NCPE Technical Summary

Vosoritide (Voxzogo®)

HTA ID: 22028

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Applicant: BioMarin International Ltd

Vosoritide for the treatment of achondroplasia in patients aged two years and older whose epiphyses are not closed.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of vosoritide (Voxzogo®). Following assessment of the Applicant's submission, the NCPE recommends that vosoritide (Voxogo®) not be considered for reimbursement.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (BioMarin International Ltd) Health Technology Assessment of vosoritide (Voxzogo®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In March 2023, Biomarin International Limited submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of vosoritide for the treatment of achondroplasia in patients aged two years and older whose epiphyses are not closed. Reimbursement is sought under the High Tech Drug Arrangement.

Although achondroplasia is an autosomal dominant condition approximately 80% of cases occur sporadically. Clinical features of achondroplasia include disproportionate short stature, rhizomelic shortening of the limbs, macrocephaly with frontal bossing, a smaller than average chest, thoracolumbar kyphosis, lumbar lordosis, hypermobile joints but limited extension and rotation of the elbow and hip, tibial bowing and brachydactyly. Diagnosis is based on clinical and radiographic examination and is confirmed by a molecular genetic test for heterozygous, gain-of-function mutations in the fibroblast growth factor receptor 3 gene (FGFR3) that leads to impaired endochondral ossification.

Vosoritide is a modified type C natriuretic peptide (CNP). Binding of vosoritide to natriuretic peptide receptor-B (NPR-B) antagonises FGFR3 downstream signalling by inhibiting the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the mitogen-activated protein kinase (MAPK) pathway at the level of rapidly accelerating fibrosarcoma serine/threonine protein kinase (RAF-1). As a result, vosoritide, like CNP, acts as a positive regulator of endochondral bone growth as it promotes chondrocyte proliferation and differentiation.

The pharmaceutical formulation is a lyophilised, preservative free, white-to-yellow powder for reconstitution with sterile water for injection. Each pack contains 10 powder vials (0.4, 0.56 or 1.2mg), 10 syringes with solvent (0.5, 0.7 or 0.6ml), 10 single use needles and 10 single use syringes. The usual dose of vosoritide is 15µg/kg body weight administered as a once daily subcutaneous injection. Treatment is stopped when there is no further growth potential, indicated by a growth velocity less than 1.5 cm per year and closure of epiphyses.

The only relevant comparator is current standard of care (SoC) which is assumed to follow the international consensus on the management of achondroplasia. The manufacturer anticipates that vosoritide will be first-line therapy for achondroplasia as it is the only licensed therapy that directly targets the underlying cause. It will be administered along with other medications and/or surgical procedures which aim to alleviate symptoms and comorbidities.

1. Comparative effectiveness of vosoritide (Voxzogo®)

The submitted dossier presents information relating to seven clinical trials and three natural history studies. The pivotal clinical trial was study 111-301 which was a randomised, double-blind, phase 3, placebo-controlled, multicentre trial which compared vosoritide with placebo in children with achondroplasia. Eligible patients had a clinical diagnosis confirmed by genetic testing, were ambulatory, had participated for 6 months in a baseline growth study and were aged 5 years to less than 18 years at enrolment. Participants received either vosoritide 15µg/kg or placebo administered by daily subcutaneous injection for a duration of 52 weeks. The primary endpoint was change from baseline in mean annualised growth velocity at 52 weeks. Of the 124 patients screened for eligibility, 121 were randomly assigned with 60 patients in the vosoritide group and 61 patients in the placebo group. The adjusted mean difference in annualised growth velocity between patients in the vosoritide group and the placebo group was 1.57 cm per year in favour of vosoritide (95% confidence interval (CI) [1.22 – 1.93]; two-sided $p < 0.0001$). Key secondary endpoints including height z-score and standing and sitting height were significantly improved with vosoritide as compared with placebo. There was no significant difference in quality of life between the treatment groups. None of the serious adverse events recorded were considered to be treatment related and no deaths occurred.

Study 111-302 is a phase 3 open-label, multicentre, long term extension of Study 111-301. After completion of the placebo-controlled study, 119 children (n=58 from the vosoritide arm and n=61 from the placebo arm) were enrolled into the extension study, where all participants received vosoritide 15µg/kg/day. The data cut for the interim study report was 2/11/2020 when all participants completed one year of follow up in the extension study (which was 104 weeks from baseline in study 111-301). In children randomised to vosoritide annualized growth velocity increased from 4.26 cm per year at baseline to 5.39 cm per year at 52 weeks (in study 111-301) and 5.52 cm per year at week 104 (after 52 weeks in the extension study). In children who crossed over from placebo to vosoritide in the extension study annualised growth velocity increased from 3.81 cm per year at week 52 to 5.43 cm per year at week 104. The improvement in height z-score observed at year 1 of vosoritide continued at year 2. No new adverse effects of vosoritide were reported. The latest interim data cut from study 111-302 on the 25/2/2022 demonstrated that the effect on growth observed in the first year of treatment with vosoritide was maintained at 3 years of treatment (mean annualised growth velocity 5.57 cm per year, mean change from baseline 1.31 cm per year) and 3.5 years of treatment (mean annualised growth velocity 5.45 cm per year, mean change from baseline

1.19 cm per year).

Supporting data was provided by three phase two studies including studies 111-202, 111-206 and 111-209 in addition to two ongoing extension studies of 111-202 and 111-206. The durability of vosoritide's treatment effect was assessed by comparing the results from the clinical extension trials against data integrated from natural history data sources. Four natural history data sources were utilised including the achondroplasia natural history multicentre clinical study (AchNH) which was defined as the primary natural history source, based on its large size (1,374 patients enrolled) and completeness of data. Natural history studies 111-901, LIAISE and KAISER were used as supportive studies to demonstrate consistency of results. The results of the pre-specified primary analysis demonstrated a statistically significant difference in height (9.08 cm) between the two groups at year 5 in favour of vosoritide. This was supported by analysis based on the other natural history studies.

2. Safety of vosoritide (Voxzogo®)

Adverse reactions that were common across the clinical trial programme included syncope, pre-syncope, dizziness, nausea, fatigue and a raised alkaline phosphatase. Very common adverse events included hypotension, vomiting and injection site reactions. The pivotal phase 3 trial reported that most adverse events were mild with no new safety findings. Injection site reactions were most commonly reported and were non-serious and transient. No clinically significant cardiovascular changes were observed however post-dose decreases in diastolic blood pressure were more frequent with vosoritide. None of the serious adverse events (influenza, radial fracture, adenoidal hypertrophy and sleep apnoea syndrome) were considered drug related in the pivotal trial. Serum total antidrug antibody titres were detected in 42% of patients but no neutralising antibodies were detected. Vosoritide was generally well tolerated in the remaining clinical trials and no new safety concerns were noted.

3. Cost effectiveness of vosoritide (Voxzogo®)

Methods

The economic evaluation was undertaken using an individual simulation model, which captured the impact of reduced stature on quality of life and the incidence of complications related to achondroplasia over the lifetime of the patient. The evaluation considered costs falling on the health care sector for treatment with vosoritide and for the management of complications associated with achondroplasia that are mitigated through vosoritide therapy. The population considered in the base case analysis were children aged between 2 years and 15 years with genetically confirmed achondroplasia whose epiphyses remain open (growth has not ended). The intervention was

vosoritide 15µg/kg administered subcutaneously once daily. The model assumed that all children ceased treatment at the age of 16 years and that 0.86% discontinued treatment each year, based on the pivotal phase 3 clinical trial. The comparator was the current standard of care. The model was run for 1,000 patients and averaged the costs and benefits across simulations on and off treatment to determine incremental costs and outcomes to generate an incremental cost-effectiveness ratio (ICER). The time cycle was one year and half-cycle correction was not applied. The annual risk of complications was a function of patient age and the percentage of average stature height achieved in each cycle. Where clinically appropriate, complications may increase the risk of mortality which was captured by applying a risk ratio to general mortality. The model considered the incidence of complications associated with achondroplasia and the primary source of data was the Lifetime Impact of Achondroplasia Study in Europe (LIAISE) study. Results in the base case represented the perspective of the Health Service Executive (HSE).

The impact of treatment with vosoritide was modelled as an increase in annualised growth velocity for each year the patient received treatment. Data on the effectiveness of vosoritide in restoring annualised growth velocity was taken from the pivotal clinical trial study 111-301. The impact of treatment was assumed to be maintained until cessation of natural growth and the increase in bone growth attributable to vosoritide was assumed to reduce the likelihood of complications arising from achondroplasia. Resource usage and costs considered in the model included drug treatment costs, healthcare resource use costs, one-off costs for interventions and ongoing costs for management of complications. A discount rate of 4% was applied to costs and quality adjusted life-years (QALYs) in line with current guidelines.

The NCPE Review Group had major concerns in relation to the assumption that the increase in bone growth attributable to vosoritide will reduce the likelihood of complications, including mortality arising from achondroplasia. The NCPE Review Group concluded:

- There was no clinical evidence to support the assumption that vosoritide is efficacious in treating any of the 13 conditions associated with achondroplasia that are mentioned in the submission e.g. foramen magnum stenosis, spinal stenosis, genu varum etc.
- There was no clinical evidence to demonstrate the efficacy of vosoritide in reducing neurological manifestations of achondroplasia in infants up to 2 years of age.
- There was no clinical evidence to support the efficacy of vosoritide in treating complications that may occur in children aged 2 to 4 years with achondroplasia including upper airway obstruction, sleep breathing disorders, obstructive sleep apnoea, hearing

impairments and difficulties with speech.

- There was no evidence to demonstrate that vosoritide reduces the requirement for surgery to prevent the impact of upper airway obstruction in children with achondroplasia.
- There was no evidence to demonstrate the ability of vosoritide to reduce sudden death in children with achondroplasia.
- Vosoritide has not been shown to impact life expectancy in patients with achondroplasia.

Results

For the treatment of achondroplasia the base-case (deterministic) incremental cost-effectiveness ratio (ICER) for vosoritide versus standard of care (SoC) was estimated at €431,228/QALY. An analysis of costs and QALYs is shown in table 1.

Table 1. Cost-effectiveness of vosoritide for the treatment of achondroplasia versus SoC.

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Vosoritide	€1,889,756	14.827			
Standard of care (SoC)	€37,428	10.531	€1,852,328	4.295	431,228

ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year
Figures in the table are rounded, and so calculations may not be directly replicable. Costs and QALY are discounted at 4%.

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in which all parameters were assigned distributions and varied jointly. A total of 1,000 Monte Carlo simulations were recorded. The ICER for vosoritide versus standard of care was estimated at €429,810/QALY which is consistent with the deterministic ICER of €431,228/QALY. The probability of vosoritide being cost-effective at the €45,000/QALY threshold was 0%.

The most important parameters that impacted the cost-effectiveness of vosoritide versus standard of care included: discounting of costs and outcomes, caregiver utility from vosoritide therapy, probability of cardiovascular disease in achondroplasia and utility weight for pain.

4. Budget impact of vosoritide (Voxzogo®)

The price to wholesaler of vosoritide for a pack size of 10 syringes is €4,930.75. The total cost per patient per year including wholesale mark-up, rebates and pharmacy fees excluding VAT is

€180,389.69. When VAT is included the total cost per patient per year is €225,125.43. The number of patients eligible for treatment ranged from 32 to 34 per annum and based on a proposed market share the 5 year gross drug budget impact was estimated at €23.36 million. The NCPE review group considered this an underestimate and a revised 5 year gross drug budget impact was €27.14 million. The net drug budget impact was considered equal to the gross drug budget impact.

5. Patient Organisation Submission

A patient organisation submission, from Little People of Ireland, was received during the course of the assessment. This will be provided to the HSE.

6. Conclusion

Due to the paucity of clinical outcome data, the very high cost and budget impact in addition to the failure to demonstrate cost-effectiveness the NCPE Review Group recommend that vosoritide not be considered for reimbursement*

*This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.