

Synthon

Safety Data Sheet Bicalutamide

Effective

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1. Identification of the substance and the company	
1.1 Product identifier	- Bicalutamide (BCM). - CAS no.: 90357-06-5
1.2.a Uses	- BCM is used as an active ingredient in pharmaceutical formulations. - BCM is a non-steroidal androgen receptor inhibitor. It is used in the management of prostate cancer.
1.2.b Uses advised against	All uses not specified under section 1.2.a.
1.3 Details of SDS supplier	Synthon BV, Microweg 22, 6545 CM, Nijmegen, The Netherlands.
1.4 Emergency Telephone	+31-(0)24-3727700
2. Hazards identification	
2.1 Classification	Carcinogenicity, Category 2. Reproductive toxicity FD, Category 1B. STOT-repeated exposure category 2. Hazardous to the aquatic environment, long-term aquatic hazard Cat. 1.
2.2 Label elements	
2.2.1 Hazard Pictogram(s)	
2.2.2 Signal word(s)	Danger.
2.2.3 Hazard statement(s)	H351: Suspected of causing cancer. H360: May damage fertility or the unborn child. H373: May cause damage to organs sensitive to androgens through prolonged or repeated exposure. H410: Very toxic to aquatic life with long lasting effects.
2.2.4 Precautionary statement(s)	P260: Do not breathe dust/fumes/gas/mist/vapours/spray. P280: Wear protective gloves/protective clothing/eye protection/face protection. P308 + P313: IF exposed or concerned: Get medical advice/attention. P391: Collect spillage. P501: Dispose of contents/container to suitable waste streams in accordance with local/regional/national/international regulations.
2.3 Other hazards	- M-factor (self classification) = 1. - See section 9, 11 and 12.
3. Composition/information on ingredients	
3.1 Chemical names	N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.
3.2 Assay	98.0 - 102.0 % (dry basis).
3.3 Molecular formula	C ₁₈ H ₁₄ F ₄ N ₂ O ₄ S
3.4 Molecular weight	430.37

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<u>3.5 CAS number</u>	90357-06-5.
<u>3.6 EC/REACH registration number</u>	618-534-3 (EC).
4. First aid measures	
<u>4.1 Description of first aid measures</u>	
<u>4.1.1 Inhalation</u>	If exposed, feeling unwell and/or concerned: get medical advice/attention (show this (D)SDS).
<u>4.1.2 Skin</u>	Rinse/wash with lukewarm, gently flowing water (and mild soap) for 5 minutes or until product is removed. If skin irritation occurs or you feel unwell: Get medical advice/attention (show this (D)SDS).
<u>4.1.3 Eyes</u>	Gently brush product off face. Do not rub eyes. Let the eyes water naturally for a few minutes. Look right and left, then up and down. If particle/dust does not come out, cautiously rinse eyes with lukewarm, gently flowing water for 5 minutes or until particle/dust is removed, while holding the eyelids open. If eye irritation persists: Get medical advice/attention. Do not attempt to manually remove anything from the eyes (show this (D)SDS).
<u>4.1.4 Ingestion</u>	If exposed, feeling unwell and/or concerned: get medical advice/attention (show this (D)SDS).
<u>4.2 Most important symptoms and effects, both acute and delayed</u>	- Acute: A single dose of BCM that results in symptoms of an overdose considered to be life threatening has not been established. - Delayed: Long-term clinical trials have been conducted with dosages up to 200 mg of BCM daily and these dosages have been well tolerated. Possible long term adverse effects may include (but not be limited to) hot flashes, gynecomastia and breast pain. - Consider effects related to the compounds classification (see section 11)
<u>4.3 Indication of any immediate medical attention and special treatment needed</u>	- Immediate medical advice may be required (show this (D)SDS). - There is no specific antidote; treatment should be symptomatic. Dialysis is not likely to be helpful since BCM is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.
5. Fire-fighting measures	
<u>5.1 Extinguishing media</u>	
<u>5.1.1 Suitable extinguishing media</u>	Use water, dry chemical powder (ABC) or appropriate foam.
<u>5.1.2 Unsuitable extinguishing media</u>	None known.
<u>5.2 Special hazards arising from the substance or mixture</u>	When heated to decomposition it emits toxic fumes and flammable vapours.
<u>5.3 Advice for firefighters</u>	- Avoid exposure to the compound. Fire fighters should use self-containing breathing apparatus and protective clothing to prevent contact with skin and eyes. - If possible keep extinguishing water away from drains, surface- and groundwater, and soil.

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6. Accidental release measures	
<u>6.1 Personal precautions, protective equipment and emergency procedures</u>	
<u>6.1.1 For non-emergency personnel</u>	Take immediate action if necessary and considered safe. Use at least a (FF)P3 (USA: N100 or P100) filter. Wear suitable protective clothing (e.g. made from Tyvek material), and safety goggles. Wear gloves, for dust any glove is suitable, check solvent compatibility of gloves where relevant. For major spills involvement of the fire brigade or other local authorities should be considered.
<u>6.1.2 For emergency responders</u>	See row above and/or section 8.
<u>6.2 Environmental precautions</u>	Keep away from drains, surface- and groundwater, and soil.
<u>6.3 Methods and material for containment and cleaning up</u>	Wear protective clothing. See section 6.1
<u>6.3.1. Containment of spill</u>	Try to moisten the compound without raising dust.
<u>6.3.2. Clean-up</u>	Clean the spill with universal sorbent sheets, towels/tissues, a HEPA-filtered vacuum cleaner etc. Work from the surrounding area towards the location of the actual spill. Dispose the spill into containers labelled as hazardous material if required. Repeat cleaning if required with a proper soap or solvent solution.
<u>6.4 Reference to other sections</u>	Refer to section 8, 11, 12 and 13 for additional information.
7. Handling and storage	
<u>7.1 Precautions for safe handling</u>	- Work in an area with general and local ventilation, if possible in a contained area. Prevent aerosol and dust generation.
<u>7.1.1 Protective measures</u>	- Measures to prevent fire: This material is assumed to be combustible. It is advisable to dissipate the potential build-up of static electricity by grounding mechanical equipment in contact with the dry material (as with all dry powders). - Measures to prevent aerosol/dust generation: See section 8.2. - Measures to protect the environment: Keep away from drains, surface- and groundwater, and soil.
<u>7.1.2 Advice on general occupational hygiene</u>	Wear protective clothing (e.g. lab coat) and safety goggles, apply hygienic working habits (e.g. no drinking, eating or smoking at the workplace).
<u>7.2 Conditions for safe storage</u>	- Store in original packaging on a dry and dark place. - Default packaging material: 2 LDPE bags inside a HDPE container. - Select storage locations and packaging material in line with relevant local chemical storage guidelines where relevant.
<u>7.3 Specific end use(s)</u>	BCM is used as an active ingredient in pharmaceutical formulations.

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8. Exposure controls/personal protection	
<u>8.1 Control parameters</u>	
8.1.1 <i>Exposure limit values</i>	- 0.01 mg/m³ 8 hr Time Weighted Average for 8 hours (originator OEL, also implemented by Synthon). - No occupational exposure limits (OELs) set by competent authorities available.
8.1.2 <i>Currently recommended monitoring procedures</i>	Please refer to local legislation. Alternatively reference to the ISPE good practice guide, ISBN 978-1-936379-35-4 is advised.
8.1.3 <i>Occupational Exposure Band</i>	- Synthon OEB: D. - OEB context and limitations: A Synthon OEB value is primarily the result of a toxicological hazard driven classification including the OEL value and hazard statements. In general the following containment strategies are considered possibly suitable for use with the assigned OEB depending on scale, dustiness and task duration: <i>Open handling within isolator or High-integrity closed coupling without external containment.</i> or <i>Local exhaust ventilation supplemented with personal protective equipment (see below).</i> Also see section 8.2.1. Please contact an EHS representative or Synthon for additional information.
<u>8.2 Exposure controls</u>	
8.2.1 <i>Generally appropriate engineering controls</i>	BCM can possibly enter the body through inhalation, ingestion and via the skin. Work in an area with general and local ventilation, if possible in a contained area. The use of weighing cabinets or fumehoods is preferred. If open manufacturing systems are used or dust is generated while transferring, weighing or pelletising, enclosed equipment and high integrity closed coupling systems should be applied when available and feasible. Otherwise, flexible local exhaust ventilation supplemented with respiratory protection equipped with a (FF)P3 filter (USA: N100 or P100) should be used. For appropriate handling precautions in specific settings consult with a health and safety representative.
8.2.2 <i>Individual protection measures, such as personal protective equipment</i>	
- <i>Respiratory control</i>	<i>If required:</i> Use a (FF)P3 filter (USA: N100 or P100).
- <i>Hand protection</i>	Wear gloves, for dust any glove is suitable, check solvent compatibility of gloves where relevant.
- <i>Eye protection</i>	Wear safety goggles.
- <i>Skin protection</i>	Wear suitable protective clothing (e.g. lab coat).
- <i>Other</i>	None.
<u>8.3 Environmental exposure controls</u>	
- Keep away from drains, surface- and groundwater, and soil. - Avoid raising dust. Moisten spilled product with water and collect in containers for disposal. Rinse remnant with plenty of water and soap.	

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9. Physical and chemical properties	
<u>9.1 General information</u>	
<i>Appearance</i>	White or almost white powder.
<i>Odour</i>	No data (publically) available or generated.
<i>Odour threshold</i>	No data (publically) available or generated.
<i>pH</i>	No data (publically) available or generated.
<i>Melting point</i>	191-193°C (crystals from a 1:1 (v/v) mix of ethylacetate and petroleum ether).
<i>Initial boiling point and range</i>	No data (publically) available or generated.
<i>Flash point</i>	No data (publically) available or generated.
<i>Evaporation rate</i>	No data (publically) available or generated.
<i>Flammability (solid/gas)</i>	No data (publically) available or generated.
<i>Upper/lower Flammability or explosive limits</i>	No data (publically) available or generated.
<i>Vapour pressure</i>	7.54×10^{-15} mm Hg at 25 °C (est.).
<i>Vapour density</i>	No data (publically) available or generated.
<i>Relative density</i>	No data (publically) available or generated.
<i>Solubility(ies)</i>	- Water: practically insoluble in water at 37°C (5 mg per 1000 mL) - Slightly soluble in chloroform and absolute ethanol, sparingly soluble in methanol, and soluble in acetone and tetrahydrofuran.
<i>Partition coefficient: n-octanol/water</i>	Log P _{ow} : 2.35 - 2.54.
<i>Auto-ignition temperature</i>	No data (publically) available or generated.
<i>Decomposition temperature</i>	No data (publically) available or generated.
<i>Viscosity</i>	No data (publically) available or generated.
<i>Explosive properties</i>	No data (publically) available or generated.
<i>Oxidising properties</i>	No data (publically) available or generated.
<u>9.2 Other information</u>	- Dissociation constant (pKa) is approximately 12. - The raw material is static.
10. Stability and Reactivity	
<u>10.1 Reactivity</u>	Not considered to be a reactive compound.
<u>10.2 Chemical stability</u>	Stable (retest period 24 months) when stored under the storage conditions given in section 7 of this (D)SDS.
<u>10.3 Possibility of hazardous reactions</u>	No hazardous reactions are expected to occur.
<u>10.4 Conditions to avoid</u>	None known, for general advice see section 7.
<u>10.5 Incompatible materials</u>	None known.
<u>10.6 Hazardous decomposition products</u>	When heated to decomposition it emits toxic fumes and flammable vapors.
11. Toxicological information	
<u>11.1 Acute toxicity</u>	
<i>11.1.1 Inhalation</i>	- No data (publically) available or generated.
<i>11.1.2 Oral</i>	- Based on available data the classification criteria are not met. - Rat LD ₅₀ > 2000 mg/kg.
<i>11.1.3 Dermal</i>	- No data (publically) available or generated.
<u>11.2 Skin corrosion/irritation</u>	- Based on available data the classification criteria are not met.

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	- Not irritant/corrosive. Non-irritant following repeated applications to rabbit skin. Unlikely to cause skin irritation in man.
11.3 Serious eye damage/irritation	- Based on available data the classification criteria are not met. - Not classified as irritant to eyes. Non-irritant to rabbit eyes causing practically no initial pain. Unlikely to cause eye irritation in man.
11.4 Respiratory sensitisation	- No data (publically) available or generated.
11.5 Skin sensitization	- Based on available data the classification criteria are not met. - Not sensitising. It is not a skin sensitizer in animal tests. Unlikely to cause skin sensitization.
11.6 Germ cell mutagenicity	- Based on available data the classification criteria are not met. - A comprehensive battery of both <i>in vitro</i> and <i>in vivo</i> genotoxicity tests (yeast gene conversion, Ames, E. coli, CHO/HGPRT, human lymphocyte cytogenetic, mouse micronucleus, and rat bone marrow cytogenetic tests) has demonstrated BCM does not have genotoxic activity.
11.7 Carcinogenicity	- Category 2, suspected human carcinogen. - Limited evidence of carcinogenic effects. Studies in animals have shown that repeated doses produce cancer in rats and mice. - The compound is not mutagenic or genotoxic; a threshold mechanism is considered to be responsible for observed effects in animal testing. Therefore, single or incidental exposure to this substance -although under all circumstances undesired- is unlikely to represent a significant hazard with respect to cancer development.
11.8 Reproductive toxicity	- Category 1B, presumed human reproductive toxicant. - None of the effects mentioned below are likely to occur in humans, provided exposure is maintained at or below the occupational exposure limit. <u>Males:</u> In animal testing reproductive performance was reduced, but reversible after cessation of dosing. <u>Females:</u> - Fertility: In animal testing no effects on female fertility were observed. - Pregnancy: In animal testing evidence of suppressed sexual development was observed in the male offspring of female rats. This is in line with the pharmacological activity of the compound (see section 1). - Lactation: It is not known if BCM is excreted in human milk. Exercise caution.
11.9 STOT-single exposure	- No data (publically) available or generated.
11.10 STOT-repeated exposure	- Category 2, specific target organ(s): organs sensitive to androgens. Also see section 1. - Note that effects are primarily related to the (intended) pharmaceutical activity of the compound.
11.11 Aspiration hazard	No data (publically) available or generated.

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11.12 Other	See section 4.2.
12. Ecological information	
12.1 Toxicity	
12.1.1 <i>LC₅₀ (96 h, fish)</i>	- LC ₅₀ Rainbow trout 96 H (static) > 7.1 mg/l; NOEC: 7.1 mg/L. - LC ₅₀ Bluegill Sunfish 96 H (static) > 4.4 mg/L; NOEC: 4.4 mg/L.
12.1.2 <i>EC₅₀ (48 h, crustacea)</i>	- LC ₅₀ Daphnia magna 48 H (static) > 5.3 mg/L.
12.1.3 <i>ErC₅₀ (72 or 96 h, for algae or other aquatic plants)</i>	- EC ₅₀ green algae growth rate > 1.1 mg/L; NOEC: 1.1 mg/L.
12.1.4 Other	- NOEC fathead minnow 124d 0.01 mg/L (OECD 210); LOEC fathead minnow 124d 0.1 mg/L (OECD 210). - NOEC Daphnia magna 21d: 0.56 mg/L. - NOEC green algae 14d 1,1 mg/L. - NOEC blue-green algae 21d 1.1 mg/L. - EC ₅₀ bacteria, aerobic > 100 mg/l (tested at concentration above water solubility). - EC ₅₀ bacteria, anaerobic > 100 mg/l (tested at concentration above water solubility). - EC ₅₀ nitrifying bacteria > 100 mg/l (tested at concentration above water solubility). - Effect on effluent treatment: There is no evidence of inhibition to the aerobic treatment process at a concentration of 100 mg/L.
12.2 Persistence and degradability	- Not rapidly degradable. There is no evidence of hydrolysis in water. - Biological Oxygen Demand (BOD) 0%. - Chemical Oxygen Demand (COD) 1.47g O ₂ /g.
12.3 Bioaccumulative potential	
12.3.1 <i>Partition coefficient: n-octanol/water</i>	Log P _{ow} : 2.35 - 2.54.
12.3.2 <i>Bioconcentration factor</i>	- No data (publically) available or generated. - According to the originator (Astra Zeneca) the substance has low potential for bioaccumulation.
12.3.3 <i>Other information</i>	-
12.4 <i>Mobility in soil</i>	- The substance has moderate mobility in groundwater. - The substance has moderate mobility in soil. - Water solubility ≥ 1 mg/L.
12.5 <i>Results of PBT and vPvB assessment</i>	Not required/available.
12.6 <i>Other adverse effects</i>	-
13 Disposal considerations	
13.1 <i>Waste treatment methods</i>	Handle as chemical waste. Dispose according to Federal-, State- or Local laws. Keep away from drains, surface- and ground-water, and soil.

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14 Transport information	
14.1 UN number	1] 3077 (BCM drug substance). 2] 3077 (BCM, finished product, in bulk, non-retail).
14.2 UN Proper shipping name	Drug substance and finished product (see 14.1): 1] and 2]: ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (Bicalutamide)
14.3 Transport hazard class(es)	1] <u>BCM, drug substance</u> : ADR/RID: Class 9, M7, packing group III. ICAO/IATA: Class 9, packing group III. TARIC drug substance: 2930 90 98 00 (also see 14.8). 2] <u>BCM, finished product (in bulk)</u> : ADR/RID: Class 9, M7, packing group III. ICAO/IATA: Class 9, packing group III. TARIC (bulk) drug product(s): 3004 90 00 00.
14.4 Packing group	1] III. 2] III.
14.5 Environmental hazards	See sections 2 and 12.
14.6 Special precautions for user	None known.
14.7 Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code	Not relevant.
14.8 Other information	- Note that when compiling this document, in annex 3 of EU regulation 1001/2013 the CN code 2930 90 99 is still applied for BCM. - Note that pharmaceutical products ready for use and packaged for retail sale or distribution to patients are not subject to ADR. - LD₅₀ acute oral toxicity (LD(o)): > 2000 mg/kg. - LD₅₀ acute dermal toxicity (LD(d)): No data available. - LC₅₀ acute inhalatory toxicity (LD(i)): No data available.
15 Regulatory information	
15.1 Safety, health and environmental regulations/legislation specific for the substance	No specific information available/required.
15.2 Chemical safety assessment	To our knowledge, no CSA is required for this compound.
16 Other information	
16.1 Revisions	- Supersedes: SDS.NL01.15161 (1.0). Updates: section 2 and 12 (environmental data & classification added), section 14 (transport classification); also 3, 4, 7, 9, 11 (minor). - (D)SDS complies with EU regulation 1272/2008.
16.2 Abbreviations	BCM: Bicalutamide Cat.: Category CLP: Classification, Labelling & Packaging EHS: Environmental Health and Safety NOEL: No Observed Effect Level OEB: Occupational Exposure Band

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	OEL: Occupational Exposure limit STOT: Specific Target Organ Toxicity
<u>16.3 Key data sources</u>	- Casodex, FDA-NDA 20-498, 1995. - CASODEX (bicalutamide) tablet, for oral use, FDA label (doc no. 020498s027lbl), 17-03-2017. - RXlist Casodex, 03-08-2017. - Iswaran et al., J Toxicol Sci. 1997 May; 22(2):75-88. - MSDS Bicalutamide, AstraZeneca, 11-02-2009. - SDS Casodex tablets, v. 2.2, Astra Zeneca, 23-05-2016. - Therapeutic Drugs, 2nd edition, Dollery, C., 1999.
<u>16.4 Training advice</u>	Distribute this (D)SDS and relevant additional information to appropriate employees. If necessary, provide sufficient training to personnel with regard to safe working with hazardous materials.
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