Safety Data Sheet

Cilazapril

according to Regulation (EU) nr. 453/2010

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1. Product identifier

Product name	Cilazapril
Product code	04 1690 8

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

Use	- pharmaceutical active substance, hypotensive: angiotensin-converting enzyme (ACE) inhibitor, INHIBACE, INIBACE

1.3. Details of the supplier of the safety data sheet

Company information	Enquiries: F. Hoffmann-La Roche AG Postfach CH-4070 Basel Switzerland Phone +41-61/688 54 80 Fax +41-61/681 72 76 E-Mail info.sds@roche.com	Local representation:

1.4. Emergency telephone number

Emergency telephone number	Phone +41-61/688 54 80

SECTION 2: Hazards identification

2.1. / 2.2. Classification of the substance or mixture / Label elements

GHS Classification

Health Hazards:
3.7_Reproductive toxicity (Category 2)
H361d Suspected of damaging the unborn child.

Signalword: Warning

Label:

Precautionary statements:
- P201 Obtain special instructions before use.
- P281 Use personal protective equipment as required.
- P308 + P313 IF exposed or concerned: Get medical advice/attention.

2.3. Other hazards

Note

- no information available

SECTION 3: Composition/information on ingredients

Characterization

pharmaceutical active agent (inhibitor of angiotensin-converting enzyme, ACE)

Chemical name

- 9(S)-[(S)-(Ethoxycarbonyl)-3-phenylpropylamino]-octahydro-10-oxo-6H-pyridazo-[1,2-a]-[1,2]-diazepine-1(S)-carboxylic acid monohydrate

Synonyms

- Cilazapril monohydrate
- INHIBACE substance
- INIBACE substance
- ACEI monohydrate

CAS number

92077-78-6

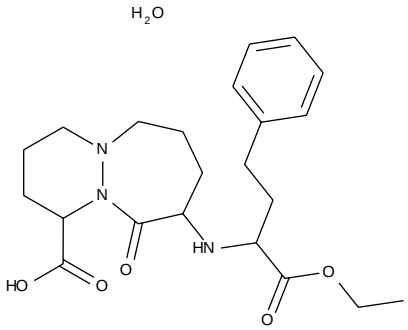
Roche number

Ro0312848-605

Empirical formula

$C_{22}H_{31}N_3O_5 \bullet H_2O$

Molecular mass	435.52 g/mol



SECTION 4: First aid measures

4.1. Description of first aid measures

Eye contact	- rinse with tap water for 10 minutes - open eyelids forcibly
Skin contact	- remove contaminated clothes, wash affected skin with water and soap - do not use any solvents
Inhalation	- remove the casualty to fresh air and keep him/her calm - in the event of symptoms get medical treatment

4.2. Most important symptoms and effects, both acute and delayed

Note	- no information available

4.3. Indication of any immediate medical attention and special treatment needed

Note to physician	- treat symptomatically

SECTION 5: Firefighting measures

5.1. Extinguishing media

Suitable extinguishing media	- water spray jet, dry powder, foam, carbon dioxide

5.2. Special hazards arising from the substance or mixture

Specific hazards	- formation of toxic and corrosive combustion gases (ammonia, hydrogen cyanide, nitrogen oxides) possible - consider dust explosion hazard

5.3. Advice for firefighters

Protection of fire-fighters	- precipitate gases/vapours/mists with water spray

SECTION 6: Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

Personal precautions	- avoid exposure

6.2. Environmental precautions

Environmental protection	- do not allow to enter drains or waterways

6.3. Methods and material for containment and cleaning up

Methods for cleaning up	- collect solids (avoid dust formation) and hand over to waste removal

SECTION 7: Handling and storage

7.1. Precautions for safe handling

Technical measures	- processing in closed systems, if possible superposed by inert gas (e.g. nitrogen) - connect the equipment to earth, avoid effective sources of ignition - avoid electric charging of dust clouds - avoid dust formation; very high dust explosion hazard - local exhaust ventilation necessary
Suitable materials	- stainless steel, aluminium, enamel, glass, polyethylene

7.2. Conditions for safe storage, including any incompatibilities

Storage conditions	- below 25 °C
Validity	- 24 months, at room temperature, under nitrogen
Packaging materials	- tightly closing; material: glass, stainless steel, aluminium (lined with polyethylene bag)

SECTION 8: Exposure controls/personal protection

8.1. Control parameters

Threshold value (Roche) air	- IOEL (Internal Occupational Exposure Limit): 0.0025 mg/m^3

8.2. Exposure controls

Respiratory protection	- in case of open handling or accidental release: particle mask or respirator with independent air supply
Hand protection	- protective gloves (eg made of neoprene, nitrile or butyl rubber)
Eye protection	- safety glasses

Analytics	-	sampling on glass fibre filter and gravimetric or chemical determination

SECTION 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

Colour	white to yellowish	
Form	fine, crystalline powder partly with lumps	 *1
Odour	none to faint	
Solubility	> 100 mg/l, water (~ 20 °C) < 100 mg/l, n-hexane (25 °C) 7’000 mg/l, diethyl ether (25 °C) 7’700 mg/l, ethyl acetate (25 °C) 25’000 mg/l, toluene (25 °C) 68’000 mg/l, n-octanol (25 °C) 233’000 mg/l, acetone (25 °C) > 500’000 mg/l, chloroform (25 °C) > 500’000 mg/l, ethanol (25 °C) > 500’000 mg/l, methanol (25 °C) > 500’000 mg/l, DMSO (dimethyl sulfoxide) (25 °C) > 500’000 mg/l, tetrahydrofuran (25 °C)	
Partition coefficient	log P_{ow} 0.8 (n-octanol/buffer) pH 7.4	
pH value	4.9 (1 % suspension in water) 4.5 to 5.5 (10 % suspension in water)	
Melting temperature	~ 98 °C (with decomposition)	

9.2. Other information

Bulk density	~ 0.56 g/cm³	*1
Sieve analysis	≥ 85 % through USP standard sieve no. 100 (Ø 150 µm) ≥ 50 % through USP standard sieve no. 140 (Ø 104 µm) ≥ 98 % through USP standard sieve no. 100 (Ø 150 µm) ≥ 90 % through USP standard sieve no. 140 (Ø 104 µm)	 *2 *2
Note	- extremely hygroscopic as an anhydrous pure substance, hence normally presenting as a monohydrate	
Dissociation constant	pK_1 3.3 pK_2 6.4	

*1 referring to: Cilazapril unmilled
*2 referring to: Cilazapril micropowder

SECTION 10: Stability and reactivity

10.1. Reactivity

Note - no information available

10.2. Chemical stability

Note - no information available

10.3. Possibility of hazardous reactions

Note - no information available

10.4. Conditions to avoid

Conditions to avoid - temperatures above 30 °C

10.5. Incompatible materials

Materials to avoid - bases, acids, oxidizing agents

10.6. Hazardous decomposition products

Note - drying operations at the lowest temperatures possible and under ensured inertisation

SECTION 11: Toxicological information

11.1. Information on toxicological effects

Acute toxicity	- LD_{50}	> 5'000	mg/kg	(oral, mouse)
	- LD_{50}	> 5'000	mg/kg	(oral, rat)
	- LD_{50}	> 30	mg/kg	(i.v., rat)
	- NOEL	0.5	mg	(oral, man); hypertensive, in dose-finding study
Local effects	- eye: moderately irritating (rabbit) - skin: non-irritant (rabbit)			
Sensitization	- not sensitizing (several species)			
Subchronic toxicity	- NOEL 10 mg/kg/d (oral, rat; 13 weeks)			
Mutagenicity	- not mutagenic (various in vivo and in vitro test systems)			
Carcinogenicity	- not carcinogenic (several species)			
Reproductive toxicity	- not teratogenic (several species) - ACE inhibitors can cause injury and death to the developing fetus			

Note	- lowers blood pressure through inhibition of angiotensin converting enzyme (ACE); cilazapril does not lower blood pressure in normotensive individuals

SECTION 12: Ecological information

12.1. Toxicity

Ecotoxicity	- barely toxic for algae (Selenastrum capricornutum) NOEC (72 h) 100 mg/l EbC_{50} (72 h) > 100 mg/l ErC_{50} (72 h) > 100 mg/l (OECD No. 201) - barely toxic for planktonic crustaceans (Daphnia magna) EC_{50} (48 h) > 987 mg/l NOEC (48 h) 987 mg/l (FDA Technical Assistance Document No. 4.08) - barely toxic for fish (carp) NOEC (96 h) 100 mg/l LC_{50} (96 h) > 100 mg/l (OECD No. 203) - no adverse influence on substrate biodegradation (activated sludge) concentration (28 d) 40 mg/l (OECD No. 301B, Modified Sturm Test) - barely toxic for microorganisms (bacteria, fungi, cyanobacteria in pure culture) NOEC 1000 mg/l (nominal concentration) (FDA Technical Assistance Document No. 4.02)

12.2. Persistence and degradability

Ready biodegradability	- not readily biodegradable ≤ 6 %, 28 d (CO_2 Evolution Test, Modified Sturm Test, OECD No. 301B)

12.3. Bioaccumulative potential

Note	- no information available

12.4. Mobility in soil

Mobility	- medium mobility K_{OC} = 184 (loam) K_{OC} = 324 (silty loam) K_{OC} = 299 (clay loam) (FDA Technical Assistance Document No. 3.08)

12.5. Results of PBT and vPvB assessment

PBT/vPvB	- substance does not meet the criteria for PBT or vPvB

12.6. Other adverse effects

Air pollution	- observe local/national regulations
Note	- does not accumulate in biological systems

SECTION 13: Disposal considerations

13.1. Waste treatment methods

Waste from residues	- incinerate in qualified installation with flue gas scrubbing - observe local/national regulations regarding waste disposal

SECTION 14: Transport information

Note	- not classified by transport regulations

SECTION 15: Regulatory information

15.1. Safety, health and environmental regulations/legislation specific for the substance or mixture

Water hazard class (Germany)	1: weakly hazardous for water (own classification according to directive VwVwS of 17.05.1999)

SECTION 16: Other information

Safety-lab number	- BS-3512 - BS-9423
Edition documentation	- changes from previous version in sections 2, 11

The information in this safety data sheet is based on current scientific knowledge. It should not be taken as expressing or implying any warranty concerning product characteristics.