HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

07 OCTOBER 2020

The legally binding text is the original French opinion version

Somatropin

NORDITROPIN FLEXPRO 5 - 10 - 15 mg / 1.5 ml solution for injection
NORDITROPIN SIMPLEXX 5 - 10 - 15 mg / 1.5 ml solution for injection
NORDITROPIN NORDIFLEX 5 - 10 - 15 mg / 1.5 ml solution for injection

New indication

Key points

Favourable opinion for reimbursement only in children with Noonan syndrome with growth retardation defined by a current height < -2 SDS.

What therapeutic improvement ?

No clinical added value in the therapeutic strategy.

Role in the care pathway ?

The management of patients with Noonan syndrome is symptomatic and multidisciplinary. Its objective is to ensure the early diagnosis and treatment of the various associated abnormalities and medical complications: heart conditions and arrhythmias, undernutrition and delayed growth, neurosensory abnormalities and cognitive difficulties, orthopaedic abnormalities, etc. Patient education and specialised medical follow-up are essential in these patients.

The aim of treatment for growth retardation is, firstly, to normalise height during childhood and, secondly, to normalise height during adulthood. Growth hormone treatment may be envisaged in the absence of hormone deficiency to promote short and long-term growth.

At present, several proprietary medicinal products exist containing somatropin: GENOTONORM, NUTROPINAQ, OMNITROPE, UMATROPE, SAIZEN, NORDITROPIN and ZOMACTON; but only NORDITROPIN has an MA in the treatment of growth retardation due to Noonan syndrome. Regular follow-up of growth and skeletal development should be conducted every six months during the growth phase.

Role of the medicinal product in the care pathway

NORDITROPIN (somatropin) is a first-line treatment that should be reserved for children with Noonan syndrome with growth retardation defined by a current height < -2 SDS according to general population growth charts. It is the only somatropin-based medicinal product to have an MA in this indication in France.

In these patients, the Committee recommends initiating treatment with NORDITROPIN :

- **following the resolution of eating disorders, associated or otherwise with inadequate weight gain, in a context in which these disorders are common before the age of 2 years and the clinical data assessing the efficacy and safety of somatropin concern prepubertal children aged at least 3 years ;**
- **after having established a genetic diagnosis, enabling optimised treatment of Noonan syndrome ;**
- **at the lowest dose in the SPC, i.e., 0.033 mg/kg/day. The dosage must be tailored to each patient and may be adjusted every 6 months on the basis of the clinical response (growth rate and height) and tolerance to treatment, via monitoring of IGF-1 levels.**

Furthermore, considering the complexity of treatment of this disease and the risks associated with the administration of this medicinal product, the Committee recommends that the prescription of NORDITROPIN (somatropin) be reserved for specialists in growth retardation (paediatric endocrinologists) and that follow-up of these patients be coordinated by reference or expertise centres in this disease.

In accordance with its SPC, treatment with NORDITROPIN (somatropin) should be discontinued at the time of closure of the epiphyseal growth plates.

The Committee reiterates that the long-term effects of somatropin are not known (maximum follow-up of 4 years of treatment in a clinical study, few data on adult height).

Special recommendations

The Transparency Committee would prefer this proprietary medicinal product to retain exception drug status. Consequently, it reiterates the importance of compliance with the recommendations in the therapeutic information sheet (TIS) for the prescription of NORDITROPIN (somatropin) in all its indications.

It recommends that :

- the prescription of NORDITROPIN (somatropin) be reserved for specialists in growth retardation (paediatric endocrinologists) and that follow-up of these patients be coordinated by reference or expertise centres in this disease, due to the complexity of management of this disease and the risks associated with the administration of this medicinal product and,
- that genetic confirmation of diagnosis of Noonan syndrome be conducted before the initiation of growth hormone treatment in order to optimise management of these patients.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Growth retardation due to Noonan disease is a serious condition, progressing to disability and a marked deterioration in quality of life.

◗ NORDITROPIN (somatropin) is a curative treatment for growth retardation, as part of a comprehensive treatment programme for Noonan disease.

◗ The efficacy of NORDITROPIN (somatropin) in terms of improvement in growth has been demonstrated in the medium term in children with Noonan syndrome in a randomised controlled study (GHLIQUID-4020), and suggested in a follow-up study (GHNOO-1658) and two observational studies.
However, in the absence of robust clinical data, there are uncertainties with respect to the efficacy of NORDITROPIN (somatropin) on adult height and its long-term safety (in particular in terms of tumour risk, blood glucose balance and cardiovascular risk). In addition, no data are available to date concerning the quality of life of patients, an endpoint judged to be relevant in this disease.
Hence, the efficacy/adverse effects ratio of NORDITROPIN (somatropin) in this indication is substantial in the medium term and inadequately established in the long term.

◗ There are therapeutic alternatives corresponding to the proprietary medicinal products containing somatropin that can be used off-label (see chapter 05 Clinically relevant comparators).

◗ NORDITROPIN (somatropin) is a first-line treatment that should be reserved for children with Noonan syndrome with growth retardation defined by a current height < -2 SDS according to general population growth charts.
It is the only somatropin-based medicinal product to have an MA in this indication in France.

◗ **<u>Public health impact</u> :**

Considering :

- the seriousness of the disease, with an impact on patients' quality of life, in particular,
- its low incidence (1/1,000 to 1/2,500 births),
- the partially met medical need,
- the absence of clinical data on morbidity or mortality or quality of life,
- the partial response to the identified need, given its demonstrated efficacy in terms of height improvement in the medium term in treated children, but the absence of data concerning its longer-term efficacy and safety,

NORDITROPIN (somatropin) proprietary medicinal products are unlikely to have an impact on public health.

Given all these elements, the Committee deems that the clinical benefit of NORDITROPIN (somatropin) is substantial only in children with Noonan syndrome with growth retardation defined by a current height < -2 SDS.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only in children with Noonan syndrome with growth retardation defined by a current height < -2 SDS.

Clinical Added Value

Considering :

- **the demonstrated efficacy of NORDITROPIN (somatropin) on growth in the medium term (4 years) with an effect size of between +0.85 and +1.84 SDS (i.e., 5 to 10 cm) in children treated for Noonan syndrome in a phase III study comparing 2 doses of somatropin (GHLIQUID-4020),**
- **and despite :**
  - **uncertainties with respect to the efficacy of NORDITROPIN on adult height and its long-term safety (in particular in terms of tumour risk, blood glucose balance and cardiovascular risk) in this indication and,**
  - **the absence of quality of life data, a relevant clinical endpoint in this disease,**

the Committee considers that NORDITROPIN (somatropin) proprietary medicinal products provide no clinical added value (CAV V) in the care pathway for growth retardation due to Noonan syndrome.