Drug Monograph

Drug Name: **Fensolvi® (leuprolide acetate) Injectable Suspension**
Drug Class: **Gonadotropin Releasing Hormone (GnRH) Agonist**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Fensolvi is available as an injectable suspension kit that contains 45 mg of leuprolide acetate.
Manufacturer:	Distributed by: Tolmar Pharmaceuticals, Inc., Fort Collins, CO 80526.
Summary of Findings:	The efficacy of Fensolvi for the treatment of central precocious puberty in pediatric patients was demonstrated in one open-label study enrolling 64 patients. The primary measurement was the percentage of participants with suppression of peak-stimulated luteinizing hormone (LH) at 6 months. LH suppression is defined as peak-stimulated LH < 4 IU/L. Peak-stimulated LH refers to the maximum LH concentration measured 30 minutes after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test. 87.1% of participants met the criteria for the primary outcome measure.

Status Recommendation:	☐ Clinical Edit ☒ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ No PA Required	☐ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1]

Central precocious puberty (CPP) is a condition that causes early sexual development in girls and boys. While puberty normally starts between ages 8 and 13 in girls and between ages 9 and 14 in boys, girls with central precocious puberty begin exhibiting signs before age 8, and boys with this disorder begin before age 9. Central precocious puberty is estimated to affect 1 in 5,000 to 10,000 girls. The condition is less common in boys, although the prevalence is unknown. The cause of central precocious puberty is often unknown. The most common known genetic cause of central precocious puberty is mutations in the MKRN3 gene. Researchers suspect that changes in genes that have not yet been identified may also be involved in central precocious puberty. The timing of puberty is influenced by several factors in addition to genetics, including nutrition, socioeconomic status, and exposure to certain chemicals in the environment.

Dosage Form [2]

Fensolvi is available as an injectable suspension kit that contains 45 mg of leuprolide acetate.

Manufacturer [2]

Distributed by: Tolmar Pharmaceuticals, Inc., Fort Collins, CO 80526.

Indication(s) [2]

Fensolvi is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty.

Clinical Efficacy [2,3,4] (mechanism of action/pharmacology, comparative efficacy)

Fensolvi, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion (luteinizing hormone (LH) and follicle stimulating hormone (FSH) when given continuously in therapeutic doses. Following an initial stimulation of GnRH receptors, chronic administration of leuprolide acetate results in downregulation of GnRH receptors, reduction in release of LH, FSH and consequent suppression of ovarian and testicular production of estradiol and testosterone respectively. This inhibitory effect is reversible upon discontinuation of drug therapy.

Pharmacokinetics:

Absorption	Initial injection mean C_{max}: 212.3 ng/mL Mean plateau serum level: 0.37 ng/mL (range of 0.18 to 0.63 ng/mL) Volume of distribution was not evaluated in pediatric patients.
Metabolism	Metabolism studies were not conducted with Fensolvi.

	Administration with different leuprolide acetate formulations has shown pentapeptide (M-1) is a major metabolite.
Excretion	Excretion studies were not conducted with Fensolvi. Administration with different formulations has shown leuprolide acetate is excreted in the urine (<5% as parent and major metabolite).
Half-life	Approximately 3 hours

Clinical Trials Experience

STUDY 1 DESIGN	Uncontrolled, open-label, single-arm, multicenter clinical trial (n=64)
INCLUSION CRITERIA	• Females age 2 to 8 years or males age 2 to 9 years • Confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but have not received prior GnRH agonist treatment for CPP • Pubertal-type LH response following an abbreviated GnRHa stimulation test before treatment initiation • Clinical evidence of puberty, defined as Tanner stage ≥ 2 for breast development in females or testicular volume ≥ 4 mL in males • Difference between bone age (Greulich and Pyle method) and chronological age ≥ 1 year
EXCLUSION CRITERIA	• Gonadotropin-independent (peripheral) precocious puberty • Prior or current GnRH treatment for CPP • Prior or current therapy with medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1) • Diagnosis of short stature (ie, 2.25 standard deviations (SD) below the mean height for age) • Known history of seizures, epilepsy, and/or central nervous system disorders that may be associated with seizures or convulsions • Any other medical condition or serious intercurrent illness that, in the opinion of the Investigator, may make it undesirable for the subject to participate in the study
TREATMENT REGIMEN	Participants received leuprolide acetate 45 mg as a subcutaneous injection at 6-month intervals for the 12 month study period.
RESULTS	The primary outcome measured was the percentage of participants with suppression of peak-stimulated luteinizing hormone (LH) at 6 months. LH suppression is defined as peak-stimulated LH < 4 IU/L. Peak-stimulated LH refers to the maximum LH concentration measured 30 minutes after a gonadotropin-releasing hormone agonist (GnRHa) stimulation test. 87.1% of participants met the criteria for the primary outcome measure.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [2,3]

- Hypersensitivity to GnRH, GnRH agonists or any of the components of Fensolvi. Anaphylactic reactions to synthetic GnRH or GnRH agonists have been reported.
- Pregnancy: Fensolvi may cause fetal harm.

Warnings and Precautions [2,3]

- Initial rise of gonadotropins and sex steroid levels: During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty including vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses. Instruct patients and caregivers to notify the physician if these symptoms continue beyond the second month after Fensolvi administration.
- Psychiatric events: Have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms.
- Convulsions: Have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.

Adverse Effects [2,3]

Most common, ≥ 5%	Fensolvi (n = 64) %
Injection site pain	31
Nasopharyngitis	22
Pyrexia	17
Headache	16
Cough	13
Abdominal pain	9
Injection site erythema	9
Nausea	8
Constipation	6
Vomiting	6
Upper respiratory tract infection	6
Bronchospasm	6
Productive cough	6
Hot flush	5

Drug Interactions [2,3]

- No pharmacokinetic drug-drug interaction studies have been conducted with Fensolvi.
- Administration with different formulations has shown leuprolide acetate may increase the levels/effects of Corifollitropin Alfa, haloperidol, and QT-prolonging agents. Leuprolide acetate may decrease the levels/effects of antidiabetic agents, Choline C 11, and Indium 111 Capromab Pendetide.

Dosage and Administration [2,3]

Fensolvi must be administered by a healthcare professional. The dose of Fensolvi is 45 mg administered by subcutaneous injection once every six months. The subcutaneous injection site should be on the abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Discontinue Fensolvi treatment at the appropriate age of onset of puberty.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Year
Leuprolide	Fensolvi	Tolmar, Inc	45 mg every 6 months	$45,156

** Wholesale Acquisition Cost

Conclusion

Fensolvi is indicated for the treatment of pediatric patients 2 years of age and older with central precocious puberty. The efficacy of Fensolvi was demonstrated in one open-label study in 64 participants with precocious puberty. The trial showed that 87% of participants had suppression of peak-stimulated LH at 6 months. The most common adverse drug reactions in patients taking Fensolvi (>5%) were injection site pain, nasopharyngitis, pyrexia, headache, cough, abdominal pain, injection site erythema, nausea, constipation, vomiting, upper respiratory tract infection, bronchospasm, and productive cough.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Central Precocious Puberty. U.S. National Library of Medicine. https://ghr.nlm.nih.gov/condition/central-precocious-puberty#:~:text=Central%20precocious%20puberty%20is%20a,disorder%20begin%20before%20age%209. Accessed August 3, 2020.
2) Product Information: Fensolvi® (leuprolide acetate). Tolmar, Inc., Fort Collins, CO 80526.
3) Fensolvi: Drug Information. Lex-Drugs. Wolters Kluwer Clinical Drug Information Inc.
4) An Open-label, single arm, multicenter study on the efficacy, safety, and pharmacokinetics of leuprolide acetate 45 mg for injectable suspension controlled release in subjects with central (Gonadotropin-dependent) precocious puberty. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02452931?cond=leuprolide&age=0&draw=2&rank=4. Accessed August 3, 2020.

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