

ABSTRACT

Histrelin

Histrelin (pGlu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NH₂; CAS 76712-82-8, free base; molecular formula C₆₆H₈₆N₁₈O₁₂; molecular weight 1323.53) is a synthetic nonapeptide analog of the hypothalamic decapeptide gonadotropin-releasing hormone (GnRH, also designated luteinizing hormone-releasing hormone, LH-RH) distinguished from other members of the clinical GnRH agonist class by exceptionally high receptor binding affinity and by a unique formulation as a once-yearly subcutaneous hydrogel polymer implant [1, 2]. The compound incorporates two structural modifications to native GnRH that collectively confer superagonist potency and metabolic stability: replacement of glycine at position 6 with D-histidine bearing an N-benzyl substituent on the imidazole ring, which eliminates the principal endopeptidase cleavage site and introduces a bulky aromatic moiety favorable to hydrophobic interaction with the GnRH receptor transmembrane domain; and replacement of the C-terminal glycinamide (position 10) with an ethylamide, which further resists carboxypeptidase degradation [3, 4]. The resulting peptide binds the type I GnRH receptor with affinity approximately 100- to 200-fold greater than native GnRH and produces the characteristic biphasic pharmacological response common to all GnRH superagonists [5, 6]. Acute administration stimulates pituitary gonadotroph secretion of luteinizing hormone and follicle-stimulating hormone, producing transient elevations in gonadal steroid output (the "flare" phase, lasting 7 to 14 days). Chronic continuous administration produces homologous desensitization of the GnRH receptor through receptor internalization, uncoupling from Gq/11-phospholipase C

DOCUMENT

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COMPOUND CLASS Synthetic gonadotropin-releasing hormone superagonist
In the peptide with C-terminal, primary amine and
suppression through GnRH receptor desensitization and
downregulation

signaling, and transcriptional downregulation of GnRH receptor
expression, resulting in profound and sustained suppression of
gonadotropin secretion and a hypogonadal state equivalent to
surgical castration in both sexes [5, 6, 7]. Histrelin was initially
developed at Ortho Pharmaceutical Corporation (a Johnson and
Johnson subsidiary) in the early 1980s and studied in daily
subcutaneous injection formulations for central precocious
puberty, prostate cancer, and endometriosis [8, 9]. The compound
was subsequently reformulated by Roberts Laboratories (later
acquired by Shire Pharmaceuticals, then Endo Pharmaceuticals)
into a diffusion-controlled hydrogel polymer reservoir
subcutaneous implant delivering approximately 65 micrograms of
histrelin acetate per day over 12 months [10, 11]. This implant
technology produced two FDA-approved products: Vantas (50 mg
histrelin acetate implant for palliative treatment of advanced
prostate cancer, approved October 2004) and Supprelin LA (50
mg histrelin acetate implant for central precocious puberty,
approved May 2007) [12, 13]. Vantas was discontinued in 2020
owing to manufacturing quality issues at the production facility;
Supprelin LA remains commercially available. Pharmacokinetics
of the implant formulation are characterized by sustained zero-
order drug release producing median steady-state serum histrelin
concentrations of approximately 0.2 to 0.4 ng/mL, with a terminal
elimination half-life of the released peptide of approximately 4
hours, 92 percent subcutaneous bioavailability, and approximately
70 percent plasma protein binding [10, 14]. Metabolism is hepatic
through peptidase-mediated degradation. The adverse-event
profile is dominated by the pharmacological consequences of
gonadal steroid suppression: hot flashes, reduced libido, erectile
dysfunction or amenorrhea, and long-term bone mineral density
reduction. Implant site reactions (bruising, pain, erythema) occur

in approximately 50 percent of recipients. The initial flare phase carries specific risk in metastatic prostate cancer, which is mitigated by co-administration of an antiandrogen during the first 2 to 4 weeks of therapy. Postmarketing surveillance has identified rare but serious adverse events including pseudotumor cerebri, seizures, psychiatric symptoms (emotional lability, depression, suicidal ideation), and severe cutaneous adverse reactions. This monograph reviews the chemistry and synthesis, the biphasic GnRH receptor pharmacology, the comprehensive human pharmacokinetic record, the clinical evidence base across prostate cancer, central precocious puberty, endometriosis, and gender-affirming therapy indications, sourcing and quality verification, reconstitution and handling, stack interactions, adverse-event signal, and a comparative assessment of five GnRH agonist candidates against histrelin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Histrelin.

Marketed names: Supprelin LA (Endo USA; central precocious puberty, once-yearly subcutaneous implant), Vantas (Endo Pharmaceuticals; advanced prostate cancer, once-yearly subcutaneous implant, discontinued 2020). Historical daily injection formulations were marketed under the Supprelin name without the "LA" designation [12, 13].

Development codes: The compound was originally developed under internal codes at Ortho Pharmaceutical Corporation (Johnson and Johnson) in the early 1980s. No single canonical development code equivalent to the leuprolide "TAP-144" or buserelin "HOE 766" designations has been widely adopted in the literature; the compound is identified by the INN "histrelin" in essentially all published pharmacology.

Chemical Abstracts Service registry numbers: 76712-82-8 (free base), 220810-26-4 (acetate salt). The acetate salt is the pharmaceutical form used in both implant products.

International Union of Pure and Applied Chemistry name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-N(pi)-benzyl-D-histidyl-L-leucyl-L-arginyl-L-proline ethylamide. The compound is the ethylamide analog of [D-His(Bzl)6]GnRH lacking the C-terminal glycine of the native decapeptide.

Sequence notation: pGlu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt. The modifications relative to native GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) are the D-histidine(N-benzyl) substitution at position 6 and the ethylamide replacement of the C-terminal glycine at position 10 [3, 4].

1.2 Structural class and chemistry

Histrelin is a synthetic nonapeptide belonging to the gonadotropin-releasing hormone agonist class, a group of modified decapeptide analogs that share the core GnRH sequence with strategic amino acid substitutions designed to enhance recep-

tor binding affinity and resistance to enzymatic degradation [3, 4, 5]. Other members of the clinical class include leuprolide, goserelin, nafarelin, triptorelin, and buserelin. Histrelin is distinguished within this class by the D-histidine(N-benzyl) modification at position 6, which is unique among the marketed GnRH agonists (leuprolide uses D-leucine, goserelin uses D-serine(tert-butyl) with a terminal hydrazide, triptorelin uses D-tryptophan, buserelin uses D-serine(tert-butyl) with a C-terminal ethylamide, nafarelin uses 3-(2-naphthyl)-D-alanine) [15].

Molecular formula: C₆₆H₈₆N₁₈O₁₂ (free base).

Exact mass: 1322.6662 g/mol (free base, monoisotopic).

Molecular weight: 1323.53 g/mol (free base).

Physical properties: White to off-white amorphous or lyophilized powder. Freely soluble in water as the acetate salt; soluble in dilute acetic acid and methanol; sparingly soluble in ethanol. The compound is hygroscopic and should be stored under desiccation. The lyophilized preparation does not exhibit a sharp melting point; decomposition occurs above approximately 200 degrees Celsius.

Stereochemistry: The peptide contains nine amino acid residues, each with defined stereochemistry. All residues except position 6 are in the natural L-configuration. Position 6 is D-histidine, a deliberate inversion that places the side chain in a conformation that resists cleavage by the endopeptidases (chymotrypsin-like enzymes, pyroglutamyl peptidases) that rapidly degrade native GnRH at the Gly6-Leu7 bond [3]. The N-benzyl substituent on the imidazole ring of the D-histidine residue provides additional steric bulk and hydrophobic surface area that enhances receptor binding through interaction with the transmembrane domain of the GnRH receptor.

1.3 Synthesis

The synthesis of histrelin proceeds by standard solid-phase peptide synthesis (SPPS) using Fmoc (9-fluorenylmethyloxycarbonyl) or Boc (tert-butyloxycarbonyl) chemistry on a resin support [16]. The general approach involves sequential coupling of protected amino acids from the C-terminus (proline, attached as the ethylamide) to the N-terminus (pyroglutamic acid). The D-His(Bzl) residue at position 6 is incorporated as the commercially available Fmoc-D-His(Bzl)-OH building block.

The C-terminal ethylamide is introduced either by starting the synthesis on a specialized amide resin that releases the ethylamide on cleavage or by solution-phase coupling of the ethylamine to the C-terminal proline carboxyl after chain assembly.

Cleavage from the resin and global side-chain deprotection are accomplished with trifluoroacetic acid (Fmoc strategy) or hydrogen fluoride (Boc strategy), with appropriate scavengers (triisopropylsilane, water, ethanedithiol) to prevent side reactions. The N-benzyl group on the D-histidine imidazole at position 6 is intentionally retained through the cleavage conditions; it is part of the final drug substance, not a protecting group to be removed.

Purification is by preparative reversed-phase high-performance liquid chromatography, typically on C18 stationary phase with acetonitrile-water gradient elution containing 0.1 percent trifluoroacetic acid. The acetate salt is formed by ion exchange or by lyophilization from dilute acetic acid. The final product is characterized by analytical HPLC (purity greater than 98 percent), mass spectrometry (electrospray ionization, expected $[M+H]^+$ at m/z 1323.67), amino acid analysis, and peptide content determination [16].

The Supprelin LA and Vantas implant formulations incorporate histrelin acetate into a hydrogel polymer reservoir system. The implant consists of a cylindrical polymer matrix (approximately 3.5 centimeters in length and 3 millimeters in diameter) composed of a non-biodegradable hydrogel polymer (2-hydroxyethyl methacrylate) that controls drug release through diffusion [10, 11]. The 50 mg histrelin acetate drug load within the implant is released at an approximately constant rate of 65 micrograms per day over 12 months, after which the implant is surgically removed and replaced if continued therapy is indicated.

2. Abstract

Histrelin (pGlu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt) is a synthetic non-peptide superagonist of the type I gonadotropin-releasing hormone receptor that achieves reversible medical castration through the paradoxical mechanism of chronic receptor desensitization and pituitary-gonadal axis suppression [1, 2, 3]. First synthesized at Ortho Pharmaceutical Corporation in the early 1980s and subsequently reformulated as a once-yearly subcutaneous hydrogel implant by Roberts Laboratories (later Endo Pharmaceuticals), histrelin is distinguished from other clinical GnRH agonists by its exceptionally high receptor binding affinity, attributable to the D-histidine(N-benzyl) modification at position 6, and by the longest approved dosing interval in the class (12 months versus 1 to 6 months for leuprolide, goserelin, and triptorelin depot formulations) [10, 11, 12].

The biphasic pharmacological mechanism is central to all clinical applications. Initial implantation produces an acute stimulatory phase ("flare") characterized by supraphysiological release of luteinizing hormone and follicle-stimulating hormone from anterior pituitary gonadotrophs, with consequent transient elevation of gonadal steroids (testosterone in males, estradiol in females). This phase typically lasts 7 to 14 days. Continued zero-order drug release from the hydrogel implant drives homologous desensitization of the GnRH receptor through receptor internalization, G-protein uncoupling, and downregulation of receptor gene expression, producing sustained suppression of gonadotropin secretion to castrate levels [5, 6, 7]. The suppressive phase is maintained for the 12-month duration of the implant and is fully reversible on removal.

Two FDA-approved products have been marketed. Vantas (50 mg histrelin acetate implant) was approved in October 2004 for palliative treatment of advanced prostate cancer and provided testosterone suppression to castrate levels (less than 50 ng/dL) in greater than 90 percent of patients within 4 weeks, with maintenance of castrate testosterone for the 12-month implant duration in pivotal clinical trials [12, 17]. Vantas was discontinued in 2020 owing to manufacturing quality issues. Supprelin LA (50 mg histrelin acetate implant) was approved in May 2007 for central precocious puberty and demonstrated suppression of luteinizing hormone to prepubertal levels in 100 percent of patients in the pivotal trial, with stabilization of bone age advancement and linear growth velocity [13, 18].

Prior to the implant formulations, histrelin was studied extensively in daily subcutaneous injection form. Neely et al. (1992) reported the first large-scale controlled clinical data establishing daily subcutaneous histrelin at 10 micrograms/kg/day as effective for gonadotropin suppression in central precocious puberty [8]. Earlier work by the same group and by Laron et al. (1989, 1990) characterized dose-response relationships and long-term outcomes in precocious puberty [9, 19]. These daily injection studies established the clinical pharmacology that supported subsequent implant development.

The compound is not approved outside the United States (Vantas received UK marketing authorization in January 2010 but has been discontinued). Research-grade histrelin acetate is available from peptide suppliers for laboratory applications. The compound is also used off-label in gender-affirming hormone therapy for pubertal suppression in adolescents.

Pharmacokinetics of the implant are characterized by sustained zero-order release producing median steady-state serum histrelin concentrations of approximately 0.2 to 0.4 ng/mL, subcutaneous bioavailability of approximately 92 percent, plasma protein binding of approximately 70 percent, hepatic peptidase-mediated metabolism, and a terminal elimination half-life of the released peptide of approximately 4 hours [10, 14]. The implant delivery system eliminates the compliance challenges inherent in daily injection or intranasal GnRH agonist regimens and provides the most consistent pharmacokinetic profile of any marketed GnRH agonist formulation.

This monograph documents chemistry, synthesis, and implant technology; the biphasic GnRH receptor pharmacology; comprehensive pharmacokinetics; the clinical evidence base across prostate cancer, central precocious puberty, endometriosis, and gender-affirming therapy; sourcing and quality verification; reconstitution and handling; stack-interaction implications; adverse-event signal; and a structured comparative assessment of five GnRH agonist candidates (leuprolide, goserelin, triptorelin, buserelin, nafarelin) against histrelin on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin

The gonadotropin-releasing hormone agonist class emerged from the Nobel Prize-winning work of Andrew Schally and Roger Guillemin, who independently characterized the hypothalamic decapeptide GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) in 1971 [20]. Within a decade, systematic structure-activity studies in multiple laboratories identified that substitution of the glycine at position 6 with D-amino acids bearing bulky hydrophobic side chains, combined with C-terminal modifications, produced analogs with dramatically increased receptor affinity and resistance to enzymatic degradation [3, 4].

Histrelin was synthesized in the early 1980s at Ortho Pharmaceutical Corporation (a subsidiary of Johnson and Johnson) as part of this structure-activity exploration. The D-histidine(N-benzyl) substitution at position 6 was selected from a series of D-amino acid analogs on the basis of high receptor binding affinity and potent *in vivo* gonadotropin suppression. The compound was among the most potent GnRH agonists characterized in early comparative binding and bioassay studies, with receptor affinity approximately 100- to 200-fold greater than native GnRH [5, 21].

3.2 Early clinical development

The initial clinical development of histrelin focused on daily subcutaneous injection formulations. Laron et al. (1989, 1990) published early clinical data demonstrating efficacy of daily subcutaneous histrelin in central precocious puberty in Israeli children, with suppression of gonadotropins and sex steroids and clinical improvement in pubertal progression [9, 19]. Neely et al. (1992) reported a larger controlled study establishing the 10 micrograms/kg/day subcutaneous dose as the optimal regimen for central precocious puberty, with documentation of gonadotropin suppression, growth velocity reduction, and bone age stabilization [8].

Concurrent clinical programs explored daily subcutaneous histrelin for advanced prostate cancer. Multiple Phase 2 studies in the mid-1980s demonstrated that daily subcutaneous histrelin at 100 to 500 micrograms/day achieved castrate

testosterone levels and objective clinical responses in hormone-responsive prostate cancer, comparable to leuprolide and other GnRH agonists at equivalent pharmacological endpoints [22, 23].

A daily subcutaneous injection formulation of histrelin (Supprelin) received FDA approval for central precocious puberty in 1991. However, the requirement for daily injections limited clinical uptake relative to the depot formulations of leuprolide (Lupron Depot, monthly or 3-monthly injection) and goserelin (Zoladex, monthly or 3-monthly implant) that were simultaneously entering the market [24].

3.3 Implant development

The transformative development in histrelin's clinical trajectory was the creation of the hydrogel polymer implant delivery system by Roberts Laboratories (subsequently acquired by Shire Pharmaceuticals and then by Endo Pharmaceuticals). The technology employed a non-biodegradable hydrogel polymer composed of 2-hydroxyethyl methacrylate, which controlled drug release through aqueous diffusion from a cylindrical reservoir containing 50 mg of histrelin acetate [10, 11]. The implant was designed for subcutaneous insertion in the inner aspect of the upper arm under local anesthesia, with surgical removal and replacement at 12-month intervals.

The implant formulation was a significant advance over existing GnRH agonist delivery systems. Monthly leuprolide acetate depot injections (Lupron Depot) required reconstitution and intramuscular injection every 28 days; 3-month and 6-month leuprolide formulations extended dosing intervals but still required periodic injection. Goserelin (Zoladex) required monthly or 3-monthly subcutaneous depot injection with a large-gauge needle. The histrelin implant replaced these with a single minor surgical procedure per year, substantially reducing the compliance burden and the pharmacokinetic variability associated with bolus depot injection pharmacology [10].

3.4 FDA approvals

Vantas (50 mg histrelin acetate implant) received FDA approval in October 2004 for the palliative treatment of advanced prostate cancer. The approval was based on a multicenter, open-label pivotal trial demonstrating testosterone suppression to cas-

trate levels in greater than 90 percent of patients within 4 weeks of implantation, maintained through the 12-month treatment period [12, 17].

Supprelin LA (50 mg histrelin acetate implant) received FDA approval in May 2007 for the treatment of central precocious puberty in children. The approval was based on a pivotal trial demonstrating suppression of stimulated and basal luteinizing hormone to prepubertal levels in all treated patients, with stabilization of clinical pubertal progression, bone age advancement, and linear growth velocity [13, 18].

Vantas also received marketing authorization from the United Kingdom Medicines and Healthcare products Regulatory Agency in January 2010. The product was subsequently discontinued globally in 2020 owing to persistent manufacturing quality issues at the production facility [25]. Supprelin LA remains commercially available in the United States.

3.5 Pricing and access considerations

Supprelin LA attracted significant public and policy attention for its pricing. At the time of approval in 2007, the implant was priced at approximately \$37,000 per year, making it one of the most expensive pediatric medications in the United States. This represented a substantial premium over monthly leuprolide depot injections, the principal alternative for central precocious puberty, which were priced at approximately \$1,000 to \$2,000 per monthly injection [26]. The pricing differential raised questions about the economic value of the convenience advantage of annual versus monthly dosing and highlighted broader issues of specialty pharmaceutical pricing in pediatric endocrinology.

4. Mechanism of Action

Histrelin is a GnRH receptor superagonist that produces its principal clinical effects through the paradoxical mechanism of chronic receptor desensitization and pituitary-gonadal axis suppression. The mechanism operates in two distinct temporal phases that are common to all GnRH superagonists but are particularly well sustained with the histrelin implant owing to the continuous zero-order drug delivery profile [5, 6, 7].

4.1 GnRH receptor pharmacology

The type I GnRH receptor (GnRHR) is a seven-transmembrane G-protein-coupled receptor expressed predominantly on anterior pituitary gonadotroph cells, with lower-density expression on gonadal tissue, breast, prostate, placenta, and selected central nervous system neurons [27, 28]. The receptor is uniquely characterized among mammalian G-protein-coupled receptors by the absence of a C-terminal cytoplasmic tail, a structural feature that limits beta-arrestin-mediated receptor internalization and contributes to the distinctive desensitization kinetics of the receptor [28].

Native GnRH is released from hypothalamic neurons in a pulsatile pattern (approximately one pulse every 60 to 120 minutes) and acts on pituitary gonadotrophs through the GnRHR to stimulate synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The pulsatile pattern of GnRH delivery is essential for maintaining normal gonadotropin secretion; continuous (non-pulsatile) GnRH exposure produces the paradoxical suppression that is exploited therapeutically [5, 27].

Histrelin binds the GnRHR with affinity approximately 100- to 200-fold greater than native GnRH [5, 21]. The enhanced affinity is attributable to the D-histidine(N-benzyl) substitution at position 6, which introduces a bulky aromatic moiety that forms favorable hydrophobic contacts with the receptor transmembrane domain and simultaneously eliminates the principal enzymatic cleavage site (the Gly6-Leu7 peptide bond in native GnRH). The C-terminal ethylamide modification further enhances metabolic stability without substantially affecting receptor binding [3, 4].

4.2 Acute stimulatory phase (flare)

Upon initial implantation and commencement of drug release, histrelin acts as a potent GnRH receptor agonist, stimulating the Gq/11-coupled phospholipase C signaling cascade in pituitary gonadotrophs. This produces inositol trisphosphate-mediated calcium mobilization and diacylglycerol-mediated protein kinase C activation, driving exocytosis of stored LH and FSH granules [27, 28]. The result is a transient surge in circulating LH and FSH levels, which in turn stimulates gonadal steroidogenesis: testosterone production from testicular Leydig cells in males and estradiol production from ovarian granulosa cells in females.

The flare phase typically peaks within 2 to 4 days of implantation and resolves within 2 to 4 weeks. During this period, serum testosterone levels in males may rise to 140 to 200 percent of baseline values before declining to castrate levels. The clinical significance of the flare is most pronounced in metastatic prostate cancer, where the transient testosterone surge can exacerbate bone pain, precipitate spinal cord compression, or cause ureteral obstruction. These risks are mitigated by co-administration of an antiandrogen (bicalutamide, flutamide, or enzalutamide) during the first 2 to 4 weeks of therapy [17, 29].

4.3 Chronic suppressive phase (desensitization)

Continuous exposure to histrelin (delivered at approximately 65 micrograms/day from the implant) produces homologous desensitization of the GnRH receptor through multiple convergent mechanisms [5, 6, 7]:

First, receptor internalization. Despite the absence of a C-terminal tail, the GnRHR is internalized through clathrin-coated pit-mediated endocytosis upon sustained agonist occupancy. The internalized receptors are directed to lysosomes for degradation rather than being efficiently recycled to the cell surface, producing a net reduction in cell-surface receptor density.

Second, G-protein uncoupling. Sustained agonist stimulation produces phosphorylation of intracellular receptor domains by G-protein-coupled receptor kinases, promoting interaction with beta-arrestin-like proteins that uncouple the receptor from the Gq/11 signaling pathway even before receptor internalization is complete.

Third, transcriptional downregulation. Chronic GnRH agonist exposure suppresses transcription of the GnRH receptor gene itself, reducing the total cellular complement of receptor protein and limiting the capacity for receptor replenish-

ment at the cell surface.

Fourth, gonadotropin subunit gene suppression. Sustained desensitization additionally suppresses transcription of the LH-beta, FSH-beta, and alpha-glycoprotein subunit genes, reducing the capacity for gonadotropin biosynthesis independent of the receptor signaling deficit.

The composite result is profound and sustained suppression of LH and FSH secretion, producing circulating testosterone levels below the castrate threshold (typically defined as less than 50 ng/dL, with more stringent modern definitions of less than 20 ng/dL) in males and suppression of estradiol to prepubertal or postmenopausal levels in females and children [12, 13, 17].

4.4 Reversibility

The suppressive effect of histrelin is fully reversible on removal of the implant or cessation of drug delivery. Recovery of the pituitary-gonadal axis typically occurs within 4 to 12 weeks after implant removal, with resumption of gonadotropin pulsatility and gonadal steroid production [18]. In children treated for central precocious puberty, pubertal progression resumes after implant removal, with subsequent achievement of normal pubertal milestones and adult height consistent with genetic potential in long-term follow-up studies [30].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and drug release from implant

The histrelin hydrogel implant provides sustained zero-order drug release through diffusion-controlled permeation of histrelin acetate from the non-biodegradable 2-hydroxyethyl methacrylate polymer reservoir [10, 11]. The 50 mg drug load is released at an approximately constant rate of 65 micrograms per day, producing measurable serum histrelin concentrations within hours of implantation and achieving steady-state concentrations within approximately 1 week.

Median maximum serum histrelin concentration (C_{max}) from the implant is approximately 0.43 ng/mL, achieved during the initial burst release phase in the first days after implantation [14]. Median steady-state serum histrelin concentrations are approximately 0.2 to 0.4 ng/mL through the 12-month treatment period, with concentrations remaining above the limit of quantification for the full duration of the implant [13, 14]. No pharmacokinetic differences have been observed between treatment-naïve and previously treated patients.

Subcutaneous bioavailability of histrelin peptide released from the implant is approximately 92 percent, consistent with the high bioavailability expected for subcutaneously delivered peptides of this molecular weight that avoid gastrointestinal degradation [14].

5.2 Distribution

Plasma protein binding of histrelin is approximately 70 percent, predominantly to albumin [14]. The volume of distribution has not been precisely characterized for the implant formulation owing to the sustained-release pharmacokinetics that preclude classical compartmental analysis from single-dose intravenous data. Studies with daily subcutaneous injection formulations suggest moderate tissue distribution consistent with the peptide character of the compound.

Histrelin crosses the blood-brain barrier minimally, as expected for a peptide of molecular weight greater than 1300 daltons. The principal site of pharmacological action is the anterior pituitary gland, which lies outside the blood-brain barrier in the hypophyseal portal system and is therefore accessible to circulating peptide [27].

5.3 Metabolism

Histrelin is metabolized principally through hepatic and renal peptidase-mediated degradation. The D-amino acid substitution at position 6 and the C-terminal ethylamide confer substantial resistance to the pyroglutamyl peptidases and chymotrypsin-like endopeptidases that rapidly degrade native GnRH (which has a plasma half-life of only 2 to 4 minutes) [3, 4]. The metabolic products are inactive peptide fragments that are cleared renally.

No cytochrome P450-mediated metabolism has been characterized for histrelin, consistent with the peptide nature of the compound. No formal drug-drug interaction studies based on CYP enzyme inhibition or induction have been conducted [13].

5.4 Elimination

The terminal elimination half-life of histrelin peptide released from the implant is approximately 4 hours [14]. This represents the disposition of free peptide after release from the polymer reservoir, not the overall pharmacokinetic profile of the implant system (which provides sustained drug delivery over 12 months through diffusion-controlled release rather than systemic elimination kinetics).

Elimination is predominantly through peptidase-mediated metabolism with renal excretion of inactive metabolites. Intact histrelin is not substantially recovered in urine.

5.5 Routes of administration

Subcutaneous implant (current): The Supprelin LA implant is placed subcutaneously in the inner aspect of the upper arm under local anesthesia using a sterile insertion trocar. The implant is a cylindrical rod approximately 3.5 cm in length

and 3 mm in diameter. The procedure is performed as an outpatient minor surgical procedure. The implant is removed surgically after 12 months through a small incision and replaced with a new implant if continued therapy is indicated [13].

Subcutaneous injection (historical): Daily subcutaneous injection of histrelin acetate solution at doses of 10 micrograms/kg/day (central precocious puberty) or 100 to 500 micrograms/day (prostate cancer) was the original route of administration. This formulation (Supprelin injection) was FDA-approved in 1991 for central precocious puberty but was largely superseded by the implant formulation and by depot formulations of leuprolide [8, 24].

Intramuscular injection: Not a registered route for histrelin. The compound has been administered intramuscularly in some early clinical studies but this route offers no advantage over subcutaneous injection.

5.6 Special populations

Pediatric: The Supprelin LA implant is approved for children aged 2 years and older with central precocious puberty. No dose adjustment is required based on body weight or age; the single 50 mg implant delivers a fixed daily dose of approximately 65 micrograms [13]. Safety and effectiveness in children below age 2 have not been established.

Geriatric: The Vantas implant was used in elderly men with advanced prostate cancer. No dose adjustment was required for age; the fixed daily release rate from the implant was independent of patient characteristics [12].

Renal and hepatic impairment: No formal pharmacokinetic studies in renal or hepatic impairment have been conducted. Given the peptidase-mediated metabolism and renal excretion of inactive metabolites, dose adjustment is unlikely to be necessary, but data are limited.

Pregnancy and lactation: Histrelin is contraindicated in pregnancy. The expected hormonal changes (suppression of gonadotropins and sex steroids) increase the risk of miscarriage and fetal harm. No human data on histrelin in breast milk are available; absorption from breast milk is not expected given the peptide nature of the compound [13].

6. Preclinical Pharmacology

6.1 In vitro receptor binding

Histrelin binds the human type I GnRH receptor with a binding affinity (K_i) in the low-picomolar to subnanomolar range, approximately 100- to 200-fold greater than native GnRH [5, 21]. In comparative binding assays using radiolabeled GnRH displacement from pituitary membrane preparations, histrelin demonstrates the highest affinity of the clinically marketed GnRH agonists. The enhanced binding is attributable to the favorable hydrophobic interactions between the D-His(Bzl) moiety and the transmembrane pocket of the receptor.

6.2 In vivo efficacy in animal models

In rodent models, subcutaneous histrelin produces dose-dependent suppression of circulating LH and FSH, with complete castrate-equivalent testosterone suppression achieved at doses corresponding to the human-equivalent implant release rate [5, 22]. In rat prostate cancer xenograft models, continuous histrelin delivery produces tumor growth inhibition equivalent to surgical castration.

In primate models, the histrelin hydrogel implant produces sustained castrate testosterone levels for 12 months with pharmacokinetics and pharmacodynamics closely predictive of the human clinical profile, which supported the pivotal clinical trial design [10, 11].

6.3 Carcinogenicity and reproductive toxicity

Animal carcinogenicity studies with GnRH agonists, including histrelin, have demonstrated increased incidence of hormonally responsive tumors at high doses, including pituitary adenomas in rats and mammary adenocarcinomas in mice [13]. These findings are considered a class effect of GnRH agonists related to the sustained alteration of the hypothalamic-pituitary-gonadal axis and are not considered predictive of human carcinogenic risk at therapeutic doses. Reproductive toxicity

studies demonstrate the expected effects of gonadotropin suppression (infertility, testicular atrophy in males, ovarian atrophy in females), all reversible on cessation of treatment.

7. Clinical Evidence Base

7.1 Advanced prostate cancer

The Vantas pivotal trial was a multicenter, open-label study in 138 patients with advanced prostate cancer (stage D) who received the 50 mg histrelin acetate subcutaneous implant [12, 17]. The primary endpoint was achievement and maintenance of castrate testosterone levels (less than 50 ng/dL) through the 12-month treatment period.

Results demonstrated that greater than 90 percent of patients achieved castrate testosterone within 4 weeks of implantation, after resolution of the initial flare phase. Castrate testosterone levels were maintained in 97 percent of patients through month 12. Serum prostate-specific antigen (PSA) levels declined progressively, with median PSA reduction of approximately 90 percent by month 6. No testosterone breakthrough (escape from castrate levels) was observed during the 12-month treatment period [17].

Shore et al. (2012) reported long-term extension data from the pivotal trial and subsequent studies, demonstrating sustained efficacy and tolerability of the histrelin implant through multiple sequential 12-month treatment cycles, with consistent testosterone suppression and PSA control across 2 to 4 years of continuous use [31]. Woolen et al. (2014) confirmed long-term efficacy and tolerability of abdominal site placement as an alternative to upper arm insertion [32].

Djavan et al. (2010) analyzed testosterone suppression kinetics in the histrelin implant program and reported that mean serum testosterone levels were maintained below 20 ng/dL (the more stringent modern castrate threshold) in the majority of patients, suggesting that the continuous zero-order drug delivery from the implant produced more consistent testosterone suppression than the pulsatile pharmacokinetics of monthly depot formulations [33].

7.2 Central precocious puberty

The Supprelin LA pivotal trial enrolled 36 children (33 females, 3 males, aged 2 to 11 years) with central precocious puberty (defined as onset of secondary sexual characteristics before age 8 in females and age 9 in males) [13, 18]. Both treatment-naïve and patients previously treated with GnRH agonist injections were included.

Results demonstrated suppression of stimulated LH to prepubertal levels in 100 percent of treatment-naïve subjects by month 1, maintained through month 12. In patients previously treated with other GnRH agonists, suppression was maintained from the time of implantation through month 12 without interruption. Estradiol was suppressed to prepubertal levels in 100 percent of girls through month 9 and in 97 percent at month 12. Testosterone suppression was maintained in all pretreated males [13, 18].

Secondary efficacy assessments demonstrated stabilization of bone age advancement (the ratio of change in bone age to change in chronological age decreased toward 1.0, indicating normalization of skeletal maturation rate) and reduction in linear growth velocity to age-appropriate rates [18].

Long-term follow-up studies have demonstrated favorable adult height outcomes in children treated with histrelin implants for central precocious puberty, with near-adult height within the range predicted by mid-parental height [30]. Pubertal progression resumes normally after implant removal, with menarche occurring at appropriate ages in girls.

Ray et al. (2023) reported long-term experience with use of a single histrelin implant beyond the labeled 12-month duration, demonstrating continued efficacy of gonadotropin suppression for periods extending to 24 months in some patients, though this extended use is not FDA-approved [34]. Villalta and Quintos (2022) reported a case of gonadotropin suppression persisting for 7 years after a single histrelin implant that was inadvertently retained, demonstrating the remarkable durability of drug release from the hydrogel polymer system [35].

7.3 Endometriosis

Histrelin has been studied for endometriosis in daily subcutaneous injection formulations, following the established GnRH agonist paradigm for this indication. GnRH agonist-induced hypoestrogenism produces atrophy of ectopic endometrial tissue and reduction in endometriosis-associated pain. The clinical evidence base

for histrelin specifically in endometriosis is limited relative to leuprolide (Lupron Depot) and goserelin (Zoladex), which are the dominant GnRH agonists in gynecological practice [36]. The Supprelin LA implant is not FDA-approved for endometriosis, and the discontinuation of Vantas has further limited the availability of histrelin for any adult indication.

7.4 Gender-affirming therapy

The Supprelin LA implant has been increasingly used off-label for pubertal suppression in adolescents with gender dysphoria, following the clinical paradigm established by the Dutch protocol for gender-affirming care [37]. The once-yearly dosing interval is an advantage over monthly or quarterly depot GnRH agonist injections in this patient population, where treatment duration may extend for several years until the patient is ready to initiate gender-affirming hormone therapy or discontinue suppression.

Pine-Twaddell et al. (2023) reported experience with extended use of histrelin implants in transgender and gender-diverse pediatric patients, demonstrating sustained pubertal suppression and tolerability over multiple treatment years [38]. Mak et al. (2023) documented trends in histrelin implantation at a pediatric tertiary care center, noting increasing utilization for gender-affirming indications [39].

The regulatory and societal context of pubertal suppression for gender dysphoria is evolving; the Supprelin LA prescribing information does not include gender dysphoria as an approved indication, and access to GnRH agonists for this purpose varies by jurisdiction and healthcare system.

7.5 Other investigated applications

Early clinical studies investigated daily subcutaneous histrelin for uterine fibroids, following the established GnRH agonist mechanism of inducing hypoestrogenic fibroid shrinkage [40]. The clinical evidence is limited and the compound is not approved for this indication. Monthly depot leuprolide and goserelin are the standard GnRH agonists for preoperative fibroid volume reduction.

Histrelin has been investigated in ovarian stimulation protocols for assisted reproduction, where GnRH agonist pituitary downregulation prevents premature LH surges during controlled ovarian hyperstimulation [41]. This application has been

explored primarily with daily injection formulations rather than the 12-month implant, which would provide unnecessarily prolonged suppression for a treatment cycle lasting weeks.

8. Sourcing and Quality Verification

Pharmaceutical-grade histrelin is available exclusively through the Supprelin LA implant product (Endo USA). The implant is supplied as a sterile, single-use device requiring surgical insertion by a qualified healthcare professional. There is no oral, injectable, or other pharmaceutical-grade histrelin formulation currently marketed in the United States following the discontinuation of Vantas and the earlier discontinuation of the daily injection Supprelin product.

Research-grade histrelin acetate is supplied by multiple peptide and pharmaceutical research suppliers (Tocris, MedChemExpress, Bachem, Selleckchem, Creative Peptides, others) as lyophilized powder at greater than 95 percent purity by HPLC. Supply is typically in milligram quantities; the compound is moderately expensive relative to smaller synthetic peptides owing to the nonapeptide chain length and the non-standard D-His(Bzl) residue.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reversed-phase high-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 1323.67 for the free base, or appropriate adduct ions)
- Amino acid analysis confirming the expected residue composition
- Peptide content determination (typically 70 to 90 percent for lyophilized peptides, with the balance consisting of counterion, residual water, and residual solvent)
- Endotoxin testing (limulus amebocyte lysate assay) for any preparation intended for in vivo research

Counterfeit or degraded GnRH agonist peptides are uncommon in the research market but lot-to-lot variability in peptide content and purity is observed. Analytical confirmation is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Histrelin acetate as supplied in the Supprelin LA implant requires no reconstitution; the device is implanted as received. Storage of the implant is at controlled room temperature (20 to 25 degrees Celsius) in the original sealed pouch until immediately before use [13].

For research-grade histrelin acetate lyophilized powder:

Reconstitution: The lyophilized peptide is reconstituted in sterile water, normal saline, or phosphate-buffered saline to the desired stock concentration. Typical stock solutions are prepared at 1 to 10 mg/mL. The peptide is freely soluble in aqueous solvents at these concentrations. For in vitro work requiring higher concentrations, dimethyl sulfoxide may be used as the primary solvent followed by dilution into aqueous buffer.

Storage: The lyophilized powder should be stored at minus 20 degrees Celsius or below, protected from moisture. Reconstituted aqueous solutions should be aliquoted for single use and stored at minus 20 degrees Celsius to prevent peptidase-mediated degradation. Repeated freeze-thaw cycles should be avoided; stability data suggest that 3 to 5 freeze-thaw cycles can be tolerated without significant potency loss, but single-use aliquoting is preferred.

Stability: The lyophilized powder is stable for at least 2 years at minus 20 degrees Celsius under desiccation. Reconstituted solutions in sterile water are stable for approximately 24 to 48 hours at 2 to 8 degrees Celsius and for at least 3 months at minus 20 degrees Celsius. Solutions should be protected from light, though histrelin is not highly photosensitive.

Handling: Standard peptide handling precautions apply. The compound should be handled with gloved hands to prevent peptidase-mediated degradation from skin contact. Glass or polypropylene containers are preferred; adsorption to some plastics may occur at very low concentrations. For in vivo research, solutions should be prepared with bacteriostatic water for injection and used within the bacteriostatic water stability window (28 days at controlled room temperature).

10. Stack Interactions and Combinations

Histrelin interacts with several drug classes through its pharmacological effects on the hypothalamic-pituitary-gonadal axis rather than through pharmacokinetic mechanisms. No formal drug-drug interaction studies have been conducted with histrelin [13]. Investigators conducting research with histrelin, especially in combination with other hormonal or reproductive agents, should consider:

Antiandrogens: Co-administration of antiandrogens (bicalutamide, flutamide, enzalutamide, apalutamide, darolutamide) during the initial 2 to 4 weeks of histrelin therapy is standard practice in prostate cancer to mitigate the flare-associated testosterone surge. This combination is pharmacologically rational and well characterized clinically [17, 29]. Extended combined androgen blockade (continuous antiandrogen plus GnRH agonist) has been extensively studied in prostate cancer and is a standard treatment paradigm.

Estrogen and progestin add-back therapy: In women receiving GnRH agonists for endometriosis or uterine fibroids, low-dose estrogen-progestin add-back therapy is co-administered to mitigate the bone density loss and vasomotor symptoms of the induced hypoestrogenic state without compromising the therapeutic suppression of endometrial tissue [36]. This combination has been characterized principally with leuprolide but the pharmacological principles apply to histrelin.

Other GnRH agonists: Concurrent use of two GnRH agonists is pharmacologically redundant and not clinically indicated. Switching between GnRH agonists (for example, from monthly leuprolide depot to annual histrelin implant) should be timed to maintain continuous gonadotropin suppression without a gap in coverage.

GnRH antagonists: GnRH antagonists (degarelix, relugolix) act by competitive blockade of the GnRH receptor and do not produce the initial flare phase. Concurrent use of a GnRH agonist and a GnRH antagonist is pharmacologically contradictory (the antagonist would block the agonist effect). Sequential use (antagonist to agonist or vice versa) requires attention to the pharmacokinetic overlap period.

QT-prolonging agents: There is no characterized QT-prolongation risk specific to histrelin. However, androgen deprivation therapy in males has been associated with QT interval prolongation as a class effect of the induced hypogonadal state. Concurrent QT-prolonging medications should be used with awareness of this potential additive risk [42].

Bone-active agents: Long-term GnRH agonist therapy produces bone mineral density reduction through gonadal steroid suppression. Co-administration of bisphosphonates (alendronate, zoledronic acid), denosumab, or calcium and vitamin D supplementation is commonly employed to mitigate skeletal effects in patients on prolonged therapy [43].

Insulin and glucose metabolism: Androgen deprivation therapy has been associated with adverse metabolic effects including insulin resistance, hyperglycemia, and increased cardiovascular risk. Investigators should consider metabolic monitoring in subjects receiving histrelin, particularly in long-term protocols [44].

11. Adverse Events and Safety

11.1 Common adverse events

The adverse-event profile of histrelin is dominated by two categories: implant-site reactions and the pharmacological consequences of gonadal steroid suppression.

Implant-site reactions (Supprelin LA pivotal trial):

- Any implant site reaction: 51.1 percent (24 of 47 patients)
- Bruising: common (exact percentage not separately reported)
- Pain and soreness: common
- Erythema and swelling: common
- Keloid scar: 6.4 percent
- Scar formation: 6.4 percent
- Suture-related complications: 6.4 percent
- Post-procedural pain: 4.3 percent

Pharmacological adverse events (GnRH agonist class effects):

- Hot flashes: 10 to 70 percent (higher incidence in adults; dose and duration dependent)
- Headache: 5 to 15 percent
- Reduced libido: common in adults
- Erectile dysfunction: common in males on androgen deprivation
- Amenorrhea: expected pharmacological effect in premenopausal females
- Weight changes: variable
- Fatigue: 5 to 10 percent
- Mood changes and emotional lability: reported in both adults and children

11.2 Rare and serious adverse events

Postmarketing surveillance has identified rare but clinically significant adverse events [13]:

Pseudotumor cerebri (idiopathic intracranial hypertension): Reported in children receiving GnRH agonists for central precocious puberty. Symptoms include headache, papilledema, blurred vision, diplopia, vision loss, eye pain, tinnitus, dizziness, and nausea. This is a class effect of GnRH agonists in the pediatric population and requires ophthalmological evaluation and potential treatment discontinuation.

Seizures and convulsions: Reported in patients with and without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors. Increased risk with concurrent medications associated with lowered seizure threshold (bupropion, SSRIs).

Psychiatric events: Emotional lability (crying, irritability, impatience, anger, aggression), depression, and rare reports of suicidal ideation have been reported in both children and adults receiving GnRH agonists [13]. The mechanism is plausibly related to the rapid changes in sex steroid levels during the flare phase and the sustained hypogonadal state during chronic therapy.

Severe cutaneous adverse reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported rarely. Treatment should be interrupted if cutaneous reactions are suspected and permanently discontinued if a severe cutaneous diagnosis is confirmed.

Implant-related complications: Implant breakage during removal has been reported in a small number of cases, requiring imaging (ultrasound, CT, or MRI) for localization of retained fragments. The implant is not radiopaque. Spontaneous implant extrusion has been reported rarely [13].

Hepatic effects: Drug-induced liver injury attributed to the histrelin implant has been reported in isolated case reports [45].

11.3 Long-term skeletal effects

Long-term GnRH agonist therapy produces clinically significant bone mineral density reduction through the induced hypogonadal state. In adults with prostate cancer, androgen deprivation therapy is associated with increased fracture risk after 1 to 2 years of treatment. In children with central precocious puberty, bone mineral density accrual may be reduced during GnRH agonist treatment but typically nor-

malizes after treatment discontinuation and resumption of puberty, with no demonstrated increase in fracture risk during or after treatment in long-term follow-up [30, 43].

11.4 Metabolic and cardiovascular effects

Androgen deprivation therapy in males is associated with adverse metabolic changes including increased body fat, decreased lean mass, insulin resistance, hyperglycemia, and unfavorable lipid changes [44]. Observational studies have suggested increased cardiovascular risk with long-term GnRH agonist therapy in men, though causality remains debated. These effects are class effects of androgen deprivation and are not specific to histrelin.

11.5 Pregnancy and lactation

Histrelin is contraindicated in pregnancy (Category X). The expected hormonal changes increase the risk of miscarriage and fetal harm. No adequate data on histrelin in breast milk are available [13].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five GnRH agonist candidates against histrelin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal clinical GnRH agonists with substantive clinical evidence bases and market presence, representing the full breadth of the class from which histrelin must be differentiated.

12.1 Leuprolide (Leuprorelin)

Mechanism: Synthetic nonapeptide GnRH superagonist with D-leucine at position 6 and ethylamide at position 10. Mechanism identical to histrelin: biphasic flare followed by chronic GnRH receptor desensitization and pituitary-gonadal axis suppression [46].

Development trajectory: Developed by Takeda and Abbott (TAP Pharmaceuticals). Lupron (daily subcutaneous injection) was approved by the FDA in 1985. Lupron Depot (monthly intramuscular depot injection) was approved in 1989. Extended depot formulations providing 3-month (1996), 4-month, and 6-month dosing intervals were subsequently approved [46]. Leuprolide is the most widely prescribed GnRH agonist globally and is the dominant compound in the class in the United States.

Novelty: Low. Leuprolide is the oldest and most established clinical GnRH agonist. The mechanism and clinical applications are comprehensively characterized over four decades of clinical use.

Effect size: Large and consistent. Castrate testosterone suppression is achieved in greater than 95 percent of prostate cancer patients within 4 weeks of depot injection. Complete gonadotropin suppression in central precocious puberty is achieved reliably across all depot formulations [46, 47].

Promising potential: High. The compound remains the dominant GnRH agonist in clinical practice and is available in the widest range of formulations (daily injection, monthly depot, 3-month depot, 4-month depot, 6-month depot, intranasal). Generic leuprolide depot formulations are available.

Side-effect profile: Identical to histrelin as a class effect of GnRH agonist-mediated gonadal suppression. The principal difference is the injection-site reaction profile, which is injection-related (pain, nodule, sterile abscess at depot injection sites) rather than implant-related (surgical site bruising, scarring, implant breakage).

Overall validation: Very high. Leuprolide has the largest clinical evidence base of any GnRH agonist, with over 40 years of clinical experience, registration across multiple indications (prostate cancer, endometriosis, uterine fibroids, central precocious puberty, breast cancer, assisted reproduction), and the broadest global regulatory approvals.

Comparison to histrelin: Leuprolide is the standard-of-care comparator for histrelin in all indications. Histrelin has the advantage of the longest dosing interval (12 months versus 6 months maximum for leuprolide depot) and more consistent testosterone suppression attributable to zero-order drug release. Leuprolide has the advantages of wider availability, lower cost, no requirement for surgical implant insertion or removal, multiple formulation options, and a substantially larger clinical evidence base. The clinical pharmacological profiles are essentially identical at the receptor level; the distinction is formulation and delivery.

12.2 Goserelin

Mechanism: Synthetic decapeptide GnRH superagonist with D-serine(tert-butyl) at position 6 and azaglycine amide replacing glycineamide at position 10. Same biphasic mechanism as histrelin [48].

Development trajectory: Developed by Imperial Chemical Industries (ICI, now AstraZeneca). Zoladex (biodegradable polyglycolic acid depot subcutaneous implant) was approved by the FDA in 1989. Available as monthly (3.6 mg) and 3-monthly (10.8 mg) depot formulations [48]. The Zoladex depot is delivered by subcutaneous injection using a large-bore (16-gauge) pre-filled syringe.

Novelty: Low. Goserelin is the second-oldest clinical GnRH agonist after leuprolide. The biodegradable depot delivery system was innovative at the time of development but is now a mature technology.

Effect size: Large and consistent, equivalent to leuprolide and histrelin at the pharmacodynamic level. Castrate testosterone suppression rates exceed 90 percent [48].

Promising potential: Moderate to high. The compound remains widely used, particularly in breast cancer and prostate cancer. Generic competition is limited owing to the specialized depot delivery system.

Side-effect profile: Class effect profile identical to histrelin. The injection site pain from the large-bore Zoladex syringe is a recognized tolerability issue that distinguishes it from the less painful monthly leuprolide depot injection but is less burdensome than the surgical implant procedure required for histrelin.

Overall validation: High. The compound has a large clinical evidence base across prostate cancer, breast cancer, endometriosis, and assisted reproduction indications, with more than 35 years of clinical experience.

Comparison to histrelin: Goserelin shares the same mechanism and pharmacodynamic endpoints as histrelin but with a shorter dosing interval (1 to 3 months versus 12 months). The Zoladex depot is biodegradable and does not require surgical removal, unlike the histrelin implant. Histrelin has the advantage of the longest dosing interval and the most consistent pharmacokinetic profile.

12.3 Triptorelin

Mechanism: Synthetic decapeptide GnRH superagonist with D-tryptophan at position 6, retaining the native glycine at position 10. Same biphasic mechanism as histrelin [49].

Development trajectory: Developed by Debiopharm and marketed by Ipsen as Trelstar (injectable depot) and Decapeptyl. Monthly (3.75 mg), 3-monthly (11.25 mg), and 6-monthly (22.5 mg) depot formulations are available. FDA-approved for prostate cancer. Used extensively in Europe for prostate cancer, endometriosis, central precocious puberty, and assisted reproduction [49, 50].

Novelty: Low. Triptorelin is the structurally simplest modification of native GnRH among the marketed agonists (only a single D-amino acid substitution at position 6, with no C-terminal modification), but the mechanism is identical to the class.

Effect size: Large and consistent, equivalent to the class. The 6-month depot formulation approaches histrelin's dosing interval and provides castrate testosterone suppression rates exceeding 90 percent [50].

Promising potential: Moderate to high. The compound is widely used in Europe and increasingly in the United States. The 6-month depot formulation is a competitive alternative to histrelin's annual implant.

Side-effect profile: Class effect profile identical to histrelin. Injection site reactions are typical of depot intramuscular formulations.

Overall validation: High. The compound has a large clinical evidence base, particularly from European registries and clinical trials, with extensive data in prostate cancer, assisted reproduction, and central precocious puberty.

Comparison to histrelin: Triptorelin's 6-month depot formulation is the closest competitor to histrelin's annual implant in terms of dosing interval. Histrelin provides a longer interval (12 versus 6 months) but requires surgical implant placement and removal. Triptorelin has the advantage of intramuscular injection administration without surgical procedure and broader international availability.

12.4 Buserelin

Mechanism: Synthetic nonapeptide GnRH superagonist with D-serine(tert-butyl) at position 6 and ethylamide at position 10. Same biphasic mechanism as histrelin [1, 2].

Development trajectory: Developed at Hoechst AG (now Sanofi-Aventis) in the mid-1970s. Marketed as Suprefact and Suprefact Depot in approximately 40 jurisdictions. Available as subcutaneous injection, intranasal spray (the first GnRH agonist to achieve medical castration via intranasal route), and 2- to 3-month subcutaneous depot implant [1, 2]. Not approved in the United States or Australia.

Novelty: Moderate historical novelty (first intranasal GnRH agonist). Low current novelty.

Effect size: Large and consistent, equivalent to the class. Castrate testosterone suppression is achieved reliably with depot formulations. The intranasal formulation has lower and more variable bioavailability (approximately 2.5 to 3.3 percent) requiring multiple daily administrations [1].

Promising potential: Moderate. The compound is well established in European, Canadian, and Asian markets but faces competition from leuprolide and goserelin in all indications. Not approved in the United States.

Side-effect profile: Class effect profile identical to histrelin. The intranasal formulation has the unique tolerability advantage of avoiding injections and surgical procedures but the disadvantage of requiring multiple daily nasal administrations with consequent compliance challenges.

Overall validation: High. The compound has more than 40 years of clinical experience and an extensive research literature.

Comparison to histrelin: Buserelin shares the C-terminal ethylamide modification with histrelin but uses D-serine(tert-butyl) rather than D-histidine(N-benzyl) at position 6. The position 6 difference accounts for histrelin's higher receptor binding affinity. Buserelin has the advantage of intranasal formulation availability and broader international registration. Histrelin has the advantage of the annual dosing interval and higher receptor potency.

12.5 Nafarelin

Mechanism: Synthetic decapeptide GnRH superagonist with 3-(2-naphthyl)-D-alanine at position 6, retaining the native glycineamide at position 10. Same biphasic mechanism as histrelin [51].

Development trajectory: Developed by Syntex (now Roche). Marketed as Synarel (intranasal spray). FDA-approved for endometriosis (1990) and central precocious puberty (1990) [51]. The compound is administered as twice-daily intranasal spray, with intranasal bioavailability of approximately 2 to 3 percent.

Novelty: Low to moderate. The 3-(2-naphthyl)-D-alanine substitution at position 6 produces very high receptor affinity (among the highest in the class, comparable to histrelin).

Effect size: Large and consistent for gonadotropin suppression when compliance with the twice-daily intranasal regimen is maintained. Compliance-dependent efficacy is the principal clinical limitation [51].

Promising potential: Low to moderate. The compound is used principally for endometriosis and central precocious puberty. The twice-daily intranasal regimen has been largely supplanted by depot injections and implants for indications requiring long-term treatment.

Side-effect profile: Class effect profile identical to histrelin. Nasal irritation and rhinitis are specific to the intranasal formulation.

Overall validation: Moderate to high. The compound has a substantial clinical evidence base in endometriosis and central precocious puberty, with more than 35 years of clinical experience.

Comparison to histrelin: Nafarelin and histrelin share the characteristic of very high GnRH receptor binding affinity attributable to their respective bulky aromatic position 6 substituents. The critical distinction is formulation: nafarelin requires twice-daily intranasal administration with inherent compliance challenges, while histrelin provides 12 months of continuous drug delivery from a single implant. For central precocious puberty in children, the histrelin implant has largely replaced nafarelin intranasal spray owing to the superior adherence profile.

12.6 Comparator summary

The five GnRH agonists share an identical mechanism of action (GnRH receptor superagonism producing biphasic flare followed by chronic receptor desensitization) and produce equivalent pharmacodynamic endpoints (castrate gonadal steroid levels). The clinical differentiation among compounds is driven almost entirely by formulation, dosing interval, route of administration, and geographic availability rather than by pharmacological differences at the receptor level.

Histrelin occupies a unique position in this comparator landscape: it provides the longest approved dosing interval (12 months) of any GnRH agonist, delivered through a non-biodegradable hydrogel implant that produces the most consistent zero-order pharmacokinetic profile in the class. This position carries the trade-off of requiring a minor surgical procedure for implant insertion and removal. The compound has the highest receptor binding affinity among the marketed GnRH agonists, attributable to the D-histidine(N-benzyl) modification at position 6.

Leuprolide remains the dominant GnRH agonist globally on the basis of widest formulation range, broadest regulatory approvals, largest clinical evidence base, and lowest cost. **Goserelin** is the principal alternative in prostate and breast cancer, with a biodegradable depot that avoids surgical removal. **Triptorelin** is widely used in Europe and provides a 6-month depot formulation that approaches histrelin's dosing interval. **Buserelin** pioneered intranasal GnRH agonist delivery but is limited by the requirement for multiple daily administrations. **Nafarelin** provides very high receptor potency comparable to histrelin but in an intranasal formulation that requires twice-daily dosing and is limited by compliance-dependent efficacy.

The principal practical question for investigators and clinicians selecting among GnRH agonists is whether the convenience of the annual dosing interval justifies the surgical procedure required for implant management and the higher acquisition cost. For pediatric central precocious puberty, where treatment extends over multiple years and adherence to injection schedules is challenging, the histrelin implant offers a clear advantage. For adult prostate cancer, the discontinuation of Vantas has rendered the question moot in the United States, with leuprolide and goserelin depot formulations as the standard options.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Histrelin is available in the United States only as Supprelin LA (central precocious puberty); Vantas (prostate cancer) was discontinued in 2020. Investigators should consult their local regulatory authority before any human research application.