according to product specification
Powder
Odor unknown
May be harmful by inhalation or if swallowed.
May be irritating to respiratory system.
Prolonged exposure may cause serious health effects.
May cause reproductive effects.
May cause developmental effects.
May cause effects to:
endocrine system
liver
male reproductive system
fetus
May cause long-term adverse effects in the aquatic environment.

EU CLASSIFICATION(S): Repr.Cat.2;R60

POTENTIAL HEALTH EFFECTS:

The following summary is based upon available information about the individual ingredients of the mixture, or of the expected properties of the mixture. Only information about the ingredients that are expected to contribute significantly to the potential health hazard profile of the formulation(s) are presented.

Flutamide is a nonsteroidal, orally active antiandrogen. Adverse effects reported during clinical therapy include breast enlargement and tenderness, gastrointestinal effects, tiredness, transient abnormal liver function, reduced sperm counts, and central nervous system effects. In animal studies, there was no indication that flutamide was secreted in breast milk.

Lactose is not expected to produce significant toxicity with workplace exposure. Lactose may cause irritation to the eyes, skin, and mucous membranes from mechanical action. Lactose may cause abdominal pain, bloating and diarrhea if ingested in large amounts or in lactose-intolerant individuals. Lactose may cause allergic reactions in sensitive individuals.

High concentrations of microcrystalline cellulose may produce respiratory tract irritation.

Corn starch is a mild skin irritant and may cause dermatitis with chronic skin exposure. Inhalation of corn starch may aggravate pre-existing lung conditions. Corn starch may cause mechanical irritation to the eye and respiratory tract.

LISTED CARCINOGENS

SECTION 3. COMPOSITION AND INFORMATION ON INGREDIENTS

PRODUCT USE: Drug product

CHEMICAL FORMULA: Mixture.

The formulations for these products are proprietary information. These formulations have the same hazardous profile; however, the presence of hazardous ingredients may vary by formulation. Only hazardous ingredients in concentrations of 1% or greater and/or carcinogenic ingredients in concentrations of 0.1% or greater are listed in the Chemical Composition table. Active ingredients in any concentration are listed. For additional information about carcinogenic ingredients see Section 2.

CHEMICAL COMPOSITION

INGREDIENT	CAS NUMBER	EC NUMBER	EU CLASSIFICATION	PERCENT
Flutamide	13311-84-7	236-341-9	Repr. Cat.2;R60-61 Xn;R48/22 R53	21-25
Lactose Monohydrate	64044-51-5	200-559-2		20-60

INGREDIENT	CAS NUMBER	EC NUMBER	EU CLASSIFICATION	PERCENT
Starch	9005-25-8	232-679-6	Not Classifed	10-20
Microcrystalline cellulose	9004-34-6	232-674-9		10-20
Povidone	9003-39-8			< 10
Sodium Lauryl Sulfate	151-21-3	205-788-1		< 10

ADDITIONAL INFORMATION: This MSDS is written to provide health and safety information for individuals who will be handling the final product formulation during research, manufacturing, and distribution. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate MSDS for each ingredient. Refer to the package insert or product label for handling guidance for the consumer.

See section 15 for EU hazard classification symbols and risk and safety phrases.

SECTION 4. FIRST AID MEASURES

INHALATION: Remove to fresh air. If any trouble breathing, get immediate medical attention. Administer artificial respiration if breathing has ceased. If irritation or symptoms occur or persist, consult a physician.

SKIN CONTACT: In case of skin contact, while wearing protective gloves, carefully remove any contaminated clothing, including shoes, and wash skin thoroughly with soap and water. If irritation or symptoms occur or persist, consult a physician.

EYE CONTACT: In case of eye contact, immediately rinse eyes thoroughly with plenty of water. If wearing contact lenses, remove only after initial rinse, and continue rinsing eyes for at least 15 minutes. If irritation occurs or persists, consult a physician.

INGESTION: Rinse mouth and drink a glass of water. Do not induce vomiting unless under the direction of a qualified medical professional or Poison Control Center. If symptoms persist, consult a physician.

SECTION 5. FIRE FIGHTING MEASURES

FLAMMABILITY DATA:

Flash Point: Not determined (liquids) or not applicable (solids).

EXPLOSION HAZARDS:
Under normal conditions of use, this material does not present a significant fire or explosion hazard. However, like most organic compounds, this material may present a dust deflagration hazard if sufficient quantities are suspended in air. This hazard may exist where sufficient quantities of finely divided material are (or may become) suspended in air during typical process operations. An assessment of each operation should be conducted and suitable deflagration prevention and protection techniques employed. The sensitivity of this material to ignition by electrostatic discharges has not been determined. In the absence of testing data, all conductive plant items and operations personnel handling this material should be suitably grounded.

SPECIAL FIRE FIGHTING PROCEDURES:
Wear full protective clothing and self-contained breathing apparatus (SCBA).

SUITABLE EXTINGUISHING MEDIA:
Carbon dioxide (CO2), extinguishing powder or water spray.

See Section 9 for Physical and Chemical Properties.

SECTION 6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS:
Avoid generation of dust during clean-up. Wear appropriate personal protective equipment as specified in Section 8. Keep personnel away from the clean-up area.

SPILL RESPONSE / CLEANUP:
All spills should be handled according to site requirements and based on precautions cited in the MSDS. In the case of liquids, use proper absorbent materials. For laboratories and small-scale operations, incidental spills within a hood or enclosure should be cleaned by using a HEPA filtered vacuum or wet cleaning methods as appropriate. For large dry or liquid spills or those spills outside enclosure or hood, appropriate emergency response personnel should be notified. In manufacturing and large-scale operations, HEPA vacuuming prior to wet mopping or cleaning is required.

See Sections 9 and 10 for additional physical, chemical, and hazard information.

SECTION 7. HANDLING AND STORAGE

HANDLING:
Keep containers adequately sealed during material transfer, transport, or when not in use. Wash face, hands, and any exposed skin after handling. Do not eat, drink, or smoke when using this substance or mixture.

Appropriate handling of this material is dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. See Section 8 (Exposure Controls) for additional guidance.

STORAGE:
Store in a cool, dry, well ventilated area.

See Section 8 for exposure controls and additional safe handling information.

SECTION 8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

The following guidance applies to the handling of the active ingredient(s) in this formulation.

OCCUPATIONAL EXPOSURE BAND (OEB):
OEB 5: <1 mcg/m^3. Materials in an OEB 5 category are considered extreme health hazards. The OEB is a range of airborne concentrations expressed as an 8-hour Time Weighted Average (8-hr. TWA) and is intended to be used with Industrial Hygiene Risk Assessment to assist with industrial hygiene sampling and selection of proper controls for worker protection. Consult your site safety and industrial hygiene staff for guidance on handling and control strategies.

EXPOSURE CONTROLS
The health hazard risks of handling this material are dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. Exposure controls for normal operating or routine procedures follow a tiered strategy. Engineering controls are the preferred means of long-term or permanent exposure control. If engineering controls are not feasible, appropriate use of personal protective equipment (PPE) may be considered as alternative control measures. Exposure controls for non-routine operations must be evaluated and addressed as part of the site-specific risk assessment.

RECOMMENDED PERSONAL PROTECTIVE EQUIPMENT (PPE):

Respiratory Protection:	Respiratory protective equipment (RPE) may be required for certain laboratory and large-scale manufacturing tasks if potential airborne breathing zone concentrations of substances exceed the relevant exposure limit(s). Workplace risk assessment should be completed before specifying and implementing RPE usage. Potential exposure points and pathways, task duration and frequency, potential employee contact with the substance, and the ability of the substance to be rendered airborne during specific tasks should be evaluated. Initial and ongoing strategies of quantitative exposure measurement should be obtained as required by the workplace risk assessment. All RPE must conform to local and regional specifications for efficacy and performance. Consult your site or corporate health and safety professional for additional guidance.
Skin Protection:	Gloves that provide an appropriate barrier to the skin are recommended if there is potential for contact with this material. Consult your site safety staff for guidance.
Eye Protection:	Safety glasses with side shields. Use of goggles or full face protection may be required based on hazard, potential for contact, or level of exposure. Consult your site safety staff for guidance.
Body Protection:	In small-scale or laboratory operations, lab coats or equivalent protection is required. Disposable Tyvek or other dust impermeable suit should be considered based on procedure or level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance. In large-scale or manufacturing operations, disposable Tyvek or other dust impermeable suit is recommended and based on level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance.

EXPOSURE LIMIT VALUES:

INGREDIENT	CAS NUMBER	ACGIH TLV (TWA)	OSHA PEL (TWA)
Starch	9005-25-8	10 mg/m^3	15 mg/m^3
Microcrystalline cellulose	9004-34-6	10 mg/m^3	15 mg/m^3

Fields in the above table(s) that do not contain data indicate that exposure limits are not available for those endpoints.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

FORM: Powder
COLOR: Color according to product specification
ODOR: Odor unknown
SOLUBILITY:

Water: Not determined

See Section 5 for flammability/explosivity information.

SECTION 10. STABILITY AND REACTIVITY

STABILITY/ REACTIVITY:
Stable under normal conditions.

INCOMPATIBLE MATERIALS / CONDITIONS TO AVOID:
None known.

HAZARDOUS DECOMPOSITION PRODUCTS / REACTIONS:
No dangerous decomposition is expected if used according to manufacturer's specifications.

SECTION 11. TOXICOLOGICAL INFORMATION

The information presented below pertains to the following individual ingredients, and not to the mixture.

ACUTE TOXICITY DATA

INHALATION:
Flutamide: Mortality did not occur in rats exposed to 0.25 mg/L (maximum attainable concentration) for 4 hours. Decreased activity, prostration, or lacrimation were observed during exposure. Effects observed after exposure included lacrimation, nasal discharge, dry rales, anogenital staining, or dried red-brown material on the face or tail. Responses were observed throughout the 14-day observation period. Moderate weight losses were also noted several days after exposure; however, recovery of weight occurred over time. Discolored lungs, dilation of kidney pelvises, and enlarged lymph nodes were noted in histopathological examination.

Microcrystalline cellulose: Inhalation LC50 (4hr): >5.05 mg/L (rat)

SKIN:
Flutamide was slightly irritating to the skin of rabbits. The primary irritation index was 0.7.

Corn starch was practically not irritating to rabbits and rats.

Microcrystalline cellulose: Dermal LD50: >2000 mg/kg (rabbit)
Microcrystalline cellulose was not irritating to the skin of rabbits.

EYE:
Flutamide was slightly irritating to the eyes of rabbits.

ORAL:
Flutamide: Oral LD50: 2768.3-3258.1 mg/kg (rats); 1653.1 (male mice); 217.8-333.2 mg/kg (guinea pigs)
Common effects observed included hypoactivity, piloerection, slow respiration, ataxia, lethargy, hypothermia, or lacrimation. Death occurred within 72 hours in rats and mice, and within 7 days in guinea pigs. No abnormalities were noted at necropsy in any animal species.

Lactose: Oral LD50: > 10g/kg (rat)

Microcrystalline cellulose: Oral LD50: >5000 mg/kg (rat)

DERMAL AND RESPIRATORY SENSITIZATION:
Microcrystalline cellulose was not a skin sensitizer in guinea pigs.

REPEAT DOSE TOXICITY DATA

SUBCHRONIC / CHRONIC TOXICITY:
Chronic studies with flutamide were conducted in rats, dogs, mice and monkeys for periods ranging from 13 weeks to 4 years. Dose-related atrophy of the prostate gland and seminal vesicles was observed in male rats given 25 to 150 mg/kg/day for 13 weeks. Hypertrophy of the liver in both sexes was also observed in rats given 75 to 150 mg/kg/day. In dogs, cardiac lesions were observed at dosages of 25 to 40 mg/kg/day for 78 weeks to 4 years. Increases in liver weight and decreases in prostate weight were also observed at dosages of 10.5 mg/kg/day and higher for 78 weeks. Effects noted in mice given 50 to 400 mg/kg/day in the diet for 3 months included discolored urine, liver hypertrophy, decreased kidney weights in males, increased incidence of excessive fibrovascular stroma in male adrenal glands, decreased adrenal gland weights in females, increased spleen weights and splenic hemosiderosis in males, atrophy of the prostate gland, testicular interstitial cell hyperplasia, or decreases in epididymal weights. Decreased size of the prostate was observed in monkeys dosed with 30 to 90 mg/kg/day for 42 days.

REPRODUCTIVE / DEVELOPMENTAL TOXICITY:
Flutamide given to rats at doses of 25 and 75 mg/kg/day prior to mating did not affect estrous cycles or interfere with mating. Males given 150 mg/kg/day failed to mate; however, mating behaviors returned to normal after cessation of dosing. Conception rates were decreased in all dosage groups. Suppression of spermatogenesis was observed in rats dosed with 32 to 182 mg/kg/day for 52 weeks and in dogs dosed with 15 to 40 mg/kg/day for 78 weeks.

Survival rate decreases were noted in the offspring of rats given 30 to 200 mg flutamide/kg/day and of rabbits given 15 mg/kg/day. Minor variations in the development of the sternebrae and vertebrae and feminization of males were observed in fetuses of rats given 100 to 200 mg/kg/day.

Corn starch had no effect on reproduction in rats given 10% to 62% in the diet.

MUTAGENICITY / GENOTOXICITY:
Flutamide was negative in bacterial mutagenicity studies and in dominant lethal tests in rats.

CARCINOGENICITY:
Daily administration of flutamide to rats for 26 to 56 weeks at doses of 30, 90, or 180 mg/kg produced testicular interstitial cell adenomas at all doses. This is a normal biologic response to antiandrogenic activity in rats and appears to be a species-specific response. Mammary adenomas, adeno-carcinomas, and fibroadenomas were also increased in treated male rats. No evidence of carcinogenicity was observed in dogs given 15 to 40 mg/kg for 78 weeks, or in monkeys given 30 to 90 mg/kg for 42 days.

SECTION 12. ECOLOGICAL INFORMATION

There are no data for the final product or its formulation(s). The information presented below pertains to the following ingredient(s).

ECOTOXICITY DATA

INGREDIENT ECOTOXICITY

Microcrystalline cellulose: 96-hr LC50 (trout): >100% saturate solution
Microcrystalline cellulose: 48-hr LC50 (daphnid): >100% saturate solution
Microcrystalline cellulose: 96-hr EC50 (algae): >100% saturate solution

ENVIRONMENTAL DATA

OTHER INGREDIENT ENVIRONMENTAL DATA:

Flutamide: log Pow (log octanol/water partition coefficient): 3.34
Flutamide is not readily biodegradable.

SECTION 13. DISPOSAL CONSIDERATIONS

MATERIAL WASTE:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations. Incineration is the preferred method of disposal, when appropriate. Operations that involve the crushing or shredding of waste materials or returned goods must be handled to meet the recommended exposure limit(s).

PACKAGING AND CONTAINERS:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations.

SECTION 14. TRANSPORT INFORMATION

This material is not subject to the transportation regulations of DOT, IATA, IMO, and the ADR.

SECTION 15. REGULATORY INFORMATION

TSCA LISTING

INGREDIENT	TSCA
Lactose Monohydrate	X
Starch	X
Microcrystalline cellulose	X
Povidone	X
Sodium Lauryl Sulfate	X

EUROPEAN UNION REGULATIONS:

This product is not subject to classification.

Indication of Danger: T - Toxic.

Risk Phrases:
R60 - May impair fertility.
R61 - May cause harm to the unborn child.
R53 - May cause long-term adverse effects in the aquatic environment.
R48/22 - Harmful: danger of serious damage to health by prolonged exposure if swallowed.

Safety Phrases:
S45 - In case of accident or if you feel unwell, seek medical advice immediately (show label where possible).
S53 - Avoid exposure - obtain special instructions before use.

SECTION 16. OTHER INFORMATION

Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained therein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequence of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

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MSDS CREATION DATE: 15-Sep-1990
SUPERSEDES DATE: 11-Mar-2010

SIGNIFICANT CHANGES (LAM SUBFORMAT): New regional format, New Language (Latin-American Spanish), OEB