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(54) Title: INJECTION SOLUTION COMPRISING AN LHRH ANTAGONIST

(54) Bezeichnung: INJEKTIONSLÖSUNG EINES LHRH-ANTAGONISTEN

(57) Abstract: The aqueous injection solution comprising an LHRH antagonist contains in addition to the LHRH antagonist, such as cetrorelix, an organic, physiologically compatible acid and optionally a surfactant and also a framework builder. The LHRH antagonist has significantly improved solubility and can be prepared in higher concentrations and with an improved bioavailability. The aggregation tendency of the LHRH antagonist is significantly reduced.

(57) Zusammenfassung: Die wässrige Injektionslösung eines LHRH-Antagonisten enthält neben dem LHRH-Antagonisten, wie Cetrorelix eine organische, physiologisch verträgliche Säure, und ggf. ein Tensid sowie einen Gerüstbildner. Der LHRH-Antagonist weist eine deutlich verbesserte Löslichkeit auf, kann in einer höheren Konzentration und besseren Bioverfügbarkeit bereitgestellt werden. Die Aggregationsneigung des LHRH-Antagonisten wird deutlich herabgesetzt.

Injection solution of an LHRH antagonist

Technical field:

The invention relates to aqueous injection solutions of an LHRH antagonist using additions of organic, physiologically tolerable acids and/or surfactants and their preparation for prevention of the aggregation of the LHRH antagonist in solution. The injection solutions prepared according to the invention additionally lead to an increase in the bioavailability and make possible the lowering of the injection volume to be administered.

Prior art:

In controlled ovarian stimulation followed by egg cell removal and techniques of assisted reproduction, besides LHRH agonists (e.g. triptorelin, buserelin), LHRH antagonists (cetrorelix, ganirelix) have especially been used for some time, since they avoid the initial increase in endogenous gonadotropin secretion and immediately lead to a competitive inhibition of gonadotropin-releasing hormone [EP 0 788 799 A2; EP 0 299 402 B1]. The LHRH antagonist ganirelix is at present used in a formulation which contains 0.25 mg of ganirelix in 0.5 ml of an aqueous, mannitol-containing solution in the form of a ready-to-use injection (Orgalutran®). The LHRH antagonist cetrorelix (Cetrotide®) is at present supplied in two administration forms: a lyophilizate containing 0.25 mg of cetrorelix combined with a ready-to-use syringe which contains 1 ml of water for reconstitution, and a lyophilizate containing 3 mg of cetrorelix combined with a ready-to-use syringe which contains 3 ml of water for reconstitution. LHRH antagonists, however, are not only used for controlled ovarian stimulation, but can also be used for the therapy of hormone-dependent types of cancer such as, for example, prostate carcinoma. Substances such as abarelix [WO 98/25642] or cetrorelix [WO 00/47234] could be used for this in that the LHRH antagonists could be an alternative to the market-dominating agonists (leuprolide, goserelin) in this therapy. On account of the relatively poor solubility of abarelix in water or physiological media, a depot formulation must be used in order to achieve a long-term action. There are indications, however, that a long-term action could also be caused by good solubility of the LHRH antagonists [G. Jiang, J. Stakewski, R. Galyean, J. Dykert, C. Schteingart, P. Broqua, A. Aebi, M. L. Aubert,

G. Semple, P. Robson, K. Akinsanya, R. Haigh, P. Riviere, J. Trojnar, J. L. Junien and J. E. Rivier, J. Med. Chem., 2001, 44, 453-467].

Presentation of the invention:

It is the object of the invention to prepare an injection solution which achieves a low injection volume together with an increased concentration of the LHRH antagonist by means of its improved solubility. At the same time, the aggregation of the LHRH antagonist in the relatively highly concentrated injection solution should be prevented.

It has surprisingly been found that the organic, physiologically tolerable acid gluconic acid, or in combination with the surfactant, Tween 80, markedly improve the solubility of LHRH antagonists and thus markedly reduce the proneness to aggregation of these substances.

Accordingly, in one aspect the invention provides an aqueous injection solution of an LHRH antagonist comprising gluconic acid, a surfactant as well as a bulking agent, characterised in that gluconic acid is present in an amount more than equimolar relating to the amount of LHRH antagonist, that gluconic acid is added in the form of gluconic acid delta-lactone, that as surfactant Tween 80 and as bulking agent mannitol are used.

In a second aspect the invention provides a process for the preparation of aqueous injection solutions of an LHRH antagonist as described above, characterised in that, alternatively

- an LHRH antagonist, gluconic acid in the form of gluconic acid delta-lactone, wherein gluconic acid is present in an amount more than equimolar relating to the amount of LHRH antagonist, Tween 80 as surfactant and mannitol as bulking agent are dissolved in water for injection, homogenized and processed for injection purposes; or
- an LHRH antagonist, Tween 80 as surfactant and mannitol as bulking agent are dissolved using an aqueous saturated solution of gluconic acid delta-lactone, homogenized and processed for injection purposes.

The invention therefore makes it possible to prepare LHRH antagonists in relatively high concentration in aqueous solutions for injection. LHRH antagonists which may be mentioned are, for example, cetrorelix, teverelix, D-63 153 (Ac-D-Nal-pCl-D-Phe-3-D-Pal-Ser-N-Me-Tyr-D-H-Cit-Nle-Arg-Pro-D-Ala-NH2) ganirelix, abarelix, antide, azaline B. It was seen that an excess of the respective carboxylic acid must be used; equimolar amounts are not sufficient. Obviously, this effect cannot be explained alone by an in-situ salt formation with basic amino acid residues present such as, for example, arginine, pyridylalanine, lysine. Likewise, the surfactant concentration must not be chosen to be too high, since otherwise the solutions foam too much and aggregation is in turn induced by the surfactants.

At the same time, these additions make possible an increase in the bioavailability, since they obviously also slow the spontaneous aggregation in the body after injection or make possible a more rapid absorption of the substance from the site of action. It was seen that the lowered pH of such injection solutions (e.g. pH = 2.5-3) has no influence on the local tolerability of the injection. By increasing the concentration, it is possible to reduce the volume administered, e.g. in the case of cetrorelix from 3 ml to 1 ml for the 3 mg form. It was likewise shown that by means of these additions a good storage stability can be achieved (see Example 1). Although storage for over 6 months at 25°C/60% produced an increase in the impurities, the

content value in each case was still clearly above 90% (as a rule the lowest value of the use period specification of pharmaceutical products). The turbidity, as a sign of aggregation, increased only slightly. Turbidity values of up to 8 FTU (formazine turbidity unit according to European Pharmacopoeia) are perfectly tolerable.

Preservatives such as, for example, phenol or p-chloro-m-cresol do not interfere and can additionally be used for the preservation of the solutions. The use of customary bulking agents, such as mannitol, lactose, glucose and fructose, is likewise possible.

Description of a route for carrying out the invention:

Example 1

500 mg	of cetrorelix
2 g	of Tween 80
2.4 g	of gluconic acid delta-lactone
95 g	of mannitol

were mixed with water for injection to 2 litres to give a homogeneous solution. The solution was then sterile-filtered and dispensed into ampoules. The ampoules were investigated analytically for purity (HPLC), content (HPLC), pH and aggregation (turbidity) initially and after a storage time of 6 months at 2-8°C and 25°C/60% rel. humidity.

Analytical results:

	Starting investigation	Investigation after 6 months at 2-8°C	Investigation after 6 months at 25°C/60% rel. humidity
Purity [%]	0.37	0.69	2.32
Content [%]	100.0	98.7	95.4
pH	3.12	3.16	3.16
Turbidity [FTU]	1.88	2.62	3.92

Example 2

About 500 mg of D-63153
About 100 mg of Tween 80
About 475 mg of mannitol

were adjusted to a pH of about 2.5 using aqueous, saturated gluconic acid delta-lactone solution. A volume of about 50 ml resulted. The mixture was stirred until a clear solution resulted.

Analytical results:

The turbidity of the solution was initially 2.4 FTU. After 24 h, 2.1 FTU were measured. The purity profile and the content of the solution (HPLC) remained unchanged.

Structure of the LHRH antagonist D-63153:

Ac-D-Nal-pCl-D-Phe-3-D-Pal-Ser-N-Me-Tyr-D-H-Cit -Nle-Arg-Pro-D-Ala-NH2

Example 3

About 100 mg of teverelix
About 100 mg of Tween 80
About 475 mg of mannitol

were adjusted to a pH of about 2.5 using aqueous, saturated gluconic acid delta-lactone solution. A volume of about 10 ml resulted. The mixture was stirred until a clear solution resulted.

Analytical results:

The turbidity of the solution was initially 6.8 FTU. After 24 h, 8.4 FTU were measured. The purity profile and the content of the solution (HPLC) remained unchanged.

Structure of the LHRH antagonist teverelix:

Ac-D-Nal-pCl-D-Phe-3-D-Pal-Ser-Tyr-D-H-Cit-Leu-iPr-Lys-Pro-D-Ala-NH2

Claims

1. Aqueous injection solution of an LHRH antagonist comprising gluconic acid, a surfactant as well as a bulking agent, characterized in that gluconic acid is present in an amount more than equimolar relating to the amount of LHRH antagonist, that gluconic acid is added in the form of gluconic acid delta-lactone, that as surfactant Tween 80 and as bulking agent mannitol are used.

2. Aqueous injection solution according to claim 1, characterized in that Cetrorelix, Teverelix, D-63 153 (Ac-D-Nal-pCl-D-Phe- 3-D-Pal-Ser-N-Me-Tyr-D-H-Cit- Nle -Arg-Pro-D-Ala-NH2), Ganirelix, Abarelix, Antide, or Azaline B are used as LHRH antagonist.

3. Aqueous injection solution of an LHRH antagonist according to claim 1, comprising

   500 mg Cetrorelix

   2,4 g Gluconic acid delta-lactone

   2,0 g Tween 80

   95,0 g Mannitol

   in 2 l Water for injection.

4. Aqueous injection solution of an LHRH antagonist according to claim 1, comprising

   500 mg D-63 153

   100 mg Tween 80

   475 mg Mannitol

   adjusted to 50 mL using saturated gluconic acid delta-lactone solution.

5. Aqueous injection solution of an LHRH antagonist according to claim 1, comprising

100 mg Teverelix

100 mg Tween 80

475 mg Mannitol

adjusted to 10 mL using saturated gluconic acid delta-lactone solution.

6. Process for the preparation of aqueous injection solutions of an LHRH antagonist according to any one of claims 1 to 5, characterized in that, alternatively

- an LHRH antagonist, gluconic acid in the form of gluconic acid delta-lactone, wherein gluconic acid is present in an amount more than equimolar relating to the amount of LHRH antagonist, Tween 80 as surfactant and mannitol as bulking agent are dissolved in water for injection, homogenized and processed for injection purposes; or

- an LHRH antagonist, Tween 80 as surfactant and mannitol as bulking agent are dissolved using an aqueous saturated solution of gluconic acid delta-lactone, homogenized and processed for injection purposes.