Synthon

Safety Data Sheet
Eltrombopag olamine

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1. Identification of the substance and the company	
1.1 Product identifier	Eltrombopag olamine (ETG.dol) EC / List no.: 629-876-8 CAS no.: 496775-62-3
1.2.a Uses	ETG.dol is used as an active ingredient in pharmaceutical formulations. ETG.dol is a thrombopoietin receptor agonist inducing proliferation and differentiation from bone marrow progenitor cells. ETG.dol is indicated for the treatment of thrombocytopenia and aplastic anaemia.
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, Cat. 4 Serious eye damage/eye irritation, Cat. 2 Specific target organ toxicity after repeated exposure, Cat. 2 Long-term aquatic hazard, Cat. 1
2.2 Label elements	
2.2.1 Hazard Pictogram(s)	
2.2.2 Signal word(s)	**Warning.**
2.2.3 Hazard statement(s)	H302: Harmful if swallowed H319: Causes serious eye irritation H373: May cause damage to organs (eye-cataract, Kidney) through prolonged or repeated exposure H410: Very toxic to aquatic life with long lasting effects
2.2.4 Precautionary statement(s)	P273: Avoid release to the environment P280: Wear protective gloves/protective clothing/eye protection/face protection. P305+P351+P338: IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing. P314: Get Medical advice/attention if you feel unwell. 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: 1 See section 9, 11 and 12.

3. Composition/information on ingredients	
3.1 Chemical names	3'-{(2Z)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid-2-aminoethanol (1:2)
3.2 Assay/purity	98-100%
3.3 Molecular formula	$C_{25}H_{22}N_4O_4.2(C_2H_7NO)$
3.4 Molecular weight	564.65 g/mol
3.5 CAS number	496775-62-3
3.6 EC/REACH registration number	EC / List no.: 629-876-8
4. First aid measures	
4.1 Description of first aid measures	
4.1.1 Inhalation	If symptoms are experienced remove source of contamination or move victim to fresh air. Obtain medical advice (show this SDS).
4.1.2 Skin	No health effects expected. If irritation does occur, flush with lukewarm, gently flowing water for 5 minutes. If irritation persists, obtain medical advice (show this SDS).
4.1.3 Eyes	Avoid direct contact. Wear chemical protective gloves if necessary. Quickly and gently blot or brush chemical off the face. Immediately flush the contaminated eye(s) with lukewarm, gently flowing water for 15-20 minutes, while holding the eyelid(s) open. If a contact lens is present, DO NOT delay irrigation or attempt to remove the lens. Take care not to rinse contaminated water into the unaffected eye or onto the face. Immediately obtain medical attention (show this SDS).
4.1.4 Ingestion	If irritation or discomfort occur, obtain medical advice (show this SDS).
4.2 Most important symptoms and effects, both acute and delayed	– Acute: overdosage of 66 times the maximum human therapeutic dose induced mild rash, transient bradycardia, and elevated liver enzymes. Platelet counts may increase excessively and result in thrombotic/thromboembolic complications. – Delayed: most common adverse reactions were anemia, nausea, pyrexia, alanine aminotransferase increased, cough, fatigue, headache, and diarrhea. Uncommonly: new or worsened cataracts. High platelet counts increases the risk for blood clots in lungs and heart. Chronic liver disease increases the risk for a type of blood clot in the stomach area. ETG.dol does not stimulate platelet production in mice, rats or dogs. Therefore, animals data do not fully model potential adverse effects related to the pharmacological effect in humans, including the reproduction and carcinogenicity studies. – Consider effects related to the classification of the compound (see section 11).

4.3 Indication of any immediate medical attention and special treatment needed	Medical advice may be required (show this SDS). In case of overdosage, oral administration of a metal cation-containing preparation should be considered to chelate ETG.dol and thus limit absorption. Platelet counts should be closely monitored. ETG.dol is not renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to enhance the elimination.
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 an (FF)P3 filter (USA: N100 or P100). 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 at room temperature in the dark, in sealed containers and protected from moisture. – Also see supplementary information, e.g. shipping documentation, CoA or contact Synthon. – Select storage locations and packaging material in line with relevant local chemical storage guidelines where relevant.
7.3 Specific end use(s)	ETG.dol is used as an active ingredient in pharmaceutical formulations.
8. Exposure controls/personal protection	
8.1 Control parameters	
8.1.1. Exposure limit values	0.100 mg/m^3 Time Weighted Average for 8 hours (Synthon and originator OEL). No 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: C 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 +/- personal protective equipment (see below).* *or* *Controlled general ventilation supplemented with personal protective equipment (see below).* Also see section 8.2.1. Please contact a EHS representative or Synthon for additional information.

8.2 Exposure controls	ETG.dol can possibly enter the body through inhalation, ingestion and via the skin.
8.2.1 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 should be used. Where necessary, safety measures should be supplemented with respiratory protection equipped with a (FF)P3 filter (USA: N100 or P100). 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).
- *Hand protection*	Wear gloves, for dust any glove is suitable, check liquid compound or 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	Red to brown crystalline solid
Odour	No data (publically) available or generated.
Odour threshold	No data (publically) available or generated.
pH	8.39 (1%w/v aq. Suspension).
Melting point/freezing point	No data (publically) available or generated.
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	No data (publically) available or generated.
Vapour density	No data (publically) available or generated.
Relative density	No data (publically) available or generated.
Solubility(ies)	Practically insoluble in water (pH 4.5) and methanol (pH 7.5). Very Sparingly soluble in Dimethyl sulphoxide.
Partition coefficient: n-octanol/water	log K_{ow} > 4.52
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	No data (publically) available or generated.
Oxidising properties	No data (publically) available or generated.
9.2 Other information	Non hygroscopic.
10. Stability and Reactivity	
10.1 Reactivity	Not considered to be a reactive compound.
10.2 Chemical stability	Stable (for 5 years) when stored under the storage conditions given in section 7 of this 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, Cat. 4 LD_{50} Dog > 300 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. Non-irritant in Reconstituted Human Epidermis.
11.3 Serious eye damage/irritation	Serious eye damage/eye irritation, Cat. 2 Severe irritant in Reconstituted Human Corneal Epithelium.
11.4 Respiratory sensitisation	No data (publically) available or generated.
11.5 Skin sensitisation	Based on available data the classification criteria are not met. Non skin sensitizer in Local Lymph Node Assay-Mouse
11.6 Germ cell mutagenicity	Based on available data the classification criteria are not met. ETG.dol was not mutagenic or clastogenic in a bacterial mutation assay or *in vivo* assays in rats (micronucleus and unscheduled DNA synthesis). In an *in vitro* mouse lymphoma assay, ETG.dol was positive.
11.7 Carcinogenicity	Based on available data the classification criteria are not met. ETG.dol was not carcinogenic in mice.
11.8 Reproductive toxicity	Based on available data the classification criteria are not met. Males: no adverse effects on fertility. Females: – Fertility: no adverse effects on fertility. – Pregnancy: no observed effects on early embryonic or embryofoetal development in rats and rabbits. In rats, there were no adverse effects on pregnancy, parturition of F0 rats at no effects on the growth, development, neurobehavioural or reproductive function of the offspring (F1). – Lactation: ETG.dol was detected in the plasma of all F1 rat pups after lactation. It is not known whether ETG.dol is excreted in human milk. Exercise caution.

11.9 STOT-single exposure	Based on available data the classification criteria are not met. In dogs, 100 mg/kg was tolerated. 300 mg/kg was poorly tolerated and was associated with decreased body weight, vomiting, abnormal feaces, decreased spontaneous motor activity and moderate body weight reduction.
11.10 STOT-repeated exposure	Specific target organ toxicity after repeated exposure, Cat. 2 Dose-dependent cataracts were detected in rodents 2 times the human clinical dose. Renal tubular toxicity in rodents starting from 0.6 times the human clinical dose. No hepatic effects, no effects on red cell mass or reticulocyte counts, and no bone changes (endosteal hyperostosis) in rodents at maximum tolerated doses 2 times the human clinical dose.
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)	Rainbow trout (Juvenile Oncorhyncus mykiss) EC_{50} = 3.19 mg/l NOEC = 2 mg/l
12.1.2 E(L)C_{50} (48 h, crustacea)	Water flea (Daphnia magna) EC_{50} = 1.9 mg/l NOEC = 0.69 mg/l
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	Activated Sludge, respiration 3 hours IC_{50} > 320 mg/l NOEC > 32 mg/l Duckweed (Lemna minor), 7 days EC_{50} = 1.53 mg/l NOEC = 0.57 mg/l, 7 days Water flea (Daphnia magna), 21 days LOEC = 0.44 mg/l NOEC = 0.15 mg/l Zebra danio (Danio rerio), 30 days LOEC = 0.2 mg/l NOEC = 0.067 mg/l
12.2 Persistence and degradability	Hydrolysis half-life = 16 days. Aerobic biodegradation-inherent, 28 days: 10 %
12.3 Bioaccumulative potential	
12.3.1. Octanol/water partition coefficient.	log K_{ow} > 4.52
12.3.2. Bioconcentration factor	14 (rainbow trout, oncorhynchus mykiss)
12.3.3. Other information	No relevant data available.
12.4 Mobility in soil	Sludge/Biomass Distribution Coefficient - log K_d =3.33-3.37 Soil/Sediment Sorption - log K_{oc} = 4.99-5.19
12.5 Results of PBT and vPvB assessment	Not required/available.

12.6 Other adverse effects	No relevant data (publically) available or generated.
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. Please contact a EHS representative for additional information.
14 Transport information	
14.1 UN number	1] 3077 (ETG.dol, drug substance). 2] Not relevant/required (finished product in bulk, non-retail).
14.2 UN Proper shipping name	1] ENVIRONMENTALLY HAZARDOUS SUBSTANCE, SOLID, N.O.S. (eltrombopag olamine). 2] Not relevant/required
14.3 Transport hazard class(es)	1] ETG.dol, drug substance: ADR/RID: Class 9, M7, Packing group III. ICAO/IATA: Class 9, Packing group III. TARIC: 2933 19 90 90 (CN code 29331990). 2] Finished product (in bulk, non-retail): ADR/RID: Not subject to ADR/RID. ICAO/IATA: Not subject to ICAO/IATA. TARIC: 3004 90 00 00.
14.4 Packing Group	1] III. 2] Not relevant/required.
14.5 Environmental hazards	Not environmentally hazardous. See section 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	LD_{50} acute oral toxicity (LD(o)): >300 mg/Kg LD_{50} acute dermal toxicity (LD(d)): no available data. LC_{50} acute inhalatory toxicity (LD(i)): no available data. 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 2021, section 2.2.61.1.6 or ICAO/IATA 61st edition, section 3.6.1.3.2). Exception for UN3082 and UN3077: Materials contained in good quality packaging in quantities ≤ 5 kg/5L (per single or inner packaging) are not regulated as dangerous goods for transport (see ICAO-TI 2017/2018 special provision A197 or ADR 2021§5.2.1.8.1).]

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 (as part of EU-REACH, (EC) No 1907/2006).	To our knowledge, no CSA is required for this compound.
16 Other information	
16.1 Revisions	Supersedes: SDS.NL01.61715 (1.0) Serious eye damage/eye irritation, changed to Cat. 2.
16.2 Abbreviations	CLP: Classification, Labelling & Packaging OEB: Occupational Exposure Band OEL: Occupational Exposure limit STOT: Specific Target Organ Toxicity
16.3 Key data sources	EPAR - Product Information. 26-04-2022. FDA label NDA 022291. 10-2021 GSK SDS. V.02. 14-04-2021 NOVARTIS product monograph. #247826. 03-11-2021
16.4 Training advice	Distribute this SDS and relevant additional information to appropriate employees. If necessary, provide sufficient training to personnel with regard to safe working with hazardous materials.