URZĄD REJESTRACJI
PRODUKTÓW LECZNICZYCH, WYROBÓW MEDYCZNYCH I PRODUKTÓW BIOBÓJCZYCH
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Informacja Prezesa Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych z dnia 31 lipca 2008 r. w sprawie nowelizacji monografii Farmakopei Europejskiej *Heparinum calcicum* i *Heparinum natricum*

Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych informuje, że zgodnie z decyzją Komisji Farmakopei Europejskiej, na podstawie Rezolucji AP-CPH (08) 5 Rady Europy z dniem 1 sierpnia 2008 r. wprowadza się jako obowiązujące znowelizowane teksty monografii *Heparinum calcicum* i *Heparinum natricum.* Powyższa informacja wraz z tekstem Rezolucji i monografiami zamieszczona jest na stronie internetowej Europejskiego Dyrektoriatu Jakości Leków i Ochrony Zdrowia (EDQM) (www.edqm.eu/ *European Pharmacopoeia/News and General Information*).

Załączniki:
1. Rezolucja AP-CPH (08) 5 Rady Europy
2. Monografie *Heparinum calcicum* i *Heparinum natricum*

COUNCIL OF EUROPE

EUROPEAN COMMITTEE ON PHARMACEUTICALS AND PHARMACEUTICAL CARE (CD-P-PH)

(Partial Agreement)

RESOLUTION AP-CPH (08) 5

Adopted by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) (Partial Agreement) on 18 July 2008

The European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH),

Considering that, under Article 1 of the Convention, the Parties have undertaken progressively to elaborate a Pharmacopoeia which shall be common to the countries concerned and which shall be entitled "European Pharmacopoeia", and to take the necessary measures to ensure that the monographs constituting the European Pharmacopoeia shall become official standards applicable within their respective countries;

Having regard to Article 4, paragraph 3, of the Convention, which makes the Public Health Committee responsible for fixing the time-limits within which decisions of a technical character relating to the European Pharmacopoeia shall be implemented within the territories of the respective Parties;

Having regard to the decisions taken by the Committee of Ministers at its 1017th meeting, on 6 February 2008, pursuant to which the European Committee on pharmaceuticals and pharmaceutical care (CD-P-PH) would carry out the tasks of the Public Health Committee set out in the Convention on the Elaboration of a European Pharmacopoeia (ETS No. 50), as amended by the Protocol (ETS No. 134), and any reference to the "Public Health Committee" in the said Convention and Protocol should now be understood as referring to the European Committee on pharmaceuticals and pharmaceutical care (CD-P-PH);

Having regard to the adoption on 25 June 2008 by the European Pharmacopoeia Commission, in accordance with the provisions of Article 6, paragraph c of the Convention, of the revised version of the monographs *Heparin calcium* (332) and *Heparin sodium* (333), the texts of which are set out in the appendix to this Resolution.

Having regard to the recommendation on 25 June 2008 by the European Pharmacopoeia Commission, in accordance with the provisions of Article 6, paragraph d of the Convention, which concerns the fixing of the date on which the revised versions of the monographs *Heparin calcium* (332) and *Heparin sodium* (333), shall be implemented within the territories of the parties,

Has decided to set 1st August 2008 the date on which the states parties to the Convention on the Elaboration of a European Pharmacopoeia shall implement, within their territories, the revised version of the monographs *Heparin calcium* (332) and *Heparin sodium* (333).

The following revised monograph was adopted by the European Pharmacopoeia Commission at its 131st session, on 25 June 2008, using the rapid implementation procedure. The implementation date is 1 August 2008.

08/2008:0332

HEPARIN CALCIUM

Heparinum calcicum

DEFINITION

Heparin calcium is a preparation containing the calcium salt of a sulphated glycosaminoglycan present in mammalian tissues. On complete hydrolysis, it liberates D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid. It has the characteristic property of delaying the clotting of freshly shed blood. The potency of heparin calcium intended for parenteral administration is not less than 150 IU/mg, calculated with reference to the dried substance. The potency of heparin calcium not intended for parenteral administration is not less than 120 IU/mg, calculated with reference to the dried substance.

PRODUCTION

It is prepared either from the lungs of oxen or from the intestinal mucosae of pigs, oxen or sheep. All stages of production and sourcing are subjected to a suitable quality assurance system.

It is produced by methods of manufacturing designed to minimise or eliminate substances lowering blood pressure and to ensure freedom from contamination by over-sulphated glycosaminoglycans.

It complies with the following additional requirements.

Nuclear magnetic resonance spectrometry (*2.2.33*). The ^{1}H NMR spectrum obtained with a frequency of at least 300 MHz complies with the specifications approved by the competent authority.

Capillary electrophoresis (*2.2.47*). The electropherogram obtained complies with the specifications approved by the competent authority.

CHARACTERS

A white or almost white powder, hygroscopic, freely soluble in water.

IDENTIFICATION

A. It delays the clotting of recalcified citrated sheep plasma (see Assay).

B. Dissolve 0.40 g in *water R* and dilute to 10.0 ml with the same solvent. The specific optical rotation (*2.2.7*) is not less than + 35.

C. Examine by zone electrophoresis (*2.2.31*) using *agarose for electrophoresis R* as the supporting medium. To equilibrate the agarose and as electrolyte solution use a mixture of 50 ml of *glacial acetic acid R* and 800 ml of *water R* adjusted to pH 3 by addition of *lithium hydroxide R* and diluted to 1000.0 ml with *water R*.

Test solution. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution. Dilute *heparin sodium BRP* with an equal volume of *water R*.

Apply separately to the strip 2 µl to 3 µl of each solution. Pass a current of 1 mA to 2 mA per centimetre of strip width at a potential difference of 300 V for about 10 min. Stain the strips using a 1 g/l solution of *toluidine blue R* and remove the excess by washing. The ratio of the mobility of the principal band or bands in the electropherogram obtained with the test solution to the mobility of the band in the electropherogram obtained with the reference solution is 0.9 to 1.1.

D. It gives the reactions of calcium (*2.3.1*).

TESTS

Appearance of solution. Dissolve a quantity equivalent to 50 000 IU in *water R* and dilute to 10 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than degree 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*). Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent. The pH of the solution is 5.5 to 8.0.

Protein and nucleotidic impurities. Dissolve 40 mg in 10 ml of *water R*. The absorbance (*2.2.25*) measured at 260 nm is not greater than 0.20 and that measured at 280 nm is not greater than 0.15.

Nitrogen. Not more than 2.5 per cent, calculated with reference to the dried substance. Carry out the determination of nitrogen by sulphuric acid digestion (*2.5.9*), using 0.100 g.

Calcium: 9.5 per cent to 11.5 per cent of Ca, calculated with reference to the dried substance. Determine the calcium by complexometric titration (*2.5.11*), using 0.200 g.

Heavy metals (*2.4.8*). 0.5 g complies with limit test C for heavy metals (30 ppm). Prepare the reference solution using 1.5 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 8.0 per cent, determined on 1.000 g by drying at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

Sulphated ash (*2.4.14*): 32 per cent to 40 per cent, determined on 0.20 g and calculated with reference to the dried substance.

Bacterial endotoxins (*2.6.14*): less than 0.01 IU per IU of heparin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. The addition of divalent cations may be necessary in order to fulfil the validation criteria.

ASSAY

Carry out the assay of heparin (*2.7.5*). The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the stated potency.

STORAGE

Store in an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

LABELLING

The label states:

- the number of International Units per milligram;
- where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

The following revised monograph was adopted by the European Pharmacopoeia Commission at its 131st session, on 25 June 2008, using the rapid implementation procedure. The implementation date is 1 August 2008.

08/2008:0333

HEPARIN SODIUM

Heparinum natricum

DEFINITION

Heparin sodium is a preparation containing the sodium salt of a sulphated glycosaminoglycan present in mammalian tissues. On complete hydrolysis, it liberates D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid. It has the characteristic property of delaying the clotting of freshly shed blood. The potency of heparin sodium intended for parenteral administration is not less than 150 IU/mg, calculated with reference to the dried substance. The potency of heparin sodium not intended for parenteral administration is not less than 120 IU/mg, calculated with reference to the dried substance.

PRODUCTION

It is prepared either from the lungs of oxen or from the intestinal mucosae of pigs, oxen or sheep. All stages of production and sourcing are subjected to a suitable quality assurance system.

It is produced by methods of manufacturing designed to minimise or eliminate substances lowering blood pressure and to ensure freedom from contamination by over-sulphated glycosaminoglycans.

It complies with the following additional requirements.

Nuclear magnetic resonance spectrometry (*2.2.33*). The ^{1}H NMR spectrum obtained with a frequency of at least 300 MHz complies with the specifications approved by the competent authority.

Capillary electrophoresis (*2.2.47*). The electropherogram obtained complies with the specifications approved by the competent authority.

CHARACTERS

A white or almost white powder, hygroscopic, freely soluble in water.

IDENTIFICATION

A. It delays the clotting of recalcified citrated sheep plasma (see Assay).

B. Dissolve 0.40 g in *water R* and dilute to 10.0 ml with the same solvent. The specific optical rotation (*2.2.7*) is not less than + 35.

C. Examine by zone electrophoresis (*2.2.31*) using *agarose for electrophoresis R* as the supporting medium. To equilibrate the agarose and as electrolyte solution use a mixture of 50 ml of *glacial acetic acid R* and 800 ml of *water R* adjusted to pH 3 by addition of *lithium hydroxide R* and diluted to 1000.0 ml with *water R*.

Test solution. Dissolve 25 mg of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution. Dilute *heparin sodium BRP* with an equal volume of *water R*.

Apply separately to the strip 2 µl to 3 µl of each solution. Pass a current of 1 mA to 2 mA per centimetre of strip width at a potential difference of 300 V for about 10 min. Stain the strips using a 1 g/l solution of *toluidine blue R* and remove the excess by washing. The ratio of the mobility of the principal band or bands in the electropherogram obtained with the test solution to the mobility of the band in the electropherogram obtained with the reference solution is 0.9 to 1.1.

D. The residue obtained in the test for sulphated ash (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

Appearance of solution. Dissolve a quantity equivalent to 50 000 IU in *water R* and dilute to 10 ml with the same solvent. The solution is clear (*2.2.1*) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (*2.2.2, Method II*).

pH (*2.2.3*). Dissolve 0.1 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent. The pH of the solution is 5.5 to 8.0.

Protein and nucleotidic impurities. Dissolve 40 mg in 10 ml of *water R*. The absorbance (*2.2.25*) measured at 260 nm is not greater than 0.20 and that measured at 280 nm is not greater than 0.15.

Nitrogen. Not more than 2.5 per cent, calculated with reference to the dried substance. Carry out the determination of nitrogen by sulphuric acid digestion (*2.5.9*), using 0.100 g.

Sodium: 9.5 per cent to 12.5 per cent of Na, calculated with reference to the dried substance and determined by atomic absorption spectrometry (*2.2.23, Method I*).

Test solution. Dissolve 50 mg of the substance to be examined in *0.1 M hydrochloric acid* containing 1.27 mg of *caesium chloride R* per millilitre and dilute to 100.0 ml with the same solvent.

Reference solutions. Prepare reference solutions containing 25 ppm, 50 ppm and 75 ppm of Na, using *sodium standard solution (200 ppm Na) R* diluted with *0.1 M hydrochloric acid* containing 1.27 mg of *caesium chloride R* per millilitre.

Measure the absorbance at 330.3 nm using a sodium hollow-cathode lamp as the source of radiation and a flame of suitable composition (for example 11 litres of air and 2 litres of acetylene per minute).

Heavy metals (*2.4.8*). 0.5 g complies with limit test C for heavy metals (30 ppm). Prepare the reference solution using 1.5 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 8.0 per cent, determined on 1.000 g by drying at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

Sulphated ash (*2.4.14*): 30 per cent to 43 per cent, determined on 0.20 g and calculated with reference to the dried substance.

Bacterial endotoxins (*2.6.14*): less than 0.01 IU per IU of heparin, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Carry out the assay of heparin (*2.7.5*). The estimated potency is not less than 90 per cent and not more than 111 per cent of the stated potency. The confidence limits of the estimated potency (P = 0.95) are not less than 80 per cent and not more than 125 per cent of the stated potency.

STORAGE

Store in an airtight container. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

LABELLING

The label states:

– the number of International Units per milligram;

– where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.