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**National Health Care Institute**
Care
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**Contact**
Ms M.J.S. de Vries
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**Our reference**
2023032734

Date 22 August 2023
Re: GVS advice oromucosal midazolam (Midazolam Xiromed®)

Dear Mr Kuipers,

In your letter of 26 June 2023 (CIBG-23-05676), the Minister of Health, Welfare and Sport requested the National Health Care Institute to assess whether the medicinal product midazolam (Midazolam Xiromed®) is interchangeable with a product that is included in the Medicine Reimbursement System (GVS). The National Health Care Institute has now completed this substantive assessment. The considerations are included in the GVS report attached to this letter.

Oromucosal midazolam (Midazolam Xiromed®) is registered for the treatment of protracted, acute convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years).

Midazolam (Midazolam Xiromed®) oromucosal solution is available in four different pre-filled syringes (2.5 mg, 5 mg, 7.5 mg and 10 mg). The recommended standard dose of oromucosal midazolam is age-dependent (see table 1).

Table 1. Standard doses per age group.

| Age range | Dose |
|---|---|
| 3 to 6 months in a hospital | 2.5 mg |
| 6 months to <1 year | 2.5 mg |
| 1 year to <5 years | 5 mg |
| 5 years to <10 years | 7.5 mg |
| 10 years to <18 years | 10 mg |

The market authorisation holder is asking for inclusion on List 1B of the Health Insurance Regulation.

**Outcome of the substantive assessment**
*Assessment of interchangeability*
Based on the criteria for interchangeability, oromucosal midazolam is not interchangeable with other medicinal products included in the GVS. Based on this, oromucosal midazolam cannot be placed on List 1A. Next, the National Health Care Institute assessed whether oromucosal midazolam is eligible for inclusion on

List 1B.

*Therapeutic value*
Reimbursement is requested for the treatment of protracted, acute convulsive seizures in the age groups from 6 months to <18 years. Infants between 3 – 6 months are excluded from the reimbursement request because these patients are treated in a hospital where monitoring is possible and resuscitation equipment is available.

If a convulsive status epilepticus lasts longer than 5 minutes, medication should be administered to stop the seizure. The first choice is oromucosal or nasal midazolam. Intramuscular midazolam and rectal diazepam are equivalent alternatives.[6]

In the Netherlands, the oromucosal form of administration of midazolam (Buccolam®) is not available (but is registered). Currently, midazolam can be used via the oromucosal route by withdrawing the appropriate dose from an ampoule for subcutaneous or intravenous use. Pharmacy preparations of disposable syringes for oromucosal use of midazolam also exist. In addition, correspondence with a number of (paediatric) neurologists has shown that the midazolam nasal spray is sometimes used orally. The marketing authorisation holder indicates that Midazolam Xiromed® is to be introduced to replace the pharmacy preparation of the oromucosal midazolam.

A direct comparison of buccal midazolam versus rectal diazepam shows that buccal midazolam is more effective than rectal diazepam in stopping the convulsion within 5 minutes. Based on an indirect comparison, there do not appear to be any major differences between oromucosal/buccal midazolam and nasal midazolam in stopping a protracted acute convulsion in children. This is in line with the expectation. It is the same active ingredient. Also, the incidence of severe adverse effects, especially respiratory depression, does not appear to differ between the two medicinal products, bearing in mind that the occurrence of these severe adverse effects is rare.

Based on the data, the National Health Care Institute concludes that oromucosal midazolam (Midazolam Xiromed®) for the treatment of protracted, acute convulsive seizures in infants, toddlers, children and adolescents (from 6 months to < 18 years) meets the established medical science and medical practice. Oromucosal midazolam is therefore eligible for inclusion on List 1B.

*Budget impact analysis*
Taking into account patient numbers, number of convulsions per patient and assumed market penetration, the inclusion on GVS list 1B of midozalam (Midozalam Xiromed®) for the treatment of protracted, acute convulsive seizures in infants, toddlers, children and adolescents (6 months to <18 years) will result in savings for the pharmaceutical budget of €-27,567 in year 3. In particular, there is uncertainty about the number of convulsions per year and the market penetration.

**Advice**
Based on the above, we advise that you include midazolam (Midazolam Xiromed®) in List 1B.

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22 August 2023

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Yours sincerely,

Sjaak Wijma
*Chairperson of the Executive Board*

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