Conitec

Recomendation report

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Vestronidase alfa for the treatment of mucopolysaccharidosis type VII

Brasília – DF
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Technology: Vestronidase alfa (Mepsevii®).

Indication: Vestronidase alfa is approved for the treatment of adults and children of all ages with mucopolysaccharidosis VII (also called Sly syndrome).

Applicant: Ultragenyx Brasil Farmacêutica Ltda.® (Brazil).

Background: Mucopolysaccharidosis VII is a genetic lysosomal storage disorder caused by a deficiency of the β-glucuronidase, an enzyme that plays an essential role in the breakdown of specific glycosaminoglycans that are part of the connective tissue, namely chondroitin sulfate, dermatan sulfate, and heparan sulfate. From the pathophysiological point of view, there is an accumulation of these substrates in tissues and organs causing a variety of clinical presentations with a wide range of manifestations, including abnormalities in the musculoskeletal, cardiovascular, respiratory and neurological systems. The natural history of this disease is not well known; patients may present with skeletal deformities, limited mobility, impaired fine and gross motor coordination, cardiomyopathy and valvular disease, breathing difficulties, cognitive limitations and intellectual disability.

Question: "Is vestronidase alfa effective and safe as an enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis VII (Sly syndrome)"?

Scientific evidence: The enzyme replacement therapy with vestronidase alfa has been associated with a rapid and sustained reduction in urinary glycosaminoglycans, showing, from a pharmacodynamic point of view, a mechanism of action consistent with the pathophysiology of mucopolysaccharidosis type VII. A study assessed its efficacy using a multi-domain responder index (MDRI), combining six clinically relevant endpoints in the context of treatment. The MDRI had an overall mean change (±SD) of +0.5 (±0.8) at treatment week 24 ($p = 0.0527$), with statistical difference between baseline and after 24 weeks (interindividual). A modified MDRI adding fatigue had a mean change (±SD) of +0.8 (±0.94) at treatment week 24 ($p = 0.01$). These positive mean changes demonstrated overall improvement in the six domains assessed. Notably, the efficacy of enzyme replacement therapy was demonstrated by a clinically significant improvement in six-minute walk test distance, an improvement in pulmonary function with a 21% increase in the forced vital capacity test in one of the patients participating in the study, and reduction in the need for respiratory support in some of them. Moreover, some patients had a clinically significant improvement in fatigue scores, with reports of increased school attendance and normalization of eating habits.

Economic evaluation: The applicant submitted a cost per outcome analysis presenting ratios between the mean changes in the multi-domain responder index (+0.5) and and in the multi-domain responder index including fatigue total score (+0.8) at treatment week 24, and the cost of treatment with vestronidase alfa. Economic models were not submitted. Moreover, the impacts of the use of vestronidase alfa on outcomes and health costs considering the natural history of mucopolysaccharidosis type VII were not presented. The ratios were estimated to be BRL 3,141,796.90 per unit of therapeutic benefit gained, and BRL 1,963,623.06 per unit of therapeutic benefit gained including change in fatigue score. However, as the applicant did not submit an economic model, it was not clear if these were incremental cost-effectiveness ratios.

Budget impact analysis: The applicant submitted a budget impact analysis over a five-year time horizon from the perspective of the Brazilian Public Health System (SUS). The number of patients eligible for treatment was estimated based on epidemiological information from a study in Brazil, ranging from 28 in 2020 to 31 in 2024. The costs were limited to the purchase price of medicines. Therefore, the budget impact of incorporating vestronidase alfa, in the scope of SUS, was estimated to be BRL 467 million in five

years, with average annual costs of BRL 93 million, assuming an initial market share of 80%, reaching 95% in 2024.

International recommendations: Vestronidase alfa has not been evaluated by the main international health technology assessment agencies.

Technology horizon scanning: Alternative drugs as a substitute to enzyme replacement therapy with vestronidase alfa for mucopolysaccharidosis type VII were not identified.

Considerations: Mucopolysaccharidosis type VII is a progressive disease, so the efficacy of enzyme replacement therapy with vestronidase alfa was demonstrated by a clinically significant improvement in some patients participating in the study, such as: increase in six-minute walk test distance (> 23 meters and 10% change from baseline); better pulmonary function, including a 21% increase in the forced vital capacity test; , and reduction in the need for respiratory support after 164 weeks of treatment; and improved gross motor coordination compared to baseline. From a pharmacodynamic point of view, the rapid and sustained reduction in urinary chondroitin and dermatan sulfate represents additional information that reinforces the activity of the enzyme, although the clinical relevance of this biochemical feature remains to be established. Vestronidase alfa is considered safe, and the anaphylactoid reactions reported in some cases can be avoided by controlling the infusion time and using appropriate medications.

Initial Recommendation: The members of CONITEC's plenary session present at the 85th Ordinary Meeting, on February 4th, 2020, decided that the subject matter should be made available in a public consultation with a preliminary recommendation against the incorporation of vestronidase alfa for mucopolysaccharidosis type VII, in the scope of SUS. It has not been on the market long enough and clinical experience is still limited. Moreover, the budget impact of incorporating enzyme replacement therapy with vestronidase alfa was considered to be significant at BRL 3 million per patient per year.

Public consultation: The Public Consultation No. 03/2020 was held from February 21st to March 17th, 2020. A total of 83 contributions were received, of which 13 were technical-scientific contributions, and 70 were experience or opinion contributions, and the majority disagreed with CONITEC's preliminary recommendation. The main evidence submitted was the extension of the observational study by Harmatz and colleagues (2020), yet to be published at the time of the writing of this report. The primary endpoint of this study was assessment of safety. Following a group of 12 patients for three years, enzyme replacement therapy with vestronidase alfa was shown to reduced urinary glycosaminoglycans excretion, and this reduction was maintained over the follow-up period. At the end of the study, there were results available for four of the 12 patients who started follow-up. Some patients also showed sustained improvement in the multi-domain responder index, used to assess the clinical progression of the disease. Regarding the economic evaluation, no cost-effectiveness analysis or other type of model indicated in the Methodological Guidelines of the Ministry of Health of Brazil was submitted, but only a cost per outcome analysis. As for the budget impact analysis, several methodological aspects were considered to be overestimated, such as the average weight of patients, the rate of technology absorption by SUS, and the number of patients, suggesting that the estimated budget impact would be overestimated by about 50%. The experience or opinion contributions were consistent with the technical contributions, reinforcing that the average weight and the number of patients in Brazil eligible for treatment would be overestimated.

Final Recommendation: CONITEC, at its 88th Ordinary Meeting, on July 7th, 2020, after analysing the contributions received in the Public Consultation, considered that there was sufficient reason to change the preliminary recommendation against the incorporation of vestronidase alfa, and decided to make a final recommendation in favour. These contributions highlighted the evidence on long-term safety and effectiveness of enzyme replacement therapy with vestronidase alfa, similar to those therapies evaluated for other mucopolysaccharidoses. Moreover, a reduction in the budget impact could be expected

according to studies and expert opinions showing that the average weight and number of patients in Brazil would be lower than those previously presented in the dossier submitted by the applicant. Therefore, CONITEC's plenary session recommended the incorporation of vestronidase alfa for the treatment of mucopolysaccharidosis type VII, subject to evaluation of effectiveness, reassessment by CONITEC after three years, and development of a Clinical Protocol and Therapeutic Guidelines. The Deliberation Record No. 532/2020 was signed.

Decision: To incorporate vestronidase alfa for the treatment of mucopolysaccharidosis type VII, subject to outcome monitoring, reassessment by CONITEC after three years of use, and development of a Clinical Protocol and Therapeutic Guidelines of the Ministry of Health of Brazil, in the scope of SUS, according to Ordinance No. 26, published in the Official Gazette of the Federal Executive No. 153, Section 1, page 40, on August 11th, 2020.