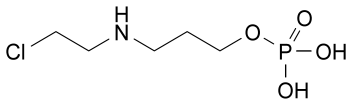
IMPURITIES

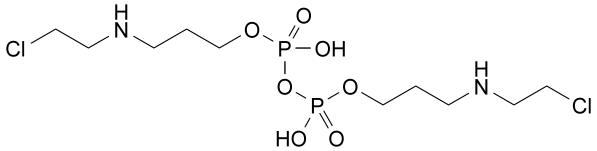
*Specified impurities*: *A, B, C, E, F.*

*Other detectable impurities: D.*

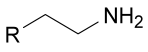
**Related substances test A**



A. 3-[(2-chloroethyl)amino]propyl dihydrogen phosphate,



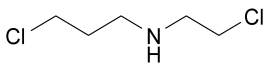
B. bis[3-[(2-chloroethyl)amino]propyl] dihydrogen diphosphate,



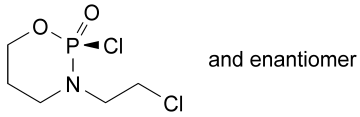
C. R = Cl: 2-chloroethanamine,

D. R = OH: 2-aminoethanol.

**Related substances test B**



E. 3-chloro-*N*-(2-chloroethyl)propan-1-amine,

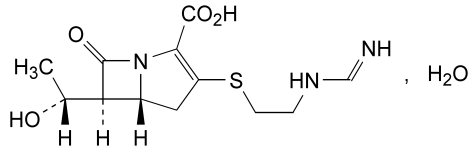



F. (*RS*)-2-chloro-3-(2-chloroethyl)-1,3,2-oxazaphosphinane 2-oxide.

**01/2008:1226**
**corrected 6.0**

# IMIPENEM

## Imipenemum



$C_{12}H_{17}N_3O_4S,H_2O$ $M_r$ 317.4

DEFINITION

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-[[2-[(iminomethyl)amino]-ethyl]sulphanyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Semi-synthetic product derived from a fermentation product.

*Content*: 98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

*Appearance*: white or almost white or pale yellow powder.

*Solubility*: sparingly soluble in water, slightly soluble in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

*Comparison*: *imipenem CRS.*

TESTS

**Appearance of solution**. The solution is not more opalescent than reference suspension II (*2.2.1*) and not more intensely coloured than intensity 6 of the range of the reference solutions of the most appropriate colour (*2.2.2, Method II*).

Dissolve 0.500 g in *phosphate buffer solution pH 7.0 R3* and dilute to 50 ml with the same solution.

**pH** (*2.2.3*): 4.5 to 7.0.

Dissolve 0.500 g in *carbon dioxide-free water R* and dilute to 100.0 ml with the same solvent.

**Specific optical rotation** (*2.2.7*): + 84 to + 89 (anhydrous substance), measured at 25 °C.

Dissolve 0.125 g in *phosphate buffer solution pH 7.0 R3* and dilute to 25.0 ml with the same solution.

**Related substances**. Liquid chromatography (*2.2.29*). *Keep the solutions in an ice-bath and use within 8 h of preparation.*

*Solvent mixture.* Mix 0.7 volumes of *acetonitrile R* and 99.3 volumes of a 0.135 g/l solution of *dipotassium hydrogen phosphate R* adjusted to pH 6.8 with *dilute phosphoric acid R.*

*Test solution.* Dissolve 40.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

*Reference solution (a).* Dissolve 40.0 mg of *imipenem CRS* in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

*Reference solution (b).* Dilute 1.0 ml of the test solution to 100.0 ml with the solvent mixture.

*Reference solution (c).* Heat 20 ml of the test solution, previously adjusted to pH 10 with *sodium hydroxide solution R*, at 80 °C for 5 min (*in situ* preparation of impurity A).

*Column*:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

*Mobile phase*: mix 0.7 volumes of *acetonitrile R* and 99.3 volumes of a 8.7 g/l solution of *dipotassium hydrogen phosphate R* adjusted to pH 7.3 with *dilute phosphoric acid R.*

*Flow rate*: 1.0 ml/min.

*Detection*: spectrophotometer at 254 nm.

*Injection*: 20 µl of the test solution and reference solutions (b) and (c).

*Run time*: twice the retention time of imipenem.

*Relative retention* with reference to imipenem (retention time = about 9 min): impurity A = about 0.8.

*System suitability*: reference solution (c):

– *resolution*: minimum 3.5 between the peaks due to impurity A and imipenem.

*Limits*:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);

- *any other impurity*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *sum of impurities other than A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1 per cent);
- *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

**Water** (*2.5.12*): 5.0 per cent to 8.0 per cent, determined on 0.200 g. Use an iodosulphurous reagent containing imidazole instead of pyridine and a clean container for each determination.

**Sulphated ash** (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

**Bacterial endotoxins** (*2.6.14*): less than 0.17 IU/mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

*Injection*: test solution and reference solution (a).

*System suitability*: reference solution (a):

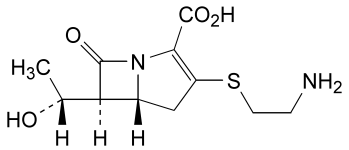
- *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

STORAGE

In an airtight container, at a temperature of 2 °C to 8 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

*Specified impurities*: *A*.

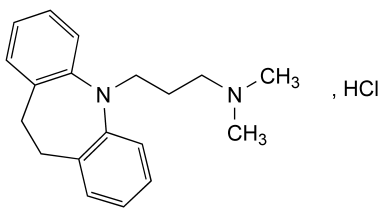



A. (5*R*,6*S*)-3-[(2-aminoethyl)sulphanyl]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (thienamycin).

**01/2008:0029**
**corrected 6.0**

# IMIPRAMINE HYDROCHLORIDE

## Imipramini hydrochloridum




$C_{19}H_{25}ClN_2$ $M_r$ 316.9
[113-52-0]

DEFINITION

Imipramine hydrochloride contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 3-(10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride, calculated with reference to the dried substance.

CHARACTERS

A white or slightly yellow, crystalline powder, freely soluble in water and in alcohol.

IDENTIFICATION

*First identification: A, C, F.*

*Second identification: A, B, D, E, F.*

A. Melting point (*2.2.14*): 170 °C to 174 °C.

B. Dissolve 20 mg in *0.01 M hydrochloric acid* and dilute to 100.0 ml with the same acid. Dilute 1.0 ml of the solution to 10.0 ml with *0.01 M hydrochloric acid*. Examined between 230 nm and 350 nm, the solution shows a single absorption maximum (*2.2.25*), at 251 nm, and a shoulder at 270 nm. The specific absorbance at the maximum is about 260.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *imipramine hydrochloride CRS*. Examine the substances prepared as discs.

D. Dissolve about 5 mg in 2 ml of *nitric acid R*. An intense blue colour develops.

E. Dissolve about 50 mg in 3 ml of *water R* and add 0.05 ml of a 25 g/l solution of *quinhydrone R* in *methanol R*. No red colour develops within 15 min.

F. About 20 mg gives reaction (a) of chlorides (*2.3.1*).

TESTS

**Solution S**. To 3.0 g add 20 ml of *carbon dioxide-free water R*, dissolve rapidly by shaking and triturating with a glass rod and dilute to 30 ml with the same solvent.

**Appearance of solution**. Solution S is clear (*2.2.1*). Immediately after preparation, dilute solution S with an equal volume of *water R*. This solution is not more intensely coloured than reference solution $BY_6$ (*2.2.2, Method II*).

**pH** (*2.2.3*). The pH of solution S, measured immediately after preparation, is 3.6 to 5.0.

**Related substances**. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel G plate R*.

*Test solution.* Dissolve 0.25 g of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent. Prepare immediately before use.

*Reference solution (a).* Dilute 1 ml of the test solution to 10 ml with *methanol R*. Dilute 1 ml of this solution to 50 ml with *methanol R*.

*Reference solution (b).* Dissolve 5 mg of *iminodibenzyl R* in *methanol R* and dilute to 100 ml with the same solvent. Prepare immediately before use.

Apply to the plate 10 µl of each solution. Develop over a path of 12 cm using a mixture of 5 volumes of *hydrochloric acid R*, 5 volumes of *water R*, 35 volumes of *glacial acetic acid R* and 55 volumes of *ethyl acetate R*. Allow the plate to dry in air for 5 min and spray with a 5 g/l solution of *potassium dichromate R* in a mixture of 1 volume of *sulphuric acid R* and 4 volumes of *water R*. Examine the plate immediately. The chromatogram obtained with the test solution shows a blue principal spot. In the chromatogram obtained with the test solution: any spot corresponding