PEPTIDES IN CANCER RESEARCH
BACHEM
PIONEERING PARTNER FOR PEPTIDES
PEPTIDE-BASED CANCER THERAPEUTICS

This brochure discusses the potential use of peptides as anti-cancer drugs highlighting current scenario and future prospects. Some peptides are also used as diagnostic tools for cancer detection. G-protein-coupled receptors are most important targets in drug development. Many of them are overexpressed in tumor cells. Amongst them, the GnRH receptor is the target of a considerable number of GnRH agonists and antagonists used in cancer management. GnRH (gonadotropin-releasing hormone) or LHRH (luteinizing hormone-releasing hormone) is a decapeptide produced in the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. Prolonged non-pulsatile administration of LHRH leads to down-regulation of LH and FSH secretion, followed by a suppression of gonadal steroid synthesis. For this reason, longer-acting GnRH agonists as well as antagonists are used for the treatment of hormone-dependent breast and prostate cancers. Most neuroendocrine tumors show a marked overexpression of somatostatin receptors, especially of sst2, which instigated the development of somatostatin agonists as octreotide. These compounds also play an important role in diagnosis. Bombesin/gastrin-releasing peptide receptors can be overexpressed in malignant cells. Antagonists of these peptides inhibit tumor growth. Active immunization by peptide vaccines is another promising strategy to fight cancer.
Introduction
Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumor mass, to vascularization and, finally, to metastasis (spread of cancer to other parts of the body). Though angiogenesis (growth of new blood vessels from existing vessels) is a normal and vital process during growth and development, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. So, angiogenesis inhibitors have been used to suppress tumor cell growth. Chemotherapy is one of the classical approaches to treat cancer, a cytotoxic agent is delivered to the cancer cells. The main problem with conventional chemotherapy is its inability to administer the correct amount of drug directly to cancer cells without affecting normal cells. Drug resistance, altered biodistribution, biotransformation and premature clearance are also common problems. Targeted chemotherapy and drug delivery techniques are emerging as a powerful method to circumvent such problems. This will allow the selective and effective localization of drugs at pre-defined targets (e.g. overexpressed receptors) while restricting its access to normal cells and thus maximizing therapeutic index and reducing toxicity. The discovery of further receptors abnormally expressed in cancer cells and tumor-related peptides and proteins is expected to lead to a ‘new wave’ of more effective and selective anti-cancer drugs in the future.

The “biologics” approach to cancer therapy includes application of proteins, monoclonal antibodies and peptides. Monoclonal antibodies (mAb) and large protein ligands have two major limitations compared to peptides: poor delivery to tumors due to their large size and a dose-limiting toxicity in liver and bone marrow due to nonspecific uptake into the reticuloendothelial system. The use of such macromolecules has therefore been restricted to vascular targets present on the luminal side of the tumor vessel endothelium and to hematological malignancies. Peptides possess many advantages such as small size, ease of synthesis and modification, they are biocompatible and can penetrate tumor tissue. Their proteolytic degradation can be conveniently prevented by chemical modifications such as incorporation of D-amino acids or cyclization. Properties of bicyclic peptides are even better and comparable to those of antibody drugs. The peptide drugs currently available on the market can be classified as analogs and antagonists of peptide hormones or tumor targeting agents carrying radionuclides.

LHRH (GnRH) Agonists and Antagonists
The first example for the introduction of peptide drugs into cancer therapy is the use of LHRH (luteinizing hormone–releasing hormone) analogs. Schally et al. developed the first GnRH agonists which later were applied in the treatment of prostate and breast cancer. Since then, peptides such as buserelin, leuprolide, goserelin, histrelin, and triptorelin have been developed and approved in cancer therapy. Depot formulations of these peptides allow for a more efficacious and convenient treatment of patients with prostate cancer. Administration of these peptides effects a down-regulation of GnRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone (FSH) and LH release, and a concomitant decrease in testosterone production. The introduction of LHRH antagonists as cetorelix resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. To date, many potent GnRH antagonists are available for therapeutic use in patients suffering from prostate cancer. A
A list of such agonists and antagonists available in the market can be found in Table 1.

### Somatostatin Analogs in Cancer Therapy

Apart from the use of peptidic LHRH agonists and antagonists for treating cancer, somatostatin analogs are the only approved cancer therapeutic peptides in the market. Potent agonists of somatostatin (SRIF) including octreotide (sandostatin) have been developed for the treatment of acromegaly, gigantism and thyrotropinoma associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas). Lanreotide, another long-acting analog of somatostatin, is used in the management of acromegaly and symptoms caused by neuroendocrine tumors.

Most neuroendocrine tumors (NETs) feature a strong overexpression of somatostatin receptors, mainly of subtype 2 (sst2). Currently, five somatostatin receptor subtypes (sst) are known (sst1-5). The density of these receptors on tumor tissue is vastly higher than on healthy tissue. Therefore, sst are attractive targets for delivery of radionuclides employing appropriately modified somatostatin analogs. Introduced in the late 1980s by Sandoz, [111 In-DTPA]-octreotide (pentetreotide, Octreoscan®), rapidly became the gold standard for diagnosis of sst-positive NETs. Numerous peptide-based tumor-imaging agents targeting sst have been developed over the past decades. Octreoscan® and NeoTect® (technetium-99m-labeled depoetrotide, cyclo(MePhe-Tyr-D-Trp-Lys-Val-Hcy(CH₃CO-β-Dap-Lys-Cys-Lys-NH₂)) are the only radiolabeled treatments on the market approved by the FDA. An octreotide scan or octreoscan is a scintigraphic method used to find carcinoids and other types of tumors and to localize sarcoidosis. DTTP-Octreotide, after radiolabeling with indium-111, is injected into a vein and travels through
THE FIVE KNOWN SOMATOSTATIN RECEPTORS ARE ATTRACTIVE TARGETS FOR TUMOR DIAGNOSIS AND THERAPY

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mostly those recognized by CD8 (+) T-cells in melanoma patients, have been clinically tested. Several melanoma TAAs have been identified and are being evaluated as peptide-based cancer vaccines in clinical trials around the world. Recent advances in the field of molecular biology have enabled the rapid identification of dozens of candidate TAAs for several important human cancers.

**Current Status and Future of Peptide Based Anti-Cancer Agents**

The application of peptides as direct therapeutic agents, in targeted drug delivery and as diagnostic tools in cancer biology is growing. Among many improvements in targeted and controlled delivery of therapeutics, specifically binding peptides have emerged as the most valuable non-immunogenic approach to target cancer cells. Various cancer treatment options using peptides are summarized in Figure 1. The RGD peptide iRGD (CRGDKGPDC) is able to specifically recognize and penetrate cancerous tumors but not normal tissues. The development of similar peptides with extraordinary tumor-penetrating properties will definitely make substantial improvements in cancer treatment in future. Chlorotoxin (Bachem product H-6086, a 36 amino acid peptide isolated from scorpion venom) has a higher affinity for glioma cells than for non-neoplastic and normal brain cells. This preferential binding has allowed the development of new methods for the treatment and diagnosis of brain cancer. Anti-angiogenesis as a therapeutic approach led to renewed interest in cilengitide. This integrin inhibitor, a cyclic RGD peptide, is being evaluated as non-small-cell lung cancer therapeutic in clinical trials. Bombesin/gastrin-releasing peptide (BN/GRP) peptides were shown to bind selectively to the G-protein-coupled receptors on the cell surface, stimulating the growth of various malignancies in murine and human cancer models. Thus, it has been proposed that the secretion of BN/GRP by neuroendocrine cells might be responsible for the development and progression of prostate cancer to androgen independence. GRP is widely distributed in lung and gastrointestinal tracts. It is produced in small cell lung cancer (SCLC), breast, prostatic, and pancreatic cancer, and functions as a growth factor. The involvement of bombesin-like peptides in the pathogenesis of a wide range of human tumors, their function as autocrine/paracrine tumoral growth factors, and the high incidence of BN/GRP receptors in various human cancers prompted the design and synthesis of BN/GRP receptor (GRPR) antagonists such as RC-3095, RC-3940-II, and RC-3950.

Currently, many researchers are focusing on the development of GHRH (growth hormone releasing hormone - a hypothalamic polypeptide) antagonists as potential anti-cancer therapeutics since GHRH is produced by various human tumors, including prostate cancer, and seems to exert an autocrine/paracrine stimulatory effect on them. Another promising approach for the therapy of prostate cancer consists of the use of cytotoxic analogues of GnRH, bombesin, and somatostatin, which can be targeted to receptors for these peptides in prostate cancers and their metastases. For example, a potential drug candidate, AEZS-108 consists of a peptide LHRH, coupled to the chemotherapeutic agent doxorubicin to directly target cells that express GnRH receptors, specifically, prostate cancer cells.

There is a tremendous effort to discover angiogenesis inhibitors, based on polypeptides as the safest and least toxic therapy for diseases associated with abnormal angiogenesis. A number of ongoing clinical trials in this area focus on peptides derived from: extracellular matrix proteins, growth factors and growth factor receptors, coagulation cascade proteins, chemokines, Type I Thrombospondin domain containing proteins and serpins.
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PEPTIDES FOR CANCER RESEARCH OFFERED BY BACHEM

A choice of our products. Besides peptides, Bachem offers enzyme substrates, inhibitors, amino acid derivatives and other compounds for numerous applications in cancer research.
**BUSERELIN AND IMPURITIES**

- **Goserein**
  - (Des-Gly¹⁰,D-Ser(tBu)⁸,Pro-NH₂⁹)-LHRH (Buserelin) H-4224
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  - (Des-Gly¹⁰,D-Pyr¹,D-Ser(tBu)⁸,Pro-NH₂⁹)-LHRH ((D-Pyr¹)-Buserelin) H-8775

- **Goserelin**
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  - (D-Ser(tBu)⁸,Azagly¹⁰)-LHRH (Goserelin (free base)) H-7296
  - (Glu¹,D-Ser(tBu)⁸,Azagly¹⁰)-LHRH ((Glu¹)-Goserelin) H-6652
  - (D-His²,D-Ser(tBu)⁸,Azagly¹⁰)-LHRH ((D-His²)-Goserelin) H-5796
  - (D-Leu⁷,D-Ser(tBu)⁸,Azagly¹⁰)-LHRH ((D-Leu⁷)-Goserelin) H-5418
  - (Ser(Ac)⁴,D-Ser(tBu)⁸,Azagly¹⁰)-LHRH ((Ser(Ac)⁴)-Goserelin) H-6666

**GOSERELIN AND IMPURITIES**

- **Buserelin**
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  - (Des-Gly³,D-Tyr⁵,D-Ser(tBu)⁸,Pro-NH₂⁹)-LHRH ((D-Tyr⁵)-Buserelin) H-8790

- **Goserelin**
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  - (D-Ser⁸,Azagly¹⁰)-LHRH ((D-Ser⁸)-Goserelin) H-6266
  - (D-Tyr⁵,D-Ser(tBu)⁸,Azagly¹⁰)-LHRH ((D-Tyr⁵)-Goserelin) H-5734
  - (Des-Gly¹⁰,D-Ser(tBu)⁸,Pro-NHN₂⁹)-LHRH ((Des-carboxamide)-Goserelin) H-5762
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<td>(Des-Gly\textsuperscript{10}, Leu\textsuperscript{8}, Pro-NH\textsubscript{Et}\textsuperscript{9})-LHRH ((Leu\textsuperscript{8})-Leuprolide)</td>
<td></td>
<td>H-6402</td>
<td>&lt;EHWSYLLRP-NH\textsubscript{Et}</td>
</tr>
<tr>
<td>(Des-Gly\textsuperscript{10}, Ser(\text{Ac})\textsuperscript{4}, D-Leu\textsuperscript{8}, Pro-NH\textsubscript{Et}\textsuperscript{9})-LHRH ((Ser(\text{Ac})\textsuperscript{4})-Leuprolide)</td>
<td></td>
<td>H-6172</td>
<td>&lt;EHWS(\text{Ac})-YLRP-NH\textsubscript{Et}</td>
</tr>
<tr>
<td>(Des-Pyr\textsuperscript{1}, Des-Gly\textsuperscript{10}, D-Leu\textsuperscript{8}, Pro-NH\textsubscript{Et}\textsuperscript{9})-LHRH ((Des-Pyr\textsuperscript{1})-Leuprolide)</td>
<td></td>
<td>H-6166</td>
<td>HWSYyLRP-NH\textsubscript{Et}</td>
</tr>
</tbody>
</table>

## TRIPTORELIN, ANALOGS AND FRAGMENTS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>CAS Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D-Trp\textsuperscript{9})-LHRH (Triptorelin)</td>
<td></td>
<td>H-4578</td>
<td>&lt;EHWSYWLRPG-NH\textsubscript{2}</td>
</tr>
<tr>
<td>(D-Trp\textsuperscript{9})-LHRH-Leu-Arg-Pro-Gly amide</td>
<td></td>
<td>H-4582</td>
<td>&lt;EHWSYWLRPLRPG-NH\textsubscript{2}</td>
</tr>
<tr>
<td>(D-Tyr\textsuperscript{8}, D-Trp\textsuperscript{9})-LHRH ((D-Tyr\textsuperscript{8})-Triptorelin)</td>
<td></td>
<td>H-4646</td>
<td>&lt;EHWSYWLRPG-NH\textsubscript{2}</td>
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<tr>
<td>(D-Trp\textsuperscript{9})-LHRH (1-6) amide (Triptorelin (1-6) amide)</td>
<td></td>
<td>H-4574</td>
<td>&lt;EHWSYW-NH\textsubscript{2}</td>
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<tr>
<td>Formyl-(D-Trp\textsuperscript{9})-LHRH (2-10) (Formyl-Triptorelin (2-10))</td>
<td></td>
<td>H-4576</td>
<td>For-HWSYWLRPG-NH\textsubscript{2}</td>
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<tr>
<td>(D-Trp\textsuperscript{9})-LHRH (2-10) ((Des-Pyr\textsuperscript{1})-Triptorelin)</td>
<td></td>
<td>H-6404</td>
<td>HWSYWLRPG-NH\textsubscript{2}</td>
</tr>
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</table>
### LHRH ANTAGONISTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetrorelix</td>
<td>H-6682 Ac-D-2Nal-D-4Cpa-D-3Pal-SY-D-Cit-LRPa-NH₂</td>
</tr>
<tr>
<td>Degarelix*</td>
<td>H-7428 Ac-D-2Nal-D-4Cpa-D-3Pal-S-4-amino-Phe(L-4,5-dihydroorotyl)-4-ureido-D-Phe-LK(isopropyl)-Pa-NH₂</td>
</tr>
</tbody>
</table>

### SOMATOSTATIN, AGONISTS AND ANTAGONISTS

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-14</td>
<td>H-1490 AGCKNFFWKFTFTSC</td>
</tr>
<tr>
<td>([ring-D₅]Phe⁶)-Somatostatin-14</td>
<td>H-7246 AGCKNF(H₃)FWKFTFTSC</td>
</tr>
<tr>
<td>BIM-23627</td>
<td>H-5886 F(4Cl)c-2Pal-WKVC-2Nal-NH₂</td>
</tr>
<tr>
<td>Cyclo-Somatostatin</td>
<td>(Somatostatin Antagonist) H-2485 c(7Aha-FwKT(Bzl))</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>(BIM-23014) H-9055 D-2Nal-CywKVCT-NH₂</td>
</tr>
<tr>
<td>Octreotide acetate salt</td>
<td>(SMS 201-995) H-5972 fCFwKTC-Thr0</td>
</tr>
<tr>
<td>Octreotide pamoate salt</td>
<td>H-8346 fCFwKTC-Thr0</td>
</tr>
<tr>
<td>([ring-D₅]Phe⁶)-Octreotide</td>
<td>H-7238 fC(H₃)FwKTC-Thr0</td>
</tr>
<tr>
<td>Octreotide trifluoroacetate salt</td>
<td>Dimer, Antiparallel H-7376 (fCFwKTC-Thr0)</td>
</tr>
<tr>
<td>Octreotide trifluoroacetate salt</td>
<td>Dimer, Parallel H-7374 (fCFwKTC-Thr0)</td>
</tr>
<tr>
<td>DOTA-(Tyr³)-Octreotate</td>
<td>(DOTATATE) H-6318 DOTA-fCywKCT</td>
</tr>
<tr>
<td>Pasireotide* NEW</td>
<td>(SOM230) H-7542 c(-Hyp(2-aminoethylcarbamoyl)-Phg-wKY(Bzl))</td>
</tr>
<tr>
<td>Tyr-(D-Dab⁴,Arg⁵,D-Trp⁸)-cyclo-Somatostatin-14</td>
<td>(KE 108) H-6276 Y-c(D-Dab-RFFwKTF)</td>
</tr>
<tr>
<td>(D-Phe⁶,Cys⁶,11,N-Me-D-Trp⁸)-Somatostatin-14</td>
<td>(5-12) amide H-5648 fCY(NMe-w)KTCT</td>
</tr>
<tr>
<td>Vapreotide</td>
<td>(RC-160) H-6634 fCywKVCW-NH₂</td>
</tr>
</tbody>
</table>

* Bachem provides this product solely for uses within the scope of any statute or law providing for an immunity, exemption, or exception to patent infringement ("Exempted Uses"), including but not limited to 35 U.S.C. § 271(e)(1) in the United States, the Bolar type exemption in Europe, and any corresponding exception to patent infringement in any other country. It is the sole responsibility of the purchaser or user of this product, and the purchaser or user of this product agrees to engage only in such Exempted Uses, and to comply with all applicable intellectual property laws and/or regulations. The purchaser of this product agrees to indemnify Bachem against all claims in connection with the performance of the respective commercial agreement (e.g. supply agreement) and possible infringements of intellectual property rights.
**BOMBESIN AND BOMBESIN/GRP ANTAGONISTS**

- **Bombesin**
  - H-2155: pEQRLGQNQAVGHL-NH₂
  - (Lys³)-Bombesin
    - H-2160: pEQKLGQNQAVGHL-NH₂
  - (Leu¹³-psi(CH₂NH)Leu¹⁴)-Bombesin (BIM 26028)
    - H-7075: pEQRLGQNQAVGHL(Ψ[CH₂NH])L-NH₂
  - (D-Phe¹²)-Bombesin
    - H-3038: pEQRLGQNQAVGHL-NH₂
  - (D-Phe⁶,Leu-NHET¹³,des-Met¹⁴)-Bombesin (6-14) (DPDMDMB)
    - H-3042: fQWAVGHL-NH₂
  - (D-Phe⁶,Leu¹³-psi(CH₂NH)p-chloro-Phe¹⁴)-Bombesin (6-14)
    - H-3028: fQWAVGHL(Ψ[CH₂NH])F(4-Cl)-NH₂
  - (Tyr⁴)-Bombesin
    - H-2165: pEQRYGNQAVGHL-NH₂
  - (Tyr⁴,D-Phe¹²)-Bombesin
    - H-9065: pEQRYGNQAVGFLM-NH₂
  - (D-2-Nal⁵,Cys⁶·¹¹,Tyr⁷,D-Trp⁸,Val¹⁰,2-Nal¹²)-Somatostatin-14 (5-12) amide (BIM 23042)
    - H-2126: D-2Nal-CYwKVC-Nal-NH
  - Acetyl-GRP (20-26) (human, porcine, canine)
    - H-6705: Ac-HWAVGHL-NH₂
  - (Deamino-Phe¹⁸,D-Ala¹⁴,D-Pro²⁶-psi(CH₂NH)Phe³⁷)-GRP (19-27) (human, porcine, canine) (BW-10, BW2258U89)
    - H-2756: Deamino-FHWAVapo(Ψ[CH₂NH])F-NH₂

**GHRH/NEUROTENSIN/SUBSTANCE P**

- Phenylacetyl-[(D-Arg¹·²·¹⁸,p-chloro-Phe⁶,Arg⁸,Abu¹⁸,Nle²²)-Homoarg²²]-GRF (1-29) amide (human) (JV-1-36)
- Phenylacetyl-[(D-Arg¹·²·¹⁸,p-chloro-Phe⁶,Homoarg⁸·²²,Tyr(Me)¹⁰,Abu¹⁸, Nle²²)]-GRF (1-29) amide (human) (JV-1-38)
- (Lys⁸-psi(CH₂NH)Lys⁹)-Neurotensin (8-13) (JMV-449)
  - H-8370: K(Ψ[CH₂NH])KPYIL
- (D-Arg¹·²·¹⁸,D-Pro¹·⁴·⁷·⁹,Leu¹¹)-Substance P (D-Pro²)-Spantide
  - H-1930: rpKPDQwFwLL-NH₂
- (D-Arg¹·²·¹⁸,D-Trp⁵·⁷·⁹,Leu¹¹)-Substance P (6-11) (Antagonist G)
  - H-1510: Rw(MeF)wLM-NH₂
- (Arg⁸,D-Trp⁷·⁹,N-Me-Phe⁸)-Substance P (6-11)
  - H-3992: rPKPwQwFwLL-NH₂
- (D-Arg¹,D-Trp⁵·⁷·⁹,Leu¹¹)-Substance P
  - H-1510: Rw(MeF)wLM-NH₂
- Ac-Trp-3,5-bis(trifluoromethyl)benzyl ester (L-732,138, Substance P Antagonist)
  - E-3135
VIP/PACAP

PACAP-38 (6-38) (human, chicken, mouse, ovine, porcine, rat)
H-2734
FTDSYSRYRKQMAVKKYLAAVLG-KRYKQRVKNK-NH₂

Acetyl-(D-Phe⁸,Lys¹⁵,Arg¹⁶,Leu²⁷)-VIP (1-7)–GRF (8-27) (PG 97–269)
H-7286
D-2Nal-Cyw-Orn-VC-2Nal-NH₂

Myristoyl-(Lys¹⁵,²⁷,²⁸)–VIP–Gly–Gly–Thr (free acid)
H-7292
Myr-HSDAVFTDNYTLRQMAVK-KYLNSIKKG

VIP Antagonist
H-9935
KPRRPYTDNYTLRQMAVKKYLN-SILN-NH₂

EPITOPES

Ovalbumin (257-264) (chicken)
H-4866
SIINFEKL

Ovalbumin (323-339) (chicken, japanese quail)
H-5532
ISQAVHAAHAINEAGR

Cytochrome C (88-104) (domestic pigeon)
H-6016
KAERADLIJAYLQATAK

Collagen Type IV α3 Chain (185-203)
H-4208
CNYYNSYSFWLASLNPER

Peptide 46
H-4054
GSRAHSSHLKSKGQSTSRHKK

Peptide 74
H-8545
TMRKPRCGNPDVAN

VARIOUS

Chlorotoxin
H-6086
MCMPCFTTDHQMARKCDDCCGGK-GRGKCYGPQCLCR-NH₂

H-Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys-OH (CTT, MMP-2/MMP-9 Inhibitor III)
H-4736
CTTHWGFTLC

Grb2 SH2 Domain Ligand
H-2708
(pY)VNV

Human CMV pp65 (495-503)
H-6218
NLVPMVATV

Tumor Targeted Pro-Apoptotic Peptide
H-6104
CNGRCGGklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklaklak-NH₂

Urinary Trypsin Inhibitor Fragment
H-2692
RGPCRAFI

Z-Val-Ala-ΔL-Asp-fluoromethyl-ketone
N-1510
Z-VAD-FMK
Tumours are caused by the uncontrolled growth of previously normal cells. The resulting growth (centre) can invade and damage surrounding tissue. Growing tumours are able to stimulate new blood vessel (red) growth which provides a direct blood supply. This process is known as angiogenesis.

KEYSTONE/SCIENCE PHOTO LIBRARY/HYBRID MEDICAL ANIMATION
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, Bachem manufactures hundreds of batches of drug substance for projects in clinical trials and for products on the market.

Bachem is currently involved in more than 150 cGMP development projects targeting NCEs and Bachem offers a range of more than 30 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 45 years of experience in the manufacture of drug substance, Bachem also has 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.
<table>
<thead>
<tr>
<th>GENERIC APIs</th>
<th>IMPURITIES OF THE LEUPRORELIN PH. EUR. MONOGRAPH</th>
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</thead>
<tbody>
<tr>
<td>Buserelin H-4224-GMP</td>
<td>Impurity A (D-Ser⁴)-Leuprolide H-6168</td>
</tr>
<tr>
<td></td>
<td>&lt;EHWS(yl)LRP-NHEt</td>
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<tr>
<td>Gonadorelin Acetate H-4005-GMP</td>
<td>Impurity B (D-His²)-Leuprolide H-4316</td>
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<tr>
<td></td>
<td>&lt;EHWS(yl)LRP-NHEt</td>
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<tr>
<td>Goserelin Acetate H-6395-GMP</td>
<td>Impurity C (Leu⁶)-Leuprolide H-6402</td>
</tr>
<tr>
<td></td>
<td>&lt;EHWS(yl)LRP-NHEt</td>
</tr>
<tr>
<td>Leuprolide Acetate H-4060-GMP</td>
<td>Impurity D (Ser(Ac)⁴)-Leuprolide H-6172</td>
</tr>
<tr>
<td></td>
<td>&lt;EHWS(Ac)yl)LRP-NHEt</td>
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<tr>
<td>Triptorelin Acetate H-4075-GMP</td>
<td>Impurity E (D-Trp³)-Leuprolide H-6636</td>
</tr>
<tr>
<td></td>
<td>&lt;EHWS(y)LRP-NHEt</td>
</tr>
<tr>
<td>Triptorelin Pamoate H-6150-GMP</td>
<td>Impurity F (D-His²,D-Ser⁴)-Leuprolide H-6638</td>
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<tr>
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<td>&lt;EHWS(y)LRP-NHEt</td>
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<td></td>
<td>Impurity G (D-Tyr⁵)-Leuprolide H-4638</td>
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<tr>
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<td>&lt;EHWS(y)LRP-NHEt</td>
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<td></td>
<td>Impurity H (D-Leu⁷)-Leuprolide H-4636</td>
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<td>&lt;EHWS(y)LRP-NHEt</td>
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<td>Impurity I (D-Pyr¹)-Leuprolide H-6642</td>
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<td>&lt;EHWS(y)LRP-NHEt</td>
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IMPURITIES OF THE GOSERELIN PH. EUR. MONOGRAPH

Impurity A
(D-Ser<sup>4</sup>)-Goserelin
H-5654
<EWYSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

Impurity B
(Ser(tBu)<sup>5</sup>)-Goserelin
H-6644
<EWWSYS(tBu)-LRP-Azagly-NH<sub>2</sub>

Impurity E
(Pro-NHNH<sub>2</sub>)<sup>9</sup>-Buserelin
H-5762
<EWWSYs(tBu)-LRP-NHNH<sub>2</sub>

Impurity F
(D-Tyr<sup>5</sup>)-Goserelin
H-5734
<EWWSYS(tBu)-LRP-Azagly-NH<sub>2</sub>

Impurity G
(D-His<sup>3</sup>)-Goserelin
H-5796
<EHWSYS(tBu)-LRP-Azagly-NH<sub>2</sub>

Impurity K
(Ser(Ac)<sup>4</sup>)-Goserelin
H-6646
<EHWS(Ac)-YS(tBu)-LRP-Azagly-NH<sub>2</sub>

Impurity L
(D-Leu<sup>7</sup>)-Goserelin
H-5418
<EHWSYs(tBu)-LRP-Azagly-NH<sub>2</sub>

IMPURITIES OF THE BUSERELIN PH. EUR. MONOGRAPH

Impurity A
(D-His<sup>3</sup>)-Buserelin
H-8780
<EHWSYS(tBu)-LRP-NHEt

Impurity B
(D-Ser<sup>4</sup>)-Buserelin
H-8785
<EWWSYS(tBu)-LRP-NHEt

Impurity D
(D-Tyr<sup>5</sup>)-Buserelin
H-8790
<EWWSYS(tBu)-LRP-NHEt

Impurity E
(D-Pyr<sup>1</sup>)-Buserelin
H-8775
<eHWSYS(tBu)-LRP-NHEt

SOMATOSTATIN AND AGONISTS

Somatostatin
H-1490-GMP
<EWWSYS(tBu)-LRP-NHEt

Lanreotide
H-9055-GMP
<EWWSYS(tBu)-LRP-NHEt

Octreotide Acetate
H-5972-GMP
<EWWSYS(tBu)-LRP-NHEt

Pasireotide Acetate*
4047875
<eHWSYS(tBu)-LRP-NHEt

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