TECHNICAL INFORMATION

Lorazepam

Ph. Eur.

1. MANUFACTURER OF THE FINAL SUBSTANCE

Evonik Operations GmbH
Gutenbergstrasse 2
69221 Dossenheim
Germany

2. PRODUCT

- Nomenclature

Recommended International Non-proprietary name (INN):

Lorazepam

Chemical name(s):

Chemical name:	(RS)-7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hyroxy-2H-1,4-benzodiazepin-2-one
Other name(s):	2H-1,4-benzodiazepin-2-one,7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-, (+)- (+)-7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one
CAS No.:	846-49-1

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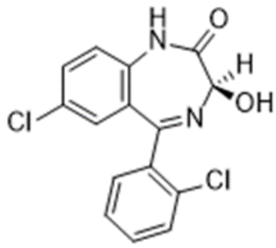
- Structure



and enantiomer

Molecular formula:	$C_{15}H_{10}Cl_2N_2O_2$
Molecular mass:	321.2 g/mol

- General Properties

Physical Form:	White to almost white crystalline powder	
Solubility:	ultrapure water:	practically insoluble
	Ethanol:	sparingly soluble
	Methylene chloride:	sparingly soluble
Melting point:	180 °C	
Polymorphism:	Lorazepam exhibits polymorphism. The control by IR of the internal quality control specification ensure that the manufactured Lorazepam is the required polymorph.	
Hygroscopicity:	Lorazepam is not known to show hygroscopicity.	
Partition coefficient (logP):	Log Pow 2.4	
Optical Activity:	No optical activity, as the substance is a racemic mixture.	

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3. SPECIFICATION

Table 1: Specification

Test Items	**Test methods**	**Acceptance Criteria**	**References**	**Frequency**
Appearance	Visual	White to off-white crystalline powder	Ph. Eur.	Each Batch
Identification	IR-Spectroscopy	Conforms to standard spectrum		
Loss on drying (LOD)	Gravimetry	nmt. 0.5%		
Sulfated ash	Residue on ignition	nmt. 0.1%		
Assay	Titration	98.5 to 102.0%		
Related Substances				
Wy4088 (Ph. Eur. Impurity B)	HPLC	nmt. 0.10%	Ph. Eur.	Each Batch
Wy4036-Dione (Ph. Eur. Impurity D)		nmt. 0.10%		
Each unspecified impurity		nmt. 0.10%		
Sum of impurities		nmt. 0.2%		
Residual Solvents:				
Ethanol	GC	nmt. 1000 ppm	---	Each Batch
Toluene		nmt. 1000 ppm		

- nmt. = not more than

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4. PACKAGING

- Container Closure System I

  Low Density Polyethylene (LDPE) flat bags

- Container Closure System II

  Fiber drums

Compliance

The material of construction of the primary packaging component, the LLDPE liner, complies with the requirements of the applicable sections of the current US Federal regulations for indirect food additives: 21 CFR parts 177, 178 and 182 or 184.

Conforms for using in the food industry and in compliant with the following guidelines and directives:

EU:	Regulation (EU) No. 10/2011
Germany:	Recommendation III Polyethylene of the German Federal Institute for Risk Assessment (formerly BgVV) from 1.1.2003
USA:	FDA 21 CFR 177.1520©2.2 (1.4.2002) and meets the extraction limit values of the BPF/BIBRA as described in the “Polymer Specification 4, Item 4, Polymer Category 1.1” (2.6% in n-hexane and 11.5% in Xylene)

Fiber drums:

The materials of construction of the secondary packaging component, a fiber drum, complies with European Parliament and Council Directive 94/62/EC on packaging waste (e.g. max concentration of heavy metals, cumulative: 100 ppm).

5. STORAGE AND STABILITY

Based on stability data, a re-test period of 36 months, if stored below 25 °C in double polyethylene bags placed in fiber drums, is defined.

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6. GENERAL INFORMATION

- GMP certificate is available.
- CEP No.: CEP 2008-142
- US-DMF No.: DMF 005041
- Residual solvents

  The residual organic solvents are controlled in the final drug substance. The acceptance criteria are compliant with the guideline ICH Q3C.

Table 2: Residual solvents

Solvent Class 1	**Acceptance criterion**	**Tested in routine**	**Method used**
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Solvent Class 2	**Acceptance criterion**	**Tested in routine**	**Method used**
Toluene*	nmt. 1000 ppm	yes	GC
Solvent Class 3	**Acceptance criterion**	**Tested in routine**	**Method used**
Ethanol	nmt. 1000 ppm	yes	GC

- *: The limit for toluene is defined in accordance with the Option 2 of ICH Q3C