Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

State Secretary of Health,
Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

2021026390

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms J.E. de Boer
T +31 (0)20 797 85 23

Our reference
2021026390

Date 29 September 2021
Subject GVS review levomepromazine (Nozinan®)

Dear Mr Blokhuis,

In the letter of 5 August 2021 (reference 3236050-1013491-GMT), the acting director of Medicinal Products and Medical Technology requested the National Health Care Institute to assess whether the substance levomepromazine (Nozinan®) can be included in the Medicine Reimbursement System (GVS) for the off-label application for palliative sedation in a home situation, as defined in the Palliative Sedation guideline. Levomepromazine (Nozinan®) is available in the following forms of administration:

- 25 mg (film-coated) tablet,[1]
- injection fluid 25 mg/ml.[2]

Registered indication
Since 1990, levomepromazine (Nozinan®) 25 mg has been available on the Dutch market for the indication *"moderate to severe pain in non-ambulatory patients*".[1, 2]

Background
Levomepromazine is a phenothiazine derivative with antipsychotic, analgesic and strong sedative effects. In addition, it has anti-α1-adrenergic and anticholinergic properties that are stronger than its antipsychotic effect.[3] This medicinal product is not included in the Medicine Reimbursement System (GVS). In 1996, the Health Insurance Funds Council, the predecessor of the National Health Care Institute, advised the Minister to exclude levomepromazine (Nozinan®) from reimbursement. This advice mentioned that "*the therapeutic value as an analgesic is lacking and the efficacy as an antipsychotic has not been demonstrated".*

For years, levomepromazine has been applied off-label as palliative sedation and to treat nausea and vomiting in the palliative phase. These applications are included in the relevant national treatment guidelines:

- The guideline on palliative sedation of the Royal Dutch Society for the Advancement of Medicine (in Dutch: Koninklijke Nederlandsche
- Maatschappij tot bevordering der Geneeskunde (KNMG); 2009, currently under review);[4]
- The guideline on nausea and vomiting of the Comprehensive Cancer Centres (in Dutch: Integraal Kankercentrum Nederland (IKNL);

2014);[5]
- The guideline on paediatric palliative care of the Dutch Pediatric Association (in Dutch: Nederlandse Vereniging voor Kindergeneeskunde (NVK); 2013).[6]

Because the medicinal product is not reimbursed from the GVS, the cost of using this medicinal product must be paid by the next of kin after the patient's death. Although the cost of this medicinal product is relatively low, this leads to painful situations.

In May 2021, for the purpose of assessment, the National Health Care Institute, with the support of the physicians' association (IKNL/guideline committee on palliative sedation) submitted a file for the justification of the placement of levomepromazine on List 1B of the Health Insurance Regulation for the off-label application in palliative sedation and for nausea and vomiting in the palliative phase.

GVS assessment

Assessment of interchangeability

According to the current guideline on palliative sedation (KNMG; 2009), levomepromazine is the second step in the treatment schedule (after midazolam) for continuous palliative sedation until the moment of death. Suggested dosage: bolus 25 mg subcutaneous/intravenous, possibly after 2 hours 50 mg; continuous administration 0.5-8 mg/hour subcutaneous/intravenous in combination with midazolam. After 3 days of dosing, the dosage must be halved due to cumulative intake.[4]

According to the guideline on nausea and vomiting (IKNL; 2014), levomepromazine is the third step in the treatment schedule for nausea and/or vomiting in palliative patients who do not respond adequately to other anti-emetics. Suggested dosage: starting dosage once daily 6.25-12.5 mg orally for the night or 3.12 mg subcutaneous (as bolus or as continuous infusion), if necessary increased to a maximum of 25 mg per day. It can also be administered in the buccal space. The antipsychotic olanzapine or a serotonin (5HT3) antagonist (in combination with dexamethasone) are named as alternatives to levomepromazine. [5]

The guideline on paediatric palliative care (NVK; 2013) states that levomepromazine can be considered in the event of nausea and vomiting, and according to experts, the medicinal product is particularly effective in refractory nausea in children at the palliative stage. There is no dosing advice. [6]

The GVS includes some medicinal products that can be applied for palliative sedation and nausea and vomiting in the palliative phase. Most of these medicinal products have, like levomepromazine, a permanent place in the treatment. For the palliative sedation indication, no alternative to levomepromazine is mentioned. For the indication of nausea and vomiting in the palliative phase, the alternative is olanzapine or serotonin (5HT3) antagonists. Olanzapine is active on the same receptors as levomepromazine and is also not registered for nausea and vomiting in the palliative phase. Olanzapine is indicated for schizophrenia and bipolar disorder, which means that the main indication of this medicinal product is the antipsychotic application. This is not the case with levomepromazine. The

serotonin (5HT3) antagonists are indicated for nausea and vomiting after chemotherapy and partly also for nausea and vomiting after radiotherapy and surgery.[7] In addition, this is the first choice of medicinal product for patients with terminal renal failure with nausea and vomiting according to the relevant treatment guideline.[5] These medicinal products are therefore widely used for the treatment of nausea and vomiting. Levomepromazine has only an off-label application in palliative phase patients with nausea and/or vomiting that do not respond adequately to other anti-emetics.[5] The medicinal product is therefore not interchangeable with these two medicinal products (groups), nor with any other medicinal product that is included in the GVS. This means that levomepromazine is, in principle, eligible for inclusion on List 1B.

Therapeutic value
The National Health Care Institute has searched the literature for studies describing the efficacy and safety of levomepromazine in the two off-label indications for which reimbursement is requested. A number of systematic literature studies were found (the most recent from 2015) in which it was concluded that there is a lack of randomized studies for levomepromazine in the palliative phase.[8-10] There was, however, one randomized study comparing levomepromazine with haloperidol in cancer-related nausea in the palliative phase. In this study, a similar effect was seen for both products.[11] In addition, some low-quality studies have been carried out (open-label, quasi experimental, retrospective, case report) which may support the effectiveness of levomepromazine.[10]

The National Health Care Institute takes the view that, given the very limited scientific evidence, a scientific discussion in accordance with the current standards set by the Scientific Advisory Board (WAR) is not possible. The therapeutic value will therefore be determined on the basis of the experience in practice and the properties of the medicinal product.

There is a well-established use. For years, levomepromazine has been applied as palliative sedation and to treat nausea and vomiting in the palliative phase. This application is included in the relevant national treatment guidelines and also in international guidelines, including the EAPC guideline. The MASCC/ESMO European guideline on nausea and vomiting in advanced cancer also mentions levomepromazine as a treatment option.[12]

The effect of levomepromazine observed in practice can be explained by the properties of the medicinal product. Levomepromazine has a strong sedative effect, which is the desired effect in palliative sedation. Levomepromazine has an antagonizing effect on the dopamine, serotonin, histamine and cholinergic receptors, which play a role in nausea and vomiting.[5]

The side effects profile of levomepromazine is known because the medicinal product has been on the market for many years. The most commonly mentioned side effects (frequency >10%) are: somnolence, tachycardia, dry mouth, nausea, vomiting.[3] In case of a continuous palliative sedation until death, these side effects are not (very) relevant, in fact they are the reason why the medicinal product is used. The physicians' association indicates that in the event of intermittent sedation and nausea/vomiting, a lower dose is chosen, partly to reduce the most relevant side effects.

National Health Care Institute
Care
Medicinal Products

Date
29 September 2021

Our reference
2021026390

Budget impact
Every year, just over 150,000 people die,[13] of which an estimated 70% require palliative care.[14] In 2015, the percentage of deaths where palliative sedation was applied was 18%, and this number is rising. [15, 16] The physicians' association estimates that approximately 25% of the deceased will have had a palliative sedation indication; in one-third of these cases, levomepromazine would have been administered. The physicians' association also indicates that about 20-50% (this assessment is based on 35%) of patients with palliative care needs suffer from nausea and/or vomiting and that for about one-third of these patients, levomepromazine will be used.

The estimated number of patients eligible annually for levomepromazine treatment for palliative sedation and nausea and vomiting applications in the palliative phase is based on prognoses of death in the coming years made by Statistics Netherlands (CBS).[17] The CBS has described a 67% forecast interval (upper and lower limits), indicating that the probability of the actual number of deaths between this interval is 67%.[18] Based on the 67% prognosis interval, the estimated number of patients eligible for levomepromazine treatment in the third year after admission (2024) is approximately between 12,395 and 14,617 patients for palliative sedation, and approximately between 12,147 and 14,324 patients for the nausea and vomiting application in the palliative phase.

The physicians' association indicates that approximately 5 ampoules of levomepromazine (Nozinan®) are used per patient for both indications. This means that the cost per patient per year is €4.58. Inclusion in the GVS of levomepromazine (Nozinan®) for palliative sedation, and for nausea and vomiting in the palliative phase will be accompanied by additional costs estimated at between €112,402 and €132,550 in the third year after inclusion in the GVS. There is some uncertainty about the number of patients for whom levomepromazine (Nozinan®) has been indicated.

Advice on inclusion in the GVS
The National Health Care Institute recommends including levomepromazine (Nozinan®) in List 1B and List 2 of the Health Insurance Regulation, and imposing the conditions stated below. Inclusion in List 1B will lead to limited additional costs.

Levomepromazine conditions
only for administration to an insured person for:
1. palliative sedation, or
2. nausea and vomiting in the palliative phase
in accordance with the guidelines accepted by the relevant physicians' associations in the Netherlands.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

National Health Care Institute
Care
Medicinal Products

Date
29 September 2021

Our reference
2021026390

References

1. CBG. Geneesmiddeleninformatiebank. Nozinan tabletten 25 mg. 2021. Geraadpleegd op 5 juli 2021 via https://www.geneesmiddeleninformatiebank.nl/nl/rvg00344.
2. CBG. Geneesmiddeleninformatiebank. Nozinan, injectievloeistof 25 mg/ml. 2021. Geraadpleegd op 5 juli 2021 via https://www.geneesmiddeleninformatiebank.nl/nl/rvg00346.
3. Farmacotherapeutisch kompas. Levomepromazine. 2021. Geraadpleegd op 5 juli 2021 via https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/l/levomepromazine.
4. KNMG. Richtlijn Palliatieve sedatie. 2009.
5. IKNL. Richtlijn Misselijkheid en braken. 2014.
6. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn Palliatieve Zorg voor Kinderen. 2013.
7. Farmacotherapeutisch Kompas. 5HT3-antagonisten. 2021. Geraadpleegd op 5 juli 2021 via https://www.farmacotherapeutischkompas.nl/bladeren/groepsteksten/5ht3_antagonisten.
8. Cox L, Darvill E and Dorman S. Levomepromazine for nausea and vomiting in palliative care. Cochrane Database Syst Rev 2015; 2015: Cd009420.
9. Darvill E, Dorman S and Perkins P. Levomepromazine for nausea and vomiting in palliative care. Cochrane Database Syst Rev 2013: Cd009420.
10. Dietz I, Schmitz A, Lampey I, et al. Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review. BMC Palliat Care 2013; 12: 2.
11. Hardy JR, Skerman H, Philip J, et al. Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open 2019; 9: e029942.
12. Walsh D, Davis M, Ripamonti C, et al. 2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. Support Care Cancer 2017; 25: 333-40.
13. CBS. Sterfte. Geraadpleegd op 5 juli 2021 via https://www.cbs.nl/nl-nl/visualisaties/dashboard-bevolking/bevolkingsgroei/overlijden.
14. PZNL. Kerncijfers palliatieve zorg. 2019. Geraadpleegd op 5 juli 2021 via https://iknl.nl/getmedia/ec16a960-d5b9-4762-b6c2-b9f360988e03/Kerncijfers_Palliatieve_Zorg_2019_PZNL_IKNL.pdf.
15. Heijltjes MT, van Thiel G, Rietjens JAC, et al. Changing Practices in the Use of Continuous Sedation at the End of Life: A Systematic Review of the Literature. J Pain Symptom Manage 2020; 60: 828-46.e3.
16. Rietjens JAC, Heijltjes MT, van Delden JJM, et al. The Rising Frequency of Continuous Deep Sedation in the Netherlands, a Repeated Cross-Sectional Survey in 2005, 2010, and 2015. J Am Med Dir Assoc 2019; 20: 1367-72.
17. CBS. Prognose bevolking; kerncijfers, 2019-2060. 2020. Geraadpleegd op 5 juli 2021 via https://www.cbs.nl/nl-nl/cijfers/detail/84645NED?dl=2E102.
18. CBS. Prognose-interval. 2021. Geraadpleegd op 5 juli 2021 via https://www.cbs.nl/nl-nl/onze-diensten/methoden/begrippen/prognose-interval#:~:text=Interval%20waarbinnen%20de%20bevolking%20(of,dan%20wel%2095%20procent%20bedraagt.