

SAFETY DATA SHEET**IRINOTECAN (Onivyde™ Active Ingredient)****SECTION 1: Identification of the substance/mixture and of the company/undertaking****1.1 Product identifier**

Product name	: IRINOTECAN (Onivyde™ Active Ingredient)
CAS number	: 100286-90-6
Chemical name	: [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, hydrochloride (1:1)
Product description	: Active pharmaceutical ingredient
Product type	: Liquid.
Other means of identification	: (1,4'-Bipiperidine)-1'-carboxylic acid, 3,4,12,14-tetrahydro-4,11-diethyl-4-hydroxy-3,4-dioxo-1H-pyrano(3',4':6,7)indolizino(1,2-b)quinolin-9-yl ester, monohydrochloride, (S)-
Chemical formula	: C33-H38-N4-O6.Cl-H

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

Not applicable.

1.3 Details of the supplier of the safety data sheet

Manufacturer / Distributor : LES LABORATOIRES SERVIER
50, rue Carnot
92284 SURESNES CEDEX
FRANCE
Tel.: +(33) (0)1 55 72 60 00

e-mail address of person responsible for this SDS : mail.reachoril@servier.com

1.4 Emergency telephone number**National advisory body/Poison Centre**

Telephone number : +(33) (0)1 40 05 48 48

Supplier

Emergency telephone number (with hours of operation) : Permanence téléphonique DRD: +(33) (0)1 55 72 60 00
Numéro ORFILA: 01 45 42 59 59
(working days and hours)

SECTION 2: Hazards identification**2.1 Classification of the substance or mixture**

Product definition : Mono-constituent substance

Classification according to Regulation (EC) No. 1272/2008 [CLP/GHS]

Acute Tox. 4, H302

Muta. 2, H341

Carc. 2, H351

Repr. 1B, H360D (Unborn child)

STOT RE 1, H372 (gastrointestinal tract and haematopoietic system)

See Section 16 for the full text of the H statements declared above.

See Section 11 for more detailed information on health effects and symptoms.

2.2 Label elements

SECTION 2: Hazards identification

Hazard pictograms

:



Signal word

: Danger

Hazard statements

: Harmful if swallowed.
May damage the unborn child.
Suspected of causing genetic defects.
Suspected of causing cancer.
Causes damage to organs through prolonged or repeated exposure. (gastrointestinal tract, haematopoietic system)

Additional warning phrases : Not available.

Precautionary statements

Prevention

: Obtain special instructions before use. Use personal protective equipment as required. Do not breathe vapour.

Response

: Get medical attention if you feel unwell. IF SWALLOWED: Call a POISON CENTER or physician if you feel unwell.

Storage

: Store locked up.

Disposal

: Dispose of contents and container in accordance with all local, regional, national and international regulations.

2.3 Other hazards

Other hazards which do not result in classification : None known.

SECTION 3: Composition/information on ingredients

Substance/mixture : Mono-constituent substance

Product/ingredient name	Identifiers	%	Classification Regulation (EC) No. 1272/2008 [CLP]	Type
IRINOTECAN (Onivyde™ Active Ingredient)	CAS: 100286-90-6	100	Acute Tox. 4, H302 Muta. 2, H341 Carc. 2, H351 Repr. 1B, H360D (Unborn child) STOT RE 1, H372 (gastrointestinal tract and haematopoietic system) See Section 16 for the full text of the H statements declared above.	[A]

There are no additional ingredients present which, within the current knowledge of the supplier, are classified and contribute to the classification of the substance and hence require reporting in this section.

Type

[A] Constituent

[B] Impurity

[C] Stabilising additive

SECTION 4: First aid measures

4.1 Description of first aid measures

Inhalation

: Move affected person to fresh air. Keep person warm and at rest. Consult immediately a doctor in case of pregnancy or nursing. If not breathing, if breathing is irregular or if respiratory arrest occurs, provide artificial respiration or oxygen by trained personnel. Get medical advice/attention. If unconscious, place in recovery position and get medical attention immediately.

Ingestion

: Wash out mouth with water. Keep person warm and at rest. Consult immediately a doctor in case of pregnancy or nursing. Seek medical attention.

SECTION 4: First aid measures

- Skin contact** : Flush contaminated skin with plenty of water. Remove contaminated clothing and shoes. Consult immediately a doctor in case of pregnancy or nursing. Seek medical attention.
- Eye contact** : Immediately flush eyes with plenty of water, occasionally lifting the upper and lower eyelids. Check for and remove any contact lenses. Continue to rinse for at least 10 minutes. Seek medical attention.
- Protection of first-aiders** : Put on appropriate personal protective equipment (see Section 8). No action shall be taken involving any personal risk or without suitable training.

4.2 Most important symptoms and effects, both acute and delayed

See section 11 for details.

4.3 Indication of any immediate medical attention and special treatment needed

- Notes to physician** : Treat symptomatically.

SECTION 5: Firefighting measures**5.1 Extinguishing media**

- Suitable extinguishing media** : Use dry chemical or CO₂.
- Unsuitable extinguishing media** : None known.

5.2 Special hazards arising from the substance or mixture

- Hazards from the substance or mixture** : In a fire or if heated, a pressure increase will occur and the container may burst. Runoff to sewer may create fire or explosion hazard.
- Hazardous combustion products** : Decomposition products may include the following materials:
carbon dioxide
carbon monoxide
nitrogen oxides
halogenated compounds

5.3 Advice for firefighters

- Special precautions for fire-fighters** : Promptly isolate the scene by removing all persons from the vicinity of the incident if there is a fire.
- Special protective equipment for fire-fighters** : Fire-fighters should wear appropriate protective equipment and self-contained breathing apparatus (SCBA) with a full face-piece operated in positive pressure mode.

SECTION 6: Accidental release measures**6.1 Personal precautions, protective equipment and emergency procedures**

- Protection of fire-fighters** : Keep unnecessary and unprotected personnel from entering. Do not touch or walk through spilt material. Avoid breathing vapour or mist. Provide adequate ventilation. Wear appropriate respirator when ventilation is inadequate. Put on appropriate personal protective equipment (see Section 8).

6.2 Environmental precautions

Inform the relevant authorities if the product has caused environmental pollution (sewers, waterways, soil or air).

6.3 Methods and material for containment and cleaning up

- Spill** : Stop leak if without risk. Prevent entry into sewers, water courses, basements or confined areas. Contain and collect spillage with non-combustible, absorbent material e.g. sand, earth, vermiculite or diatomaceous earth and place in container for disposal according to local regulations.

SECTION 6: Accidental release measures

- 6.4 Reference to other sections** :
- See Section 1 for emergency contact information.
 - See Section 8 for information on appropriate personal protective equipment.
 - See Section 13 for additional waste treatment information.

SECTION 7: Handling and storage

7.1 Precautions for safe handling

- Protective measures** :
- Must be handled preferentially under strictly containment. Avoid contact during pregnancy or while nursing. Put on appropriate personal protective equipment (see Section 8). Avoid exposure - obtain special instructions before use. Do not get in eyes or on skin or clothing. Avoid breathing vapour or mist. Use only with adequate ventilation. Wear appropriate respirator when ventilation is inadequate.
- Advice on general occupational hygiene** :
- Remove contaminated clothing and protective equipment before entering eating areas. Workers should wash hands and face before eating, drinking and smoking.

7.2 Conditions for safe storage, including any incompatibilities

- :
- Store between the following temperatures: 2 to 8°C (35.6 to 46.4°F). Store in accordance with local regulations. Store in original container protected from direct sunlight in a dry, cool and well-ventilated area, away from incompatible materials (see Section 10) and food and drink. Store locked up. Use appropriate containment to avoid environmental contamination. Keep container tightly closed and sealed until ready for use.

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Occupational exposure limits

No exposure limit value known.

8.2 Exposure controls

- Appropriate engineering controls** :
- If this product contains ingredients with exposure limits, use process enclosures, local exhaust ventilation or other engineering controls to keep worker exposure below any recommended or statutory limits.

Individual protection measures

- Hygiene measures** :
- Wash hands, forearms and face thoroughly after handling chemical products, before eating, smoking and using the lavatory and at the end of the working period.
- Respiratory protection** :
- Must be handled preferentially under strictly containment. Gaz mask with A2B2E2K cartridge or mask with air adduction should be worn.
- Eye/face protection** :
- Goggles should be worn.
- Hand protection** :
- Wear suitable gloves.
- Body protection** :
- Wear clothes dedicated to handling of chemical products. Suitable protective footwear. Disposable outer garments when there is a risk of contact with the material.
- Environmental exposure controls** :
- In some cases, fume scrubbers, filters or engineering modifications to the process equipment will be necessary to reduce emissions to acceptable levels.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

Physical state	: Liquid.
Molecular weight	: 623.21 g/mole
pH	: 7 to 7.5
Initial boiling point and boiling range	: 100°C
Solubility(ies)	: Easily soluble in the following materials: cold water.

SECTION 10: Stability and reactivity

10.1 Reactivity	: No specific test data related to reactivity available for this product or its ingredients.
10.2 Chemical stability	: The product is stable.
10.3 Possibility of hazardous reactions	: Under normal conditions of storage and use, hazardous reactions will not occur.
10.4 Conditions to avoid	: No specific data.
10.5 Incompatible materials	: No specific data.
10.6 Hazardous decomposition products	: Under normal conditions of storage and use, hazardous decomposition products should not be produced.

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity

Product/ingredient name	Result	Species	Dose	Exposure
IRINOTECAN (Onivyde™ Active Ingredient)	LD50 Oral	Rat	867 mg/kg	-

Irritation/Corrosion

Conclusion/Summary : Not available.

Sensitiser

Conclusion/Summary : Not available.

Mutagenicity

Conclusion/Summary : Although irinotecan was negative in the Ames bacterial mutagenicity assay, it was positive in several short-term screening tests for chromosomal aberrations in vitro and/or in vivo.

Carcinogenicity

Conclusion/Summary : In rats, there was a significant linear trend between non-liposomal irinotecan (as anhydrous free base) dosage (1.7 and 22 mg/kg, IV, once weekly for 13 weeks followed by a 91 week treatment-free period) and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Reproductive toxicity

Conclusion/Summary : Caused reproductive organ atrophy in rodents and dogs administered repeat doses of 20 mg/kg and 0.4 mg/kg, respectively, however no significant adverse effects on fertility were observed following IV administration of up to 6 mg/kg in rats and rabbits.

Teratogenicity

Conclusion/Summary : Caused embryotoxicity and teratogenicity in both rats and rabbits. The NOAELs for developmental toxicity in rats and rabbits are 0.24 and 0.06 mg/kg/ day, IV respectively

Specific target organ toxicity (single exposure)

Not available.

SECTION 11: Toxicological information

Specific target organ toxicity (repeated exposure)

Product/ingredient name	Category	Route of exposure	Target organs
IRINOTECAN (Onivyde™ Active Ingredient)	Category 1	All	gastrointestinal tract and haematopoietic system

Aspiration hazard

Not available.

- Ingestion** : Harmful if swallowed.
- Conclusion/Summary** : Irinotecan has an effect on tissues with high proliferative activity such as bone marrow, thymus gland, spleen, lymph nodes and testes
- General** : Causes damage to organs through prolonged or repeated exposure.

SECTION 12: Ecological information

12.1 Toxicity

Conclusion/Summary : Not available.

12.2 Persistence and degradability

Conclusion/Summary : Not available.

12.3 Bioaccumulative potential

Not available.

12.4 Mobility in soil

Soil/water partition coefficient (K_{oc}) : Not available.

SECTION 13: Disposal considerations

13.1 Waste treatment methods

- Methods of disposal** : Send to an appropriate hazardous waste incineration facility, in compliance with legislation. Disposal of this product, solutions and any by-products should at all times comply with the requirements of environmental protection and waste disposal legislation and any regional local authority requirements. Care should be taken when handling emptied containers that have not been cleaned or rinsed out. Empty containers or liners may retain some product residues. Avoid dispersal of spilt material and runoff and contact with soil, waterways, drains and sewers.
- Hazardous waste** : The classification of the product may meet the criteria for a hazardous waste.

SECTION 14: Transport information

	ADR/RID	IATA
14.1 UN number	Not available.	Not available.
14.2 UN proper shipping name	Not available.	Not available.
14.3 Transport hazard class(es)	Not available.	Not available.
14.4 Packing group	-	-

SECTION 14: Transport information

14.5 Environmental hazards	No.	No.
14.6 Special precautions for user	Transport within user's premises: always transport in closed containers that are upright and secure. Ensure that persons transporting the product know what to do in the event of an accident or spillage.	Transport within user's premises: always transport in closed containers that are upright and secure. Ensure that persons transporting the product know what to do in the event of an accident or spillage.
Additional information	-	-

SECTION 15: Regulatory information**15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture****EU Regulation (EC) No. 1907/2006 (REACH)****Annex XIV - List of substances subject to authorisation****Substances of very high concern**


None of the components are listed.

Annex XVII - Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles

Restricted to professional users.

Other EU regulations**Europe inventory** : Not determined.

Product/ingredient name	Carcinogenic effects	Mutagenic effects	Developmental effects	Fertility effects
IRINOTECAN (Onivyde™ Active Ingredient)	Carc. 2, H351	Muta. 2, H341	Repr. 1B, H360D (Unborn child)	-

SECTION 16: Other information
 Indicates information that has changed from previously issued version.

Abbreviations and acronyms :

- ATE = Acute Toxicity Estimate
- CLP = Classification, Labelling and Packaging Regulation [Regulation (EC) No. 1272/2008]
- DNEL = Derived No Effect Level
- EUH statement = CLP-specific Hazard statement
- PNEC = Predicted No Effect Concentration
- RRN = REACH Registration Number

Procedure used to derive the classification according to Regulation (EC) No. 1272/2008 [CLP/GHS]

Classification	Justification
Acute Tox. 4, H302 Muta. 2, H341 Carc. 2, H351 Repr. 1B, H360D (Unborn child) STOT RE 1, H372 (gastrointestinal tract and haematopoietic system)	On basis of test data Expert judgment based on generated data. Expert judgment based on generated data. Expert judgment based on generated data. Expert judgment based on generated data.

Full text of abbreviated H statements :

- H302 Harmful if swallowed.
- H341 Suspected of causing genetic defects.
- H351 Suspected of causing cancer.
- H360D May damage the unborn child.
- (Unborn child)
- H372 Causes damage to organs through prolonged or repeated exposure.
- (gastrointestinal tract and haematopoietic system)
- and
- haematopoietic

SECTION 16: Other information

system)

Full text of classifications [CLP/GHS]	: Acute Tox. 4, H302 Carc. 2, H351 Muta. 2, H341 Repr. 1B, H360D (Unborn child) STOT RE 1, H372 (gastrointestinal tract and haematopoietic system)	ACUTE TOXICITY (oral) - Category 4 CARCINOGENICITY - Category 2 GERM CELL MUTAGENICITY - Category 2 TOXIC TO REPRODUCTION (Unborn child) - Category 1B SPECIFIC TARGET ORGAN TOXICITY (REPEATED EXPOSURE) (gastrointestinal tract and haematopoietic system) - Category 1
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The information provided herein is derived from tests carried out by **SERVIER** or accredited laboratories. To the best of our knowledge, the information contained herein is accurate.

All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards that exist.