Injection solution of an LHRH antagonist

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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,

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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 organic, physiologically tolerable acids, particularly carboxylic acids, in particular hydroxycarboxylic acids, but preferably gluconic acid on its own or in combination with surfactants such as, for example, Tween, markedly improve the solubility of LHRH antagonists and thus markedly reduce the proneness to aggregation of these substances.

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-Iso-Leu-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-Iso-Leu-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

Patent claims

1. Aqueous injection solution of an LHRH antagonist, characterized in that an organic, physiologically tolerable acid is added to the LHRH antagonist.

2. Aqueous injection solution according to Claim 1, characterized in that a carboxylic acid is added.

3. Aqueous injection solution according to Claims 1 and 2, characterized in that a hydroxycarboxylic acid is added.

4. Aqueous injection solution according to Claims 1 to 3, characterized in that gluconic acid is added.

5. Aqueous injection solution according to Claims 1 to 4, characterized in that a surfactant is added.

6. Aqueous injection solution according to Claims 1 to 5, which contains Tween as a surfactant.

7. Aqueous injection solution according to Claim 1, which as LHRH antagonist contains cetrorelix, teverelix, D-63 153 (Ac-D-Nal-pCl-D-Phe-3-D-Pal-Ser-N-Me-Tyr-D-H-Cit-Iso-Leu-Arg-Pro-D-Ala-NH2), ganirelix, abarelix, antide or azaline B.

8. Aqueous injection solution according to Claims 1 to 4, characterized in that the acid is present in an at least equimolar amount, based on the amount of the LHRH antagonist.

9. Aqueous injection solution of an LHRH antagonist according to Claims 1 to 8, comprising 500 mg of cetrorelix
2.4 g of gluconic acid delta-lactone
2.0 g of Tween 80
95.0 g of mannitol
in 2 l of water for injection.

10. Aqueous injection solution of an LHRH antagonist according to Claims 1 to 8, comprising 500 mg of D-63 153
100 mg of Tween 80
475 mg of mannitol
adjusted to 50 ml using saturated gluconic acid delta-lactone solution.

11. Aqueous injection solution of an LHRH antagonist according to Claims 1 to 8, comprising 100 mg of teverelix
100 mg of Tween 80
475 mg of mannitol
adjusted to 10 ml using saturated gluconic acid delta-lactone solution.

12. Process for the preparation of aqueous injection solutions of an LHRH antagonist, characterized in that, alternatively
-an LHRH antagonist, an organic, physiologically tolerable acid and optionally a surfactant and a bulking agent are dissolved in water for injection, homogenized and processed for injection purposes, or

-an LHRH antagonist and optionally a surfactant and a bulking agent are dissolved using an aqueous saturated solution of an organic, physiologically tolerable acid, homogenized and processed for injection purposes.

13. Process according to Claim 12, characterized in that a carboxylic acid, in particular hydroxycarboxylic acid, but preferably gluconic acid, is employed.