POLICY: Gonadotropin-Releasing Hormone Agonists Implants
- Supprelin® LA (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)
- Vantas® (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)
- Zoladex® (goserelin acetate subcutaneous implant – TerSera Therapeutics)

DATE REVIEWED: 01/15/2020; Selected revision, 3/11/2020

OVERVIEW

Supprelin LA, Vantas, and Zoladex are gonadotropin-releasing hormone (GnRH) agonists implants.[1-4] Vantas and Zoladex are indicated for the palliative treatment of advanced prostate cancer.[1-3] Zoladex is also FDA-approved for use in combination with flutamide for the management of locally confined prostate cancer (3.6 mg and 10.8 mg implants).[2,3] In addition, Zoladex 3.6 mg is indicated for the management of endometriosis, for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding, and for the palliative treatment of advanced breast cancer in pre- and perimenopausal women.[2] Supprelin LA is a GnRH agonist indicated for the treatment of children with central precocious puberty.[3] Although Vantas is not indicated for use in children with central precocious puberty, it contains the same chemical entity as that of Supprelin LA, and can be used for this condition.

Guidelines

The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 4.2019 – August 19, 2019) list both Vantas and Zoladex as androgen deprivation therapy (ADT) therapy options for use in various settings (all category 2A): clinically localized disease, regional disease, prostate specific antigen (PSA) persistence/recurrence after radical prostatectomy (RP) or external beam radiation therapy (EBRT) [castration-naïve disease], and metastatic castration-naïve disease.[5]

The NCCN compendium and guidelines for breast cancer (version 3.2019 – September 6, 2019) does not note the use of Zoladex implants for advanced breast cancer.[6] However, the guidelines note that ovarian suppression with GnRH agonists (e.g., Zoladex) administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.

Central precocious puberty, also known as gonadotropin-dependent precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis.[7] The standard of care for central precocious puberty is GnRH agonists. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[8] The panel noted that the available GnRH agonists (including leuprolide, triptorelin, and histrelin implant) are effective despite different routes of administration, dosing, and duration of action. An update by the International Consortium (2019) reiterates the use of GnRH agonists (e.g., leuprolide, triptorelin, and histrelin implant) for the treatment of central precocious puberty.[9] GnRH agonists are generally well-tolerated in children and adolescents.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Supprelin LA, Vantas, and Zoladex. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas and Zoladex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that as with Supprelin LA, when Vantas is prescribed for use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Vantas is recommended in patients who meet the following criteria:

FDA-Approved Indications

1. Prostate Cancer. Approve for 1 year if the medication is prescribed by, or in consultation with, an oncologist.

Dosing. Approve one implant (50 mg) up to once every 12 months (inserted subcutaneously in the upper arm).

Other Uses with Supportive Evidence

2. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one implant (50 mg) up to once every 12 months (inserted subcutaneously in the upper arm).

II. Coverage of Supprelin LA is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

1. Central Precocious Puberty. Approve for 1 year.

Dosing. Approve one implant (50 mg) up to once every 12 months (inserted subcutaneously in the upper arm).

III. Coverage of Zoladex is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

1. Prostate Cancer. Approve for 1 year if the medication is prescribed by, or in consultation with, an oncologist.

Dosing. Approve the following dosage regimens (inserted subcutaneously into the anterior abdominal wall):
A) Zoladex 3.6 mg implant up to once every 28 days; OR
B) Zoladex 10.8 mg implant up to once every 12 weeks.

2. Breast Cancer. Approve for 1 year if the patient meets the following conditions (A and B):
A) Zoladex is used in premenopausal or perimenopausal women; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve Zoladex 3.6 mg implant up to once every 28 days (inserted subcutaneously into the anterior abdominal wall).

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3. Endometriosis. Approve for 6 months if the patient meets the following conditions (A and B):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by, or in consultation with, an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

Dosing. Approve Zoladex 3.6 mg implant up to once every 28 days (inserted subcutaneously into the anterior abdominal wall)

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4. Abnormal Uterine Bleeding. Approve for 2 months if the patient meets the following conditions (A and B):
- **A)** Zoladex is used as an endometrial-thinning agent prior to endometrial ablation; AND
- **B)** The medication is prescribed by, or in consultation with, an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

Dosing. Approve Zoladex 3.6 mg implant up to once every 28 days (inserted subcutaneously into the anterior abdominal wall).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).

Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[8] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vantas® Subcutaneous Implant [prescribing information]. Malvern, PA: Endo Pharmaceuticals Inc.; November 2019.
2. Zoladex® 3.6 mg Implant [prescribing information]. Lake Forest, IL; February 2019.
3. Zoladex® 10.8 mg Implant [prescribing information]. Lake Forest, IL; February 2019.
4. Supprelin® LA [prescribing information]. Malvern, PA; Endo Pharmaceuticals Solutions Inc., November 2019.
5. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – August 19, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 7, 2020.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019 © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 7, 2020.
7. Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972..
8. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics.* 2009 Apr;123(4):e752-62.

9. Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;91:357-372.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	01/03/2019
Selected revision	Revised Precocious Puberty (also known as GnRH-independent precocious puberty or peripheral precocious puberty) to Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).	09/18/2019
Update	Changed policy name from "Gonadotropin-Releasing Hormone Agonists – Supprelin LA, Vantas, Zoladex Implants" CC to "Gonadotropin-Releasing Hormone Agonists – Implants (Supprelin LA, Vantas, and Zoladex)" CC	11/21/2019
Annual revision	No criteria changes. Policy Statement: Removed Supprelin LA from this sentence: Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas, and Zoladex as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated (Supprelin LA was inadvertently included. Approval of Central Precocious Puberty does not require that it be prescribed by or in consultation with a specialist).	01/15/2020
Selected revision	Vantas: Added approval for central precocious puberty. Dosing. Approve one implant (50 mg) up to once every 12 months (inserted subcutaneously in the upper arm). Policy Statement: Added this sentence: Note that as with Supprelin LA, when Vantas is prescribed for use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.	03/11/2020