Pharmaceutical form of administration for peptides, methods for its production and use

The invention relates to novel pharmaceutical forms for the parenteral administration of peptides which are prone to aggregation, in particular of LHRH analogs or LHRH antagonists and agonists, and methods for their production and use.

It is known from EP 0 299 402 to employ pharmaceutically active decapeptides such as SB-030, SB-075 (cetrorelix) and SB-088 in the form of their pharmaceutically acceptable, nontoxic acid addition salts such as hydrochlorides, hydrobromides, sulfates, phosphates, fumarates, gluconates, tannates, maleates, acetates, citrates, benzoates, succinates, alginates, pamoates, ascorbates and tartrates, etc.

A lyophilized peptide or protein preparation is further known from JP 06321800-A which contains gluconate salts as stabilizers. In an example, the solution contains 2.5% magnesium gluconate, with vasopressin, LHRH and insulin, inter alia, being described as active compound.

It is known from the literature, inter alia from Powell, M.F., Pharmaceutical Research, 1258-1263(8) 1991; Dathe, M., Int. J. Peptide Protein Res. 344-349(36) 1990, and Szejtli, J. Pharmaceutical Technology International 16-22, 1991, that oligopeptides, namely particularly those having a terminal acid amide function, are prone to gel formation.

In EP 0 611 572, a preparation process for a lyophilizate of a peptide having 3-15 amino acids is described, according to which 100-10 000 parts by weight of the peptide are dissolved in acetic acid and treated with bulking substances such as mannitol, and subsequently lyophilized in order to obtain a sterile-

filtered lyophilizate of the peptide and to avoid gel formation.

In DE A 195 42 873, pharmaceutical forms of administration of complicated composition in the form of microparticles are described, according to which an ABA triblock copolymer is used whose A block is a polymer of milk and glycolic acid and whose B polymer is a polyethylene glycol chain together with an additive from the group consisting of the serum proteins, polyamino acids, cyclodextrins, cyclodextrin derivatives, saccharides, amino sugars, amino acids, detergents or carboxylic acids, and mixtures of these substances. The microparticles described should also continuously release the polypeptide over a relatively long period after inclusion of small or aggregation-sensitive amounts of polypeptide.

In DD 141 996, the preparation of pharmaceutical forms of native LHRH is described, which are stable over a relatively long period and comply with the requirements for a parenterally administrable preparation. The key point here is the improvement of the storability of these preparations (page 2, lines 19-23). No statement is made about the filterability of the solutions. Moreover, for the improvement of the storability, buffer substances (also acetic acid) are also employed in order to establish a pH range of pH 3.5 - 6.5. The problem of preparing sterile lyophilizates from gel-forming peptide salts is not solved there.

In EP 0 175 506, an aqueous solution of the peptide is treated with 1N acetic acid and then lyophilized in order to obtain the acetate salt of the peptide. The subject of this application is thus the synthesis of the peptide salts.

However, it has been shown that in the case of the known acetate salts of the peptides which are prone to aggregation, such as, for example, the LHRH antagonists, the preparation of sterile solutions for

parenteral administration is indeed possible by means of filtration, especially at high concentrations, but aggregates can form shortly before injection after the dissolution of the lyophilizate. The aggregates then lead to a concentration-dependent lowering of the bioavailability from a peptide concentration of 0.5 mg/ml.

The problem mentioned occurs not only in the case of injection solutions which are administered for the purpose of rapid release of active compound, but is also observed in the case of injection preparations which exhibit delayed release. Thus peptides, incorporated in matrices which are intended to control the release of active compound, exhibit an undesirably low release on account of their proneness to aggregation. Thus the bioavailability is lowered here as well.

Starting from the fact that the preferred administration of pharmaceutically active peptides such as LHRH agonists and antagonists, for example antarelix and cetrorelix, is the parenteral pharmaceutical form, there was a need for the preparation of stable injection preparations having acceptable bioavailability, which can be conveniently prepared, sterile-filtered and formulated. This applies in particular to injection preparations in the form of reconstituted lyophilizates of soluble peptide salts and to microparticles, microcapsules or implants.

This is all the more of importance in consideration of the versatile areas of application of LHRH antagonists, which are becoming more and more known.

A wider selection of parenterally injectable, in particular subcutaneously injectable, stable peptide solutions is desirable with respect to the rapidly growing indication areas of this class of substance.

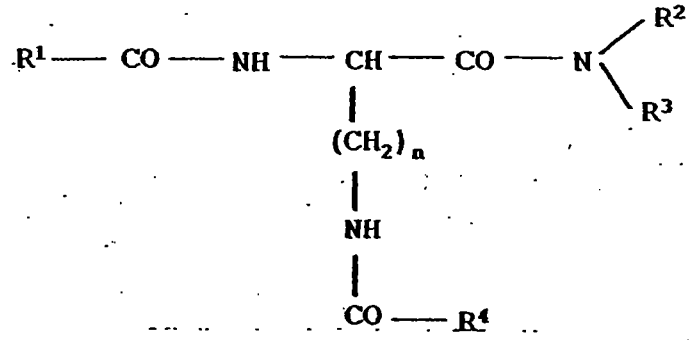
In a first aspect of the present invention, there is provided a pharmaceutical composition suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form, characterised in that the peptides are present in the form of their acetate, gluconate, glucoronate, lactate, citrate, ascorbate, benzoate or phosphate salts and in that the composition additionally contains one of the above-mentioned acids as the free acid. One embodiment may relate to pharmaceutical composition which according to the first aspect can be dissolved or dispersed in water or in aqueous solventmixtures.

According to a further embodiment, the pharmaceutical compositions can also be present in dissolved or dispersed form in a physiologically tolerable oil, preferably medium-chain triglycerides (neutral oils, Miglyol®) or castor oil, sesame oil, cottonseed oil, corn oil, groundnut oil, olive oil, or in mixtures of such oils.

The peptides used are the LHRH antagonisys antide, A75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix and antarelix and the antagonists according to the patents US 5,942,493 and DE 19911771.3.

The antagonists disclosed in US patent 5,942,493 include:

(i) Compounds of the general formula (I)



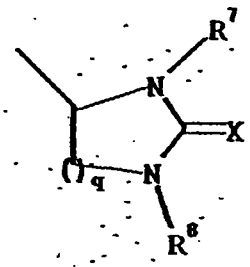
(I)

in which n is the number 3 or 4, R^1 is an alkyl group, an alkyloxy group, an aryl group, a heteroaryl group, an aralkyl group, a heteroaralkyl group, an aralkyloxy group or a heteroaralkyloxy group, in each case unsubstituted or substituted, R^2 and R^3 independently of one another are each a hydrogen atom, an alkyl group, an aralkyl group or a heteroralkyl group, in each case unsubstituted or substituted, where the substitution can in turn consist of an aryl group or heteroaryl group, or $-NR^2R^3$ is an amino acid group, and R^4 is a group having the formula (II)

$$-(CH_2)_p-CO-NR^5R^6 \qquad (II)$$

in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl or heteroararyl group,

or R^4 is a ring of the general formula (III)



(III)

in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, where the aromatic or heteroaromatic radicals can be partially or completely

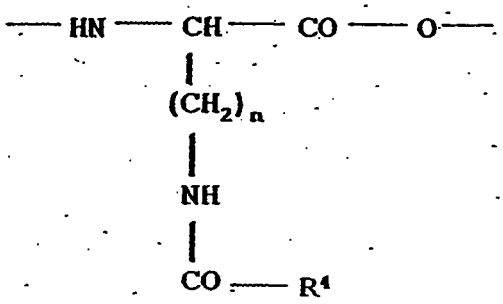
hydrogenated and chiral carbon atoms can have the R- or S-configuration, and its salts with pharmaceutically acceptable acids; and

(ii) Compounds of the general formula (V)

Ac-D-Nal(2)^1-D-(pCl)Phe^2-D-Pal(3)^3-Ser^4-Tyr^5-D-Xxx^6-Leu^7-Arg^8-Pro^9-D-Ala^{10}-NH$_2$ (V)

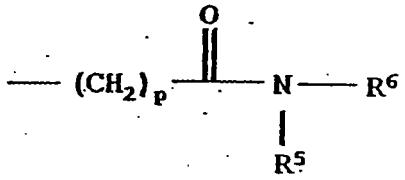
in which D-Xxx is an amino acid group of the general formula (VI)

(VI)



in which n is the number 3 or 4, R^4 is a group of the formula (II)

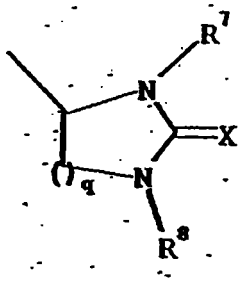
(II)



in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl group or heteroaryl group,

or R^4 is a ring of the general formula (III)

(III)



in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, and its salts with pharmaceutically acceptable acids

The antagonists disclosed in DE 1991171.3 (from which US patent 6,627,609 is derived) include:

Compounds of the general formula (a)

$A\text{-}Xxx^1\text{-}Xxx^2\text{-}Xxx^3\text{-}Xxx^4\text{-}Xxx^5\text{-}Xxx^6\text{-}Xxx^7\text{-}Xxx^8\text{-}Xxx^9\text{-}Xxx^{10}\text{-}NH_2$ (a)

in which

A is an acetyl or a 3-(4-fluorophenyl)propionyl group,

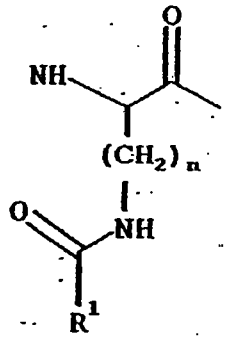
Xxx^1 is D-Nal(1) or D-Nal(2),

$Xxx^2\text{-}Xxx^3$ is D-Cpa-D-Pal(3) or a single bond,

Xxx^4 is Ser,

Xxx^5 is N-Me-Tyr,

Xxx^6 is D-Cit, D-Hci or a D-amino acid group of the general formula (b)

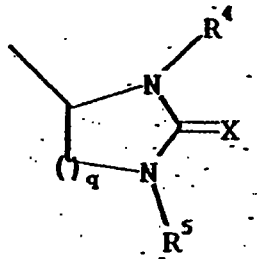


(b)

in which n is the number 3 or 4, where R^1 is a group having the general formula (c)

$$-(CH_2)_p\text{-}CO\text{-}NR^2R^3 \qquad (c)$$

where p is an integer from 1 to 4, R^2 is hydrogen or an alkyl group and R^3 is an unsubstituted aryl group or heteroaryl group, or R^1 is a 3-amino-1,2,4-triazole-5-carbonyl group or R^1 is a ring of the general formula (d)



(d)

in which q is the number 1 or 2, R^4 is a hydrogen atom or an alkyl group, R^5 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom,

Xxx^7 is Leu or Nie,

Xxx^8 is Arg or Lys(iPr),

Xxx^9 is Pro and

Xxx^{10} is Ala, D-Ala or Sar

and their salts with pharmaceutically acceptable acids.

Acids employed in the excipient function are gluconic acid, glucuronic acid, galacturonic acid, glucaric acid, citric acid, ascorbic acid and amino acids.

It is thus possible to suppress the aggregation of the peptide and thus to fulfill the requirements of a preparation having good bioavailability, thus to enrich the pharmaceutical wealth and to do so with an efficient pharmaceutical technology.

It has further surprisingly been found that by the addition of gluconic, glucuronic, citric, lactic or ascorbic acid the stability of various cetrorelix salts can moreover be considerably improved.

According to the invention, the preparation and formulation of sterile-filtered, stable compositions are thus possible without problems.

It is additionally advantageous to add suitable excipients. These excipients can be acids, surface-active substances, polymers, lipids or sugars. Examples of acids are gluconic acid, glucuronic acid, galacturonic acid, glucaric acid, lactic, citric acid, ascorbic acid and amino acids. Surface-active substances which can be employed are polyethylene glycol 12-(hydroxy)stearate (Solutol®), polyoxyethylene ricinoleate (Cremophor®), polysorbates, poloxamers, phospholipids, lecithins or benzalkonium chloride. Suitable polymers are albumins, polyethylene glycols, cellulose derivatives, starch derivatives or polyvinylpyrrolidone. Examples of sugars are cyclodextrins or cyclodextrin derivatives. "Chaotropic" substances such as urea can also be used as additives or excipients.

In a second aspect of the present invention, there is provided a process for the production of a pharmaceutical composition according to the first aspect or its embodiments, characterised in that, by double decomposition of peptide salts with acetic acid, glucuronic acid, gluconic acid, lactic acid, citric acid or ascorbic acid, the corresponding salts are prepared in a stoichoimetric ratio, dissolved in water for injection, then sterile-filtered, dispensed into injection vials and lyophilized.

The area of use of the compositions according to the invention in particular lies in the prevention and therapy of all sex hormone-dependent conditions and diseases which can be influenced by LHRH analogues, i.e. LHRH agonists and LHRH antagonists.
The following are to be emphasized here:
Benign prostate hyperplasia, prostate carcinoma, precocious puberty, hirsutism, endometrial hyperplasia and its concomitant symptoms, endometrial carcinoma, in vitro fertilization (IVF/COS/ART), contraception, premenstrual syndrome (PMS), uterine myomatosis, breast cancer, tubal obstruction (PTO), ovarian cancer, uterine carcinoma. Particularly preferred LHRH

antagonists for the composition according to the invention are the following substances:
cetrorelix, antarelix, antide, A-75998, ganirelix, the Nal-Glu antagonist and LHRH antagonists according to the patents US 5,942,493 and DE 19911771.3., as described previously.

Example 1

By means of polarization microscopy, aggregation investigations were carried out on solutions of various cetrorelix salts without or with addition of excipients.

In a polarization light microscope having crossed polarizers, aggregated peptide solutions show images which are very similar to those of liquid-crystalline structures. In contrast to this, aggregate-free peptide solutions produce no such effects.

Table 1: Influence of a gluconic acid addition on the aggregation behavior of cetrorelix acetate solutions.

Concentration of cetrorelix acetate, mg/ml	Gluconic acid in the reconstitution medium, %	pH	Days without aggregation
2.5	0	4.7	1
2.5	0.0071	4.5	2
2.5	0.071	3.7	2
2.5	0.71	3.1	12

Thus the addition of gluconic acid brings about an improvement in the stability of cetrorelix acetate solutions by delaying or preventing the aggregation.

Further experiments concentrate on cetrorelix gluconate without or with addition of gluconic acid. The most important results are summarized in Table 2.

Table 2: Aggregation behavior of various solutions which were prepared from bulk cetrorelix gluconate product.

Gluconic acid addition:	Yes		No	
Concentration of cetrorelix, mg/ml	pH	Days without aggregation	pH	Days without aggregation
2.5	3.0	> 30		
5	3.6	4	4.8	1
5	3.8	4	4.7	1
7.5	3.4	1	4.7	0
7.5	3.7	1	4.8	0

Cetrorelix gluconate thus offers advantages in comparison to the acetate salt. The addition of gluconic acid increases the storability of cetrorelix gluconate solutions.

Moreover, the stabilizing influence of glucuronic acid on cetrorelix acetate solutions and, as a further salt, also cetrorelix glucuronate was tested for its aggregation behavior. The results are summarized in Table 3.

Table 3: Aggregation behavior of various concentrated solutions of cetrorelix acetate and cetrorelix glucuronate without or with addition of glucuronic acid.

	Glucuronic acid addition:	Yes		No	
Salt form	Concentration of cetrorelix, mg/ml	pH	Days without aggregation	pH	Days without aggregation
Acetate	2.5	3.0	> 21	4.7	0
Acetate	5	3.0	0		
Glucuronate	2.5	2.9	> 30	4.5	3
Glucuronate	5	2.7	> 30	4.6	0

Significant improvements with respect to the aggregation stability of cetrorelix solutions can also be obtained by the replacement of the acetate salt by a glucuronate salt, similarly to the gluconate salt. By the addition of glucuronic acid to cetrorelix glucuronate solutions, the aggregation stability of these solutions can be even further improved.

Table 4: Aggregation-free period in days of cetrorelix acetate solutions after addition of 10% of α-cyclodextrin, 20% of hydroxypropyl-β-cyclodextrin or 20% of γ-cyclodextrin.

Concentration of cetrorelix acetate, mg/ml	α-Cyclodextrin	Hydroxypropyl-β-cyclodextrin	γ-Cyclo-dextrin
2.5	7	24	98 + (168,182,189)
5	0	7	31 + (140,147,182)
7.5	0	10	5 + (20, 20, 20)
10	0	2	2 + (4, 4, 4)
15		0	0

The aggregation stability of cetrorelix acetate solutions can be significantly improved by the addition of hydroxypropyl-β-cyclodextrin and particularly of γ-cyclodextrin.

Table 5: Aggregation-free period in days of 2.5 mg/ml cetrorelix gluconate solutions after addition of α-cyclodextrin, hydroxypropyl-β-cyclodextrin or γ-cyclo-dextrin.

Cyclodextrin type	Concentration of cyclodextrin, %	Days without aggregation
γ-Cyclodextrin	20	182
	6.8	126
Hydroxypropyl-β-cyclodextrin	20	189
	6.8	91
α-Cyclodextrin	10	140
	5	1

The aggregation stability of cetrorelix gluconate solutions can also be significantly improved by the

addition of hydroxypropyl-β-cyclodextrin or of γ-cyclodextrin.

Table 6: Aggregation-free period in days of cetrorelix acetate solutions with addition of polyvinylpyrrolidone (Kollidon® 12 PF or 17 PF)

Concentration of cetrorelix, mg/ml	Concentration of Kollidon®, %	Days without aggregation with Kollidon® 12 PF	Days without aggregation with Kollidon® 17 PF
2.5	0	0	0
	5	1	2
	10	1	2
	15	77	63
	20	84	98
5	15	0	1
	20	0	1

The aggregation stability of cetrorelix acetate solutions can also be significantly improved by the addition of various types of polyvinylpyrrolidone.

Table 7: Aggregation behavior of cetrorelix solutions with addition of various excipients assessed by means of polarization microscopy and according to the visual image (appearance).

Excipient	Conc. of excipient	Conc. of cetrorelix	Aggregation (microscopy)	Appearance
Solutol® HS 15	5.00%	2.5 mg/ml	yes, after 14 days	clear solution
	10.00%	2.5 mg/ml	≥ 112 days without aggregation	clear solution

	20.00%	2.5 mg/ml	≥ 112 days without aggregation	clear solution
Cremophor® EL	5.00%	2.5 mg/ml	yes, after 10 days	clear solution
	10.00%	2.5 mg/ml	≥ 112 days without aggregation	clear solution
	20.00%	5 mg/ml	yes, after 1 day	clear, viscous
L-Glutamic acid	0.80%	2.5 mg/ml	yes, after 2 days	clear solution, pH 3.8
Glucaric acid	2.50%	2.5 mg/ml	≥ 12 days without aggregation	clear solution, pH 2.5
Galacturonic acid	2.50%	2.5 mg/ml	≥ 12 days without aggregation	clear solution, pH 2.6

Example 2

Cetrorelix bulk product is dissolved in 30% strength acetic acid in a concentration of 10 mg/ml and diluted with an aqueous solution of the additives to a final concentration of 1 mg/ml of peptide in 3% acetic acid. This solution is then sterilized and lyophilized (5 mg per vial).

After reconstruction of these lyophilizates, the solutions (2.5 mg/ml of cetrorelix) are investigated for aggregate formation and release behavior in the following tests:

- polarization microscopy (pol. mic.): days without aggregation.
- filterability in %:
  Cetrorelix solutions are prepared according to a standardized process and filtered through 0.22 µm or 0.45 µm filters by means of centrifugation. The concentration of cetrorelix in the filtrate is determined by HPLC and indicated as a % value, based on the starting concentration before filtration (filterability in %).

- in-vitro release abbreviated form (RRS, release in Ringer's solution):

  % released after 1 h and after 6 h.

  The in-vitro release behavior is determined in a flow-through process using Ringer's solution as a medium at 37°C. The concentration measurement is carried out by HPLC. Cetrorelix samples, corresponding to 10 mg of cetrorelix base, are weighed into the flow-through cell, mixed with 4 ml of water and stirred for 10 min. After addition of 6 ml of Ringer's solution to the sample, Ringer's solution is pumped through the flow-through cell while stirring uniformly with a flow of 0.5 ml/min.

- rat animal experiment: cetrorelix residual content in the muscle in % of the administered dose 168 h after injection.

Some cetrorelix acetate lyophilizate batches prepared and the corresponding test results of 2.5 mg/ml cetrorelix acetate solutions prepared therefrom are listed in Table 8a.

Table 8a

Cetrorelix acetate lyophilizate batches (5 mg)...	Pol. mic., days w/o aggr.	0.22 µm filter-able	RRS, [%] after		Rat % i.m. after
Excipients		[%]	1h	6h	168h
Only mannitol (= control)	0				about 55
Solutol®/mannitol	48	100			
Cremophor®/mannitol	46	101			
Solutol®/alanine	16	98	17	24	
Solutol®/alanine/	19	101	57	68	5.7

gluconic acid					
Solutol®/mannitol/ gluconic acid	> 45	100	84	88	3.8
Cremophor®/mannitol/ gluconic acid	> 45	101			
Solutol®/tryptophan/ mannitol	Impos-sible				
Solutol®/tryptophan/ gluconic acid	6				9.6
Cyclodextrin molar ratio 1:10/mannitol	2	101	16	27	10
Cyclodextrin molar ratio 1:10/mannitol/ gluconic acid	> 45	102	68	74	
Cyclodextrin molar ratio 1:30/mannitol	17	100	68	76	
Cyclodextrin molar ratio 1:10/alanine/gluconic acid	5	101	39	52	6.3
Mannitol/citric acid	1	102	45	53	
Solutol®/mannitol/ citric acid	> 36	100	84	91	7.4
Solutol®/alanine/ citric acid	1	99	47	54	
Solutol®/glycine	> 36	97	24	31	
Solutol®/urea	21	100	32	40	
Solutol®/glycine/ gluconic acid	> 36	99	82	89	
Solutol®/urea/ gluconic acid	> 36	100			
Cremophor®/alanine/ gluconic acid	(36)				
Cremophor®/urea/ gluconic acid	(36)				
Pluronic® F127/mannitol	1				

5% Tween® 80/mannitol	> 16				
Polyethylene glycol 4000/mannitol	1				
Dextran/mannitol	1				
Phenylmercuric acetate/mannitol	2				

From the examples mentioned, it is evident that with a large number of the excipients from various substance groups tested (surface-active substances, acids, amino acids, polymers, sugars, sugar alcohols, cyclodextrins, preservatives), individually or with mixtures of these excipients, stabilizing effects can be achieved in vitro (polarization microscopy, filterability, in vitro release) and in vivo. This lowered tendency to aggregation and thus improved in vitro active compound release also leads in the rat experiment to improved bioavailability of the peptide compound and thus to reduced residual contents in the rat muscle.

Further in vitro and in vivo data of batches containing various cetrorelix salts without or with addition of stabilizing excipients are listed in Table 8b below.

Table 8b:

Cetrorelix salts (reconstituted with water)	Conc. of cetro-relix from lyo	Pol. mic days w/o aggr.	RRS, [%] after		Rat % i.m. after
Excipients	mg/ml		1h	6h	168h
- Acetate	2.5	0	12	24.5	about 55
- Acetate	2.5	0	13	35.9	about 55

- Acetate	5	0	10	35	
- Acetate reconstituted with gluconic acid	2.5	18	50	63.2	15.2
- Acetate + Kollidon® 12 PF	2.5	84	15	43.4	20.2
- Acetate + Kollidon® 17 PF	2.5	98	22	50.6	
- Acetate + benzalkonium chloride	2.5		6.3	30.3	
- Acetate + phospholipids	2.5		7.3	23.3	
- Acetate + γ-cyclodextrin (1:10)	2.5		22.6	44.5	10
- Acetate + γ-cyclodextrin (1:30)	2.5		28	56.7	
- Acetate + γ-cyclodextrin (1:50)	2.5		35.1	56.6	
- Acetate + γ-cyclodextrin (1:90)	2.5	> 168	34.5	60.2	3.6
- Acetate + γ-cyclodextrin (1:90)	5	140	19	47.8	
- Acetate + γ-cyclodextrin (1:90)	7.5	20			
- Acetate + γ-cyclodextrin (1:90)	10	4			45.2
- Acetate reconstituted with gluconic acid	15				49.1
- Gluconate	2.5		18	45.3	
- Gluconate	2.5		11.3	46	
- Gluconate reconstituted with gluconic acid	2.5		77.5	83.6	
- Citrate	15	-	9	20.3	
- Lactate	Bulk		20	55.2	

- Embonate	15		13	43	

Example 3

Cetrorelix formulations which are less prone/slower to aggregate (better filterability/polarization microscopy) and exhibit more rapid in-vitro release in Ringer's solution stand out in the rat muscle experiment due to their lower cetrorelix residual content after 168 h. A higher bioavailability is expected of such formulations.

Some results of rat muscle experiments have already been listed in Tables 8a and 8b.

In the further rat muscle experiments shown in Table 9, in addition to the residual content in the muscle the cetrorelix content in the plasma was further determined. Also on the basis of these data, we the stabilizing influence of the excipients tested clear. Moreover, it was possible by the replacement of the acetate salt by other salt forms of cetrorelix to achieve an improved bioavailability and, accompanying this, a reduced residual amount in the rat muscle experiment.

Table 9:

Substance (Cetrorelix)	Dose (mg/kg)	Cetrorelix concentration of the inj. soln. (mg/ml)	Cetrorelix content in the muscle (168 h) % of the dose	Cetrorelix content in the plasma % of the dose
Acetate + Solutol® + alanine +	1.5	2.5	5.7	

gluconic acid				
Acetate + Solutol® + tryptophan + gluconic acid	1.5	2.5	9.6	
Acetate + cyclodextrin 1:10	1.5	2.5	10.0	83.4
Acetate + cyclodextrin 1:10, alanine, gluconic acid	1.5	2.5	6.3	81.8
Acetate + Solutol® + gluconic acid	1.5	2.5	3.8	
Acetate + Solutol® + citric acid	1.5	2.5	7.4	
Acetate	1.5	3	55.1	92.2
Acetate in Miglyol®	1.5	3	22.3	74.2
Acetate + benzalonium chloride	1.5	3	76.9	39.8
Acetate + 20% cyclodextrin	1.5	3	3.6	106.2
Acetate + 20% Kollidon®	1.5	3	20.2	88.4
Acetate + glucuronic acid	1.5	3	23.6	106.1
Acetate + gluconic acid	1.5	3	15.2	95.5
Acetate + 20% cyclodextrin	3.0	10	25.2	60.9

Acetate	3.0	15	56.5	28.7
Acetate in Miglyol®	3.0	15	24.2	57.2
Acetate + 0.025% benzalkon.	3.0	15	10.5	21.4
Acetate + glucuronic acid	3.0	15	78.1	43.8
Acetate + gluconic acid	3.0	15	49.1	45.5
Gluconate	1.5	15	37.9	46.9
Gluconate in mannitol	1.5	3	24.6	58.0
Gluconate in mannitol	1.5	3	25.4	75.2
Gluconate in Miglyol®	1.5	3	28.8	46.3
Gluconate in gluconic acid	1.5	3	13.2	120.0
Gluconate in gluconic acid	3.0	3	29.2	
Gluconate in gluconic acid	3.0	15	43.5	74.2
Glucuronate	1.5	3	16.5	78.6
Glucuronate	3.0	15	18.8	
Lactate	3.0	15	33.2	72.1
Lactate	1.5	3	30.7	67.1
Citrate-lyo/a	1.5	3	22.8	36.6
Citrate in Miglyol®	1.5	3	14.8	53.1
Base	1.5	3	27.2	122.2
Base in	1.5	3	38.9	55.9

Miglyol®				
Benzoate in mannitol	1.5	3	34.2	32.7
Benzoate in Miglyol®	1.5	3	33.1	21.1
Phosphate	1.5	3	32.9	22.6

28 September 2006

CLAIMS:

1. A pharmaceutical composition suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form, characterized in that the peptides are present in the form of their acetate, gluconate, glucuronate, lactate, citrate ascorbate, benzoate or phosphate salts and in that the composition additionally contains one of the above-mentioned acids as the free acid.

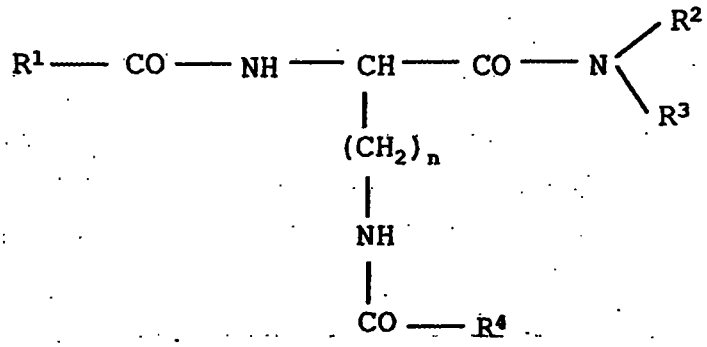
2. The pharmaceutical composition of claim 1 dissolved or dispersed in water or in aqueous solvent mixtures.

3. The pharmaceutical composition of claim 1 dissolved or dispersed in a physiologically tolerable oil.

4. The pharmaceutical composition of claim 3, wherein the oil is selected from medium-chain triglycerides (neutral oils) or castor oil, sesame oil, cottonseed oil, corn oil, groundnut oil, olive oil or mixtures of such oils.

5. The pharmaceutical composition of any of claims 1 to 4, characterized in that the peptides are the LHRH antagonists antide, A-75998, ganirelix or Nal-Glu antagonist.

6. The pharmaceutical composition of any of claims 1 to 4, wherein the peptides are:
- cetrorelix;
- antarelix;
- compounds of the general formula (I)



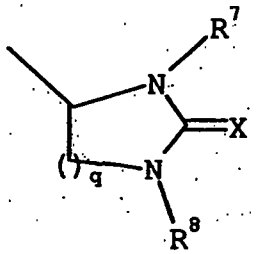
(I)

in which n is the number 3 or 4, R^1 is an alkyl group, an alkyloxy group an aryl group, a heteroaryl group, an aralkyl group, a heteroaralkyl group, an aralkyloxy group or a heteroaralkyloxy group, in each case unsubstituted or substituted, R^2 and R^3 independently of one another are each a hydrogen atom, an alkyl group, an aralkyl group or a heteroralkyl group, in each case unsubstituted or substituted, where the substitution can in turn consist of an aryl group or heteroaryl group, or $-NR^2R^3$ is an amino acid group, and R^4 is a group having the formula (II)

$$-(CH_2)_p-CO-NR^5R^6 \qquad (II)$$

in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl or heteroararyl group,

or R^4 is a ring of the general formula (III)



(III)

in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, where the aromatic or heteroaromatic radicals can be partially or completely

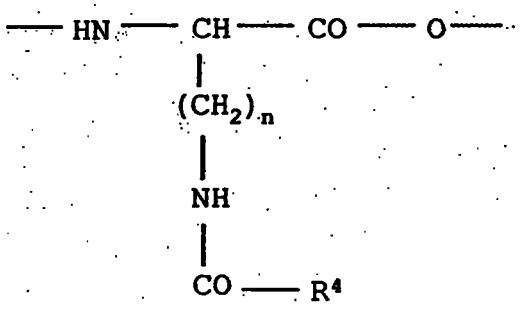
hydrogenated and chiral carbon atoms can have the R- or S-configuration, and its salts with pharmaceutically acceptable acids;

- compounds of the general formula (V)

Ac-D-Nal(2)^1-D-(pCl)Phe^2-D-Pal(3)^3-Ser^4-Tyr^5-D-Xxx^6-Leu^7-Arg^8-Pro^9-D-Ala^{10}-NH_2 (V)

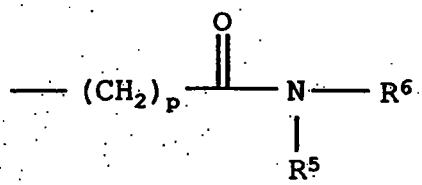
in which D-Xxx is an amino acid group of the general formula (VI)

(VI)



in which n is the number 3 or 4, R^4 is a group of the formula (II)

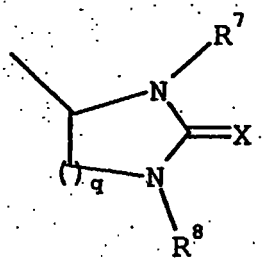
(II)



in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl group or heteroaryl group,

or R^4 is a ring of the general formula (III)

(III)



in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, and its salts with pharmaceutically acceptable acids; or

- compounds of the general formula (a)

$A\text{-}Xxx^1\text{-}Xxx^2\text{-}Xxx^3\text{-}Xxx^4\text{-}Xxx^5\text{-}Xxx^6\text{-}Xxx^7\text{-}Xxx^8\text{-}Xxx^9\text{-}Xxx^{10}\text{-}NH_2$ (a)

in which

A is an acetyl or a 3-(4-fluorophenyl)propionyl group,

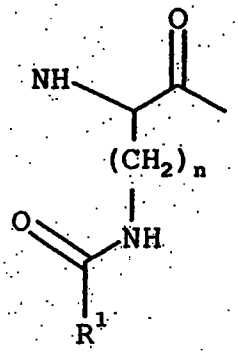
Xxx^1 is D-Nal(1) or D-Nal(2),

Xxx^2-Xxx^3 is D-Cpa-D-Pal(3) or a single bond,

Xxx^4 is Ser,

Xxx^5 is N-Me-Tyr,

Xxx^6 is D-Cit, D-Hci or a D-amino acid group of the general formula (b)

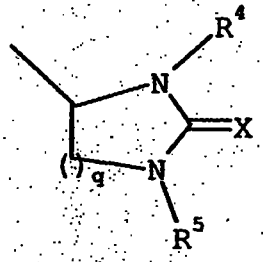


(b)

in which n is the number 3 or 4, where R^1 is a group having the general formula (c)

$$-(CH_2)_p\text{-}CO\text{-}NR^2R^3 \qquad (c)$$

where p is an integer from 1 to 4, R^2 is hydrogen or an alkyl group and R^3 is an unsubstituted aryl group or heteroaryl group, or R^1 is a 3-amino-1,2,4-triazole-5-carbonyl group or R^1 is a ring of the general formula (d)



(d)

in which q is the number 1 or 2, R^4 is a hydrogen atom or an alkyl group, R^5 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom,

Xxx^7 is Leu or Nie,
Xxx^8 is Arg or Lys(iPr),
Xxx^9 is Pro and
Xxx^{10} is Ala, D-Ala or Sar
and their salts with pharmaceutically acceptable acids.

7. The pharmaceutical composition of any preceding claim, further comprising additives and excipients from the group consisting of acids, surface-active substances, polymers, lipids or sugars.

8. The pharmaceutical composition of claim 7, characterized in that the acids employed in the excipient function are gluconic acid, glucuronic acid, galacturonic acid, glucaric acid, citric acid, ascorbic acid or amino acids.

9. The pharmaceutical composition of claim 7, characterized in that the surface-active substances employed are polyethylene glycol 12-(hydroxy)stearate, polyoxyethylene ricinoleate, polysorbates, poloxamers, phospholipids lecitins or in the form of preservatives.

10. The pharmaceutical preparation of claim 9, wherein the surface-active substance employed is benzalkonium chloride or phenylmercuric acetate.

11. The pharmaceutical composition of claim 7, characterized in that the polymers employed are albumins, polyethylene glycols, cellulose derivatives, starch derivatives or polyvinylpyrrolides.

12. The pharmaceutical composition of claim 7, characterized in that the sugars employed are cyclodextrins or its derivatives, and sugar alcohols.

13. The pharmaceutical composition of claim 7, characterized in that urea or other chaotropic substances are employed as excipient.

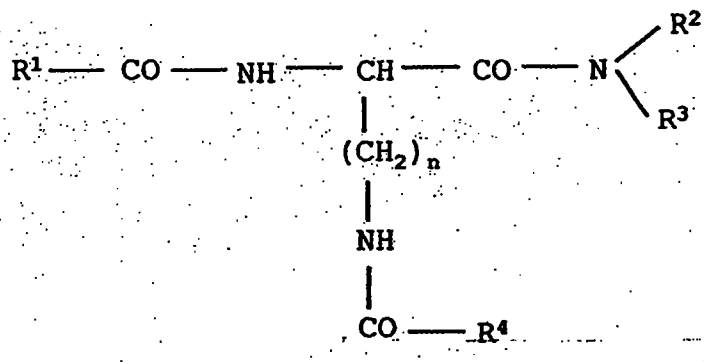
14. The pharmaceutical composition of any preceding claim, characterized in that the peptide salts of acetic acid, gluconic acid, glucuronic acid, lactic acid, citric acid or of ascorbic acid are present in solutions in a concentration of higher than 0.5 mg/ml

15. The pharmaceutical composition according to any of claims 1 to 13, characterized in that the release of active compound is delayed by the use of polymers.

16. The pharmaceutical composition of claim 15 wherein the polymers are homo- or copolymers of lactic and glycolic acid.

17. The pharmaceutical composition according to any of claims 1, 2, 5 to 7 or 14, characterized in that the peptides employed are:

- cetrorelix;
- antarelix;
- compounds of the general formula (I)



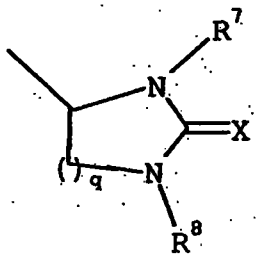
(I)

in which n is the number 3 or 4, R^1 is an alkyl group, an alkyloxy group an aryl group, a heteroaryl group, an aralkyl group, a heteroaralkyl group, an aralkyloxy group or a heteroaralkyloxy group, in each case unsubstituted or substituted, R^2 and R^3 independently of one another are each a hydrogen atom, an alkyl group, an aralkyl group or a heteroralkyl group, in each case unsubstituted or substituted, where the substitution can in turn consist of an aryl group or heteroaryl group, or $-NR^2R^3$ is an amino acid group, and R^4 is a group having the formula (II)

$$-(CH_2)_p-CO-NR^5R^6 \quad (II)$$

in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl or heteroararyl group,

or R^4 is a ring of the general formula (III)



(III)

in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, where the aromatic or heteroaromatic radicals can be partially or completely

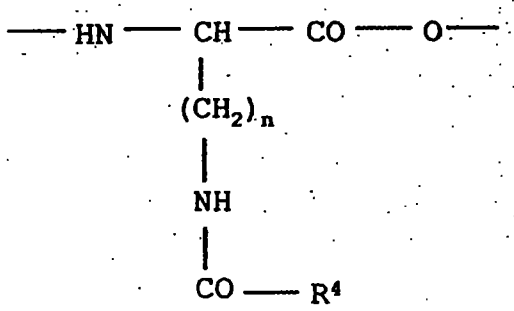
hydrogenated and chiral carbon atoms can have the R- or S-configuration, and its salts with pharmaceutically acceptable acids;

- compounds of the general formula (V)

$Ac\text{-}D\text{-}Nal(2)^1\text{-}D\text{-}(pCl)Phe^2\text{-}D\text{-}Pal(3)^3\text{-}Ser^4\text{-}Tyr^5\text{-}D\text{-}Xxx^6\text{-}Leu^7\text{-}Arg^8\text{-}Pro^9\text{-}D\text{-}Ala^{10}\text{-}NH_2$ (V)

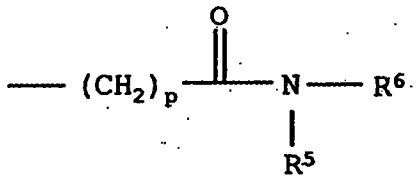
in which D-Xxx is an amino acid group of the general formula (VI)

(VI)



in which n is the number 3 or 4, R^4 is a group of the formula (II)

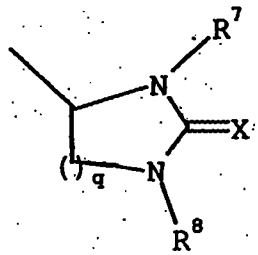
(II)



in which p is an integer from 1 to 4, R^5 is hydrogen or an alkyl group and R^6 is an unsubstituted or substituted aryl group or heteroaryl group,

or R^4 is a ring of the general formula (III)

(III)



in which q is the number 1 or 2, R^7 is a hydrogen atom or an alkyl group, R^8 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom, and its salts with pharmaceutically acceptable acids; or

- compounds of the general formula (a)

$A\text{-}Xxx^1\text{-}Xxx^2\text{-}Xxx^3\text{-}Xxx^4\text{-}Xxx^5\text{-}Xxx^6\text{-}Xxx^7\text{-}Xxx^8\text{-}Xxx^9\text{-}Xxx^{10}\text{-}NH_2$ (a)

in which

A is an acetyl or a 3-(4-fluorophenyl)propionyl group,

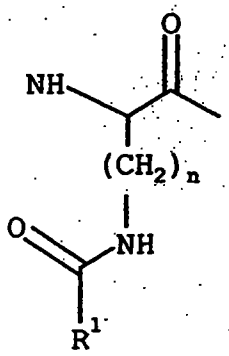
Xxx^1 is D-Nal(1) or D-Nal(2),

$Xxx^2\text{-}Xxx^3$ is D-Cpa-D-Pal(3) or a single bond,

Xxx^4 is Ser,

Xxx^5 is N-Me-Tyr,

Xxx^6 is D-Cit, D-Hci or a D-amino acid group of the general formula (b)

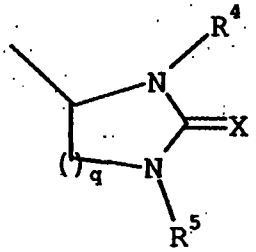


(b)

in which n is the number 3 or 4, where R^1 is a group having the general formula (c)

$$-(CH_2)_p\text{-}CO\text{-}NR^2R^3 \qquad (c)$$

where p is an integer from 1 to 4, R^2 is hydrogen or an alkyl group and R^3 is an unsubstituted aryl group or heteroaryl group, or R^1 is a 3-amino-1,2,4-triazole-5-carbonyl group or R^1 is a ring of the general formula (d)



(d)

in which q is the number 1 or 2, R^4 is a hydrogen atom or an alkyl group, R^5 is a hydrogen atom or an alkyl group and X is an oxygen or sulphur atom,

Xxx^7 is Leu or Nie,
Xxx^8 is Arg or Lys(iPr),
Xxx^9 is Pro and
Xxx^{10} is Ala, D-Ala or Sar
and their salts with pharmaceutically acceptable acids;

and are employed in solutions in a concentration of higher than 0.5 mg/ml.

18. A process for the production of a pharmaceutical composition according to any of claims 1 or 5 to 7, characterized in that, by double decomposition of peptide salts with acetic acid, glucuronic acid, gluconic acid, lactic acid, citric acid or ascorbic acid, the corresponding salts are prepared in a stoichiometric ratio, dissolved in water for injection, then sterile-filtered, dispensed into injection vials and lyophilized.

19. The process of claim 18, wherein excipients as claimed in claims 8 to 13 are mixed into the solution prior to the sterile filtration step.

20. A process for the production of a pharmaceutical composition according to any of claims 1 or 5 to 7, characterized in that, by double decomposition of peptide salts with acetic acid, glucuronic acid, gluconic acid, lactic acid, citric acid of ascorbic acid, the corresponding salts are prepared in a stoichiometric ratio, these salts are incorporated into delayed-release microparticles of homo- or copolymers of lactic and glycolic acid and these microparticles are suspended in a physiologically tolerable medium for injection purposes.

21. The pharmaceutical composition according to any of claims 1 to 17 for use in therapy.

22. Use of the pharmaceutical composition according to any of claims 1 to 17, for the manufacture of a medicament for treating, by parenteral administration, sex hormone-dependent, benign and malignant diseases.

23. The use of claim 22, wherein the sex hormone-dependent, benign and malignant diseases are selected from the group consisting of benign prostate hyperplasia, prostate carcinoma, precocious puberty, hirsutism, endometrial hyperplasia and their concomitant symptoms, endometrial carcinoma, *in vitro* fertilization (IVF/COS/ART) contraception, premenstral syndrome (PMS), uterine myomatosis, breast cancer, tubal obstruction (PTO), ovarian cancer and uterine carcinoma.