Brief Therapeutic Update from PES Drugs and Therapeutics Committee

(VOXZOGO™)

VOXZOGO™ (vosoritide) is a biological analog of C-type natriuretic peptide (CNP), which stimulates cartilaginous bone growth via endochondral ossification. In achondroplasia, there is severe disproportionate short stature and failure to convert cartilage to bone caused by activating mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene (1). CNP counteracts negative growth effects of FGFR3 in the cellular signaling pathway of chondrocytes, increasing their proliferation (2), thus stimulating linear growth. On November 19, 2021, the FDA approved VOXZOGO™ for the treatment of children over five years of age with achondroplasia and open epiphyses to increase linear growth (3). The FDA approved VOXZOGO ™ under the accelerated pathway based on improved annualized growth velocity (AGV) and is contingent upon continued review and verification of clinical benefit in ongoing clinical trials (3).

VOXZOGO™ is administered as a daily subcutaneous injection at a dose of approximately 15 mcg/kg. The medication is packaged as a lyophilized powder in a single-dose vial at 0.4 mg, 0.56 mg, or 1.2 mg and requires reconstitution with a prefilled co-packed diluent delivered in a syringe (Sterile Water for Injection, USP) (3). The injection volume is based on both patient weight and concentration of reconstituted VOXZOGO™ (FDA Prescribing Information, Table 1) (3). VOXZOGO should be refrigerated but should be brought to room temperature before reconstitution. Once reconstituted, it can be held in the vial at temperatures of 20°C to 25°C (68°F to 77°F) for a maximum of 3 hours. Proper training by a medical professional on the preparation and administration of VOXZOGO™ is required. A missed dose can be administered up to 12 hours from the scheduled time, after which it is recommended to skip the dose and deliver the usual dose the next day (3). A transient decrease in blood pressure has been observed with VOXZOGO™ (see safety information below); to reduce the risk of low blood pressure, the patient needs to be well fed and hydrated (approximately 240-300 mL of fluid) an hour prior to administration of the medication (3).

The efficacy and safety of VOXZOGO™ was evaluated in a phase 3 randomized, double-blind, placebo-controlled, multicenter trial of 121 subjects age 5 to < 18 years with achondroplasia (mean [SD] age of 8.35 [2.43] and 9.06 [2.47] in vosoritide [15 mcg/kg] and placebo groups, respectively) (4). Out of 121 patients enrolled, 119 completed 52 weeks of treatment. The adjusted mean difference in AGV was 1.57 cm/year between vosoritide and placebo groups favoring the former (95% CI [1·22-1·93]; two-sided p<0·0001) at the end of 52 weeks (4). The height z-scores least-squares mean difference between vosoritide and placebo groups was 0.28 SD (95% CI, 0.17 – 0.39, p < 0.0001). There was no difference between the groups in body segment ratio and functional and quality of life assessments (*e.g*. the Pediatric Quality of Life Inventory, Quality of Life of Short Statured Youth tools, or functional independence) at 52 weeks (4). While vosoritide appeared to be an effective treatment to increase growth in children with achondroplasia, the effects on final adult height are not yet known.

In the pivotal phase 3 study, the most common adverse events observed were injection site reactions (85% in the treatment group compared to 82% in placebo), vomiting (27% vs 20%), arthralgia (15% vs 7%), and gastroenteritis (13% vs 8%) (3). Eight (13%) of 60 subjects in the VOXZOGO™ group had a total of 11 events of transient low blood pressure compared to 3 (5%) of 61 subjects in the placebo group (3,4). The median onset of low blood pressure from the injection was 31 minutes (18-120) with resolution on average within 31 minutes (5 to 90) (3). Two patients in the vosoritide group each had a symptomatic hypotension episode after an injection that was associated with vomiting and/or dizziness (3, 4). The events were reported to be transient and self-limiting. Subjects with significant cardiac or vascular disease and patients on anti-hypertensive meds were excluded from

clinical trials. There were nine serious AEs in seven patients: four patients in the placebo group and three patients in the vosoritide group (4). AEs in the vosoritide group included grade 3 influenza, radius fracture, and sleep apnea and grade 2 adenoidal hypertrophy (4). None of the serious AEs were considered to be treatment related. No anaphylaxis, deaths, AEs related to disproportionate skeletal growth, or clinically significant adverse cardiovascular effects were observed (4).

Recently, two-year data from the phase 3 extension study were published presenting efficacy and safety over 104 weeks (5). AGV in children on vosoritide increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at 104 weeks showing a sustained increase (5). In addition, patients who crossed over from placebo to vosoritide at 52 weeks showed an increase in AGV from 3.81 cm/year at week 52 to 5.43 cm/year at 104 weeks (a difference in LS mean change in height *Z*-score [95% CI] of 0.44 [0.25, 0.63]). After 2 years, the mean standard deviation change in bone age from baseline was 2.58 (1.33) years in males (*n* = 18) and 1.58 (1.42) years in females (*n* = 18), which was considered to be within normal range for progression over the 104-week period (5). There was a decrease in the upper-to-lower segment ratio in the vosoritide group at 104 weeks (LS mean change from baseline [95% CI] was −0.05 [−0.09, −0.01]). The authors reported no new adverse effects of vosoritide (5).

REFERENCES:

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Prepared on behalf of PES Drugs and Therapeutics Committee by,
Anna Ryabets-Lienhard, DO

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