SAFETY DATA SHEET

SECTION 1 - IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/ UNDERTAKING

Contact information

General

AMAG Pharmaceuticals, Inc
1100 Winter Street, Waltham, MA 02451
Main: +1 (617) 498-3300
Fax: +1 (617) 649-1632
sds@amagpharma.com

Emergency telephone number

Chemtrec *(24-hour availability)*:
+1 (800) 424-9300 (USA and Canada)
+1 (703) 527-3887 (International; collect calls accepted)

Product identifier

Hydroxyprogesterone Caproate for Injection

Synonyms

HPC; 17α-Hydroxyprogesterone Caproate; 17α-Hexanoyloxypregn-4-ene-3,20-dione

Trade names

MAKENA®

Chemical family

Mixture

Relevant identified uses of the substance or mixture and uses advised against

Bulk formulated pharmaceutical product/Formulated pharmaceutical product packaged in final form and intended for the final user.

Note

This SDS is written to address potential worker health and safety issues associated with the handling of the formulated drug product.

SECTION 2 - HAZARDS IDENTIFICATION

Classification of the substance or mixture

Drugs in the finished state and intended for the final user are not subject to labeling in the US, EU or Canada. Please consult the prescribing/packaging information. **The classification and labeling listed below is for bulk drug product.**

Globally Harmonized System [GHS]

Reproductive Toxicity - Category 1A. Aquatic toxicity (acute) - Category 1.

SECTION 2 - HAZARDS IDENTIFICATION …continued

Label elements

GHS hazard pictogram

GHS signal word

Danger

GHS hazard statements

H360DF - May damage fertility or the unborn child. H400 - Very toxic to aquatic life.

GHS precautionary statements

P201 - Obtain special instructions before use. P202 - Do not handle until all safety precautions have been read and understood. P273 - Avoid release to the environment. P281 - Use personal protective equipment as required. P308 + P313 - If exposed or concerned: get medical advice/attention. P391 - Collect spillage. P405 - Store locked up. P501 - Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Other hazards

Each 5 mL multidose vial contains 1250 mg hydroxyprogesterone caproate. Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.** The most commonly reported adverse effects include injection site reactions (pain, swelling, itchiness) gastrointestinal (GI) discomfort, headache, dizziness, depression, chest discomfort, difficulty breathing, and urinary tract infections, changes to the cervix, and premature rupture of membranes. An increased incidence of fetal and maternal complications was observed, including miscarriage and stillbirth, preterm labor, gestational hypertension, and gestational diabetes. There are no adequate and well-controlled studies of Makena use in women during the first trimester of pregnancy. Data from a placebo-controlled clinical trial did not demonstrate any teratogenic risks to infants from in utero exposure to Makena during the second or third trimesters. Though not currently indicated for this purpose, hydroxyprogesterone caproate has been used in non-pregnant women to treat menstrual disorders.

Note

This product is classified as hazardous according to Regulation EC No 1272/2008 (EU CLP) and Hazard Communication Standard No. 1910.1200 (US OSHA).

SECTION 3 - COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient	CAS #	EINECS/ ELINCS#	Amount	GHS Classification
Benzyl benzoate	120-51-4	204-402-9	40-50%	ATO4: H302; AA1: H400
Hydroxyprogesterone Caproate	630-56-8	211-138-8	20-30%	RT1A: H360DF
Benzyl alcohol	100-51-6	202-859-9	<5%	ATO4: H302; ATI4: H332

Note The ingredient(s) listed above are considered hazardous and/or are the active ingredient. The remaining components are non-hazardous and/or present at amounts below reportable limits. See Section 16 for full text of GHS classifications.

SECTION 4 - FIRST AID MEASURES

Description of first aid measures

Immediate Medical Attention Needed Yes. If exposed or concerned: Get medical advice/attention.

Eye Contact If easy to do, remove contact lenses, if worn. Immediately flush eyes with copious quantities of water for at least 15 minutes. If irritation occurs or persists, notify medical personnel and supervisor.

Skin Contact Wash exposed area with soap and water and remove contaminated clothing/shoes. If irritation occurs or persists, notify medical personnel and supervisor.

Inhalation Immediately move exposed subject to fresh air. If not breathing, give artificial respiration. If breathing is labored, administer oxygen. Immediately notify medical personnel and supervisor.

Ingestion If swallowed, call a physician immediately. Do not induce vomiting unless directed by medical personnel. Do not give anything to drink unless directed by medical personnel. Never give anything by mouth to an unconscious person. Notify medical personnel and supervisor.

Protection of first aid responders See Section 8 for Exposure Controls/Personal Protection recommendations.

Most important symptoms and effects, both acute and delayed See Sections 2 and 11.

Indication of immediate medical attention and special treatment needed, if necessary Medical conditions aggravated by exposure: hormone-sensitive cancers, liver disease, thromboembolic disorders, or uncontrolled hypertension. Treat symptomatically and supportively. If accidental exposure occurs to an individual who is also taking one or more concomitant medications, consult the respective package or prescribing information for potential drug-drug interactions.

SECTION 5 - FIREFIGHTING MEASURES

Extinguishing media	Use water spray (fog), foam, dry powder, or carbon dioxide, as appropriate for surrounding fire and materials.
Specific hazards arising from the substance or mixture	May emit carbon monoxide or carbon dioxide.
Flammability/ Explosivity	No information identified for product.
Advice for firefighters	Wear full protective clothing and a self-contained breathing apparatus with a full facepiece operated in the pressure demand or other positive pressure mode. Decontaminate all equipment after use.

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures	If product is released or spilled, take proper precautions to minimize exposure by using appropriate personal protective equipment (see Section 8). Do not breathe mist/vapors/spray.
Environmental precautions	Do not empty into drains. Avoid release to the environment.
Methods and material for containment and cleaning up	If vials are crushed or broken, DO NOT CAUSE MATERIAL TO BECOME AIRBORNE. For small spills, soak up material with absorbent, e.g., paper towels. For large spills, cordon off spill area and minimize the spreading of spilled material. Soak up material with absorbent. Collect spilled material, absorbent, and rinse water into suitable containers for proper disposal in accordance with applicable waste disposal regulations (see Section 13). Decontaminate the area twice.
Reference to other sections	See Sections 8, 9 and 13 for more information.

SECTION 7 - HANDLING AND STORAGE

Precautions for safe handling	Follow recommendations for handling bulk formulated/packaged pharmaceutical agents (i.e., use of engineering controls and/or other personal protective equipment if needed). Wash thoroughly after handling.
Conditions for safe storage including any incompatibilities	Store at room temperature. Protect from freezing, light, and extreme heat.
Specific end use(s)	No information identified.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION

Note Dispose of broken vials/syringes in a sharps container.

Control Parameters/ Occupational Exposure Limit Values

Compound	Issuer	Type	OEL
Benzyl benzoate	--	--	--
Hydroxyprogesterone Caproate	Lumara	8-hour TWA (DRAFT)	10 μg/m3
Benzyl alcohol	AIHA	TWA-8 HR	10 ppm
	Bulgaria, Latvia	TWA-8 HR	5 mg/m^3
	Czech Republic	TWA-8 HR	40 mg/m^3
	Czech Republic	Ceiling	80 mg/m^3
	Lithuania	TWA-8 HR	5 mg/m^3 (skin)
	Poland	TWA-8 HR	240 mg/m^3

Exposure/Engineering controls None required for normal handling of packaged product. If vials are crushed or broken: Control exposures to below the OEL (if available). Otherwise, selection and use of containment devices and personal protective equipment should be based on a risk assessment of exposure potential. Open handling should not be performed when handling potent substances, or substances of unknown toxicity. Material should be handled inside a closed process, ventilated enclosure, isolator or device of equivalent or better control that is suitable for dusts and/or aerosols.

Respiratory protection None required for normal handling of packaged product. If vials are crushed or broken: Choice of respiratory protection should be appropriate to the task and the level of existing engineering controls. For routine powder handling tasks, an approved and properly worn powered air-purifying respirator equipped with HEPA filters or combination filters should provide ancillary protection based on the known or foreseeable limitations of existing engineering controls. Use a positive-pressure air-supplied respirator if there is any potential for an uncontrolled release, when exposure levels are not known, or in any other circumstances where air purifying respirators may not provide adequate protection.

Hand protection None required for the normal handling of packaged product. Wear nitrile or other impervious gloves if skin contact is possible. Double gloves should be considered.

Skin protection Wear appropriate gloves, lab coat, or other protective overgarment if skin contact is likely. Base the choice of skin protection on the job activity, potential for skin contact and solvents and reagents in use.

Eye/face protection Wear safety glasses with side shields, chemical splash goggles, or full face shield, if necessary. Base the choice of protection on the job activity and potential for contact with eyes or face. An emergency eye wash station should be available.

SECTION 8 - EXPOSURE CONTROLS/PERSONAL PROTECTION …continued

Environmental Exposure Controls	Avoid release to the environment and operate within closed systems wherever practicable. Air and liquid emissions should be directed to appropriate pollution control devices. In case of spill, do not release to drains. Implement appropriate and effective emergency response procedures to prevent release or spread of contamination and to prevent inadvertent contact by personnel.
Other protective measures	Wash hands in the event of contact with this substance, especially before eating, drinking or smoking. Protective equipment is not to be worn outside the work area (e.g., in common areas or out-of-doors).

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance	Solution in pre-filled vial.
Color	Colorless to slightly yellow.
Odor	No information identified.
Odor threshold	No information identified.
pH	No information identified.
Melting point/ freezing point	No information identified.
Initial boiling point and boiling range	No information identified.
Flash point	No information identified.
Evaporation rate	No information identified.
Flammability (solid, gas)	No information identified.
Upper/lower flammability or explosive limits	No information identified.
Vapor pressure	No information identified
Vapor density	No information identified.
Relative density	No information identified.
Water solubility	No information identified.
Solvent solubility	No information identified.

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES …continued

Partition coefficient (*n-octanol/water*)	No information identified.
Auto-ignition temperature	No information identified.
Decomposition temperature	No information identified.
Viscosity	No information identified.
Explosive properties	No information identified.
Oxidizing properties	No information identified.

Other information

Molecular weight	Not applicable (Mixture)
Molecular formula	Not applicable (Mixture)

SECTION 10 - STABILITY AND REACTIVITY

Reactivity	No information identified.
Chemical stability	Stable under normal handling and storage conditions.
Possibility of hazardous reactions	Not expected to occur.
Conditions to avoid	No information identified.
Incompatible materials	No information identified.
Hazardous decomposition products	No information identified.

SECTION 11 - TOXICOLOGICAL INFORMATION

Note	No data for this product/mixture were identified. The following data describe the active ingredient and/or the individual ingredients where applicable.

Information on toxicological effects

Route of entry	May be absorbed by inhalation, skin contact and ingestion.

Acute toxicity

Compound	Type	Route	Species	Dose
Benzyl benzoate	LD_{50}	Oral	Rat	1700 mg/kg
	LD_{50}	Dermal	Rat	4000 mg/kg
	LD_{50}	Oral	Rabbit	1680 mg/kg
	LD_{50}	Dermal	Rabbit	4000 mg/kg
	LD_{50}	Oral	Mouse	1400 mg/kg
Hydroxyprogesterone Caproate	--	--	--	--
Benzyl alcohol	LC_{50}	Inhalation	Rat	8.8 mg/L/4 hours
	LD_{50}	Oral	Rat	1230 - 3100 mg/kg
	LD_{50}	Dermal	Rabbit	2000 mg/kg
	LD_{50}	Oral	Mouse	1150 - 1580 mg/kg

Irritation/Corrosion Benzyl alcohol was slightly irritating to rabbit skin and irritating to rabbit eyes.

Sensitization Benzyl alcohol is not a skin sensitizer. No data were identified for the other ingredients.

STOT-single exposure No studies identified.

STOT-repeated exposure/Repeat-dose toxicity No studies identified.

Reproductive toxicity In a multi-generation study, the offspring of treated rats were followed throughout adulthood and their reproductive parameters were assessed. Fertility and embryofetal development were not affected following IM doses of up to 150 mg/kg/week.

Developmental toxicity There are no adequate and well-controlled studies of Makena use in women during the **first trimester** of pregnancy. Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received Makena at weekly doses of 250 mg by intramuscular injection in their second and third trimesters, as well as long-term (2-5 years) follow-up safety data on 194 of their infants, did not demonstrate any teratogenic risks to infants from in utero exposure to Makena. Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Makena. Makena administration produced embryolethality in rhesus monkeys but not in cynomolgus monkeys exposed to 1 and 10 times the human dose equivalent every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either species.

Genotoxicity Hydroxyprogesterone caproate, benzyl benzoate, and benzyl alcohol were negative in genotoxicity assays

Carcinogenicity None of the components of the mixture present at levels greater than or equal to 0.1% are listed by NTP, IARC, ACGIH or OSHA as a carcinogen.

Aspiration hazard No data available.

SECTION 12 - ECOLOGICAL INFORMATION

Toxicity

Compound	Type	Species	Concentration
Benzyl benzoate	LC_{50}/96h	Danio rerio (zebra fish)	1.34 mg/L
	EC_{50}/72h	Algae	0.475 mg/L
	LC_{50}/24h	Gammarus fasciatus (fresh water shrimp)	9.8 mg/L
	LC_{50}/96h	Gammarus fasciatus (fresh water shrimp)	4.8 mg/L
Hydroxyprogesterone Caproate	--	--	--
Benzyl alcohol	LC_{50}/48h	*Leuciscus idus* (freshwater fish)	646 mg/L
	LC_{50}/96h	Fathead minnow	460 mg/L
	EC_{50}/48h	Daphnia magna	≥100-360 mg/L
	EC_{50}/48h	Bacteria (*E.coli*)	1000 mg/L

Additional toxicity information No data available.

Persistence and Degradability Benzyl alcohol is readily biodegradable. No data were identified for the other ingredients.

Bioaccumulative potential No data available.

Mobility in soil No data available.

Results of PBT and vPvB assessment Not performed.

Other adverse effects No data available.

Note The environmental characteristics of this mixture have not been fully investigated. Releases to the environment should be avoided.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste treatment methods Used product should be disposed of according to local, state, and federal regulations. Do not send down the drain or flush down the toilet. All wastes containing the material should be properly labeled. Dispose of wastes in accordance to prescribed federal, state, and local guidelines, e.g., appropriately permitted chemical waste incinerator. Rinse waters resulting from spill cleanups should be discharged in an environmentally safe manner, e.g., appropriately permitted municipal or on-site wastewater treatment facility.

SECTION 14 - TRANSPORT INFORMATION

Transport	Based on the available data, this product/mixture may be regulated as a hazardous material/dangerous good under EU ADR/RID, US DOT, Canada TDG, IATA, or IMDG. Limited Quantity Exemptions may apply for the product packaged in final form for patient use.
UN number	3082
UN proper shipping name	Environmentally Hazardous Substance, liquid, n.o.s (contains benzyl benzoate)
Transport hazard classes and packing group	Hazard Class - 9; Packing Group III.
Environmental hazards	Based on the available data, this product/mixture is regulated as an environmental hazard or a marine pollutant.
Special precautions for users	Avoid release to the environment.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.

SECTION 15 - REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture	This SDS generally complies with the requirements listed under current guidelines in the US, EU and Canada.
Chemical safety assessment	Not conducted.
WHMIS classification	H360DF - May damage fertility or the unborn child, H400 - Very toxic to aquatic life.
TSCA status	Drugs are exempt from TSCA.
SARA section 313	Not listed.
California proposition 65	Not listed.
Additional information	No other information identified.

SECTION 16 - OTHER INFORMATION

Full text of H phrases and GHS classifications	RT1A - Reproductive toxicity Category 1A. H360DF - May damage fertility or the unborn child. ATO4 - Acute Toxicity (Oral) Category 4. H302 - Harmful if swallowed. AA1- Acute aquatic toxicity Category 1. H400 - Very toxic to aquatic life. ATI4 - Acute Toxicity (Inhalation) Category 4. H332 - Harmful if inhaled.
Sources of data	Information from published literature and internal company data.
Abbreviations	ACGIH - American Conference of Governmental Industrial Hygienists; ADR/RID - European Agreement Concerning the International Carriage of Dangerous Goods by Road/Rail; AIHA - American Industrial Hygiene Association; CAS# - Chemical Abstract Services Number; CLP - Classification, Labelling, and Packaging of Substances and Mixtures; DNEL - Derived No Effect Level; DOT - Department of Transportation; EINECS - European Inventory of New and Existing Chemical Substances; ELINCS - European List of Notified Chemical Substances; EU - European Union; GHS - Globally Harmonized System of Classification and Labeling of Chemicals; IARC - International Agency for Research on Cancer; IDLH - Immediately Dangerous to Life or Health; IATA - International Air Transport Association; IMDG - International Maritime Dangerous Goods; LOEL - Lowest Observed Effect Level; LOAEL - Lowest Observed Adverse Effect Level; NIOSH - The National Institute for Occupational Safety and Health; NOEL - No Observed Effect Level; NOAEL - No Observed Adverse Effect Level; NTP - National Toxicology Program; OEL - Occupational Exposure Limit; OSHA - Occupational Safety and Health Administration; PNEC - Predicted No Effect Concentration; SARA - Superfund Amendments and Reauthorization Act; STEL - Short Term Exposure Limit; TDG - Transportation of Dangerous Goods; TSCA - Toxic Substances Control Act; TWA - Time Weighted Average; WHMIS - Workplace Hazardous Materials Information System
Issue Date	29 June 2015
Revisions	This is the first version of this SDS.
Disclaimer	The above information is based on data available to us and is believed to be correct. Since the information may be applied under conditions beyond our control and with which we may be unfamiliar, we do not assume any responsibility for the results of its use and all persons receiving it must make their own determination of the effects, properties and protections which pertain to their particular conditions. No representation, warranty, or guarantee, express or implied (including a warranty of fitness or merchantability for a particular purpose), is made with respect to the materials, the accuracy of this information, the results to be obtained from the use thereof, or the hazards connected with the use of the material. Caution should be used in the handling and use of the material because it is a potent pharmaceutical product. The above information is offered in good faith and with the belief that it is accurate. As of the date of issuance, we are providing all information relevant to the foreseeable handling of the material. However, in the event of an adverse

Disclaimer …continued	incident associated with this product, this Material Safety Data Sheet is not, and is not intended to be, a substitute for consultation with appropriately trained personnel.