Xtandi (enzalutamide) Tablets 40 mg and 80 mg

Safety Data Sheet

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SECTION 1: IDENTIFICATION

1.1. Product Identifier

Product Form: Mixture

Product Name: Xtandi (enzalutamide) Tablets 40 mg and 80 mg

CAS No of Active Ingredient: 915087-33-1

Chemical Name of Active Ingredient: 4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide

Chemical Formula of Active Ingredient: $C_{21}H_{16}F_4N_4O_2S$

1.2. Intended Use of the Product

Use of the substance/mixture: Androgen receptor inhibitor indicated for the treatment of patients with cancer. For professional use only.

1.3. Name, Address, and Telephone of the Responsible Party

Company

Astellas US LLC
2375 Waterview Drive
Northbrook, IL 60062
Tel.: 800-888-7704
www.us.astellas.com

1.4. Emergency Telephone Number

SECTION 2: HAZARDS IDENTIFICATION

This product is a drug, as defined by the US Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) It is in solid, final form for direct administration to the patient. Therefore, it is exempt from labeling, as defined in the 29 CFR 1910.1200(b)(5)(iii).

Potential to cause seizures, especially in those predisposed to seizure activity. The toxicological, physical and other potential hazards associated with this compound have not been fully characterized. Should avoid ingestion, inhalation, skin and eye contact.

Given anti-androgen effects of the compound, histopathological changes have been observed in endocrine and reproductive organs in rats and dogs. As teratogenicity was induced at a low dose level (10 mg/kg) in the embryo-fetal development study in mice, pregnant women and women suspected to be pregnant should avoid contact with this material.

ADI=300 µg/day

SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

This product is a drug, as defined by the US Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) It is in solid, final form for direct administration to the patient. Therefore, it is exempt from the US 2012 Hazard Communication Standard, as defined in the 29 CFR 1910.1200(b)(6)(vii).

SECTION 4: FIRST AID MEASURES

4.1. Description of First Aid Measures

First-aid Measures General: Never give anything by mouth to an unconscious person. If you feel unwell, seek medical advice (show the label if possible).

First-aid Measures After Inhalation: Remove to fresh air and keep at rest in a position comfortable for breathing. Obtain medical attention if breathing difficulty persists.

First-aid Measures After Skin Contact: Gently wash with plenty of soap and water. Obtain medical attention if irritation develops or persists.

First-aid Measures After Eye Contact: Rinse cautiously with water for at least 5 minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Obtain medical attention if pain, blinking, or redness persist.

First-aid Measures After Ingestion: Do not induce vomiting. Rinse mouth. Immediately call a POISON CENTER or doctor/physician.

4.2. Most important symptoms and effects, both acute and delayed

Symptoms/Injuries: Pharmaceutical. When handling in workplace settings, in quantities that are most likely above the therapeutic dose, this product may be harmful if absorbed through the eyes, skin, or respiratory tract.

Symptoms/Injuries After Inhalation: If tablet is crushed: May cause respiratory irritation.

Symptoms/Injuries After Skin Contact: If tablet is crushed: May cause skin irritation.

Symptoms/Injuries After Eye Contact: If tablet is crushed: May cause eye irritation.

Symptoms/Injuries After Ingestion: Ingestion may cause nausea, vomiting and diarrhea.

Chronic Symptoms: Potential to cause seizures, especially in those predisposed to seizure activity. May damage fertility or the unborn child (oral). May damage organs (reproductive organs, kidneys, liver, pituitary gland, thyroid gland) through prolonged or repeated exposure (oral).

4.3. Indication of Any Immediate Medical Attention and Special Treatment Needed

If you feel unwell, seek medical advice (show the label where possible).

SECTION 5: FIRE-FIGHTING MEASURES

5.1. Extinguishing Media

Suitable Extinguishing Media: Water spray, fog, alcohol-resistant foam, or dry chemical.

Unsuitable Extinguishing Media: Do not use carbon dioxide. Do not use a heavy water stream. Use of heavy stream of water may spread fire.

5.2. Special Hazards Arising From the Substance or Mixture

Fire Hazard: Not considered flammable but may burn at high temperatures.

Explosion Hazard: Product is not explosive.

Reactivity: Hazardous reactions will not occur under normal conditions.

5.3. Advice for Firefighters

Precautionary Measures Fire: Exercise caution when fighting any chemical fire.

Firefighting Instructions: Use water spray or fog for cooling exposed containers.

Protection During Firefighting: Do not enter fire area without proper protective equipment, including respiratory protection.

Other Information: Refer to Section 9 for flammability properties.

SECTION 6: ACCIDENTAL RELEASE MEASURES

6.1. Personal Precautions, Protective Equipment and Emergency Procedures

General Measures: Use only as directed.

6.1.1. For Non-emergency Personnel

Protective Equipment: Use appropriate personal protection equipment (PPE).

Emergency Procedures: Evacuate unnecessary personnel.

6.1.2. For Emergency Responders

Protective Equipment: Equip cleanup crew with proper protection.

Emergency Procedures: Upon arrival at the scene, a first responder is expected to recognize the presence of dangerous goods, protect oneself and the public, secure the area, and call for the assistance of trained personnel as soon as conditions permit.

6.2. Environmental Precautions

Prevent entry to sewers and public waters. Notify authorities if product enters sewers or public waters.

6.3. Methods and Material for Containment and Cleaning Up

For Containment: Contain and collect as any solid.

Methods for Cleaning Up: Clean up spills immediately and dispose of waste safely. Take up mechanically (sweeping, shoveling) and collect in suitable container for disposal. Contact competent authorities after a spill.

6.4. Reference to Other Sections

See Heading 8. Exposure controls and personal protection. For further information refer to section 13.

SECTION 7: HANDLING AND STORAGE

7.1. Precautions for Safe Handling

Additional Hazards When Processed: Avoid breaking or crushing tablets.

Hygiene Measures: Handle in accordance with good industrial hygiene and safety procedures. Wash hands and other exposed areas with mild soap and water before eating, drinking or smoking and when leaving work.

7.2. Conditions for Safe Storage, Including Any Incompatibilities

Technical Measures: Comply with applicable regulations.

Storage Conditions: Store in a dry, cool and well-ventilated place. Keep container closed when not in use. Keep/Store away from direct sunlight, extremely high or low temperatures and incompatible materials.

Incompatible Products: Oxidizers.

Storage Temperature: 20 - 25 °C (68 °F - 77 °F). Excursions permitted from 15 °C to 30 °C (59 °F to 86 °F).

7.3. Specific End Use(s)

Androgen receptor inhibitor indicated for the treatment of patients with cancer. For professional use only.

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Control Parameters

For substances listed in section 3 that are not listed here, there are no established exposure limits from the manufacturer, supplier, importer, or the appropriate advisory agency including: ACGIH (TLV), AIHA (WEEL), NIOSH (REL), or OSHA (PEL).

Xtandi (enzalutamide) Tablets 40 mg and 80 mg (915087-33-1)		
Internally derived drug substance OEL:	Internal TWA (mg/m^3) for an 8-hour day	30 $\mu g/m^3$

Silica, amorphous (7631-86-9)		
USA NIOSH	NIOSH REL (TWA) (mg/m^3)	6 mg/m^3
USA IDLH	US IDLH (mg/m^3)	3000 mg/m^3
USA OSHA	OSHA PEL (TWA) (mg/m^3)	6 mg/m^3
USA OSHA	OSHA PEL (TWA) (ppm)	20 mppcf (80mg/m^3/%SiO_2)

Particulates not otherwise classified (PNOC)		
USA ACGIH	ACGIH TWA (mg/m^3)	3 mg/m^3 Respirable fraction 10 mg/m^3 Total Dust
USA OSHA	OSHA PEL (TWA) (mg/m^3)	5 mg/m^3 Respirable fraction 15 mg/m^3 Total Dust

8.2. Exposure Controls

Appropriate Engineering Controls : Ensure adequate ventilation, especially in confined areas. Emergency eye wash fountains and safety showers should be available in the immediate vicinity of any potential exposure. Ensure all national/local regulations are observed.

Personal Protective Equipment : Not generally required. The use of personal protective equipment may be necessary as conditions warrant.

Materials for Protective Clothing : Chemically resistant materials and fabrics.

Hand Protection : Wear chemically resistant protective gloves.

Eye Protection : Chemical goggles or safety glasses.

Skin and Body Protection : Wear suitable protective clothing.

Respiratory Protection : None required under normal product handling conditions.

Environmental Exposure Controls : Do not allow the product to be released into the environment.

Consumer Exposure Controls : Do not eat, drink or smoke during use.

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

9.1. Information on Basic Physical and Chemical Properties

Physical State : Solid

Appearance : **40 mg:** round, yellow film-coated tablets, debossed with E 40
80 mg: oval, yellow film-coated tablets, debossed with E 80

Odor : No data available

Odor Threshold : No data available

pH : No data available

Evaporation Rate : No data available

Melting Point : 201 °C (394 °F)

Freezing Point : No data available

Boiling Point : No data available

Flash Point : No data available

Auto-ignition Temperature : No data available

Decomposition Temperature : No data available

Flammability (solid, gas) : No data available

Vapor Pressure : No data available

Relative Vapor Density at 20 °C : No data available

Relative Density : No data available

Solubility : Practically insoluble in water, somewhat soluble in isopropanol (13 mg/mL) and acetonitrile (90 mg/mL)

Partition Coefficient: N-Octanol/Water : 3.0 (was experimentally established for the ERA)

Viscosity : No data available

Molecular Weight Of Active Ingredient : 464.44 g/mol

9.2. Other Information No additional information available.

SECTION 10: STABILITY AND REACTIVITY

10.1. Reactivity: Hazardous reactions will not occur under normal conditions.

10.2. Chemical Stability: Enzalutamide is stable if stored at 20°C to 25°C (68°F to 77°F).

10.3. Possibility of Hazardous Reactions: Hazardous polymerization will not occur.

10.4. Conditions to Avoid: Direct sunlight. Extremely high or low temperatures. Ignition sources. Incompatible materials.

10.5. Incompatible Materials: Oxidizers.

10.6. Hazardous Decomposition Products: Carbon oxides (CO, CO_2). Nitrogen oxides. Sulfur dioxide. Fluorine compounds.

SECTION 11: TOXICOLOGICAL INFORMATION

11.1. Information On Toxicological Effects

Acute Toxicity: Not classified

Xtandi (enzalutamide) Tablets 40 mg and 80 mg (915087-33-1)	
LD50 Oral Rat	400 mg/kg lethal dose, mouse

Dextrin (9004-53-9)	
LD50 Oral Rat	> 2000 mg/kg
LD50 Dermal Rat	> 2000 mg/kg
LC50 Inhalation Rat	> 5 mg/l/4h

Silica, amorphous (7631-86-9)	
LD50 Oral Rat	> 5000 mg/kg
LD50 Dermal Rabbit	> 2000 mg/kg
LC50 Inhalation Rat	> 2.2 mg/l (Exposure time: 1 h)

Croscarmellose sodium (74811-65-7)	
LD50 Oral Rat	> 5050 mg/kg
LD50 Dermal Rabbit	> 2000 mg/kg
LC50 Inhalation Rat	> 0.13 mg/l/4h

Magnesium stearate (557-04-0)	
LD50 Oral Rat	> 2000 mg/kg
LC50 Inhalation Rat	> 2 mg/l/4h

Skin Corrosion/Irritation: Not classified

Enzalutamide (915087-33-1)	
Additional information	Negative phototoxicity in vitro.

Serious Eye Damage/Irritation: Not classified

Respiratory or Skin Sensitization: Not classified

Germ Cell Mutagenicity: Not classified

Enzalutamide (915087-33-1)	
Additional information	Enzalutamide was negative in the in vitro Ames Bacterial Reverse Mutation Assay and the Mouse Lymphoma Assay. Enzalutamide was also negative in the in vivo Mouse Micronucleus Assay.

Carcinogenicity: Not classified

Enzalutamide (915087-33-1)	
Additional information	In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day. Daily oral dosing of rats with enzalutamide at 10 to 100 mg/kg/day for 2 years increased the incidence of neoplastic findings (compared to control) that was considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumor in the testes in males; benign granulosa cell tumor in the ovaries in females; adenoma in the pars distalis of the pituitary in both sexes. In addition, urothelial papilloma and carcinoma of urinary bladder in male rats were observed at the 100 mg/kg/day dose and were considered secondary to the irritation caused by the increased urinary crystal/calculi which is known to occur in rodent species., Leydig cell tumors in rats are

	generally not considered relevant to humans based on experience with other anti-androgens. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out.

Silica, amorphous (7631-86-9)	
IARC group	3

Reproductive Toxicity: May damage fertility or the unborn child.

Enzalutamide (915087-33-1)	
Additional information	An effect on male fertility may be expected given the anti-androgen effects of the compound. Similarly, potential to cause birth defects (in particular, the feminization of male offspring) may exist. Embryo-fetal development study in mice: NOAEL = 1 mg/kg based on increased post-implantation loss and shortened anogenital distance. In dams, spontaneous abortion was observed at a dose of 30 mg/kg. In a rabbit embryo-fetal development study, the maternal NOAEL was 10 mg/kg and in fetuses the NOAEL was 10 mg/kg.

Specific Target Organ Toxicity (Single Exposure): Not classified

Specific Target Organ Toxicity (Repeated Exposure): May cause damage to organs through prolonged or repeated exposure.

Enzalutamide (915087-33-1)	
Additional information	Convulsions were observed in mice at doses > 100 mg/kg/day and in dogs at doses of 60 mg/kg/day. In addition, in the 39-week dog study, 1 animal at the 45 mg/kg/day dose was observed to have convulsions. Mild hematological effects (slight reduction in red blood cell parameters) and an increase in plasma testosterone occurred in dogs at oral doses of 15 to 60 mg/kg/day. Changes in male reproductive organ weights may be related to the pharmacologic action of this androgen receptor inhibitor. 26-week repeated dose rat study: MTD 100 mg/kg/day, PO based on the following findings in males - decreased weights of prostate, epididymis and seminal vesicle, decreased prostate and seminal vesicle secretions. The following findings were observed in female reproductive organs – lumen dilation of the uterine glands and dilation of mammary gland. In addition, mild decreases in red blood cell counts and parameters, mild elevated cholesterol, increased liver and pituitary weights were reported. Histopathological findings included hepatocellular hypertrophy, hyperplasia/hypertrophy in the pituitary, thyroid follicular cell hyperplasia/hypertrophy, mammary gland hyperplasia in females, mammary gland atrophy in males, and slight to mild chronic progressive renal nephropathy. 39-week repeated dose dog study: decreased prostate and epididymis weight, atrophy in the prostate, hypertrophy and/or hyperplasia of the Leydig cells in the testes, and atrophy and/or epithelial vacuolation, atrophy in the epididymides at 5 mg/kg/day and greater, atrophy and oligospermia/germ cell debris in the epididymis, and hypospermatogenesis consistent with pharmacological effects.

Aspiration Hazard: Not classified

Symptoms/Injuries After Inhalation: If tablet is crushed: May cause respiratory irritation.

Symptoms/Injuries After Skin Contact: If tablet is crushed: May cause skin irritation.

Symptoms/Injuries After Eye Contact: If tablet is crushed: May cause eye irritation.

Symptoms/Injuries After Ingestion: Ingestion may cause nausea, vomiting and diarrhea.

Chronic Symptoms: Potential to cause seizures, especially in those predisposed to seizure activity. May damage fertility or the unborn child (oral). May damage organs (reproductive organs, kidneys, liver, pituitary gland, thyroid gland) through prolonged or repeated exposure (oral).

SECTION 12: ECOLOGICAL INFORMATION

12.1. Toxicity

Silica, amorphous (7631-86-9)	
LC50 Fish 1	5000 mg/l (Exposure time: 96 h - Species: Brachydanio rerio [static])
EC50 Daphnia 1	7600 mg/l (Exposure time: 48 h - Species: Ceriodaphnia dubia)

12.2. Persistence and Degradability No additional information available.

12.3. Bioaccumulative Potential

Silica, amorphous (7631-86-9)	
BCF fish 1	(no bioaccumulation expected)

12.4. Mobility in Soil No additional information available.

12.5. Other Adverse Effects

Other Information : Avoid release to the environment.

SECTION 13: DISPOSAL CONSIDERATIONS

13.1. Waste treatment methods

Waste Disposal Recommendations: Dispose of contents and container according to local, regional, national, and international regulations.

Ecology – Waste Materials: Avoid release to the environment.

SECTION 14: TRANSPORT INFORMATION

14.1. In Accordance with DOT Not regulated for transport.

14.2. In Accordance with IMDG Not regulated for transport.

14.3. In Accordance with IATA Not regulated for transport.

SECTION 15: REGULATORY INFORMATION

15.1 US Federal Regulations Not applicable

15.2 US State Regulations Not applicable

SECTION 16: OTHER INFORMATION, INCLUDING DATE OF PREPARATION OR LAST REVISION

Revision Date : 08/05/2019

Other Information : This document has been prepared in accordance with the SDS requirements of the OSHA Hazard Communication Standard 29 CFR 1910.1200.

This information is based on our current knowledge and is intended to describe the product for the purposes of health, safety and environmental requirements only. It should not therefore be construed as guaranteeing any specific property of the product.

Astellas US GHS SDS