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National Health Care Institute
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Our reference
2022042437

Date 29 November 2022
Subject GVS advice doxylamine succinate/pyridoxine hydrochloride (Xonvea®)

Dear Mr Kuipers,

In your letter of 3 May 2022 (CIBG-22-03786), you requested the National Health Care Institute to carry out a substantive review of whether doxylamine succinate/pyridoxine hydrochloride (Xonvea®) is interchangeable with a product that is included in the Medicine Reimbursement System (GVS). The National Health Care Institute has now completed the substantive assessment. The considerations are included in the pharmaco-therapeutic report attached to this letter.

Doxylamine succinate/pyridoxine hydrochloride is indicated for the treatment of nausea and vomiting during pregnancy in women who do not respond to conservative management. The recommended starting dose is two tablets before bedtime. If this dose adequately controls the symptoms the next day, the patient may continue to take two tablets before bedtime. Guided by the symptoms, the dose can be increased to four tablets per day.

The marketing authorisation holder is asking for doxylamine succinate/pyridoxine hydrochloride to be included on List 1B of the Health Insurance Regulation.

Outcome of the substantive assessment
Therapeutic value conclusion
The treatment with doxylamine succinate/pyridoxine hydrochloride in the above indication has been studied in a randomized double-blind placebo-controlled study. The results of this study show that doxylamine succinate/pyridoxine hydrochloride compared to placebo after 15 days of treatment probably does not have a clinically relevant effect on the relevant outcome parameters. The National Health Care Institute, advised by its Scientific Advisory Board (WAR), concluded that doxylamine succinate/pyridoxine hydrochloride *does not* meet the criterion of established medical science and medical practice for nausea and vomiting during pregnancy in women who do not respond to conservative management.
The available data, although sufficient for market registration, does not show a clinically relevant difference and therefore no positive decision can be made regarding inclusion in the health insurance package.

Context of the assessment

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Doxylamine succinate/pyridoxine hydrochloride is currently not included in Dutch guidelines. The Dutch Society for Obstetrics and Gynaecology (NVOG) advises meclozine/pyridoxine (Emesafene®) as a first-line treatment for severe pregnancy nausea and vomiting, but this is not included in the guideline of the Dutch College of General Practitioners (NHG).
Currently, meclozine/pyridoxine is the only medicinal product included in the GVS for pregnancy nausea and vomiting and that is reimbursed for this indication. Meclozine monotherapy is only available as an over-the-counter medicinal product.
The assessment, in which an indirect comparison was made between doxylamine succinate/pyridoxine hydrochloride and meclozine/pyridoxine, has shown that there is also no proof of a clinically relevant effect on relevant outcome parameters for meclozine/pyridoxine.

Advice on inclusion in the GVS
Based on the above-mentioned considerations, the National Health Care Institute recommends that doxylamine succinate/pyridoxine hydrochloride should not be included in the GVS.
In addition, the National Health Care Institute recommends that meclozine/pyridoxine should no longer be designated as an insured benefit for the treatment of nausea and vomiting during pregnancy, and that meclozine/pyridoxine should no longer be included in the GVS for this indication.
The National Health Care Institute therefore recommends to apply the following reimbursement conditions:
Condition for meclozine/pyridoxine
only for an insured person when the medicinal product is used to treat nausea and vomiting after surgery or after radiotherapy.

According to the GIP database, 32,607 insured persons used Emesafene in 2021. The National Health Care Institute has calculated an estimated 73% of users used the medicinal product for nausea and vomiting during pregnancy (nearly 24,000 women). The total expenditure for Emesafene was estimated to be €1,442,000.

A negative assessment by the National Health Care Institute does not mean that doxylamine succinate/pyridoxine hydrochloride is not available to pregnant women. It is still available on prescription from the pharmacy but will have to be paid for by the patient. This will be approximately €15 - €45 per treatment.

Future developments
The National Health Care Institute is of course prepared to reconsider the package eligibility of doxylamine succinate/pyridoxine hydrochloride and meclozine/pyridoxine if additional research data not previously assessed by the National Health Care Institute leads to scientific publications.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board