LHRH AGONISTS AND ANTAGONISTS

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PIONEERING PARTNER FOR PEPTIDES
LHRH AGONISTS AND ANTAGONISTS OFFERED BY BACHEM

LHRH (luteinizing hormone-releasing hormone) is a decapeptide hormone which is synthesized in neurosecretory cells within the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. Since it controls the secretion of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone) from the anterior pituitary gland, it is also designated as GnRH (gonadotropin-releasing hormone). Pulsatile secretion is essential for reproductive functions, sexual development and differentiation. Prolonged non-pulsatile administration of LHRH results in a down-regulation of LH and FSH secretion from the anterior pituitary gland, followed by a suppression of gonadal steroid synthesis. This effect, which is shared by longer-acting GnRH agonists, is used for the treatment of hormone-dependent breast and prostate cancers but also for the treatment of endometriosis and precocious puberty. In reproductive medicine, continuous administration of LHRH agonists serves to prevent a premature LH surge prior to stimulation of ovulation.

In this brochure we present our LHRH agonists and antagonists for endocrinological research and its generic APIs in this field.
LHRH Agonists and Antagonists

LHRH, also known as GnRH (gonadotropin-releasing hormone) or gonadorelin, is an important hypothalamic hormone which regulates reproductive functions and the development and maintenance of secondary sex characteristics in males and females. It acts directly on the pituitary gland and stimulates the release of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone).

Back in the 1930s it was already known that the central nervous system in mammals was able to control the release of LH and FSH from the pituitary gland. Electrophysiological studies hinted at the hypothalamus as a link between the central nervous system and the pituitary gland. The mechanism of this hypothalamic control, however, was not elucidated at that time. The discovery of the hypothalamo-hypophyseal portal system, a blood vessel system linking the hypothalamus to the anterior pituitary, led to the hypothesis that neurosecretory cells of the hypothalamus synthesize hormones which are released into the portal system and thereby stimulate the secretion of hypophyseal hormones. This concept of the hypothalamic control of the adenohypophysis was strongly supported by the findings by J.D. Green and G.W. Harris. They discovered that interruption of the blood vessels between the hypothalamus and the anterior pituitary, by sectioning the pituitary stalk, prevented ovulation in their experimental animals. In 1960, S.M. McCann and coworkers demonstrated that an extract from rat hypothalami contained an activity which could cause the release of LH from the pituitary. After a tremendous effort to isolate and determine the structure of this LHRH activity, A.V. Schally et al. were able to present the structure of porcine LHRH at the congress of the Endocrine Society in San Francisco in 1971. Porcine LHRH was shown to be a decapeptide with the following structure:

\[\text{Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH}_2\]

\(<\text{EWSYGLRP amide}\>

Since LHRH also stimulates the release of FSH from the pituitary gland, it was also designated as GnRH (gonadotropin-releasing hormone, gonadorelin).

In the following years, LHRHs from other species were isolated and sequenced. It turned out that most vertebrates produce two, and fishes even three LHRH isoforms, LHRH, LHRH II, and LHRH III. The LHRH isoform I from all mammalian species examined had the same amino acid sequence as the porcine peptide. The sequence of GnRH II, \(<\text{EHWSHGYP amide}\>\>, which was first isolated from chicken brains in 1984, is conserved even stronger. It could be detected in all jawed vertebrates examined. In contrast to the other vertebrate classes, the sequences of the piscine GnRH isoforms show a considerable diversity. One of them, lamprey GnRH III (peforelin), has found use in veterinary medicine. After the primary structure of gonadorelin had been elucidated, an enormous research interest focused on the determination of the structure-activity relationship. Since GnRH has a very short half-life of several minutes only, the fundamental aim behind this effort was to find more potent and longer-acting agonists for clinical applications. Until now, several thousand LHRH analogs have been synthesized. It became clear that the amino acids at the positions 1 and 4-10 were essential for binding to the receptors and for exerting conformational effects. Modification at position 6 with a D-amino acid and/or the replacement of the glycine amide residue with an ethylamide group yielded several potent long-acting LHRH agonists.
yielded several potent long-acting LHRH agonists such as buserelin ((Des-Gly\textsuperscript{10},D-Ser(tBu)\textsuperscript{6},Pro-NHEt\textsuperscript{9})-LHRH), deslorelin ((Des-Gly\textsuperscript{10},D-Trp\textsuperscript{6},Pro-NHEt\textsuperscript{9})-LHRH), fertirelin ((Des-Gly\textsuperscript{10},Pro-NHEt\textsuperscript{9})-LHRH), lecirelin ((Des-Gly\textsuperscript{10},tBu-D-Gly\textsuperscript{6},Pro-NHEt\textsuperscript{9})-LHRH), leuprorelin (leuprolide) (Des-Gly\textsuperscript{10},tBu-D-Gly\textsuperscript{6},Pro-NHEt\textsuperscript{9})-LHRH), nafarelin ((D-2-Nal\textsuperscript{6})-LHRH), and triptorelin ((D-Trp\textsuperscript{6})-LHRH). Substitution of the C-terminal glycine amide with an azaglycine residue in combination with an O-t-butylated D-serine residue (D-Ser(tBu)) in position 6 led to another well-known agonist, goserelin ((D-Ser(tBu)\textsuperscript{6},Azagly\textsuperscript{10})-LHRH). Azagly-nafarelin, a nafarelin sequence analogously modified at the C-terminus, is a GnRH agonist used in veterinary medicine. The enhanced biological activity of these analogs is due to their increased resistance to enzymatic degradation and their higher affinity for the GnRH receptors. Appropriate salt forms allow to obtain prolonged-release formulations of these LHRH agonists.

The elucidation of the primary structure of LHRH and the availability of synthetic GnRH and GnRH analogs have contributed to the understanding of the physiological role and mode of action of the hormone. LHRH secretion occurs in a pulsatile fashion which is due to oscillations in the electrical activity of the LHRH pulse generator in the medial basal hypothalamus. The pulsatile secretion pattern, which is different in males and females, changes during sexual maturation. Regulation of the secretion pattern is essential for proper development and maintenance of reproductive functions.

The diverse effects of LHRH and its agonists, dependent on the way of administration either as a single injection, multiple injections, or continuous infusion, have found their use in reproductive medicine and in the treatment of various disorders. Continuous administration first results in an increase in the release of LH and FSH, followed by a down-regulation due to pituitary desensitization. As a consequence, gonadal steroid plasma concentrations are lowered to castrate levels. The inhibiting effect of GnRH agonists on gonadal steroids is used in the treatment of hormone-dependent prostate and breast cancer. Continuous administration of LHRH agonists is also indicated for the treatment of endometriosis since reduction of the estrogen levels results in a shrinking of the uterine and ectopic endometrial tissue. Besides these indications, LHRH-induced suppression of gonadal hormone levels also allows the treatment of central precocious puberty, which is manifested by the premature development of sexual characteristics. Most children with this disorder grow fast at first, but also finish growing before reaching their full potential height. Normal puberty is resumed after discontinuation of GnRH agonist administration. In assisted reproduction, LHRH agonists are used to prevent a premature LH surge and consequent ovulation prior to ovarian stimulation with gonadotropins.

GnRH and its agonists have found broad use in veterinary medicine and animal husbandry. Generally, variation of the dosage regimen of these drugs allows to induce either reproduction or infertility in animals. The most important application of gonadorelin itself is the synchronization of ovulation in dairy cattle. Other LHRH agonists are used in the reproduction management of companion animals and horses. For example, administration of deslorelin triggers ovulation in estrous mares and a single dose of buserelin induces ovulation in bitches in heat.

GnRH agonists can be conveniently applied in humans and animals as slow-release depot formulation. Diffusion-controlled drug delivery systems for subcutaneous implantation allow continuous administration of the drugs during months or even years. For example, once-yearly histrelin-releasing implants for the treatment of prostate cancer in men or deslorelin-releasing reservoirs implanted for the prolonged reversible castration of male dogs and the suppression of the oestrus of bitches. The elevation of LH with the dysregulation of the hypothalamic-pituitary-gonadal axis at menopause and andropause could play a role in modulating the susceptibility to, and
progression of Alzheimer’s disease (AD). This hypothesis has raised substantial interest in GnRH agonists as potential drugs for the therapeutic intervention in AD patients. A beneficial effect could be observed in mild-to-moderate cases when administering leuprolide to female AD patients.

Apart from LHRH agonists, LHRH antagonists have also found their way into assisted reproduction. The severe side-effects of the active compounds developed initially, which were caused by concomitant histamine release, could be vastly reduced in the safe and effective “third-generation” (e.g. abarelix, acyline, antide (iturelix), cetrorelix, ganirelix) and “fourth-generation” (e.g. degarelix, ozarelix) GnRH antagonists. Cetrorelix and ganirelix have gained approval for the inhibition of premature LH surges in women undergoing controlled ovarian (hyper)stimulation.

A major disadvantage of LHRH agonists in the treatment of hormone-dependent cancer has been attributed to their potential stimulatory effects on the hormone-dependent cancer cells due to initial stimulation of LH and FSH and the concomitant increase in gonadal steroid levels. Antagonists have therefore been suggested to offer a safer treatment option. Abarelix and degarelix have been approved by the FDA for the treatment of advanced prostate cancer in patients who can’t be treated by other options.

Since the isolation and characterization of LHRH about 50 years ago, we have enormously improved our understanding about its function in physiological and developmental processes. The search for potential GnRH analogs has provided us with information about a multitude of agonists and antagonists. Research in this field is still active, and there is a persistent interest in finding more sophisticated drug regimens, especially as long-lasting depot formula-
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LHRH AGONISTS AND ANTAGONISTS
### BUSERELIN AND IMPURITIES

- **(Des-Gly^{10}, D-Ser(tBu)^8, Pro-NHET^9)-LHRH (Buserelin)**
  - H-4224
  - <EHWSYs(tBu)-LRP-NHET

- **(Des-Gly^{10}, D-His^2, D-Ser(tBu)^8, Pro-NHET^9)-LHRH ((D-His^2)-Buserelin)**
  - H-8780
  - <ehWSYs(tBu)-LRP-NHET

- **(Des-Gly^{10}, D-Pyr^1, D-Ser(tBu)^8, Pro-NHET^9)-LHRH ((D-Pyr^1)-Buserelin)**
  - H-8775
  - <eHWSYs(tBu)-LRP-NHET

- **(Des-Gly^{10}, D-Ser^4, D-Ser(tBu)^6, Pro-NHET^9)-LHRH ((D-Ser^4)-Buserelin)**
  - H-8785
  - <EHWSYs(tBu)-LRP-NHET

- **(Des-Gly^{10}, D-Tyr^5, D-Ser(tBu)^8, Pro-NHET^9)-LHRH ((D-Tyr^5)-Buserelin)**
  - H-8790
  - <EHWSys(tBu)-LRP-NHET

### DESLORELIN, ANALOGS AND FRAGMENTS

- **(Des-Gly^{10}, D-Trp^6, Pro-NHET^9)-LHRH (Deslorelin High acetate salt)**
  - H-4116
  - <EHWSYwLRP-NHET (High acetate salt)

- **(Des-Gly^{10}, D-His^2, D-Trp^6, Pro-NHET^9)-LHRH ((D-His^2)-Deslorelin)**
  - H-4986
  - <EHWSYwLRP-NHET

- **(Des-Gly^{10}, D-Trp^6, D-Leu^7, Pro-NHET^9)-LHRH ((D-Leu^7)-Deslorelin)**
  - H-4994
  - <EHWSYwLRP-NHET

- **(Des-Gly^{10}, D-Ser^4, D-Trp^6, Pro-NHET^9)-LHRH ((D-Ser^4)-Deslorelin)**
  - H-4988
  - <EHWSYwLRP-NHET

- **(Des-Gly^{10}, D-Tyr^5, D-Trp^6, Pro-NHET^9)-LHRH ((D-Tyr^5)-Deslorelin)**
  - H-4992
  - <EHWSywLRP-NHET

### GONADORELIN, ANALOGS AND FRAGMENTS

- **LHRH (Acetate salt)**
  - (Gonadorelin Acetate salt)
  - H-4005
  - <EHWSYGLRPG-NH₂ (Acetate salt)

- **LHRH (Hydrochloride salt)**
  - (Gonadorelin Hydrochloride salt)
  - H-6728
  - <EHWSYGLRPG-NH₂ (Hydrochloride salt)

- **LHRH (free acid)**
  - H-6010
  - <EHWSYGLRPG

- **(D-Ala^6)-LHRH**
  - H-4020
  - <EHWSYaLRPG-NH₂

- **Biotinyl-(Gln^1)-LHRH**
  - H-4792
  - Biotinyl-QHWSYGLRPG-NH₂

- **(Des-Pyr^1)-LHRH**
  - H-9200
  - HWSYGLRPG-NH₂

- **(3,5-Diido-Tyr^5)-LHRH**
  - H-1375
  - <EHWSY(3,5-diido)GLRPG-NH₂
## Gonadorelin, Analogs and Fragments (Continued)

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<td>For-HWSYGLRPG-NH₂</td>
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## Goserelin and Impurities

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GOSERELIN AND IMPURITIES (CONTINUED)

(D-Ser<sup>6</sup>, Azagly<sup>10</sup>)-LHRH
((D-Ser<sup>6</sup>)-Goserelin)
H-6266
<EHWSysLRP-Azagly-NH<sub>2</sub>

(D-Tyr<sup>5</sup>, D-Ser<sup>(tBu)</sup><sup>6</sup>, Azagly<sup>10</sup>)-LHRH
((D-Tyr<sup>5</sup>)-Goserelin)
H-5734
<EHWSys(tBu)-LRP-Azagly-NH<sub>2</sub>

(H-6266, D-Ser<sup>(tBu)</sup> <sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH (Des-carboxamide)-Goserelin)
H-5762
<EHWSys(tBu)-LRP-NHNH<sub>2</sub>

(H-5734, D-Ser<sup>(tBu)</sup> <sup>6</sup>, Azagly<sup>10</sup>)-LHRH
((D-Pyr<sup>1</sup>)-Goserelin)
H-6648
HWSys(tBu)-LRP-Azagly-NH<sub>2</sub>

HISTRELIN, ANALOGS AND FRAGMENTS

(Des-Gly<sup>4</sup>, D-His(Bzl)<sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH (Histrelin)
H-9210
<EHWSYh(Bzl)-LRP-NH<sub>Et</sub>

(Des-Gly<sup>4</sup>, His(Bzl)<sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH ((His(Bzl)<sup>6</sup>)-Histrelin)
H-4656
<EHWSYH(Bzl)-LRP-NH<sub>Et</sub>

(Des-Gly<sup>4</sup>, D-His<sup>1</sup>, D-His(Bzl)<sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH ((D-His<sup>1</sup>)-Histrelin)
H-4652
<EHWSYh(Bzl)-LRP-NH<sub>Et</sub>

(Des-Gly<sup>4</sup>, D-His<sup>1</sup>, D-Leu<sup>7</sup>, Pro-NH<sub>2</sub>)-LHRH ((D-Leu<sup>7</sup>)-Histrelin)
H-4658
<EHWSYh(Bzl)-LRP-NH<sub>Et</sub>

(H-4656, D-Ser<sup>(tBu)</sup> <sup>6</sup>, D-His(Bzl)<sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH (Histrelin (1-7))
H-4704
<EHWSYh(Bzl)-LRP-NH<sub>Et</sub>

(Des-Gly<sup>4</sup>, D-Tyr<sup>5</sup>, D-His(Bzl)<sup>6</sup>, Pro-NH<sub>2</sub>)-LHRH ((D-Tyr<sup>5</sup>)-Histrelin)
H-4654
<EHWSYh(Bzl)-LRP-NH<sub>Et</sub>

(D-His(Bzl)<sup>6</sup>)-LHRH (Histrelin (1-7)) (free acid)
H-4804
<EHWSYh(Bzl)-L

(Des-Gly<sup>4</sup>, tBu-D-Gly<sup>4</sup>, Pro-NH<sub>2</sub>)-LHRH (Lecirelin Trifluoroacetate salt)
H-5936
<EHWSY-D-Tle-LRP-NH<sub>Et</sub> (Trifluoroacetate salt)
LEUPROLIDE AND IMPURITIES

(Des-Gly\(^{10}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH (Leuprolide)
H-4060
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([Leu\(^{6}\)]-Leuprolide)
H-6402
\(<\text{EHWSYLLRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Leu\(^{6}\),\([^{13}C]_{7}\)Leu\(^{7}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH (([\([^{13}C]_{7}\)Leu\(^{7}\)]-Leuprolide)
H-6258
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Leu\(^{6}\),D-Leu\(^{7}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([D-Leu\(^{7}\)]-Leuprolide)
H-4636
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Leu\(^{6}\),D-His\(^{2}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([D-His\(^{2}\)]-Leuprolide)
H-4316
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-His\(^{2}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(D-His\(^{2}\),D-Ser\(^{4}\)]-Leuprolide)
H-6398
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Lys\(^{3}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(D-Lys\(^{3}\),D-Trp\(^{3}\)]-Leuprolide)
H-6716
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Ser\(^{4}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(D-Ser\(^{4}\)]-Leuprolide)
H-4638
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Ser\(^{4}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(D-Ser\(^{4}\)]-Leuprolide)
H-6168
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(Des-Pro-NH\(_{Et}\)]-Leuprolide)
H-6398
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(D-Leu\(^{6}\)]-LHRH (1-8) (free acid) ([(Des-Pro-NH\(_{Et}\)]-Leuprolide)
H-6714
\(<\text{EHWSYILRP-NH}_{Et}\)

(Des-Gly\(^{10}\),Des-Ser\(^{4}\),D-Leu\(^{6}\),Pro-NH\(_{Et}\))\(^{b}\)-LHRH ([(Des-Ser\(^{4}\)]-Leuprolide)
H-4008
\(<\text{EHWSYILRP-NH}_{Et}\)

PISCINE LHRH

LHRH (lamprey III) (Peforelin)
H-4258
\(<\text{EHWSHDWKPG-NH}_{2}\)

LHRH (salmon)
H-6845
\(<\text{EHWSYGWLPG-NH}_{2}\)
### PISCINE LHRH (CONTINUED)

<table>
<thead>
<tr>
<th>LHRH (sea bream)</th>
<th>(Des-Gly¹⁰,D-Ala⁶,Pro-NH₂⁹⁹)-LHRH (salmon)</th>
<th>(Des-Gly¹⁰,D-Trp⁶,Pro-NH₂⁹⁹)-LHRH (sea bream)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-4262</td>
<td>H-9205</td>
<td>H-4284</td>
</tr>
<tr>
<td>&lt;EHWSYGLSPG-NH₂</td>
<td>&lt;EHWSYrWLP-NHEt</td>
<td>&lt;EHWSYwLSP-NHEt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Des-Gly¹⁰,D-Ala⁶,Pro-NH₂⁹⁹)-LHRH (salmon)</td>
<td></td>
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<tr>
<td>H-7525</td>
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</tr>
<tr>
<td>&lt;EHWSYwWLP-NHEt</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Des-Gly¹⁰,D-Ala⁶,Pro-NH₂⁹⁹)-LHRH (sea bream)</td>
<td></td>
<td></td>
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<tr>
<td>H-4282</td>
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<tr>
<td>&lt;EHWSYwLSP-NHEt</td>
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</tbody>
</table>

### TRIPTORELIN, ANALOGS AND FRAGMENTS

<table>
<thead>
<tr>
<th>(D-Trp⁶)-LHRH (Triptorelin Acetate salt)</th>
<th>(Trp⁹)-LHRH ((Trp⁹)-Triptorelin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-4075</td>
<td>H-4578</td>
</tr>
<tr>
<td>&lt;EHWSYwLRPG-NH₂ (Acetate salt)</td>
<td>&lt;EHWSYwLRPG-NH₂</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(D-Trp⁶)-LHRH (Triptorelin Pamoate salt)</th>
<th>(D-Trp⁹)-LHRH ((D-Trp⁹)-Triptorelin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-6150</td>
<td>H-4582</td>
</tr>
<tr>
<td>&lt;EHWSYwLRPG-NH₂ (Pamoate salt)</td>
<td>&lt;EHWSYwLRPGLRPG-NH₂</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(D-Trp⁹)-LHRH (Triptorelin (free acid))</th>
<th>(D-Tyr⁶,D-Trp⁹)-LHRH ((D-Tyr⁶)-Triptorelin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3078</td>
<td>H-4646</td>
</tr>
<tr>
<td>&lt;EHWSYwLRPG</td>
<td>&lt;EHWSYwLRPG-NH₂</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(D-His²,D-Trp⁹)-LHRH ((D-His²)-Triptorelin)</th>
<th>(D-Trp⁹)-LHRH (1-6) amide (Triptorelin (1-6) amide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-4642</td>
<td>H-4574</td>
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<tr>
<td>&lt;EHWSYwLRPG-NH₂</td>
<td>&lt;EHWSYw-NH₂</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(D-Trp⁴,D-Leu⁷)-LHRH ((D-Leu⁷)-Triptorelin)</th>
<th>Formyl-(D-Trp⁹)-LHRH (2-10) (Formyl-Triptorelin (2-10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-4648</td>
<td>H-4576</td>
</tr>
<tr>
<td>&lt;EHWSYwLRPG-NH₂</td>
<td>For-HWSYwLRPG-NH₂</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(D-Ser⁴,D-Trp⁹)-LHRH ((D-Ser⁴)-Triptorelin)</th>
<th>(D-Trp⁹)-LHRH (2-10) ((Des-Pyr¹)-Triptorelin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-4644</td>
<td>H-6404</td>
</tr>
<tr>
<td>&lt;EHWSYwLRPG-NH₂</td>
<td>HWSYwLRPG-NH₂</td>
</tr>
</tbody>
</table>
FURTHER LHRH ANALOGS AND FRAGMENTS

LHRH (chicken)
H-3106
<EHWSYGLQPG-NH₂

LHRH II
H-4278
<EHWSHGWYPG-NH₂

(Des-Gly₁₀,D-Ala⁶,Pro-NH₂⁹)-LHRH (Alarelin)
H-4070
<EHWSYaLRP-NH₂

(Des-Gly₁₀,Pro-NH₂⁹)-LHRH (Fertirelin)
H-4055
<EHWSYGLRP-NH₂

(D-2-Nal⁶)-LHRH (Nafarelin)
H-6095
<EHWSY-D-2-Nal-LRP-NH₂

(Des-Gly₁₀,D-Ala⁶,Pro-NH₂⁹)-LHRH II (chicken)
H-4286
<EHWSHaWYP-NH₂

(Des-Gly₁₀,D-Arg⁶,Pro-NH₂⁹)-LHRH II (chicken)
H-4288
<EHWSHrWYP-NH₂

LUTEINIZING HORMONE-RELEASING HORMONE (LHRH) ANTAGONISTS

Antide (Iturelix)
H-9215
Ac-D-2Nal-D-4Cpa-D-3Pal-SK(nicotinoyl)-k(nicotinoyl)-LK(isopropyl)-Pa-NH₂

Cetrorelix
H-6682
Ac-D-2Nal-D-4Cpa-D-3Pal-S-Y-D-Cit-LRPa-NH₂

Degarelix
H-7428
Ac-D-2-Nal-D-4-Cpa-D-3-Pal-Ser-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-Leu-Lys(isopropyl)-Pro-D-Ala-NH₂

Acetyl-(D-Trp¹,4-chloro-D-Phe³,D-Trp³,D-Arg⁶,D-Ala¹⁰)-LHRH (LRF-147)
H-5575
Ac-w-4Cpa-fwSYLRPa-NH₂

(D-Phe²⁶,Pro¹)-LHRH
H-4045
<EFPSYCLRPG-NH₂

Luteinizing Hormone-Releasing Hormone Antagonist
H-5076
Ac-D-2Nal-D-4Cpa-D-3Pal-GRPa-NH₂

Ozarelix
H-7384
Ac-D-2Nal-D-4-Cpa-D-3Pal-S-N-Me-Y-D-Hci-Nle-RPa-NH₂
False-colour transmission electron micrograph (TEM) of a cell of the human anterior pituitary gland (adenohypophysis) showing the secretion of gonadotrophic hormones (gonadotrophins). The cell nucleus at bottom left is coloured orange: circular “packets” of hormone in the surrounding cytoplasm are coloured dark pink. The group of gonadotrophins includes any hormones synthesised & secreted by the pituitary that act on the sex organs to produce sex hormones and sperm or ova. Important examples include follicle-stimulating hormone and luteinizing hormone.

KEYSTONE/SCIENCE PHOTO LIBRARY/STR
Bachem is the world’s leading independent manufacturer of peptide active pharmaceutical ingredients (APIs) and a well established manufacturer of small molecules APIs. Each year, we manufacture hundreds of batches of drug substance for projects in clinical trials and for products on the market.

We are currently involved in more than 100 cGMP development projects targeting NCEs and we offer over 80 generic drug substances. We have the capacity to produce peptide APIs from gram scale up to annual quantities of hundreds of kilograms and small molecules APIs from gram scale up to annual quantities of tens of tons. Our GMP manufacturing facilities are located in Switzerland and the United States and are regularly inspected by the FDA and local authorities.

In addition to more than 40 years of experience in the manufacture of drug substance, we also have a strong regulatory background and we are well prepared to fully support you with the required regulatory documentation such as drug master files (DMFs). For complex development projects we support you with dedicated project teams comprising of our experts from R&D, production, quality control, quality assurance and regulatory affairs. A team of experienced Business Development Managers and Generics Managers look forward to working with you for your future requirements.
### GENERIC ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

<table>
<thead>
<tr>
<th>Name</th>
<th>Code</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buserelin</td>
<td>H-4224-GMP</td>
<td>&lt;EHWSYs(tBu)-LRP-NH&lt;sub&gt;Et&lt;/sub&gt;</td>
</tr>
<tr>
<td>Gonadorelin Acetate</td>
<td>H-4005-GMP</td>
<td>&lt;EHWSYGLRP-NH&lt;sub&gt;3&lt;/sub&gt; (Acetate salt)</td>
</tr>
<tr>
<td>Gosserelin Acetate</td>
<td>H-6395-GMP</td>
<td>&lt;EHWSYs(tBu)-LRP-Azagly-NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Leuprolide Acetate</td>
<td>H-4060-GMP</td>
<td>&lt;EHWSYILRP-NH&lt;sub&gt;Et&lt;/sub&gt;</td>
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<tr>
<td>Triptorelin Acetate</td>
<td>H-4075-GMP</td>
<td>&lt;EHWSYwLRPG-NH&lt;sub&gt;3&lt;/sub&gt; (Acetate salt)</td>
</tr>
<tr>
<td>Triptorelin Pamoate</td>
<td>H-6150-GMP</td>
<td>&lt;EHWSYwLRPG-NH&lt;sub&gt;3&lt;/sub&gt; (Pamoate salt)</td>
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</table>

### IMPURITIES OF THE LEUPRORELIN PH. EUR. MONOGRAPH

| Impurity A | (D-Ser<sup>4</sup>)-Leuprolide | H-6168 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity B | (D-His<sup>2</sup>)-Leuprolide | H-4316 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity C | (Leu<sup>6</sup>)-Leuprolide | H-6402 | <EHWSYLLRP-NH<sub>Et</sub> |
| Impurity D | (Ser(Ac)<sup>4</sup>)-Leuprolide | H-6172 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity E | (D-Trp<sup>3</sup>)-Leuprolide | H-6636 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity F | (D-His<sup>2</sup>,D-Ser<sup>4</sup>)-Leuprolide | H-6638 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity G | (D-Tyr<sup>5</sup>)-Leuprolide | H-4638 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity H | (D-Leu<sup>7</sup>)-Leuprolide | H-6636 | <EHWSYILRP-NH<sub>Et</sub> |
| Impurity I | (D-Pyr<sup>1</sup>)-Leuprolide | H-6642 | <EHWSYILRP-NH<sub>Et</sub> |
IMPURITIES OF THE GOSERELIN PH. EUR. MONOGRAPH

Impurity A (D-Ser\(^4\))-Goserelin
H-5654
"EHWSYs(tBu)-LRP-Azagly-NH\(_2\)"

Impurity B (Ser(tBu)\(^6\))-Goserelin
H-6644
"EHWSYS(tBu)-LRP-Azagly-NH\(_2\)"

Impurity E (Pro-NHN\(_2\)\(^9\))-Buserelin
H-5762
"EHWSYS(tBu)-LRP-NHN\(_2\)"

Impurity F (D-Tyr\(^5\))-Goserelin
H-5734
"EHWSYS(tBu)-LRP-Azagly-NH\(_2\)"

Impurity G (D-His\(^2\))-Goserelin
H-5796
"EHWSYS(tBu)-LRP-Azagly-NH\(_2\)"

Impurity K (Ser(Ac)\(^4\))-Goserelin
H-6646
"EHWS(Ac)-Ys(tBu)-LRP-Azagly-NH\(_2\)"

Impurity L (D-Leu\(^7\))-Goserelin
H-5418
"EHWSYS(tBu)-LRP-Azagly-NH\(_2\)"

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IMPURITIES OF THE BUSERELIN PH. EUR. MONOGRAPH

Impurity A (D-His\(^2\))-Buserelin
H-8780
"EHWSYS(tBu)-LRP-NHEt"

Impurity B (D-Ser\(^4\))-Buserelin
H-8785
"EHWSYS(tBu)-LRP-NHEt"

Impurity D (D-Tyr\(^5\))-Buserelin
H-8790
"EHWSYS(tBu)-LRP-NHEt"

Impurity E (D-Pyr\(^1\))-Buserelin
H-8775
"EHWSYS(tBu)-LRP-NHEt"
# Custom Synthesis at Bachem

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Quality**   | GMP and non-GMP quality  
                 State of the art analytical capabilities                                                                                                  |
| **Chemistry** | Fmoc-, Boc-, Z- and other synthetic strategies  
                 Synthesis of complex peptides                                                                                                             |
| **Capacity**  | Largest production facilities in the market (Europe and the USA)  
                 Up-to-date technology  
                 Short to complex peptides from mg to multi-kg and beyond                                                                                   |
| **Modifications** | Acylation, acetylation, amidation, etc.  
                 Cyclizations  
                 Stabilizing modifications                                                                                                               |
| **Support**   | Highly motivated and experienced support team  
                 Documentation  
                 Confidentiality                                                                                                                              |
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