Letrozole

Section 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME
Letrozole

STATEMENT OF HAZARDOUS NATURE

NFPA

SUPPLIER
Company: Santa Cruz Biotechnology, Inc.
Address:
2145 Delaware Ave
Santa Cruz, CA 95060
Telephone: 800.457.3801 or 831.457.3800
Emergency Tel: CHEMWATCH: From within the US and Canada: 877-715-9305
Emergency Tel: From outside the US and Canada: +800 2436 2255 (1-800-CHEMCALL) or call +613 9573 3112

PRODUCT USE
Antineoplastic which suppresses oestrogen synthesis. Treatment of breast cancers. Also used to induce ovulation. Letrozole has also been used to treat endometriosis. Letrozole is an oral non-steroidal aromatase inhibitor that has been introduced for the adjuvant treatment of hormonally-responsive breast cancer. Estrogens are produced by the conversion of androgens through the activity of the aromatase enzyme. Letrozole blocks production of oestrogens in this way by competitive, reversible binding to the haeme of its cytochrome P450 unit. The action is specific, and letrozole does not reduce production of mineralo- or corticosteroids. In contrast, the antioestrogenic action of tamoxifen, the major medical therapy prior to the arrival of aromatase inhibitors, is due to its interfering with the estrogen receptor, rather than inhibiting estrogen production. Letrozole has also been shown to delay the fusing of the growth plates in adolescents. This may boost the effectiveness of growth hormone, and thus Letrozole is used to treat adolescents and children with short stature. Letrozole has shown to reduce estrogen levels by 98 percent while raising testosterone levels. The anti-estrogen action of letrozole is preferred by athletes and bodybuilders for use during a steroid cycle to reduce bloating due to excess water retention and prevent the formation of gynecomastia related breast tissue that is a side effect of some anabolic steroids. Use, above 5mg/day for extended periods, may cause kidney problems.

SYNONYMS
C17-H11-N5, "4, 4'-(1H-1, 2, 4-triazol-1-yl)methylene)bisbenzonitrile", "4, 4'-(1H-1, 2, 4-triazol-1-yl)methylene)bisbenzonitrile", "1-[bis(4-cyanophenyl)methyl]-1, 2, 4-triazole", "4-[1-(4-cyanophenyl)methyl]-1, 2, 4-triazole", "4-[1-(4-cyanophenyl)-1-1, 2, 4-triazol-1-yl)methyl]benzonitrile", "4-[1-(4-cyanophenyl)-1-1, 2, 4-triazol-1-yl)methyl]benzonitrile", CGS-20267, "letrazole (sic)", Femara, "fadrozole analogue", "nonsteroidal aromatase inhibitor", antineoplastic, "ovulation inducer"
Azole fungicides show a broad antifungal activity and are used either to prevent fungal infections or to cure an infection. Therefore, they are important tools in integrated agricultural production. According to their chemical structure, azole compounds are classified into triazoles and imidazoles; however, their antifungal activity is due to the same molecular mechanism. The cell membrane assembly of fungi and yeast is disturbed by blocking the synthesis of the essential membrane component ergosterol. This fundamental biochemical mechanism is the basis for the use ofazole fungicides in agriculture and in human and veterinary antimycotic therapies. The enzyme involved is sterol 14[alpha]-demethylase, which is found in several phyla. In mammals, it converts lanosterol into the meiosis-activating sterols (MAS) which regulate or modify cell division. These precursors of cholesterol have been discovered to moderate the development of male and female germ (sexual) cells. Several metabolites of lanosterol have been regarded only as precursors of cholesterol without any biological function in animals. This view dramatically changed recently with the observation that FF-MAS isolated from human follicle fluid and T-MAS isolated from bull testis as well as the MAS-412 and MAS-414 induced resumption of meiosis in cultivated mouse oocytes (Byskov et al. 1995).

Aromatase is another target enzyme of azole compounds. In steroidogenesis, it converts androgens into the corresponding oestrogens. Androgens or oestrogens for the development of reproductive organs, for fertility, and in certain sex steroid-dependent diseases is well known. Therefore, azole compounds can be directed against aromatase to treat oestrogen-responsive diseases. Based on the inhibitory activity of azoles on key enzymes involved in sex steroid hormone synthesis, it is likely that effects on fertility, sexual behavior, and reproductive organ development will occur depending on dose level and duration of treatment of laboratory animals. Several azole compounds were shown to inhibit the aromatase and to disturb the balance of androgens and estrogens in vivo. In fact, the clinical use of azole compounds in estrogen-dependent diseases is based on this effect. Additionally, azole antifungals developed to inhibit the sterol 14[alpha]-demethylase of fungi and yeast in agriculture and medicine are also inhibiting aromatase. Therefore, these antifungals may unintentionally disturb the balance of androgens and estrogens. Until now, it is not clear whether this effect is compensated by an increased expression of aromatase by other unknown mechanisms.

The broad use of biologically active compounds in human therapy as well as in nonhuman applications may involve some risks, as exemplified by emerging antibiotic resistance. In agriculture, fungi and yeast are well known to develop resistance to azoles, and some molecular mechanisms of resistance development have been described. The significance of the agricultural azole resistance for human clinical antimycotic therapies has been discussed in Europe, but it is not clarified yet. The actual target enzyme of azole antifungals, the fungal sterol 14[alpha]-demethylase, is expressed in many species including humans, and it is highly conserved through evolution. Hence, it seems reasonable to assume that most of the azole antifungals used in agriculture and medicine as well as azoles used in management of breast cancer also act as inhibitors in human sterol 14[alpha]-demethylase to an unknown extent. The toxicologic profiles of individual azole fungicides provide evidence for endocrine effects. In fact, many of these fungicides have effects on prostate, testis, uterus, and ovaries as well as on fertility, development, and sexual behavior. The current database does not allow us to establish causal relationships of these effects with inhibition of sterol 14[alpha]-demethylase and/or aromatase, but the overall view strongly suggests a connection with disturbed steroidogenesis.

Zam et al; Environmental Health Perspectives - 3/1/2003
Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. Extensive structural activity data from the family of triazole pesticides suggests that may induce hepatocellular adenomas in animal models. The significance of this finding in human carcinogenicity is equivocal.

**Section 3 - COMPOSITION / INFORMATION ON INGREDIENTS**

**HAZARD RATINGS**

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<th>Max</th>
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<tr>
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<tr>
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**NAME**

<table>
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<tr>
<th>letrozole</th>
<th>CAS RN</th>
<th>%</th>
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<tbody>
<tr>
<td></td>
<td>112809-51-5</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

**Section 4 - FIRST AID MEASURES**

**SWALLOWED**

- If swallowed do NOT induce vomiting.
- If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration.
- Observe the patient carefully.
- Never give liquid to a person showing signs of being sleepy or with reduced awareness; i.e. becoming unconscious.
- Give water to rinse out mouth, then provide liquid slowly and as much as casually can comfortably drink.
- Seek medical advice.

**EYE**

- If this product comes in contact with the eyes:
  - Wash out immediately with fresh running water.
  - Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.
  - If pain persists or recurs seek medical attention.
- Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.

**SKIN**

- If skin or hair contact occurs:
  - Flush skin and hair with running water (and soap if available).
  - Seek medical attention in event of irritation.

**INHALED**

- If fumes or combustion products are inhaled remove from contaminated area.
- Other measures are usually unnecessary.

**NOTES TO PHYSICIAN**

- Treat symptomatically.

**Section 5 - FIRE FIGHTING MEASURES**

<p>| | |</p>
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</tr>
<tr>
<td>Specific Gravity (water=1):</td>
<td>Not Available</td>
</tr>
<tr>
<td>Lower Explosive Limit (%):</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

**EXTINGUISHING MEDIA**

- Foam.
- Dry chemical powder.
- BCF (where regulations permit).
- Carbon dioxide.
- Water spray or fog - Large fires only.

**FIRE FIGHTING**

- Alert Emergency Responders and tell them location and nature of hazard.
- Wear breathing apparatus plus protective gloves.
- Prevent, by any means available, spillage from entering drains or water course.
- Use water delivered as a fine spray to control fire and cool adjacent area.
DO NOT approach containers suspected to be hot.
Cool fire exposed containers with water spray from a protected location.
If safe to do so, remove containers from path of fire.
Equipment should be thoroughly decontaminated after use.

GENERAL FIRE HAZARDS/HAZARDOUS COMBUSTIBLE PRODUCTS

- Combustible solid which burns but propagates flame with difficulty.
- Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust may burn rapidly and fiercely if ignited.
- Dry dust can be charged electrostatically by turbulence, pneumatic transport, pouring, in exhaust ducts and during transport.
- Build-up of electrostatic charge may be prevented by bonding and grounding.
- Powder handling equipment such as dust collectors, dryers and mills may require additional protection measures such as explosion venting.

Combustion products include: carbon monoxide (CO), carbon dioxide (CO2), nitrogen oxides (NOx), other pyrolysis products typical of burning organic material.

FIRE INCOMPATIBILITY

- Avoid contamination with oxidizing agents i.e. nitrates, oxidizing acids, chlorine bleaches, pool chlorine etc. as ignition may result.

PERSONAL PROTECTION

Glasses:
Chemical goggles.

Gloves:
Respirator:
Particulate

Section 6 - ACCIDENTAL RELEASE MEASURES

MINOR SPILLS

- Environmental hazard - contain spillage.
- Clean up waste regularly and abnormal spills immediately.
- Avoid breathing dust and contact with skin and eyes.
- Wear protective clothing, gloves, safety glasses and dust respirator.
- Use dry clean up procedures and avoid generating dust.
- Vacuum up or sweep up. NOTE: Vacuum cleaner must be fitted with an exhaust micro filter (HEPA type) (consider explosion-proof machines designed to be grounded during storage and use).
- Dampen with water to prevent dusting before sweeping.
- Place in suitable containers for disposal.

MAJOR SPILLS

- Environmental hazard - contain spillage.
- Moderate hazard.
- CAUTION: Advise personnel in area.
- Alert Emergency Responders and tell them location and nature of hazard.
- Control personal contact by wearing protective clothing.
- Prevent, by any means available, spillage from entering drains or water courses.
- Recover product wherever possible.
- IF DRY: Use dry clean up procedures and avoid generating dust. Collect residues and place in sealed plastic bags or other containers for disposal. IF WET: Vacuum/shovel up and place in labelled containers for disposal.
- ALWAYS: Wash area down with large amounts of water and prevent runoff into drains.
- If contamination of drains or waterways occurs, advise emergency services.

PROTECTIVE ACTIONS FOR SPILL

PROTECTIVE ACTION ZONE

Isolation Distance

wind direction

down wind distance

evacuation direction

half downwind distance

From IERG (Canada/Australia)
Isolation Distance -
Downwind Protection Distance 10 meters

FOOTNOTES

1 PROTECTIVE ACTION ZONE is defined as the area in which people are at risk of harmful exposure. This zone assumes that random changes in wind direction confines the vapour plume to an area within 30 degrees on either side of the predominant wind direction, resulting in a crosswind protective action distance equal to the downwind protective action distance. 2 PROTECTIVE ACTIONS should be initiated to the extent possible, beginning with those closest to the spill and working away from the site in the downwind direction. Within the protective action zone a level of vapour concentration may exist resulting in nearly all unprotected persons becoming incapacitated and unable to take protective action and/or incurring serious or irreversible health effects.

3 INITIAL ISOLATION ZONE is determined as an area, including upwind of the incident, within which a high probability of localised wind reversal may expose
nearly all persons without appropriate protection to life-threatening concentrations of the material.

4 SMALL SPILLS involve a leaking package of 200 litres (55 US gallons) or less, such as a drum (jerrican or box with inner containers). Larger packages leaking less than 200 litres and compressed gas leaking from a small cylinder are also considered "small spills". LARGE SPILLS involve many small leaking packages or a leaking package of greater than 200 litres, such as a cargo tank, portable tank or a "one-tonne" compressed gas cylinder.


6 IERG information is derived from CANUTEC - Transport Canada.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGL) (in ppm)

AEGL 1: The airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL 2: The airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL 3: The airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Section 7 - HANDLING AND STORAGE

PROCEDURE FOR HANDLING

- Avoid all personal contact, including inhalation.
- Wear protective clothing when risk of exposure occurs.
- Use in a well-ventilated area.
- Prevent concentration in hollows and sumps.
- DO NOT enter confined spaces until atmosphere has been checked.
- DO NOT allow material to contact humans, exposed food or food utensils.
- Avoid contact with incompatible materials.
- When handling, DO NOT eat, drink or smoke.
- Keep containers securely sealed when not in use.
- Avoid physical damage to containers.
- Always wash hands with soap and water after handling.
- Work clothes should be laundered separately.
- Launder contaminated clothing before re-use.
- Use good occupational work practice.
- Observe manufacturer’s storing and handling recommendations.
- Atmosphere should be regularly checked against established exposure standards to ensure safe working conditions are maintained.

Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the presence of an appropriate ignition source.

- Do NOT cut, drill, grind or weld such containers
- In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit.

RECOMMENDED STORAGE METHODS

- Glass container.
- Polyethylene or polypropylene container.
- Check all containers are clearly labelled and free from leaks.

STORAGE REQUIREMENTS

- Observe manufacturer’s storing and handling recommendations.

SAFE STORAGE WITH OTHER CLASSIFIED CHEMICALS

X: Must not be stored together
O: May be stored together with specific preventions
+: May be stored together

Section 8 - EXPOSURE CONTROLS / PERSONAL PROTECTION

EXPOSURE CONTROLS

The following materials had no OELs on our records

- letrozole: CAS:112809-51-5

MATERIAL DATA

LETRAZOLE:

- It is the goal of the ACGIH (and other Agencies) to recommend TLVs (or their equivalent) for all substances for which there
is evidence of health effects at airborne concentrations encountered in the workplace. At this time no TLV has been established, even though this material may produce adverse health effects (as evidenced in animal experiments or clinical experience). Airborne concentrations must be maintained as low as is practically possible and occupational exposure must be kept to a minimum.

NOTE: The ACGIH occupational exposure standard for Particles Not Otherwise Specified (P.N.O.S) does NOT apply. Airborne particulate or vapor must be kept to levels as low as is practicably achievable given access to modern engineering controls and monitoring hardware. Biologically active compounds may produce idiosyncratic effects which are entirely unpredictable on the basis of literature searches and prior clinical experience (both recent and past).

PERSONAL PROTECTION

Consult your EHS staff for recommendations

EYE
- When handling very small quantities of the material eye protection may not be required.
- For laboratory, larger scale or bulk handling or where regular exposure in an occupational setting occurs:
  - Chemical goggles
  - Face shield. Full face shield may be required for supplementary but never for primary protection of eyes
  - Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lens or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience.
  - Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59]

HANDS/FEET
- Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include: such as:
  - frequency and duration of contact,
  - chemical resistance of glove material,
  - glove thickness and dexterity
- Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739).
  - When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374) is recommended.
  - When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374) is recommended.
- Contaminated gloves should be replaced.
- Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.
  - Rubber gloves (nitrile or low-protein, powder-free latex). Employees allergic to latex gloves should use nitrile gloves in preference.
  - PVC gloves.
  - Protective shoe covers.
- Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.
  - polychloroprene
  - nitrile rubber
  - butyl rubber
  - fluorocaoutchouc
  - polyvinyl chloride
- Gloves should be examined for wear and/ or degradation constantly.

OTHER
- For quantities up to 500 grams a laboratory coat may be suitable.
- For quantities up to 1 kilogram a disposable laboratory coat or coverall of low permeability is recommended. Coveralls should be buttoned at collar and cuffs.
- For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.
- For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.
- Eye wash unit.
- Ensure there is ready access to an emergency shower.
- For Emergencies: Vinyl suit
- Respirators may be necessary when engineering and administrative controls do not adequately prevent exposures.
- The decision to use respiratory protection should be based on professional judgment that takes into account toxicity information, exposure measurement data, and frequency and likelihood of the worker’s exposure - ensure users are not subject to high thermal loads which may result in heat stress or distress due to personal protective equipment (powered, positive flow, full face apparatus may be an option).
- Published occupational exposure limits, where they exist, will assist in determining the adequacy of the selected respiratory . These may be government mandated or vendor recommended.
- Certified respirators will be useful for protecting workers from inhalation of particulates when properly selected and fit tested.
as part of a complete respiratory protection program.
- Use approved positive flow mask if significant quantities of dust becomes airborne.
- Try to avoid creating dust conditions.

**RESPIRATOR**

<table>
<thead>
<tr>
<th>Protection Factor</th>
<th>Half-Face Respirator</th>
<th>Full-Face Respirator</th>
<th>Powered Air Respirator</th>
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<tr>
<td>10 x PEL</td>
<td>P1</td>
<td>-</td>
<td>PAPR-P1</td>
</tr>
<tr>
<td>50 x PEL</td>
<td>Air-line*</td>
<td>P2</td>
<td>PAPR-P2</td>
</tr>
<tr>
<td>100 x PEL</td>
<td>P3</td>
<td>Air-line*</td>
<td>-</td>
</tr>
<tr>
<td>100+ x PEL</td>
<td>-</td>
<td>Air-line**</td>
<td>PAPR-P3</td>
</tr>
</tbody>
</table>

* - Negative pressure demand  ** - Continuous flow

Explanation of Respirator Codes:
Class 1 low to medium absorption capacity filters.
Class 2 medium absorption capacity filters.
Class 3 high absorption capacity filters.
PAPR Powered Air Purifying Respirator (positive pressure) cartridge.
Type A for use against certain organic gases and vapors.
Type AX for use against low boiling point organic compounds (less than 65°C).
Type B for use against certain inorganic gases and other acid gases and vapors.
Type E for use against sulfur dioxide and other acid gases and vapors.
Type K for use against ammonia and organic ammonia derivatives

Class P1 intended for use against mechanically generated particulates of sizes most commonly encountered in industry, e.g. asbestos, silica.
Class P2 intended for use against both mechanically and thermally generated particulates, e.g. metal fume.
Class P3 intended for use against all particulates containing highly toxic materials, e.g. beryllium.

The local concentration of material, quantity and conditions of use determine the type of personal protective equipment required.

Use appropriate NIOSH-certified respirator based on informed professional judgement. In conditions where no reasonable estimate of exposure can be made, assume the exposure is in a concentration IDLH and use NIOSH-certified full face pressure demand SCBA with a minimum service life of 30 minutes, or a combination full facepiece pressure demand SAR with auxiliary self-contained air supply. Respirators provided only for escape from IDLH atmospheres shall be NIOSH-certified for escape from the atmosphere in which they will be used.

**ENGINEERING CONTROLS**

- Enclosed local exhaust ventilation is required at points of dust, fume or vapor generation.
- HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapors.
- Barrier protection or laminar flow cabinets should be considered for laboratory scale handling.
- The need for respiratory protection should also be assessed where incidental or accidental exposure is anticipated: Dependent on levels of contamination, PAPR, full face air purifying devices with P2 or P3 filters or air supplied respirators should be evaluated.
- Fume-hoods and other open-face containment devices are acceptable when face velocities of at least 1 m/s (200 feet/minute) are achieved. Partitions, barriers, and other partial containment technologies are required to prevent migration of the material to uncontrolled areas. For non-routine emergencies maximum local and general exhaust are necessary. Air contaminants generated in the workplace possess varying "escape" velocities which, in turn, determine the "capture velocities" of fresh circulating air required to effectively remove the contaminant.

**PHYSICAL PROPERTIES**

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<th>Molecular Weight</th>
<th>Flash Point (°F)</th>
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<td>357.8 - 361.4</td>
<td>Viscosity</td>
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<tr>
<td>Boiling Range (°F)</td>
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<td>Solubility in water (g/L)</td>
<td>Partly Miscible</td>
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<tr>
<td>Flash Point (°F)</td>
<td>Not Available</td>
<td>pH (1% solution)</td>
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</table>

**Section 9 - PHYSICAL AND CHEMICAL PROPERTIES**
Decomposition Temp (°F) Not Available  pH (as supplied) Not Applicable
Autoignition Temp (°F) Not Available  Vapour Pressure (mmHG) Negligible
Upper Explosive Limit (%) Not Available  Specific Gravity (water=1) Not Available
Lower Explosive Limit (%) Not Available  Relative Vapor Density (air=1) Not Applicable
Volatile Component (%vol) Negligible  Evaporation Rate Not Applicable

APPEARANCE
White crystalline solid; does not mix well with water. Flammability Color Physical State Odor Miscibility with water - White Solid Partly Miscible

Section 10 - CHEMICAL STABILITY

CONDITIONS CONTRIBUTING TO INSTABILITY

- Presence of incompatible materials.
- Product is considered stable.
- Hazardous polymerization will not occur.

STORAGE INCOMPATIBILITY

- Avoid reaction with oxidizing agents.

For incompatible materials - refer to Section 7 - Handling and Storage.

Section 11 - TOXICOLOGICAL INFORMATION

letrozole

TOXICITY AND IRRITATION

- unless otherwise specified data extracted from RTECS - Register of Toxic Effects of Chemical Substances.

**TOXICITY**

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<th>Route</th>
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<td>150 D</td>
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<tr>
<td>Oral (Woman)</td>
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<td>14 D</td>
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<tr>
<td>Intravenous (Woman)</td>
<td>4.55</td>
<td>91 D</td>
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</table>

| Tumours of skin and appendages, changes in luteinising hormone and gonadotropins recorded. |

Section 12 - ECOLOGICAL INFORMATION

Refer to data for ingredients, which follows:

**LETRZOLE**

- Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
- Do NOT allow product to come in contact with surface waters or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment wash-waters.
- Wastes resulting from use of the product must be disposed of on site or at approved waste sites.
- For azole-containing substances.
- Azole fungicides and systemically used antifungal drugs directly interfere with steroidogenesis by acting as potent inhibitors of steroidogenic enzymes and are known to cause endocrine disruption mainly via this mechanism.
- An important P450 enzyme involved in the steroidogenesis is aromatase. Aromatase demethylates C10 and specifically converts androstenedione and testosterone. On the protein level, the amino acid sequence homology between aromatase from fish and humans is about 50% and between rats and humans is about 78%. In mammals, aromatase is mainly expressed in the brain and the gonads, but it is also found in placental, adipose, and bone tissue. The physiologic balance between different sex steroid hormones is crucial for the development, maintenance, and function of the reproductive system as well as for the differentiation of the sexual phenotype during ontogeny. Oestrogens (estrone and estradiol) are products of the androgens (androstenedione and testosterone), and the reaction is catalysed by aromatase. In mammals, differentiation of the male phenotype depends not only on testosterone but also on estradiol generated from testosterone by neuronal aromatase in central nervous system. Therefore, disturbances in aromatase expression and/or changes in its catalytic activity are expected to exhibit negative effects on reproduction parameters.
- Azole-containing compounds produce profound effects in the environment. In part this is due to inhibition of several enzyme systems including those involving sterol 14[alpha]-demethylase. Sterol 14[alpha]-demethylase is a member of the superfamily of haeme-containing cytochrome P450 enzymes involved in metabolism of endogenous and xenobiotic substances. The antifungal effect of azoles is due to inhibition of sterol 14[alpha]-demethylase in fungi and yeast, thereby blocking the biosynthesis of ergosterol. The subsequent lack of ergosterol is detrimental because ergosterol is an essential steroid component in the membranes of fungi and yeast. Sterol 14[alpha]-demethylase is not only expressed in fungi and yeast but is also found in many other species ranging from bacteria to mammals. In plants, the sterol 14[alpha]-demethylase reaction metabolises obtusifoliol and provides precursors for biosynthesis of phytosterols. In animals, the sterol 14[alpha]-demethylase reaction is part of the metabolic pathway leading to biosynthesis of cholesterol. Cholesterol in turn is the substrate for the production of many other sterols (e.g., the sex steroid hormones).
- The DNA sequences encoding sterol 14[alpha]-demethylase of many fungi and yeast are known, as well as the sequences of mice, rats, pigs, and humans. On the protein level, the amino acid sequences are highly conserved along the phylogenetic tree. This fact is considered by many authors as an indication of the pivotal role of sterol 14[alpha]-demethylase in all organisms. The homology of the amino acid sequence level between rats and humans is 93% and 40% between fungi and humans. In humans, the sterol 14[alpha]-demethylase is expressed in many different tissues.
- DO NOT discharge into sewer or waterways.

Section 13 - DISPOSAL CONSIDERATIONS
Disposal Instructions

All waste must be handled in accordance with local, state and federal regulations.

- Puncture containers to prevent re-use and bury at an authorized landfill.
- Legislation addressing waste disposal requirements may differ by country, state and/or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.
- A Hierarchy of Controls seems to be common - the user should investigate:
  - Reduction
  - Reuse
  - Recycling
  - Disposal (if all else fails)

This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.

- DO NOT allow wash water from cleaning equipment to enter drains. Collect all wash water for treatment before disposal.
- Recycle wherever possible.
- Consult manufacturer for recycling options or consult Waste Management Authority for disposal if no suitable treatment or disposal facility can be identified.
- Dispose of by: Burial in a licensed land-fill or Incineration in a licensed apparatus (after admixture with suitable combustible material)
- Decontaminate empty containers. Observe all label safeguards until containers are cleaned and destroyed.

Section 14 - TRANSPORTATION INFORMATION

DOT:

| Symbols: | G | Hazard class or Division: | 9 |
| Identification Numbers: | UN3077 | PG: | III |
| Label Codes: | 9 | Special provisions: | 8, 146, 335, B54, IB8, IP3, N20, T1, TP33 |
| Packaging: Exceptions: | 155 | Packaging: Non-bulk: | 213 |
| Packaging: Exceptions: | 155 | Quantity limitations: | Passenger aircraft/rail: No limit |
| Quantity Limitations: Cargo aircraft only: | No limit | Vessel stowage: Location: | A |

- Vessel stowage: Other: None

Hazardous materials descriptions and proper shipping names:

Environmentally hazardous substance, solid, n.o.s

Air Transport IATA:

| ICAO/IATA Class: | 9 | ICAO/IATA Subrisk: | % |
| UN/ID Number: | 3077 | Packing Group: | III |
| Special provisions: | A97 |

Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. *(CONTAINS LETROZOLE)

Maritime Transport IMDG:

| IMDG Class: | 9 | IMDG Subrisk: | None |
| UN Number: | 3077 | Packing Group: | III |
| EMS Number: | F-A,S-F | Special provisions: | 274 909 944 |
| Limited Quantities: | 5 kg |

Shipping Name: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S.(contains letrozole)

No data for letrozole (CAS: , 112809-51-5)

Section 15 - REGULATORY INFORMATION

LIMITED EVIDENCE

- Ingestion may produce health damage*.
- Limited evidence of a carcinogenic effect*.

*limited evidence).

Germany Hazard classification and labelling of medicines with antineoplastic effects (ATC Code L01 and L02)
<table>
<thead>
<tr>
<th>INN</th>
<th>CAS</th>
<th>Danger</th>
<th>CMR effects</th>
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<td>112809-51-5</td>
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<td>R 60 R 61</td>
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Classification of the mixture and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references. A list of reference resources used to assist the committee may be found at: www.chemwatch.net/references.

The (M)SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

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