Glycopyrronium bromide (Sialanar®) for the symptomatic treatment of severe sialorrhoea

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 9 April 2019

Zorginstituut Nederland carried out an assessment of the medicinal product glycopyrronium bromide (Sialanar®) and came to the following conclusion.

In a letter dated 21 January 2019 (CIBG-19-07506), the Ministry of Health, Welfare and Sport (VWS) asked *Zorginstituut Nederland* to assess whether the product glycopyrronium bromide (Sialanar®) is interchangeable with any product included in the insured package. *Zorginstituut Nederland* has completed its assessment.

Registered indication

The full registered indication for glycopyrronium bromide (Sialanar®) is:
The symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and infants aged 3 years and older with chronic neurological disorders.
Glycopyrronium bromide is available as a drink for oral use. Every ml contains 400 microgram glycopyrronium bromide (equivalent to 320 microgram glycopyrronium). The starting dose is 12.8 microgram/kg per dose, three times a day, increasing every 7 days to a maximum of 64 microgram/kg or 6 ml three times a day. Glycopyrronium bromide is generally given for short-term use (< 24 weeks).

Background

Sialorrhoea is described as the involuntary loss of saliva from the mouth. This is normal in growing children from 18 months. After the age of 4 years, continued drooling is regarded as pathological. Patients with severe sialorrhoea are currently treated, if medicinal therapy is being considered, with glycopyrronium bromide in the form of a pharmacy preparation. These are children with chronic neurological disorders (mainly cerebral palsy). Based on national and international literature and the manual of the Dutch Association of Paediatrics, glycopyrronium bromide is the preferred choice for patients with severe sialorrhoea, if medicinal therapy is being considered.
Glycopyrronium bromide (Sialanar®) is registered based on *well-established use*. When *well-established use* is being assessed, the applicant does not have to submit new clinical research to the registration authority (EMA). Where new clinical research is lacking, the registration authority uses available scientific literature and current European treatment guidelines for the assessment. The registration of Sialanar® is based mainly on two randomised, placebo-controlled studies in which Sialanar® itself was not studied.

GVS assessment

The manufacturer of glycopyrronium bromide (Sialanar®) has asked for its inclusion on List 1B of the Health Insurance Decree (Rzv).
Zorginstituut Nederland concludes that no other products in the GVS are eligible to assess the interchangeability with glycopyrronium bromide (Sialanar®). Therefore, Sialanar® is not interchangeable with any other products included in the GVS. Additionally, we examined whether this medicinal product is eligible for List 1B.

The scientific basis for assessing the therapeutic value is limited. Despite these limitations, the EMA gave approval . *Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Sialanar in the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions: Conditions or restrictions regarding supply and use, Periodic Safety Update Reports, conditions or restrictions with regard to the safe and effective use of the medicinal product and additional risk minimisation measures.*
Despite the limited data, the *Zorginstituut* concludes that the use of the substance glycopyrronium bromide on patients with severe sialorrhoea can be considered as *well-established use* of a known substance. In comparison with placebo, the use of glycopyrronium bromide reduced sialorrhea. Unfavourable effects – mainly related to its anticholinergic mechanism of action – were also more prevalent, though generally not severe. An optimal balance should be obtained, by means of dose titration, between favourable and unfavourable effects.
In principle, based on the above-mentioned considerations, glycopyrronium bromide (Sialanar®) is eligible for inclusion on List 1B.

Other considerations

- Sialanar® in the form of a pharmacy preparation has been used for severe sialorrhoea for a long time. Health insurers have been reimbursing this pharmacy preparation. Glycopyrronium bromide (Sialanar®) was recently registered for this indication.
- In the Netherlands, patients generally start with speech therapy and behavioural therapy, followed by botulin toxin injections. If anticholinergic medication is chosen, then the possibilities include glycopyrronium bromide, scopolamine, trihexyphenidyl or atropine. Based on national and international literature and the guidelines of the Dutch Association of Paediatrics, the preferred choice is glycopyrronium bromide.
- Despite limited clinical data, the registration authority arrived at a positive assessment after receiving additional information from the applicant and after the applicant made changes in the SmPC.
- As we mentioned in our letter dated 21 December 2015 regarding 6-tioguanine (Thiosix®), the EMA wants to minimise off-label use, and from this perspective, they appreciate the initiative to register medicines for the indication concerned. The question is whether it would be realistic to demand controlled research for an application such as this, which arose in clinical practice. On the other hand, by approving this use based on relatively few clinical studies, the EMA could be setting a precedent, and this would be extremely undesirable. The EMA continues to prefer controlled clinical research. The *Zorginstituut* agrees with these considerations.

Budget impact analysis

Taking into account the estimated numbers of patients, the estimated dose, duration of treatment and the total costs of the pharmacy preparation, including glycopyrronium bromide (Sialanar®) for symptomatic sialorrhoea on List 1B of the GVS will be accompanied by additional costs to the pharmacy budget of between €0.7 million and €2.2 million. Uncertainty exists about the number of patients who will be treated with Sialanar® and the total costs of the current pharmacy

preparation.
Advice
Based on the criteria for interchangeability, glycopyrronium bromide (Sialanar®) is not eligible for inclusion on List 1A. Glycopyrronium bromide (Sialanar®) is registered on the basis of *well-established use*. In principle, based on the above-mentioned consideration, glycopyrronium bromide (Sialanar®) is eligible for inclusion on List 1B. Inclusion on List 1B will be accompanied by additional costs to the pharmacy budget of between €0.7 and €2.2 million.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.