Safety Data Sheet
Irinotecan Hydrochloride Injection

1 - Identification of the substance/mixture and of the company undertaking

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MATERIAL IDENTIFICATION:

Product Name: **Irinotecan Hydrochloride Injection**

Synomyms: CPT-11, Camptosar, Campto.

Chemical Name: (*S*)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxol*H*pyrano[3',4':6,7]-indolizino[1,2-b]quniolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate; (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4'-bipiperidine]-1' carboxylate hydrochloride trihydrate.

Chemical Formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$.

Product Type: Regulated sterile injectible prescription drug.

Intended Use: Antineoplastic enzyme inhibitor primarily used in the treatment of colorectal cancer.

Product Supply: 40 mg/2 ml or 100 mg/5 ml or 500mg /25 ml in amber glass vials.

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 Irinotecan Hydrochloride.**

Hazard Statement(s): H302 - Harmful if swallowed.
Active ingredient is cytotoxic and will produce severe toxic effects to rapidly dividing tissues upon over-exposure. Suspected of damaging

the unborn child. Possible mutagen. Gastrointestinal effects. Blood effects. May cause allergic reactions.

Specific hazards: Possible foetal development hazard that may adversely affect the developing foetus.

EU Hazard Symbols:

Label elements

Pictogram

Signal word Warning

Hazard statement(s)

H341 Suspected of causing genetic defects.
H361 Suspected of damaging fertility or the unborn child.

Precautionary statement(s)

P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P281 Use personal protective equipment as required.
P308 + P313 If exposed or concerned: Get medical advice/attention.
P405 Store locked up.
P501 Dispose of contents/container in accordance with national regulations.

EU Risk Phrases: R61 – May cause harm to the unborn child.
R68 – Possible risk of irreversible effects.

EU Indication of Danger: Toxic to reproduction, Category 2.
Mutagenic, Category 3.

Principle Routes of Entry: Eye/skin contact or ingestion.

Inhalation: Inhalation is not considered likely under normal usage conditions.

Ingestion: May be harmful if swallowed (based upon animal data). Gastrointestinal effects (may include nausea/vomiting, abdominal pain, diarrhoea, dry mouth, colic). Blood effects (may include anaemia, neutropenia, thrombocytopenia, bone marrow depression). Dermatologic effects (may include exfoliative dermatitis, photosensitivity, rash, itching). Nervous system effects (headache, dizziness, light headedness). Cardiovascular effects (may include fluctuations in heart rate, changes in blood pressure, chest pain). Anaemia.

Skin Contact: May cause irritation and/or allergic reactions, particularly to cut or abraded skin.

Eye Contact: Potential for eye irritation. May cause allergic reaction.

3. COMPOSITION

Hazardous

Ingredients	CAS Number	EU EINECS/ ELINCS List	Classification	%
Irinotecan hydrochloride trihydrate	136572-09-3	Not listed	Mut. Cat. 3; R68; Repr. Cat. 2; R60; R61; T; R22	1-5
Lactic acid	79-33-4	200-018-0	Not listed	0-1%
Sodium hydroxide	1310-73-2	215-185-5	C; R35 T; R23	trace

Sodium hydroxide is present in trace quantities for pH adjustment.

Non-Hazardous

Ingredients	CAS Number	EU EINECS/ELINCS List	Classification	%
Water for Injection	7732-18-5	231-791-2	Not listed	>95
Sorbitol	50-7-4	200-061-5	Not listed	1-5

The product typically contains 2 % Irinotecan, as irinotecan hydrochloride trihydrate. It is a sterile solution in water with a pH of 3.5 and is intended for dilution prior to intravenous infusion.

This document has been prepared in accordance with standards for workplace safety, which require the inclusion of all known hazards of the substances, regardless of the potential risk. This document does not serve as a risk assessment. The precautionary statements and warnings included may not apply in all cases. Any workplace risk assessment should take into account the hazards detailed within this document.

4. FIRST AID MEASURES

See patient insert for additional information.

Inhalation: Remove to fresh air and keep patient still. Seek medical attention immediately. If patient is unconscious, provide artificial respiration. If breathing is difficult, give oxygen.

Skin contact: Remove contaminated clothing and footwear. Flush affected area of skin with copious quantity of soap and water. Seek medical attention if irritation occurs. Wash contaminated clothing before reuse.

Prophylactic or therapeutic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine may be considered in employees experiencing rhinitis, increased salivation, miosis, lachrymation, diaphoresis, flushing, abdominal cramping or diarrhoea (occurring shortly after exposure to irinotecan). These symptoms are expected to occur more frequently with higher irinotecan exposures.

Eye contact: Immediately irrigate eye/s with water, whilst holding eyelids open, for at least 15 minutes. Seek medical attention if irritation occurs.

Ingestion: Wash out mouth with water. Do NOT induce vomiting unless directly by medical personnel. Seek medical attention immediately.

5. FIRE FIGHTING MEASURES

Suitable extinguishing media: Use carbon dioxide, dry chemical or water spray as appropriate to surroundings.

Unsuitable extinguishing media: Not known.

Special hazards in fire: During thermal decomposition, the formation of irritating vapours or fumes may be possible (i.e. oxides of carbon, oxides of nitrogen and hydrogen chloride).

Firefighting instructions: Wear appropriate personal protective equipment, including self-contained breathing apparatus (SCBA).

6. ACCIDENTAL RELEASE MEASURES

Personnel precautions: Wear suitable protective clothing and gloves (see Section 8 – Exposure Controls).

Environmental precautions: Eliminate releases to drains, water courses and emissions to atmosphere.

Methods for cleaning: Contain spills with absorbent material (i.e. booms, towels, granules) and then place soiled materials in suitable sealed container for disposal as chemical waste. Clean affected area with soapy water.
Solutions of Irinotecan Hydrochloride will fluoresce blue/white under an ultraviolet light at a wavelength of 365 nm. This property can be used to assess the extent of any spill or the effectiveness of the cleanup operation.

Additional considerations: If a large spill occurs, evacuate non-essential personnel. Report emergency situations immediately. Clean-up operations should only be performed by trained personnel.

7. HANDLING AND STORAGE

Handling: Wash hands thoroughly after handling and before eating, drinking or smoking.

As with all potent pharmaceutical products, avoid contact and inhalation of dust, fumes, mist and/or vapours associated with the product.

Storage: To prevent deterioration of the product, keep in sealed container until time of use. Store between 15-30 ºC and out of direct sunlight.

Incompatible products: No special restrictions on storage with other products.

Special precautions: Persons with known hypersensitivities to irinotecan products, pregnant women, or women who want to become pregnant, should consult an occupational health and/or safety professional prior to handling this material.

8. EXPOSURE CONTROLS

Engineering measures: During dilution or reconstitution, use a biological safety cabinet or other ventilated enclosure designed to miminise airborne exposure. This should discharge HEPA filtered air external to the room environment.

Ensure a safety shower and eye wash is available for personnel involved in handling larger quantities of product (i.e. during dilution or reconstitution). Ensure an eyewash is available during drug administration.

Respiratory protection: Not usually required for normal final use conditions. Where there is potential to exceed the exposure limit, suitable respiratory protective equipment will be required.

Personal protection: Wear suitable disposable protective clothing. For dilution or reconstitution, wear close-front lab coat, gown or smock with long sleeves and knit cuffs, as appropriate.

Eye protection: Wear suitable eye protection during dilution or reconstitution. Where eye contact is possible during final product use, wear suitable eye protection.

Hand protection: Wear suitable chemical-resistant impervious gloves (i.e. nitrile rubber).

Hygiene measures: Wash hands and arms thoroughly after handling this product.

Exposure limits:

Irinotecan

None have been assigned by any regulatory authority, however, for the bulk material the innovators of the drug utilised an in-house control limit during manufacture of 0.4 mcg/m3, expressed as an 8 hour Time Weighted Average.

Sodium Hydroxide

The following occupational exposure limits currently apply (this list is not exhaustive):

ACGIH Threshold Limit Value	2 mg/m^3
Australia PEAK	2 mg/m^3
Austria OEL – MAKs	2 mg/m^3
Belgium OEL – TWA	2 mg/m^3
Bulgaria OEL – TWA	2 mg/m^3
Czech Republic OEL – TWA	1 mg/m^3
Finland OEL – TWA	2 mg/m^3
France OEL – TWA	2 mg/m^3
Greece OEL – TWA	2 mg/m^3

Hungary OEL – TWA	2 mg/m^3
Japan OEL – Ceiling	2 mg/m^3
Latvia OEL – TWA	0.5 mg/m^3
OSHA PEL – TWA	2 mg/m^3
Poland OEL – TWA	0.5 mg/m^3
Slovakia OEL- TWA	2 mg/m^3
Slovenia OEL - TWA	2 mg/m^3
Sweden OEL - TWA	1 mg/m^3

Analytical Methods: Contact Sindan Pharma for further details on available analytical methods for occupational hygiene personal exposure monitoring to the active ingredient.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance:	Transparent aqueous solution, colourless to pale yellow in appearance
Odour:	None
pH:	3.5
Molecular Weight:	Mixture
Boiling point:	100 ºC
Melting point:	0 ºC
Flashpoint:	Not known
Explosive properties:	Not known
Vapour pressure:	23 hPa (20 ºC)
Relative density:	Not known
Viscosity:	0.952 mPa*s (20 ºC)
Solubility:	Freely miscible with water

10. STABILITY AND REACTIVITY

Stability: Stable under normal temperature conditions.

Conditions to Avoid: Exposure to light.

Hazardous Polymerisation: Will not occur.

Incompatible Materials: Reactive with strong oxidizing agents.

11. TOXICOLOGICAL INFORMATION

This product is intended for therapeutic use only when prescribed by a physician. Potential adverse reactions from prescribed doses are described in the package insert. Reported warnings and adverse patient effects may include: diarrhoea, neutropenia, hypersensitivity reactions, colitis, ileus, renal impairment or failure, thromboembolism, nausea, vomiting, anorexia, constipation, flatulence, stomatitis, dyspepsia, leucopenia, anaemia, asthenia, fever, pain, headache, back pain, chills, minor infection, oedema, abdominal enlargement, weight loss, elevated alkaline phosphatase and SGOT levels, hair loss, sweating, rash, dyspnoea, coughing, rhinitis, dizziness and vasodilation.

Signs and Symptoms of Exposure/Overexposure: Occupational exposure has not been fully investigated.

Medical Conditions
Aggravated by Exposure: Individuals with hypersensitivity to Irinotecan Hydrochloride Injection or any of its excipients. Pre-existing bone marrow, blood, cardiovascular, gastrointestinal, central nervous system, pulmonary, liver or skin ailments; or pregnancy.

Irinotecan Hydrochloride in bulk form

ORAL LD_{50} (RAT):	867-1026 mg/kg
ORAL LD_{50} (MOUSE):	765-1064 mg/kg
INTRAPERITONEAL LD_{50} (MOUSE):	177 mg/kg
INTRAVENOUS LD_{50} (RAT):	84 mg/kg
INTRAVENOUS LD_{50} (MOUSE):	132 mg/kg
INTRAVENOUS LD_{50} (DOG):	40-80 mg/kg

Sorbitol

ORAL LD_{50} (RAT):	15900 mg/kg
ORAL LD_{50} (MOUSE):	17800 mg/kg

Sodium Hydroxide

INTRAPERITONEAL LD_{50} (MOUSE):	40 mg/kg

Lactic Acid

ORAL LD_{50} (RAT):	3543 mg/kg
ORAL LD_{50} (MOUSE):	4875 mg/kg
DERMAL LD_{50} (RABBIT):	>2000 mg/kg

Water for Injection

ORAL LD_{50} (RAT):	>50000 mg/kg

Irritation / Sensitisation:

Irinotecan Hydrochloride in bulk form

Eye Irritation (RABBIT):	Minimal
Skin Irritation (RABBIT):	No Effect
Antigenicity-Passive Cutaneous Anaphylaxis (MOUSE):	Negative

Lactic Acid

Eye Irritation (RABBIT):	Severe
Skin Irritation (RABBIT):	Moderate/Severe

Sodium Hydroxide

Eye Irritation (RABBIT):	Severe
Skin Irritation (RABBIT):	Severe

Reproductive Effects:

In animal studies, no significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan to rats and rabbits at dosages of up to 6 mg/kg/day. In repeat-dose studies, testicular atrophy was noted in rodents at a dosage of 20 mg/kg/day, and in dogs at a dosage of 0.4 mg/kg/day. Intravenous administration to rats and rabbits at a dose of 6 mg/kg/day during organogenesis produced embryotoxicity, characterised by increased post-implantation loss and decreased numbers of live foetuses. Irinotecan was found to be teratogenic in rats at dosages greater than 1.2 mg/kg/day, and in rabbits at a dosage of 6 mg/kg/day. Irinotecan administered to rat dams for the period following organogenesis through weaning at a dosage of 6 mg/kg/day decreased learning ability and decreased female body weights in the offspring.

Mutagencity:

Neither irinotecan, nor its major metabolite, was found to be mutagenic in the *in vitro* Ames assay. Irinotecan was clastogenic in *in vitro* tests on Chinese hamster ovarian cells and in *in vivo* tests on mice micronuclei.

Carcinogenicity:

Long-term carcinogenicity studies with irinotecan have not been conducted. However, intravenous administration of irinotecan to rats at dosages of 2 mg/kg or 25 mg/kg irinotecan once a week for 13 weeks, followed by 91 weeks recovery, resulted in a significant dose-related trend for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas

12. ECOLOGICAL INFORMATION

The environmental characteristics of this material have not been fully evaluated. Releases to environment should be prevented.

Irinotecan photodegrades rapidly and is not anticipated to persist in the aquatic environment.

13 DISPOSAL CONSIDERATIONS

Dispose of waste by incineration in accordance with all applicable laws and regulations. EU Member State-specific and Community-specific provisions must be considered.

Packaging should be disposed of in keeping with all local and national legislation.

Treat all contaminated waste as bulk product and dispose of as pharmaceutical waste.

14. TRANSPORT INFORMATION

Classification data: Not regulated for transport under USDOT, IATA or IMDG regulations. May be subject to state and/or local transportation requirements.

15. REGULATORY INFORMATION

Ingredients are not listed as carcinogenic by IARC, NTP or OSHA.

EU Risk Phrases:
R61 – May cause harm to the unborn child.
R68 – Possible risk of irreversible effects.

EU Safety Phrases:
S23 – Do not breathe spray.
S24 – Avoid contact with the skin.
S25 – Avoid contact with the eyes.
S53 – Avoid exposure – obtain special instructions before use.
S36/37 – Wear suitable protective clothing and gloves.
S60 – Material and its container must be disposed of as hazardous waste.

16. OTHER INFORMATION

Recommendations/ restrictions:	The information relates only to the specific material designated and may not be valid for such materials used in combination with other materials or in any process. Such information is, to the best of the company's knowledge and belief, accurate and reliable as of the date of issue. However, no warranty guarantee of representation is made to its accuracy, reliability or completeness. It is the user's responsibility to satisfy himself as to the suitability of such information for his own particular use.
Note:	There is limited evidence that personnel involved in the preparation and administration or parenteral antineoplastic agents may be at some risk due to mutagenicity and/or teratogenicity and/or carcinogenicity of these agents. The actual risk has not been adequately quantified. Cautious handling is required in both preparation and disposal of antineoplastic agents. Precautions suggested include the use of biological safety cabinets during reconstitution and dilution of parenteral medications, use of surgical gloves and masks, good techniques to prevent worker and workplace contamination and proper disposal of needles, syringes, vials or ampoules.
Data Sources:	Proprietary drug development information and publicly available toxicity information.
Prepared by:	Registered professional occupational hygienists working for Actavis Corporate Environmental, Health and Safety.
Reasons for Revision:	Not applicable (first issue).