CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

SUMMARY REVIEW

Division Director Memorandum

Date	*See Stamp Date*
From	Jean-Marc Guettier, MDCM
Subject	Division Director Review
NDA/BLA # Supplement#	208956
Applicant	Arbor Pharmaceuticals, LLC
Date of Submission	8/29/2016
PDUFA Goal Date	6/29/2017
Proprietary Name / Established (USAN) names	TRIPTODUR (triptorelin) for extended-release injectable suspension, for intramuscular use
Dosage forms / Strength	Powder, lyophilized for suspension/ 22.5 (b) (4)
Proposed Indication(s)	For the treatment of children (> 2 years) with central precocious puberty
Indication Granted	For the treatment of children (> 2 years) with central precocious puberty
Recommended:	*Approval*

On 29 August 2016, Arbor Pharmaceuticals submitted a New Drug Application (NDA) for TRIPTODUR (triptorelin pamoate) pursuant to Section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act. The product is an extended-release injectable suspension, for intramuscular use and comes in a single dosage strength of 22.5 mg to be administered by a trained healthcare professional every 24 weeks.

The product in this application is a synthetic gonadotropin releasing hormone (GnRH) agonist that is already approved in the United States under the tradename TRELSTAR for the palliative treatment of advanced prostate cancer. TRELSTAR strengths approved include: a 3.75 mg strength approved in 2000 under NDA# 20715, an 11.25 mg strength approved in 2001 under NDA# 21288, and a 22.5 mg strength approved in 2010 under NDA# 22437. The Sponsor has obtained the right of reference to all three TRELSTAR NDAs.

This NDA proposes to indicate the approved 22.5 mg strength and schedule (i.e., injection every 24 weeks) for the treatment of children (> 2 years) with central precocious puberty. The application has been reviewed in details by Drs. Sullivan (clinical), Chen (clinical pharmacology), Basso (pharmacology-toxicology), He (statistics), and Tran (CMC). Dr. Zemskova has summarized the key findings from each of these reviews in her cross-discipline team leader memorandum. My memorandum serves to provide concurrence with the review team's decision to recommend approval.

Central precocious puberty (CPP) is a rare disorder characterized by early onset pubertal development (i.e., puberty onset prior to age 8 in girls and age 9 in boys). The disorder is caused by premature activation of the hypothalamic pituitary gonadal axis and affects approximately 1 in every 5,000 to 10,000 children and approximately 20 girls for every 1 boy. The diagnosis of CPP is established by excluding causes of peripheral precocious puberty (i.e., primary adrenal or gonadal steroid hormone over-production) and by demonstrating a luteinizing hormone response in the pubertal range (i.e., greater than or equal to 6 IU/L) following pituitary stimulation with an immediate release GnRH agonist.

Early onset puberty in CPP often causes extreme psychological distress and social isolation. Additionally, the higher than normal estradiol levels (from the ovaries in girls and via conversion from testosterone in boys) that result from the disorder, accelerate bone growth, can cause premature fusion of epiphyseal growth plates and can decrease final achieved adult height.

Drugs used in the treatment of CPP aim to improve the above psychosocial and physical complications. The mainstay of therapy consists in arresting premature pubertal development by suppressing the hypothalamic pituitary gonadal axis with GnRH agonist drugs. There are currently three GnRH agonist drugs indicated for CPP that are approved and marketed in the United States: LUPRON DEPOT PED (leuprolide), a monthly or every three months intramuscular injection (NDA# 020263, AbbVie); SUPRELIN LA (histrelin), a yearly subcutaneous implant (NDA# 22058, Endo Pharmaceuticals); and SYNAREL (nafarelin), a daily intra-nasal spray (NDA# 020109, Pfizer). Major safety concerns related to GnRH agonists as a class include injection site reactions, rare hypersensitivity reactions, side effects attributed to the drug's pharmacology (e.g., vaginal bleeding in girls), and side effects related to HPG axis suppression (e.g., hot flashes).

The applicant established the efficacy of TRIPDODUR for the treatment of CPP in a single arm, open-label, trial that enrolled 44 participants between 2 to 9 years of age with CPP. The 12-months study was well executed and had excellent follow-up (i.e., little to no missing information). The applicant demonstrated in this study that injection of TRIPTODUR at baseline resulted in normalization of abnormally high baseline GnRH stimulated LH levels[1] in the majority of patients at all time points examined [e.g., 93% of individuals (95% CI; 81-99%) at 24-weeks; the pre-specified primary time point]. The applicant also demonstrated through secondary analyses that non-stimulated circulating LH levels, follicle stimulating hormone (FSH) levels and circulating sex steroids levels (i.e., estradiol in girls and testosterone in boys) decreased from high baseline levels to age appropriate levels with treatment (i.e., two injections and 52 weeks of follow-up). Finally, treatment with TRIPTODUR induced changes in height velocity, bone age and secondary sexual characteristics that were consistent with pubertal arrest. In aggregate the applicant demonstrated that TRIPTODUR was effective at arresting puberty in a cohort of children with CPP. Pubertal arrest is expected to reduce psychosocial and physical complications of this disease and is an accepted surrogate of clinical benefit that supports the full approval of GnRH products for this indication.

The applicant adequately characterized the risks of TRIPTODUR in the intended use. The most common adverse reactions were injection site pain, menstrual bleeding, and an initial reversible increase in signs and symptoms of puberty due to the initial stimulatory effect on the HPG axis. Adverse reactions were comparable in nature and frequency to those observed in other CPP programs for long-acting GnRH agonists and no unique adverse reaction was identified with TRIPTODUR. Risks will be mitigated through labeling and will include risks detected in the post-market setting for other members of the class and attributed to the class of product as a whole. Dr. Zemsokova describes PMR studies in her memorandum.

Overall I agree that the applicant has established that the clinical benefits of TRIPTODUR for the treatment of CPP far outweigh the identified risks. The product belongs to a class of products with established effectiveness in this condition, no issues that would preclude approval in any disciplines review were identified and I therefore concur with the decision to recommend approval.

[1] LH≤ 5 IU/L 30 minutes after GnRH agonist stimulation with 20 µg/kg leuprolide acetate

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/s/

JEAN-MARC P GUETTIER
06/29/2017