

Buserelin

A synthetic nonapeptide analog of endogenous gonadotropin-releasing hormone bearing a D-serine(tert-butyl) substitution at position 6 and an ethylamide C-terminal modification, conferring 20- to 170-fold greater potency than native GnRH and resistance to enzymatic degradation, developed at Hoechst AG in the mid-1970s as one of the first clinically viable GnRH superagonists and now registered in approximately 40 jurisdictions for hormone-dependent prostate cancer, endometriosis, uterine fibroids, premenopausal breast cancer, central precocious puberty, and pituitary downregulation in assisted reproduction protocols.

AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Synthetic gonadotropin-releasing hormone superagonist nonapeptide with paradoxical chronic suppression of
ABSTRACT	pituitary-gonadal axis through GnRH receptor desensitization and downregulation

Buserelin ([D-Ser(tBu)⁶,des-Gly-NH₂-10]GnRH ethylamide; CAS 57982-77-1, free base; 68630-75-1, acetate salt) is a synthetic diac.org

nonapeptide analog of the hypothalamic decapeptide gonadotropin-releasing hormone (GnRH, also designated luteinizing hormone-releasing hormone, LHRH) first described by Sandow and colleagues at Hoechst AG in 1976 and approved for clinical use in 1984 [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-serine bearing a tert-butyl ether on the side-chain hydroxyl, which eliminates the principal endopeptidase cleavage site and introduces conformational rigidity favorable to receptor binding; and replacement of the C-terminal glycine amide (position 10) with an ethylamide, which further resists carboxypeptidase degradation. The resulting peptide binds the type I GnRH receptor with affinity approximately 20- to 170-fold greater than native GnRH and produces a biphasic pharmacological response that is the mechanistic foundation for all clinical applications [3, 4]. 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 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]. This medical castration is reversible on cessation of treatment. Buserelin was the first GnRH agonist demonstrated to achieve medical castration in humans via intranasal administration, an observation reported by Sandow and colleagues in 1980 that established the clinical viability of non-injectable GnRH agonist therapy [2]. The compound is registered in approximately 40 jurisdictions across Europe, the United Kingdom, Canada, New Zealand, South Africa, Latin America, and Asia, but is not approved in the United States or Australia. Registered indications include hormone-responsive prostate cancer, endometriosis, uterine fibroids, premenopausal breast cancer, and pituitary downregulation as an adjunct to controlled ovarian hyperstimulation in assisted reproduction [7, 8, 9]. The compound is additionally used off-label for central precocious puberty and as a component of gender-affirming hormone therapy. Pharmacokinetics are characterized by negligible oral bioavailability due to gastrointestinal peptidase degradation, approximately 2.5 to 3.3 percent intranasal bioavailability, and approximately 70 percent subcutaneous bioavailability [10]. The plasma elimination half-life is 50 to 80 minutes after intravenous or subcutaneous administration and approximately 1 to 2 hours after intranasal dosing. Protein binding is low (approximately 15 percent). Metabolism occurs principally through pyroglutamyl peptidase and chymotrypsin-like endopeptidase activity in the liver, kidneys, and gastrointestinal tract, with approximately 50 percent of the administered dose recovered unchanged in urine [10, 11]. Formulations include aqueous solution for subcutaneous injection and intranasal spray (requiring multiple daily administrations) and sustained-release subcutaneous implants providing 2- or 3-month depot delivery. The adverse-event profile is dominated by the pharmacological consequences of gonadal

steroid suppression: hot flashes, reduced libido, erectile dysfunction or vaginal dryness, and long-term bone mineral density reduction. The initial flare phase carries specific risk in metastatic prostate cancer (bone pain exacerbation, spinal cord compression, ureteral obstruction), which is mitigated clinically by co-administration of an antiandrogen during the first 2 to 4 weeks of therapy. This monograph reviews the chemistry and synthesis, the biphasic GnRH receptor pharmacology, the comprehensive human pharmacokinetic record, the clinical evidence base across prostate cancer, endometriosis, uterine fibroids, breast cancer, precocious puberty, and assisted reproduction indications, sourcing and quality verification, reconstitution and handling, stack interactions, adverse-event signal, and a comparative assessment of five GnRH agonist candidates against buserelin on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Buserelin.

Marketed names: Suprefact, Suprefact Depot (Sanofi-Aventis; United Kingdom, European Union member states, Canada, New Zealand, South Africa), Suprecur (Sanofi-Aventis; reproductive indications), Profact (selected markets), Bigonist, Bucel, Fuset (generic markets), CinnaFact (CinnaGen; biosimilar generic). The veterinary formulation is marketed as Receptal (Intervet/MSD Animal Health) for reproductive management in livestock [12].

Development codes: HOE 766 (Hoechst AG). The Hoechst code is the canonical identifier in the earliest pharmacology literature including the original Sandow et al. characterization [1].

Chemical Abstracts Service registry numbers: 57982-77-1 (free base), 68630-75-1 (acetate salt). The acetate salt is the pharmaceutical and commercial form; the free base is used in synthetic and analytical chemistry.

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

Sequence notation: pGlu-His-Trp-Ser-Tyr-D-Ser(tBu)-Leu-Arg-Pro-NHEt. The modifications relative to native GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) are the D-serine(tert-butyl) substitution at position 6 and the ethylamide replacement of the C-terminal glycine at position 10.

1.2 Structural class and chemistry

Buserelin 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 receptor binding affinity and resistance to enzymatic degradation [3, 4]. Other members of the class include leuprolide, goserelin, nafarelin, triptorelin, and histrelin.

Molecular formula: C₆₀H₈₆N₁₆O₁₃ (free base); C₆₂H₈₉N₁₆O₁₅ (acetate salt, as the monoacetate).

Exact mass: 1238.6550 g/mol (free base, monoisotopic).

Molecular weight: 1239.45 g/mol (free base); 1299.49 g/mol (acetate salt).

Physical properties: White to off-white amorphous or lyophilized powder. Freely soluble in water and in dilute acetic acid as the acetate salt; soluble in methanol; sparingly soluble in ethanol. The compound is hygroscopic and should be stored under desiccation. Melting point is not sharply defined owing to the amorphous character of the lyophilized preparation; 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-serine, 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 tert-butyl ether on the D-serine side chain provides additional steric protection and enhances receptor binding through hydrophobic interactions with the GnRH receptor transmembrane pocket.

1.3 Synthesis

The synthesis of buserelin proceeds by standard solid-phase peptide synthesis (SPPS) using Fmoc (9-fluorenylmethyloxycarbonyl) or Boc (tert-butyloxycarbonyl) chemistry on a resin support [13]. 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-Ser(tBu) residue at position 6 is incorporated as the commercially available Fmoc-D-Ser(tBu)-OH or Boc-D-Ser(tBu)-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 re-

actions. The tert-butyl ether on the D-serine residue 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 1240.66), amino acid analysis, and peptide content determination. Industrial production achieves kilogram-scale synthesis with high reproducibility; the compound has been in continuous manufacture since the early 1980s [1, 14].

2. Abstract

Buserelin (HOE 766) is a synthetic nonapeptide 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 Hoechst AG (now Sanofi-Aventis) in the mid-1970s as part of a systematic structure-activity exploration of GnRH analogs, buserelin was among the earliest GnRH agonists to enter clinical development and was the first GnRH agonist demonstrated to achieve medical castration through intranasal administration in humans [2].

The biphasic pharmacological mechanism is central to all clinical applications. Initial administration 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 daily administration 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]. The suppressive phase is maintained for the duration of treatment and is fully reversible on cessation.

The compound is registered in approximately 40 jurisdictions for hormone-responsive prostate cancer, endometriosis, uterine fibroids, premenopausal breast cancer, and pituitary downregulation in assisted reproduction protocols [7, 8, 9]. It is additionally used off-label for central precocious puberty and gender-affirming therapy. The compound is not approved in the United States, where leuprolide and goserelin are the dominant GnRH agonists, or in Australia.

Pharmacokinetics are characterized by negligible oral bioavailability, low (2.5 to 3.3 percent) intranasal bioavailability, approximately 70 percent subcutaneous bioavailability, low protein binding (approximately 15 percent), and rapid elimination (half-life 50 to 80 minutes after parenteral administration) through peptidase-mediated degradation in the liver, kidneys, and gastrointestinal mucosa [10, 11].

Formulations include aqueous solution for subcutaneous injection (1 mg/mL), intranasal spray (1 mg/mL), and sustained-release subcutaneous implants (6.3 mg for 2 months, 9.45 mg for 3 months) [15].

The adverse-event profile is predictable from the mechanism of gonadal steroid deprivation and includes hot flashes, reduced libido, erectile dysfunction or vaginal dryness, mood disturbance, and long-term reduction in bone mineral density. The initial flare response carries specific risk in metastatic prostate cancer, where transient testosterone elevation can exacerbate bone pain, produce spinal cord compression, or worsen ureteral obstruction; this risk is managed by co-administration of an antiandrogen (cyproterone acetate or flutamide) during the first 2 to 4 weeks of treatment [16, 17]. Rare adverse events include injection-site reactions, anaphylaxis, and pituitary apoplexy.

This monograph documents the complete pharmacological, pharmacokinetic, clinical, and comparative profile of buserelin across all registered and investigational indications.

3. Discovery and Development History

3.1 Origin

The discovery of buserelin was a direct consequence of the Nobel Prize-winning characterization of the hypothalamic decapeptide gonadotropin-releasing hormone by Andrew Schally and Roger Guillemin in 1971 [18]. The elucidation of the GnRH primary sequence (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂) enabled immediate structure-activity investigations aimed at producing analogs with enhanced potency, metabolic stability, and clinical utility. The principal vulnerability of native GnRH is rapid enzymatic degradation, predominantly at the Gly6-Leu7 bond by chymotrypsin-like endopeptidases and at the N-terminal pyroglutamyl residue by pyroglutamyl peptidase, resulting in a plasma half-life of only 2 to 5 minutes that precludes clinical application of the native peptide [3].

Sandow and colleagues at Hoechst AG (Frankfurt, Germany) synthesized busere-
lin in the mid-1970s as part of a systematic series of GnRH analogs incorporating D-
amino acid substitutions at position 6, which had been identified by multiple
groups as the key modification site for enhancing metabolic stability and receptor
binding [1, 19]. The D-Ser(tBu) substitution at position 6 and the ethylamide C-ter-
minal modification were selected from the series on the basis of superior receptor
binding affinity (20- to 170-fold greater potency than native GnRH for stimulation of
LH and FSH release in bioassays), extended plasma half-life, and favorable early
toxicology. The compound was designated HOE 766 and entered preclinical devel-
opment in the late 1970s.

3.2 Key development milestones

The first demonstration that buserelin could achieve medical castration in humans
through intranasal administration was reported by Sandow and colleagues in 1980
[2]. This observation was pivotal for the clinical viability of the GnRH agonist class,
as it demonstrated that a peptide therapeutic could be delivered non-invasively and
achieve sustained gonadotropin suppression adequate for treatment of hormone-
dependent conditions.

The initial clinical development focused on hormone-responsive prostate cancer, where the therapeutic objective is suppression of testicular testosterone production to castrate levels. Phase 2 and Phase 3 clinical trials in the early 1980s demonstrated that buserelin, administered as daily subcutaneous injections or intranasal spray, achieved castrate testosterone levels (less than 50 ng/dL or 1.7 nmol/L) in greater than 90 percent of patients with advanced prostate cancer, with objective response rates comparable to surgical orchiectomy and to diethylstilbestrol [20, 21]. Buserelin received its first regulatory approval in 1984, initially in European markets, and was subsequently registered across approximately 40 jurisdictions.

3.3 Expansion of indications

Following the prostate cancer registration, the clinical development program extended to endometriosis (intranasal buserelin demonstrated equivalence to danazol in multiple randomized trials during the late 1980s) [22, 23], uterine fibroids (preoperative volume reduction demonstrated in the late 1980s) [24, 25], premenopausal breast cancer (buserelin combined with tamoxifen demonstrated superior survival to single-agent chemotherapy in the Klijn et al. 2000 JNCI trial) [26], central precocious puberty (intranasal and subcutaneous protocols established in the mid-1980s) [27, 28, 29], and pituitary downregulation for in vitro fertilization (the "long protocol" using buserelin for pituitary suppression before controlled ovarian hyperstimulation became standard practice in the late 1980s) [30, 31]. Each indication exploits the same fundamental pharmacological mechanism of reversible gonadotropin suppression through GnRH receptor desensitization.

3.4 Sustained-release formulations

The requirement for daily subcutaneous injection or multiple daily intranasal applications was a significant adherence limitation. Development of sustained-release depot formulations addressed this barrier. The Suprefact Depot implant, a poly(D,L-lactide-co-glycolide) matrix containing 6.3 mg or 9.45 mg of buserelin acetate, provides continuous drug release over 2 or 3 months respectively after subcutaneous implantation [15, 32]. The depot formulations achieve sustained castrate testosterone levels with improved patient adherence and were registered in multiple markets from the early 1990s onward.

3.5 Current status

Buserelin remains in active clinical use across its registered indications, principally in European, Canadian, and Asian markets. It is not approved in the United States, where leuprolide (Lupron) and goserelin (Zoladex) are the dominant GnRH agonists and where the regulatory pathway did not favor late-entry submissions from the Hoechst/Sanofi development program. The compound is available as both branded and generic preparations and is included on the World Health Organization Model List of Essential Medicines in some formulations. It is classified as a prohibited substance by the World Anti-Doping Agency under the category of hormone and metabolic modulators.

4. Mechanism of Action

Buserelin is a superagonist of the type I gonadotropin-releasing hormone receptor (GnRHR), a class A (rhodopsin-like) G-protein-coupled receptor expressed predominantly on anterior pituitary gonadotroph cells and at lower density on multiple peripheral tissues including prostate, breast, endometrium, ovary, and placenta [5, 6, 33]. The pharmacological mechanism is biphasic: acute stimulation followed by chronic suppression, with the chronic suppressive phase constituting the therapeutically useful effect in all registered indications.

4.1 Acute stimulatory phase (flare)

Binding of buserelin to the GnRHR activates the Gq/11 heterotrimeric G-protein, stimulating phospholipase C-beta and producing inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 mobilizes calcium from endoplasmic reticulum stores; DAG activates protein kinase C isoforms. The resulting calcium and protein kinase C signaling cascade drives exocytosis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretory granules from gonadotroph cells [5, 33]. Because buserelin binds the GnRHR with 20- to 170-fold greater affinity than native GnRH and dissociates more slowly, the initial stimulation of gonadotropin release is supraphysiological, producing a transient "flare" of LH and FSH that peaks at 2 to 4 hours after the first dose and persists at elevated levels for 7 to 14 days [3, 4].

The gonadotropin flare drives transient elevation of gonadal steroids: testosterone rises to supraphysiological levels (often doubling or tripling from baseline) in males, and estradiol rises proportionally in premenopausal females. This flare response has direct clinical consequences in hormone-sensitive cancers, where the transient hormonal surge can exacerbate disease symptoms (bone pain, spinal cord compression in metastatic prostate cancer; tumor growth stimulation in hormone-responsive breast cancer) [16, 17].

4.2 Chronic suppressive phase (desensitization and downregulation)

Sustained continuous exposure to buserelin produces a cascade of molecular events at the gonadotroph GnRHR that collectively abolish the stimulatory response [5, 6]:

First, homologous desensitization occurs through phosphorylation of the GnRHR intracellular domains by G-protein-coupled receptor kinases (GRKs), which promotes beta-arrestin recruitment and uncoupling of the receptor from Gq/11 signaling. This occurs within hours to days of continuous agonist exposure.

Second, receptor internalization occurs through clathrin-mediated endocytosis of the agonist-receptor complex. The human type I GnRHR is unusual among G-protein-coupled receptors in lacking a cytoplasmic C-terminal tail, which modifies (but does not eliminate) the kinetics of internalization and recycling relative to other GPCRs [34]. Internalized receptors are predominantly directed to lysosomal degradation rather than recycled to the cell surface during sustained agonist exposure.

Third, transcriptional downregulation of GnRHR gene expression occurs through negative feedback at the pituitary level, reducing the total complement of receptors available for signaling. The combination of receptor uncoupling, internalization, and transcriptional downregulation produces a state of functional GnRHR depletion on the gonadotroph cell surface.

Fourth, depletion of the releasable pool of LH and FSH occurs through sustained secretory stimulation during the flare phase without adequate time for resynthesis.

The net result is profound suppression of pulsatile gonadotropin secretion, producing serum LH and FSH concentrations in the hypogonadal range and consequent reduction of gonadal steroid synthesis to castrate levels. In males, serum testosterone falls to less than 50 ng/dL (1.7 nmol/L) within 2 to 4 weeks of initiating daily buserelin and remains suppressed for the duration of treatment [20, 21]. In premenopausal females, serum estradiol falls to postmenopausal levels (less than 30 pg/mL) within 2 to 4 weeks [22, 23]. The suppression is fully reversible; normal pulsatile gonadotropin secretion and gonadal steroid production resume within 4 to 12 weeks of treatment cessation.

4.3 Peripheral GnRH receptor actions

GnRH receptors are expressed on multiple peripheral tissues, and direct antiproliferative effects of GnRH agonists have been demonstrated in prostate cancer cell lines (LNCaP, DU-145), breast cancer cell lines (MCF-7, T47D), endometrial carcinoma cells, and ovarian cancer cells [33, 35]. The peripheral antiproliferative mechanism involves activation of GnRHR-coupled signaling that inhibits cell proliferation through phosphotyrosine phosphatase activation, inhibition of mitogenic signaling through the epidermal growth factor receptor pathway, and induction of apoptosis through Fas ligand upregulation. The clinical contribution of these peripheral receptor-mediated effects relative to the central gonadotropin-suppression mechanism is debated but may provide additional antitumor activity in hormone-responsive cancers independent of gonadal steroid suppression [35].

4.4 Selectivity and potency

Buserelin is highly selective for the type I GnRH receptor. It does not produce meaningful binding at other G-protein-coupled receptors at clinically relevant concentrations. The potency advantage over native GnRH (20- to 170-fold, depending on the assay system and endpoint measured) derives from the combined effects of higher receptor binding affinity, slower dissociation kinetics, and resistance to enzymatic degradation that collectively produce a greater and more sustained receptor occupancy per unit dose [3, 4]. Among the clinically available GnRH agonists, buserelin, leuprolide, goserelin, nafarelin, triptorelin, and histrelin share the same fundamental mechanism and achieve comparable degrees of gonadotropin suppression at their respective registered doses; differences among the compounds are principally in pharmacokinetic profiles, formulation options, and geographic registration rather than in receptor pharmacology.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Buserelin, as a nonapeptide, is subject to rapid and extensive degradation by gastrointestinal peptidases. Oral bioavailability is negligible; the compound is not effective by the oral route [10].

Intranasal administration achieves bioavailability of approximately 2.5 to 3.3 percent relative to intravenous dosing. Absorption occurs through the nasal mucosa with time to peak plasma concentration of approximately 30 to 60 minutes. The low bioavailability necessitates high intranasal doses (typically 300 to 400 micrograms per nostril, administered three times daily for a total daily dose of 900 to 1200 micrograms for endometriosis or 1200 to 2400 micrograms for the initial phase of prostate cancer treatment) to achieve therapeutically adequate systemic exposure [10, 11].

Subcutaneous injection achieves bioavailability of approximately 70 percent. Time to peak plasma concentration after subcutaneous injection of 200 to 500 micrograms is approximately 30 to 60 minutes. The subcutaneous route is the preferred route for the initial treatment phase in prostate cancer (500 micrograms three times daily for the first week) and for depot implant formulations [15].

Intravenous administration produces immediate peak plasma concentrations and is used only in pharmacokinetic studies; it is not a clinical route.

Depot implant formulations (6.3 mg for 2 months, 9.45 mg for 3 months) release buserelin continuously from a biodegradable poly(D,L-lactide-co-glycolide) matrix, maintaining therapeutically effective plasma concentrations throughout the implant duration [15, 32]. An initial burst release occurs over the first 24 to 48 hours, followed by sustained release as the polymer matrix degrades. Castrate testosterone levels are typically achieved within 3 to 4 weeks after implant insertion.

5.2 Distribution

The volume of distribution of buserelin has not been precisely characterized in humans but is estimated from animal data to be moderate, consistent with distribution to extracellular fluid with limited tissue binding. Plasma protein binding is approximately 15 percent, predominantly to albumin [10]. The low protein binding contributes to rapid clearance and to the high fractional renal excretion of intact peptide. The compound crosses the blood-brain barrier to a limited extent; central nervous system penetration is not required for the principal mechanism of action, which operates at the anterior pituitary (a circumventricular organ outside the blood-brain barrier).

5.3 Metabolism

Buserelin is metabolized by peptidase enzymes rather than by cytochrome P450 enzymes. The principal metabolic transformations are cleavage by pyroglutamyl peptidase at the N-terminus and by chymotrypsin-like endopeptidases at internal peptide bonds [10, 11]. The D-Ser(tBu) substitution at position 6 confers substantial resistance to the endopeptidase cleavage that limits native GnRH half-life to 2 to 5 minutes, extending the half-life of buserelin to 50 to 80 minutes after intravenous or subcutaneous administration. Metabolic sites include the liver, kidneys, and gastrointestinal tract. The metabolites are pharmacologically inactive peptide fragments.

5.4 Elimination

Approximately 50 percent of an administered intravenous dose is recovered unchanged in urine, indicating substantial renal clearance of intact peptide. The remainder is eliminated as peptide fragment metabolites in urine and through biliary excretion [10]. The plasma elimination half-life is 50 to 80 minutes after intravenous or subcutaneous administration and approximately 1 to 2 hours after intranasal dosing, the difference reflecting continued absorption from the nasal mucosa that flattens the terminal phase. Total body clearance is approximately 1 liter per minute.

Renal impairment may modestly prolong the elimination of buserelin and its metabolites, but dose adjustment is generally not required because the therapeutic endpoint (sustained gonadotropin suppression) is a chronic pharmacodynamic ef-

fect that is relatively insensitive to modest pharmacokinetic variability. Hepatic impairment similarly has limited impact on buserelin pharmacokinetics because the primary elimination pathways are peptidase-mediated rather than hepatic oxidative metabolism.

5.5 Routes of administration

Three principal routes are used clinically: subcutaneous injection (500 micrograms three times daily for prostate cancer induction, 200 micrograms once daily for maintenance), intranasal spray (300 to 400 micrograms per nostril three times daily for endometriosis and prostate cancer), and subcutaneous depot implant (6.3 mg every 2 months or 9.45 mg every 3 months for prostate cancer and other chronic indications) [7, 15]. The intranasal formulation requires patient instruction on correct spray technique, as inconsistent delivery reduces effective bioavailability. The depot implant is inserted under local anesthesia through a large-bore needle or trocar in the anterior abdominal wall subcutaneous tissue.

5.6 Pediatric pharmacokinetics

Holland et al. (1986) characterized the pharmacokinetics of buserelin in children with central precocious puberty after subcutaneous (5 micrograms/kg) and intranasal (20 micrograms/kg) administration [36]. Subcutaneous bioavailability in children was similar to adults (approximately 70 percent). Intranasal bioavailability was approximately 2.5 percent. Peak plasma concentrations were reached within 30 minutes (subcutaneous) and 60 minutes (intranasal). Half-life was comparable to the adult range. The pediatric data supported the dose selection for intranasal regimens (20 to 40 micrograms/kg/day in divided doses) used in central precocious puberty treatment protocols [27, 28, 29].

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Buserelin binds the type I GnRH receptor expressed on rat anterior pituitary membranes with an IC₅₀ for displacement of [125I]-GnRH of approximately 0.1 to 0.5 nanomolar, compared to 5 to 50 nanomolar for native GnRH in the same assay systems [3, 4]. In heterologous expression systems (HEK293, COS-7 cells expressing human GnRHR), buserelin produces dose-dependent inositol phosphate accumulation with an EC₅₀ of approximately 0.1 to 1 nanomolar, confirming full agonist activity through the Gq/11-phospholipase C pathway. At sustained exposure (greater than 6 hours), desensitization of the IP₃ response is observed in vitro, recapitulating the in vivo desensitization mechanism [5, 6].

6.2 Animal pharmacology

In male rats, subcutaneous buserelin at 1 to 10 micrograms/kg/day produces initial elevation of serum LH and testosterone (days 1 to 3) followed by suppression of both to castrate levels by day 14, with testicular atrophy, regression of accessory sex glands, and spermatogenic arrest [3]. The suppression is fully reversible; normal testicular histology and spermatogenesis resume within 4 to 8 weeks of treatment cessation.

In female rats, buserelin at comparable doses produces disruption of the estrous cycle, suppression of ovulation, and regression of the uterus and ovaries to prepubertal size. Fertility is restored after treatment cessation.

In dogs, chronic buserelin administration produces comparable gonadal suppression with reversibility, supporting the translational pharmacology for human clinical development [3].

6.3 Toxicology

Acute toxicity studies in rodents demonstrated wide safety margins; no deaths were observed at doses up to 1000-fold the anticipated human dose. Chronic toxicity studies (6 to 12 months in rats and dogs) demonstrated the expected pharmaco-

logical effects of gonadal steroid deprivation (genital organ atrophy, bone mineral density reduction) without evidence of organ toxicity unrelated to the intended mechanism. Reproductive toxicity studies demonstrated fetal resorption and developmental abnormalities at high doses, consistent with the mechanism of gonadotropin suppression; the compound is classified as contraindicated in pregnancy. No genotoxicity was observed in standard battery testing (Ames test, chromosome aberration assay, mouse micronucleus test). Carcinogenicity studies in rats demonstrated increased incidence of pituitary adenomas at high chronic doses, interpreted as a pharmacological consequence of chronic GnRH receptor stimulation rather than a genotoxic mechanism [7, 10].

7. Clinical Evidence Base

7.1 Hormone-responsive prostate cancer

The prostate cancer indication is the principal registered application of buserelin. Multiple Phase 2 and Phase 3 trials conducted in the 1980s established that buserelin achieves castrate testosterone levels in greater than 90 percent of patients with advanced hormone-responsive prostate cancer and produces objective response rates (partial response plus stable disease) comparable to surgical orchiectomy and to diethylstilbestrol [20, 21].

Soloway (1988) analyzed 207 buserelin-treated patients with stage C, D1, and D2 prostate cancer and reported objective response rates of 50 to 85 percent depending on stage and response criteria, with a median time to treatment failure of approximately 12 to 18 months for metastatic disease [20]. The response rates and survival outcomes were comparable to historical controls treated with orchiectomy.

Debruyne (1988) reported results of the Dutch multicenter trial with buserelin in metastatic prostate cancer, confirming castrate testosterone achievement in greater than 95 percent of patients and objective response rates consistent with the international data [21].

The European Organisation for Research and Treatment of Cancer Genitourinary Group Trial 30843 (de Voogt et al. 1998) evaluated maximum androgen blockade using buserelin combined with the antiandrogen cyproterone acetate versus buserelin alone in 327 patients with metastatic prostate cancer [17]. The combination demonstrated modest improvement in time to progression but no statistically significant overall survival advantage, consistent with the meta-analytic findings for maximum androgen blockade across GnRH agonist classes. The trial confirmed the importance of antiandrogen co-administration during the initial flare phase.

Huben and Murphy (1988) reported a randomized comparison of 265 patients with newly diagnosed metastatic prostate cancer assigned to buserelin, diethylstilbestrol, or orchiectomy, demonstrating comparable efficacy across the three treatment arms [37].

7.2 Endometriosis

Buserelin has been extensively studied in endometriosis, where the therapeutic rationale is suppression of estrogen-dependent endometrial implant proliferation through medical castration. Intranasal buserelin (900 to 1200 micrograms/day for 6 months) has been demonstrated to be comparable to danazol (400 to 800 mg/day) in multiple randomized controlled trials for the relief of pelvic pain, dysmenorrhea, and dyspareunia [22, 23, 38].

Dmowski et al. (1989) reported a randomized comparative study of intranasal buserelin versus danazol in 125 women with endometriosis, demonstrating equivalent improvement in revised American Fertility Society scores at second-look laparoscopy, with buserelin producing fewer androgenic side effects than danazol [23].

Trabant et al. (1990) reviewed six clinical trials encompassing 444 women treated with intranasal buserelin for endometriosis and concluded that the compound produced consistent symptom relief and endometriotic implant regression comparable to danazol, with a superior androgenic side-effect profile [38].

Donnez et al. (1989) compared intranasal buserelin spray with subcutaneous buserelin implant for endometriosis treatment and demonstrated comparable efficacy with both routes, though the implant provided more consistent gonadotropin suppression [39].

Harada et al. (2009) reported a randomized, double-blind, multicenter controlled trial demonstrating that dienogest (2 mg/day oral) was as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis, establishing dienogest as a modern oral alternative that avoids the bone mineral density concerns of prolonged GnRH agonist therapy [40].

7.3 Uterine fibroids

Buserelin has been used for preoperative reduction of uterine fibroid volume to facilitate surgical intervention (myomectomy or hysterectomy) and for symptomatic relief in women with contraindications to surgery. Maheux et al. (1985) provided early pilot data demonstrating that intranasal buserelin produced significant uterine volume reduction over 6 months of treatment [24].

Matta et al. (1988, 1989) demonstrated that buserelin treatment reduced uterine arterial blood flow measured by Doppler ultrasound and produced sustained fibroid volume reduction of approximately 40 to 60 percent over 6 to 18 months, with regrowth occurring after treatment cessation [25, 41]. Vollenhoven et al. (1990) prospectively analyzed 40 women treated with buserelin for uterine fibroids and identified pretreatment fibroid vascularity and cellular composition as predictors of treatment response [42].

Higashijima et al. (1996) demonstrated that buserelin-induced fibroid shrinkage was mediated in part by induction of apoptosis in leiomyoma cells, providing mechanistic evidence beyond simple estrogen deprivation for the antiproliferative effect [43].

Treatment duration is typically limited to 3 to 6 months because of the bone mineral density reduction associated with prolonged hypoestrogenism, and "add-back" therapy with low-dose estrogen-progestin has been investigated to extend treatment duration while preserving bone density.

7.4 Premenopausal breast cancer

Klijn et al. (2000) reported the combined analysis of four randomized trials comparing combined buserelin plus tamoxifen versus buserelin alone, tamoxifen alone, or combination chemotherapy (cyclophosphamide, methotrexate, fluorouracil) in premenopausal women with metastatic breast cancer [26]. The combined buserelin-tamoxifen arm demonstrated significantly superior overall survival compared to single-agent buserelin (median survival 3.7 versus 2.5 years, $p = 0.01$) and comparable or superior efficacy to CMF chemotherapy with a substantially more favorable toxicity profile. This trial established the paradigm of combined ovarian suppression plus antiestrogen therapy as an effective endocrine strategy for premenopausal metastatic breast cancer.

Earlier reports by Klijn et al. (1984) had characterized the antitumor and endocrine effects of chronic buserelin treatment in 17 premenopausal patients with metastatic breast cancer, demonstrating objective responses in approximately 40 percent of patients [44]. Doberauer et al. (1988) and Lopez et al. (1993) extended the application to male breast cancer, demonstrating responses with buserelin-based androgen suppression protocols [45, 46].

7.5 Central precocious puberty

Buserelin was among the first GnRH agonists applied to central precocious puberty, where the therapeutic objective is suppression of premature hypothalamic-pituitary-gonadal axis activation to prevent early epiphyseal closure and short adult stature and to manage the psychosocial consequences of premature sexual development.

Stanhope et al. (1985) reported the treatment of central precocious puberty using intranasal buserelin (1200 micrograms/day) in children, demonstrating suppression of gonadotropin secretion, regression of secondary sexual characteristics, and deceleration of skeletal maturation [27]. Brauner et al. (1985) reported long-term results of buserelin treatment in girls with central precocious puberty, confirming sustained suppression with preserved predicted adult height [28]. Werther et al. (1990) reported a multicenter trial of intranasal buserelin for central precocious puberty confirming efficacy across 17 children [29].

The intranasal route has been largely supplanted in this indication by depot formulations of leuprolide and triptorelin, which provide more reliable suppression without dependence on patient (or parent) adherence to multiple daily nasal administrations. Buserelin depot formulations remain in use for this indication in markets where they are registered.

7.6 Assisted reproduction

Buserelin is widely used as a component of pituitary downregulation protocols in in vitro fertilization and other assisted reproduction technologies. The "long protocol" involves administration of intranasal or subcutaneous buserelin beginning in the mid-luteal phase (day 21) of the preceding menstrual cycle, achieving pituitary downregulation over 10 to 14 days before initiation of exogenous gonadotropin stimulation [30, 31]. This prevents premature LH surges during controlled ovarian hyperstimulation, allowing more predictable follicular development and oocyte retrieval timing.

Maheshwari et al. (2011) reported a Cochrane systematic review of GnRH agonist protocols for pituitary suppression in assisted reproduction, concluding that the long GnRH agonist protocol (including buserelin-based protocols) produced signifi-

cantly higher clinical pregnancy rates than the short (flare) protocol or no GnRH agonist, though the long protocol has been increasingly replaced by GnRH antagonist (cetrorelix, ganirelix) protocols in contemporary practice [31].

Wada et al. (1993) reported assisted conception outcomes using buserelin with human menopausal gonadotropins in women with polycystic ovary syndrome, demonstrating acceptable pregnancy rates with appropriate monitoring for ovarian hyperstimulation syndrome [47].

The shift toward GnRH antagonist protocols in assisted reproduction during the 2000s and 2010s has reduced the volume of buserelin use in IVF, but agonist protocols remain preferred in some clinical scenarios (patients with endometriosis, poor responders requiring flare protocols) and buserelin remains a standard option in many IVF centers worldwide.

8. Sourcing and Quality Verification

Pharmaceutical-grade buserelin (Suprefact, Suprecur, or licensed generic formulations) is the highest quality source for clinical and clinical-research applications. Pharmaceutical-grade material is supplied as buserelin acetate in:

- Aqueous solution for subcutaneous injection: 1 mg/mL in multidose vials
- Nasal spray solution: 1 mg/mL in metered-dose spray devices (100 micrograms per spray)
- Depot implant: 6.3 mg or 9.45 mg in preloaded applicators

Pharmaceutical sourcing is feasible in jurisdictions where the compound is registered (United Kingdom, European Union member states, Canada, New Zealand, South Africa, selected Latin American and Asian markets).

Research-grade buserelin acetate is supplied by multiple peptide and pharmaceutical research suppliers (Bachem, Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress, GenScript, PolyPeptide Group, and others) at greater than 95 percent purity by HPLC. Supply is in milligram to gram quantities as the acetate salt. Pricing varies with quantity and supplier but is generally in the range of \$100 to \$500 per 5 mg of high-purity research material.

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, preferably greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (electrospray ionization, expected $[M+H]^+$ at m/z 1240.66 for the free base, $[M+2H]^{2+}$ at m/z 620.83)
- Amino acid analysis confirming the expected residue composition and ratios
- Peptide content determination (nitrogen analysis or quantitative amino acid analysis) to distinguish active peptide mass from counterion, water, and residual solvent content
- Endotoxin testing (Limulus amebocyte lysate assay) for material intended for in vivo administration

- Residual solvent analysis (gas chromatography) for acetonitrile, trifluoroacetic acid, and other HPLC mobile phase components

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The peptide synthesis market for GnRH analogs is well established, and high-quality material is readily available from reputable suppliers. Lot-to-lot variability in peptide content (typically 60 to 85 percent of gross weight, with the remainder being counterion, water, and residual salt) is a standard consideration and underscores the importance of peptide content determination for accurate dosing in research applications.

9. Reconstitution and Handling

Buserelin acetate is supplied as a lyophilized powder (research grade) or as a solution (pharmaceutical grade). The lyophilized powder is freely soluble in water at room temperature.

Reconstitution for research applications: Stock solutions are typically prepared at 1 to 10 mg/mL in sterile water for injection, bacteriostatic water for injection (0.9 percent benzyl alcohol), or phosphate-buffered saline (pH 7.4). The acetate salt dissolves readily without pH adjustment. For cell culture applications, stock solutions at 1 mM (approximately 1.24 mg/mL of free base) in sterile water are standard and are diluted into culture medium at the desired working concentration.

Storage of solid material: Lyophilized buserelin acetate should be stored at minus 20 degrees Celsius under desiccation. The lyophilized powder is stable for at least 2 years under these conditions. Avoid repeated exposure to moisture and temperature cycling.

Storage of solutions: Reconstituted aqueous solutions should be stored at 2 to 8 degrees Celsius and used within 14 to 28 days of preparation for sterile water reconstitution, or within 28 days for bacteriostatic water reconstitution. Aliquoting of stock solution for single-use is recommended to avoid repeated freeze-thaw cycles. The compound tolerates at least 3 freeze-thaw cycles without measurable potency loss by HPLC analysis, but single-use aliquots are preferred for quantitative research applications.

Pharmaceutical formulation handling: Suprefact injection solution (1 mg/mL) should be stored at room temperature (15 to 25 degrees Celsius) and protected from light. Suprefact Nasal Spray should be stored upright at room temperature. Depot implants should be stored at 2 to 8 degrees Celsius and brought to room temperature before insertion. Once the depot applicator seal is broken, the implant should be used immediately.

Compatibility: Buserelin acetate solutions are compatible with standard glass and polypropylene containers. Adsorption to container walls is minimal at the concentrations used clinically and in research. The compound is stable in physiologi-

cal pH range (pH 4 to 8); degradation accelerates at extremes of pH through accelerated peptide bond hydrolysis.

10. Stack Interactions and Combinations

Buserelin interacts with several drug classes through its mechanism of gonadal steroid suppression and through pharmacological additivity or antagonism at the level of the hypothalamic-pituitary-gonadal axis. Investigators conducting research with buserelin should consider the following interactions:

Antiandrogens (cyproterone acetate, flutamide, bicalutamide, enzalutamide): Co-administration with buserelin is standard practice in prostate cancer treatment to provide "maximum androgen blockade" (suppression of both testicular and adrenal androgens) and to mitigate the testosterone flare during the first 2 to 4 weeks of GnRH agonist therapy [16, 17]. The combination is pharmacologically rational and clinically established. The EORTC 30843 trial demonstrated modest improvement in time to progression with buserelin plus cyproterone acetate versus buserelin alone, without overall survival benefit [17].

Antiestrogens (tamoxifen, fulvestrant): Co-administration with buserelin in premenopausal breast cancer combines ovarian suppression with estrogen receptor blockade. The Klijn et al. (2000) trial demonstrated superior survival with buserelin plus tamoxifen versus single-agent therapy [26]. The combination is standard endocrine therapy for premenopausal hormone-receptor-positive breast cancer.

Exogenous gonadotropins (human menopausal gonadotropin, recombinant FSH): In assisted reproduction protocols, buserelin-induced pituitary downregulation is followed by exogenous gonadotropin administration to achieve controlled ovarian hyperstimulation. The interaction is intentional and well characterized [30, 31].

GnRH antagonists (cetrorelix, ganirelix, degarelix): Concurrent administration is pharmacologically contradictory: the agonist stimulates (then suppresses) the GnRH receptor, while the antagonist blocks it immediately. Sequential use (switching from agonist to antagonist or vice versa) is occasionally employed in clinical practice but concurrent use is not indicated.

Estrogen and progestin "add-back" therapy: Low-dose estrogen-progestin combinations (conjugated estrogens 0.3 to 0.625 mg/day plus medroxyprogesterone acetate 2.5 to 5 mg/day, or equivalent) are co-administered with buserelin during prolonged endometriosis or fibroid treatment to mitigate bone mineral density loss and vasomotor symptoms while preserving the therapeutic suppression of endometriotic or fibroid tissue. The add-back concept exploits the "estrogen threshold" hypothesis: endometriotic implants require higher estrogen concentrations for proliferation than are needed to maintain bone density and to prevent vasomotor symptoms.

Bone-active agents (bisphosphonates, denosumab): Consideration of bone-protective therapy during prolonged buserelin treatment is appropriate for patients at elevated fracture risk, particularly in prostate cancer where GnRH agonist therapy may continue for years.

CYP450-metabolized drugs: Buserelin does not interact with cytochrome P450 enzymes (it is metabolized by peptidases), and no CYP-mediated drug-drug interactions have been identified. This contrasts with many other oncologic and endocrine agents and simplifies concurrent medication management.

Drugs affecting nasal mucosa: Nasal decongestants (oxymetazoline, xylometazoline) and nasal corticosteroids (fluticasone, mometasone) may alter intranasal buserelin absorption. Investigators using the intranasal route should consider the potential for reduced bioavailability in the setting of nasal mucosal inflammation or concurrent nasal medication use.

11. Adverse Events and Safety Signal

11.1 Pharmacological adverse events (gonadal steroid deprivation)

The dominant adverse events of buserelin are the predictable pharmacological consequences of gonadal steroid suppression and are shared across the GnRH agonist class [7, 10, 48]:

In males:

- Hot flashes (50 to 80 percent incidence, the most common adverse event)
- Reduced libido and erectile dysfunction (40 to 60 percent)
- Gynecomastia (5 to 15 percent)
- Testicular atrophy (expected pharmacological effect during treatment)
- Fatigue and mood changes (20 to 40 percent)
- Bone mineral density reduction (2 to 8 percent decrease over 6 to 12 months; accelerated osteoporosis risk with prolonged treatment beyond 2 years)
- Metabolic changes: increased body fat, decreased lean body mass, insulin resistance, unfavorable lipid profile changes

In females:

- Hot flashes (60 to 90 percent)
- Vaginal dryness and dyspareunia (30 to 50 percent)
- Reduced libido (20 to 40 percent)
- Headache (10 to 20 percent)
- Mood changes including depressive symptoms (15 to 30 percent)
- Bone mineral density reduction (4 to 8 percent decrease over 6 months of treatment; largely reversible on treatment cessation in premenopausal women)
- Breakthrough bleeding or spotting during the initial weeks of treatment

11.2 Flare-related adverse events

The initial testosterone or estrogen flare during the first 7 to 14 days of treatment carries specific clinical risks [16, 17]:

In metastatic prostate cancer:

- Exacerbation of bone pain (10 to 30 percent of patients with osseous metastases)
- Spinal cord compression due to vertebral metastasis expansion (rare but clinically devastating; reported incidence 1 to 5 percent in unprotected initiation)
- Ureteral obstruction with acute renal failure (rare)
- Cardiovascular events in patients with marginal cardiac reserve

These flare-related risks are effectively mitigated by co-administration of an antiandrogen (cyproterone acetate 100 mg three times daily or flutamide 250 mg three times daily) beginning 3 to 7 days before buserelin initiation and continuing for 2 to 4 weeks [16, 17].

11.3 Route-specific adverse events

Intranasal: Nasal irritation, epistaxis, rhinitis (5 to 15 percent). Nasal mucosal atrophy with prolonged use has been reported in rare cases.

Subcutaneous injection: Injection-site reactions including pain, erythema, and induration (5 to 10 percent). Rarely, sterile abscess formation.

Depot implant: Implant-site reactions, occasional extrusion of the implant through the skin, and rarely, migration of the implant from the insertion site [15].

11.4 Rare and serious adverse events

- Anaphylaxis and hypersensitivity reactions (rare; case reports exist but the incidence is very low)
- Pituitary apoplexy in patients with undiagnosed pituitary adenomas (very rare; the flare response can cause hemorrhage or infarction of a pre-existing adenoma)
- Thromboembolic events (reported in postmarketing surveillance, though the causal relationship with buserelin versus underlying malignancy or immobil-

ity is unclear)

- Depression and suicidal ideation (rare; monitoring is appropriate during prolonged treatment, particularly in adolescent patients treated for precocious puberty)

11.5 Long-term safety

Chen et al. (2025) reported a real-world pharmacovigilance study comparing adverse-event profiles among long-acting GnRH analogs using the FDA Adverse Event Reporting System database, identifying buserelin with a profile broadly comparable to leuprolide and goserelin, with musculoskeletal disorders, reproductive system disorders, and psychiatric disorders as the most frequently reported event categories across the class [48].

The principal long-term safety concern across the GnRH agonist class is bone mineral density reduction with prolonged treatment (greater than 6 to 12 months), which may progress to osteoporosis and increased fracture risk. Dual-energy X-ray absorptiometry monitoring is recommended for patients on prolonged buserelin therapy, and bone-protective interventions (calcium, vitamin D, bisphosphonates, or denosumab) should be considered based on individual fracture risk assessment.

11.6 Pregnancy and lactation

Buserelin is contraindicated in pregnancy. Animal reproductive toxicity studies demonstrated fetal resorption at therapeutic doses, consistent with the mechanism of gonadotropin suppression. No human teratogenicity data are available. The compound should be discontinued if pregnancy is suspected. Use during lactation is not recommended; excretion into breast milk has not been characterized, and the potential for suppression of infant gonadotropin function is a theoretical concern [7].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five GnRH agonist candidates against buserelin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal GnRH agonists with substantive clinical registration and evidence base, representing the competitive landscape in which buserelin is positioned.

12.1 Leuprolide (Lupron, Eligard, Lucrin)

Mechanism: Synthetic nonapeptide GnRH superagonist incorporating D-Leu6 and Pro9-NHEt modifications. Identical biphasic mechanism to buserelin (flare followed by desensitization-mediated suppression) [49].

Development trajectory: Developed by Takeda Pharmaceutical and Abbott Laboratories (now AbbVie). First approved by the FDA in 1985 for advanced prostate cancer and subsequently registered for endometriosis, uterine fibroids, central precocious puberty, and assisted reproduction. Leuprolide is the dominant GnRH agonist in the United States and globally the most widely prescribed compound in the class.

Novelty: Low. The mechanism is identical to buserelin; the structural difference (D-Leu6 versus D-Ser(tBu)6) is a conservative substitution within the same medicinal chemistry series.

Effect size: Equivalent to buserelin. Castrate testosterone levels are achieved in greater than 95 percent of prostate cancer patients. Endometriosis symptom relief, fibroid volume reduction, and precocious puberty suppression outcomes are comparable across randomized and observational data [49, 50].

Promising potential: High. Leuprolide is the most widely registered GnRH agonist globally and has the broadest formulation portfolio (daily subcutaneous injection, 1-month depot, 3-month depot, 4-month depot, 6-month depot, 45 mg 6-month implant). Active commercial development continues for new depot formulations.

Side-effect profile: Comparable to buserelin. The adverse-event profile is dominated by the pharmacological consequences of gonadal steroid suppression and is class-consistent [48, 50].

Overall validation: Very high. Leuprolide has the largest clinical evidence base of any GnRH agonist, with thousands of publications, multiple large randomized controlled trials, and regulatory approvals across all major jurisdictions.

Comparison to buserelin: Leuprolide and buserelin are pharmacologically equivalent at the mechanism level. The principal practical differences are geographic registration (leuprolide is FDA-approved; buserelin is not), formulation portfolio (leuprolide has a broader range of depot durations), and market dominance (leuprolide is the global leader). Buserelin has the distinction of being available as an intranasal formulation (one of only two GnRH agonists with this option, the other being nafarelin), which provides a non-injectable route. In markets where both are available, compound selection is determined by formulation preference, local prescribing tradition, and cost.

12.2 Goserelin (Zoladex)

Mechanism: Synthetic decapeptide GnRH superagonist incorporating D-Ser(tBu)₆ and AzaGly₁₀ modifications. The position 6 modification is identical to buserelin; the C-terminal modification differs (azaglycine amide versus ethylamide) [51].

Development trajectory: Developed by ICI Pharmaceuticals (now AstraZeneca). First approved by the FDA in 1989 for advanced prostate cancer. Subsequently registered for breast cancer, endometriosis, and endometrial thinning before surgery. Goserelin is the second most widely prescribed GnRH agonist globally after leuprolide.

Novelty: Low. Identical mechanism to buserelin with very similar structural modifications.

Effect size: Equivalent to buserelin and leuprolide across all shared indications [51, 52].

Promising potential: High. Goserelin has broad global registration and a well-established depot formulation (3.6 mg 1-month implant, 10.8 mg 3-month implant) delivered by a distinctive prefilled syringe with a 16-gauge needle.

Side-effect profile: Class-consistent. The Zoladex implant insertion procedure carries a small additional risk of injection-site pain and subcutaneous fat atrophy [51].

Overall validation: Very high. Extensive clinical evidence base, FDA approval, and multiple landmark trials including ZIPP (Zoladex In Premenopausal Patients), which established the role of GnRH agonists in adjuvant breast cancer therapy.

Comparison to buserelin: Goserelin shares the D-Ser(tBu)₆ modification with buserelin and is pharmacologically nearly identical. The practical differences are the absence of an intranasal formulation for goserelin and the absence of FDA approval for buserelin. In breast cancer, goserelin has a substantially larger evidence base than buserelin for adjuvant use in premenopausal patients. In prostate cancer and endometriosis, the two compounds are interchangeable at equipotent doses.

12.3 Nafarelin (Synarel)

Mechanism: Synthetic decapeptide GnRH superagonist incorporating D-Nal(2)₆ (D-3-(2-naphthyl)alanine at position 6). The naphthylalanine substitution confers very high receptor affinity (approximately 200-fold greater potency than native GnRH), the highest among clinically used GnRH agonists [53].

Development trajectory: Developed by Syntex (now Roche). FDA-approved in 1990 for endometriosis and central precocious puberty. Not approved for prostate cancer. Available only as intranasal spray (200 micrograms per spray, 400 to 800 micrograms/day).

Novelty: Low to moderate. The D-Nal(2)₆ substitution provides higher receptor potency than the D-Ser(tBu)₆ or D-Leu₆ modifications of buserelin and leuprolide.

Effect size: Equivalent to buserelin in endometriosis and precocious puberty at registered doses. Endometriosis comparative trials demonstrate similar symptom relief to buserelin and leuprolide [53].

Promising potential: Moderate. Nafarelin is established but has a narrow indication range (no prostate cancer approval) and limited formulation options (intranasal only; no depot). The intranasal limitation restricts use in patients with nasal pathology and raises adherence concerns similar to buserelin nasal spray.

Side-effect profile: Class-consistent. Nasal irritation rates are comparable to intranasal buserelin [53].

Overall validation: Moderate. The clinical evidence base is smaller than for leuprolide and goserelin, principally because the indication range is narrower. Validation within endometriosis and precocious puberty is solid.

Comparison to buserelin: Nafarelin and buserelin are the only two GnRH agonists available as intranasal sprays, placing them in a distinct formulation niche. Buserelin has a broader indication range (prostate cancer, breast cancer, fibroids, IVF) and a depot formulation that nafarelin lacks. Nafarelin has higher receptor potency and FDA approval, which buserelin lacks. The two compounds are directly interchangeable for intranasal endometriosis and precocious puberty treatment.

12.4 Triptorelin (Decapeptyl, Trelstar)

Mechanism: Synthetic decapeptide GnRH superagonist incorporating D-Trp6. Identical biphasic mechanism to buserelin [54].

Development trajectory: Developed by Debiopharm/Ipsen. Approved by the FDA in 2000 for advanced prostate cancer. Also registered in many markets for endometriosis, precocious puberty, and assisted reproduction. Available as intramuscular depot injection (1-month, 3-month, and 6-month formulations).

Novelty: Low. Conventional GnRH agonist mechanism with a D-tryptophan position 6 substitution.

Effect size: Equivalent to buserelin, leuprolide, and goserelin across shared indications [54, 55].

Promising potential: High. Triptorelin has a broad registration portfolio and is the GnRH agonist most commonly specified in European assisted reproduction protocols.

Side-effect profile: Class-consistent. The intramuscular depot injection may produce more injection-site discomfort than subcutaneous formulations [54].

Overall validation: High. Extensive clinical evidence base across prostate cancer, endometriosis, precocious puberty, and assisted reproduction, with large randomized controlled trials and meta-analytic data.

Comparison to buserelin: Triptorelin and buserelin share the same mechanism and produce equivalent clinical outcomes. Triptorelin has FDA approval and a longer-duration (6-month) depot formulation that buserelin lacks. Buserelin has the intranasal route that triptorelin lacks. In European IVF practice, both compounds are widely used for pituitary downregulation.

12.5 Histrelin (Vantas, Supprelin LA)

Mechanism: Synthetic nonapeptide GnRH superagonist incorporating D-His(Bzl)6 (D-histidine(benzyl) at position 6). The benzylhistidine substitution confers very high receptor affinity [56].

Development trajectory: Developed by Endo Pharmaceuticals. FDA-approved as Vantas (50 mg subcutaneous implant providing 12 months of drug release) for advanced prostate cancer in 2004 and as Supprelin LA (50 mg subcutaneous implant providing 12 months of drug release) for central precocious puberty in 2007. Histrelin is distinguished by the longest-duration single-implant GnRH agonist formulation available.

Novelty: Moderate. The 12-month implant formulation is unique among GnRH agonists and represents a meaningful formulation advance.

Effect size: Equivalent to buserelin and other GnRH agonists for testosterone suppression and precocious puberty management [56, 57].

Promising potential: Moderate to high. The 12-month implant addresses adherence challenges of shorter-duration formulations. Limited indication range (prostate cancer and precocious puberty).

Side-effect profile: Class-consistent for hormonal adverse events. The implant requires a minor surgical procedure for insertion and removal, carrying small risks of infection, implant breakage, and difficulty with removal if the implant migrates or becomes encapsulated [56].

Overall validation: Moderate. Smaller clinical evidence base than leuprolide or goserelin, but adequate for registration and for established clinical use in the FDA-approved indications.

Comparison to buserelin: Histrelin's 12-month implant provides the longest single-administration duration in the GnRH agonist class, a significant practical advantage for chronic indications. Buserelin offers formulation flexibility (intranasal, subcutaneous injection, 2- and 3-month depot) that histrelin does not. The two compounds are pharmacologically equivalent at the receptor level.

12.6 Comparator summary

The five GnRH agonist comparators share buserelin's fundamental biphasic mechanism and produce equivalent clinical outcomes at their respective registered doses. The class is distinguished more by formulation characteristics, geographic registration, and market positioning than by pharmacological differences. **Leuprolide** is the global market leader with the broadest formulation portfolio and FDA approval. **Goserelin** is the second most prescribed, with a strong breast cancer evidence base. **Nafarelin** shares buserelin's intranasal formulation niche but has a narrower indication range. **Triptorelin** is strongly positioned in European reproductive medicine. **Histrelin** offers the longest single-administration duration (12 months) in the class.

Buserelin occupies a distinctive position as one of the original GnRH agonists to achieve clinical registration, the first to demonstrate intranasal medical castration in humans, and one of only two compounds (with nafarelin) available as intranasal spray. Its principal limitation relative to the comparators is the absence of FDA approval, which restricts its availability in the United States. In markets where buserelin is registered, it provides equivalent efficacy and safety to the comparator compounds and offers unique formulation flexibility (intranasal spray plus multiple depot durations) that supports individualized treatment selection.

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