Synthon

Safety Data Sheet
Anastrozole

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1. Identification of the substance and the company	
1.1 Product identifier	- Anastrozole (ANA). - CAS no.: 120511-73-1
1.2.a Uses	- ANA is used as an active ingredient in pharmaceutical formulations. - ANA is a selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations. It is indicated for the treatment of postmenopausal women with hormone receptor positive (or unknown) breast 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	Acute toxicity (oral), Category 3 Carcinogenicity, Category 2. Reproductive toxicity, 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)	H301: Toxic if swallowed. H351: Suspected of causing cancer. H360: May damage fertility or the unborn child. H373: May cause damage to organs sensitive to estrogens 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) = 10. - See section 9, 11 and 12.

3. Composition/information on ingredients	
3.1 Chemical names	1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5- (1H-1,2,4-triazol-1-ylmethyl).
3.2 Assay	98.0-102.0 % (HPLC, anhydrous basis).
3.3 Molecular formula	$C_{17}H_{19}N_5$.
3.4 Molecular weight	293.4
3.5 CAS number	120511-73-1
3.6 EC/REACH registration number	601-715-6 (EC).
4. First aid measures	
4.1 Description of first aid measures	
4.1.1 Inhalation	-Take proper precautions to ensure your own safety before attempting rescue (e.g. wear appropriate protective equipment). - If exposed, feeling unwell and/or concerned: get medical advice/attention (show this (D)SDS).
4.1.2 Skin	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).
4.1.3 Eyes	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).
4.1.4 Ingestion	If exposed, feeling unwell and/or concerned: get medical advice/attention (show this (D)SDS).
4.2 Most important symptoms and effects, both acute and delayed	- Acute: In a clinical setting, single doses up to 60 mg and daily doses up to 10 mg were tolerated. Exposure to ANA is not expected to result in severe acute effects. - Delayed: Reported side effects in clinical trials include amongst others asthenia, pain, headache, vasodilatation, hypertension, nausea, lymphoedema, arthritis, arthralgia, depression, rash and pharyngitis. - Consider effects related to the compounds classification (see section 11)
4.3 Indication of any immediate medical attention and special treatment needed	- Immediate medical advice may be required (show this (D)SDS). - There is no specific antidote to overdosage and treatment must be symptomatic.
5. Fire-fighting measures	
5.1 Extinguishing media	
5.1.1 Suitable extinguishing media	Use water, dry chemical powder (ABC) or appropriate foam.
5.1.2 Unsuitable extinguishing media	None known.
5.2 Special hazards arising from the substance or mixture	When heated to decomposition it emits toxic fumes and flammable vapours.

5.3 Advice for firefighters	- 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.
6. Accidental release measures	
6.1 Personal precautions, protective equipment and emergency procedures	
6.1.1 For non-emergency personnel	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.
6.1.2 For emergency responders	See row above and/or section 8.
6.2 Environmental precautions	Keep away from drains, surface- and groundwater, and soil.
6.3 Methods and material for containment and cleaning up	Wear protective clothing. See section 6.1
6.3.1. Containment of spill	Try to moisten the compound without raising dust.
6.3.2. Clean-up	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.
6.4 Reference to other sections	Refer to section 8, 11, 12 and 13 for additional information.
7. Handling and storage	
7.1 Precautions for safe handling	- Work in an area with general and local ventilation, if possible in a contained area. Prevent aerosol and dust generation.
7.1.1 Protective measures	- 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.
7.1.2 Advice on general occupational hygiene	Wear protective clothing (e.g. lab coat) and safety goggles, apply hygienic working habits (e.g. no drinking, eating or smoking at the workplace).
7.2 Conditions for safe storage	- Store in original packaging on a dry and dark place. - Default packaging material: Double low density polyethylene (LDPE) bags inside a high density polyethylene (HDPE) container. - Select storage locations and packaging material in line with relevant local chemical storage guidelines where relevant.
7.3 Specific end use(s)	ANA is used as an active ingredient in pharmaceutical

	formulations.
8. Exposure controls/personal protection	
8.1 Control parameters	
8.1.1 Exposure limit values	- 0.0001 mg/m^3 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 Currently recommended monitoring procedures	Please refer to local legislation. Alternatively reference to the ISPE good practice guide, ISBN 978-1-936379-35-4 is advised.
8.1.3 Occupational Exposure Band	- Synthon OEB: D (*deviation from default based on overall compound properties).* - 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: *Open handling within isolator or High-integrity closed coupling without external containment.* or *Local exhaust ventilation supplemented with personal protective equipment (see below).* Also see section 8.2.1. Please contact an EHS representative or Synthon for additional information.
8.2 Exposure controls	ANA can possibly enter the body through inhalation, ingestion and via the skin.
8.2.1 Generally Appropriate engineering controls	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 Individual protection measures, such as personal protective equipment	
- *Respiratory control*	*If required:* Use a (FF)P3 filter (USA: N100 or P100). The use of these filters in combination with a half/full face masks should be considered. Alternatively, using equipment suitable for use with a TH3 helmet/hood (higher assigned protection factor) can be considered.
- *Hand protection*	Wear gloves, for dust any glove is suitable, check solvent compatibility of gloves where relevant.

- *Eye protection*	Wear safety goggles.
- *Skin protection*	Wear suitable protective clothing (e.g. lab coat).
- *Other*	None.
8.3 Environmental exposure controls	- 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.
9. Physical and chemical properties	
9.1 General information	
Appearance	White to almost white powder.
Odour	No data (publically) available or generated.
Odour threshold	No data (publically) available or generated.
pH	No data (publically) available or generated.
Melting point	83 - 86 ˚C.
Initial boiling point and range	No data (publically) available or generated.
Flash point	No data (publically) available or generated.
Evaporation rate	No data (publically) available or generated.
Flammability (solid/gas)	No data (publically) available or generated.
Upper/lower Flammability or explosive limits	No data (publically) available or generated.
Vapour pressure	1.19 x 10^{-8} mm Hg at 25 deg C (est.).
Vapour density	No data (publically) available or generated.
Relative density	No data (publically) available or generated.
Solubility(ies)	- Water: 0.53 mg/ml at 25˚C. - Soluble in alcohols, acetone, acetonitrile, tetrahydrofuran.
Partition coefficient: n-octanol/water	Log P_{ow}: 1.56 °C.
Auto-ignition temperature	No data (publically) available or generated.
Decomposition temperature	No data (publically) available or generated.
Viscosity	No data (publically) available or generated.
Explosive properties	Dust explosion related data: *Minimum ignition temperature:* 500-550 ˚C. *Minimum ignition energy:* 2.5-10 mJ.
Oxidising properties	No data (publically) available or generated.
9.2 Other information	pKa: 2.4 (estimated, protonated form).
10. Stability and Reactivity	
10.1 Reactivity	Not considered to be a reactive compound.
10.2 Chemical stability	Stable (retest period 24 months) when stored under the storage conditions given in section 7 of this (D)SDS.
10.3 Possibility of hazardous reactions	No hazardous reactions are expected to occur.
10.4 Conditions to avoid	None known, for general advice see section 7.
10.5 Incompatible materials	None known.
10.6 Hazardous decomposition products	When heated to decomposition it emits toxic fumes and flammable vapors.

11. Toxicological information	
11.1 Acute toxicity	
11.1.1 Inhalation	- No data (publically) available or generated.
11.1.2 Oral	- Acute toxicity (oral), category 3. - Rat LD_{50}: 100 mg/kg < LD_{50} < 250 mg/kg.
11.1.3 Dermal	- No data (publically) available or generated.
11.2 Skin corrosion/irritation	- Based on available data the classification criteria are not met. - *In vitro and in vivo* data indicate that ANA has low topical irritant potential. - In a clinical setting, following oral dosing, skin rash and dermatitis have been reported.
11.3 Serious eye damage/irritation	- Based on available data the classification criteria are not met. - *In vivo* data indicate that ANA is non-irritating to eyes.
11.4 Respiratory sensitisation	- No data (publically) available or generated.
11.5 Skin sensitization	- Based on available data the classification criteria are not met. - *In vivo* data indicate that ANA does not induce an anaphylactic response.
11.6 Germ cell mutagenicity	- Based on available data the classification criteria are not met. - Not mutagenic in *in vitro* tests (Ames and E. coli bacterial tests, CHO-K1 gene mutation assay) or clastogenic either *in vitro* (chromosome aberrations in human lymphocytes) or *in vivo* (micronucleus test in rats).
11.7 Carcinogenicity	- Category 2, suspected human carcinogen. - Studies in animals have shown that repeated doses produce cancer in rats and mice some of which may be specific to animal species. The significance to humans is unknown. - 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. <u>Males:</u> No effects on fertility expected. However, in animal testing, exposure to ANA resulted in (reversible) effects on male reproductive organs. Fertility was however not compromized. <u>Females:</u> - Fertility: May impair fertility, studies in animals have shown that repeated doses produce adverse reproductive effects; recovery of fertility has been observed. - Pregnancy: Can cause fetal harm following exposure of a pregnant woman. A study in animals has shown that repeated doses produce embryo/foetotoxic effects in the absence of maternal toxicity. - Lactation: It is not known whether ANA is excreted in human milk. Contraindicated during breastfeeding. Withhold breastfeeding for 10 days following single exposures.

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 estrogens or containing/dependent on aromatase. Also see section 4. - ANA is a type II aromatase inhibitor and therefore all cells/organs containing aromatase will be affected following repeated exposure to ANA. These include breast tissue, reproductive organs and adipose tissue. Note that effects are primarily related to the (intended) pharmaceutical activity of the compound.
11.11 Aspiration hazard	No data (publically) available or generated.
11.12 Other	See section 4.2.
12. Ecological information	
12.1 Toxicity	
12.1.1 LC_{50} (96 h, fish)	- Bluegill fish: 84 mg/L; NOEC: 10 mg/L (96 hr). - Rainbow trout 75 mg/L; NOEC: 32 mg/L (96 hr).
12.1.2 EC_{50} (48 h, crustacea)	No data (publically) available or generated.
12.1.3 ErC_{50} (72 or 96 h, for algae or other aquatic plants)	No data (publically) available or generated.
12.1.4 Other	- Fish: NOEC Pimephales promelas (fathead minnow, flow through) 0.01 mg/L (104 Days). - Daphnia Magna LC_{50} > 18 mg/L (21 days), NOEC: 3.2 mg/L. Repeated doses produce no adverse reproductive effects up to the concentration of < 5.6 mg/L; no adverse effects on length up to the concentration of < 5.6 mg/L. - Green algae: No observed effect concentration (NOEC, growth rate, cell density): 27 mg/L (14 d). - NOEC (growth rate) blue-green algae: 3.0 mg/L (14 d). - NOEC (cell density) blue-green algae: 1.5 mg/L (14 d).
12.2 Persistence and degradability	- Percentage Aerobic Biodegradation: < 5% (OECD 301F). - Considered to be not readily biodegradable.
12.3 Bioaccumulative potential	
12.3.1 Partition coefficient: n-octanol/water	Log P_{ow}: 1.56.
12.3.2 Bioconcentration factor	- No data (publically) available or generated. - Considered to have low potential for bioaccumulation.
12.3.3 Other information	-
12.4 Mobility in soil	- The mobility depends on soil type. - Low mobility in soil (pH <5.8); Moderate mobility in soil (pH 7.7).
12.5 Results of PBT and vPvB assessment	Not required/available.
12.6 Other adverse effects	-

13 Disposal considerations	
13.1 Waste treatment methods	Handle as chemical waste. Dispose according to Federal-, State- or Local laws. Keep away from drains, surface- and ground-water, and soil.
14 Transport information	
14.1 UN number	1] 3077 (ANA drug substance). 2] 3077 (ANA, 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. (Anastrozole)
14.3 Transport hazard class(es)	1] ANA, drug substance: ADR/RID: Class 9, M7, packing group III. ICAO/IATA: Class 9, packing group III. TARIC drug substance: 2933 99 80 00. 2] ANA, finished product (in bulk): 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 pharmaceutical products ready for use and packaged for retail sale or distribution to patients are not subject to ADR. - LD_{50} acute oral toxicity (LD(o)): 100 mg/kg < LD_{50} < 250 mg/kg. - LD_{50} acute dermal toxicity (LD(d)): No data available. - LC_{50} acute inhalatory toxicity (LD(i)): No data available. Regulated under ADR/RID and/or ICAO/IATA due to compound classification as described in section 2 of this (D)SDS (therefore, classification not based on oral, dermal or inhalatory LD_{50} values; also see ADR 2017, section 2.2.61.1.6 or ICAO/IATA 57th edition, section 3.6.1.3.2).
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.NL01.15304 (1.0). Updates: Section 2 & 12 (environmental data & classification added) and 14 (transport classification); also 1, 4, 8, 9, 11 (minor changes). - (D)SDS complies with EU regulation 1272/2008.
16.2 Abbreviations	ANA: Anastrozole Cat.: Category CLP: Classification, Labelling & Packaging EHS: Environmental Health and Safety NOEL: No Observed Effect Level OEB: Occupational Exposure Band OEL: Occupational Exposure limit STOT: Specific Target Organ Toxicity
16.3 Key data sources	- Arimidex, RXlist, 09-08-2017. - Arimidex, website FASS.se, 09-08-2017. - Drugs during pregnancy and lactation, 2nd edition, Schaefer et al., 2007. - FDA-NDA 20-541, 20-541S006, 20-541S010, 20-541S016. - J. Endocrinol. 2000 Feb;164(2):225-38. - Safety data sheet Anastrozole, v.16.1, Astrazeneca, 08-07-2016. - Safety data sheet Arimidex, v.3.1, Astrazeneca, 03-10-2016.
16.4 Training advice	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.