Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health,
Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

2021044712

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
P.K. Cheung

Case number
2020022675

Our reference
2021044712

Your reference
1681288-204715-GMT

Your letter of
12 May 2020

Date 13 April 2022
Re: Advice on the clustering of combination preparations and ghost clusters in GVS (part 2)

Dear Mr Kuipers,

In your letter of 12 May 2020, your predecessor asked the National Health Care Institute for advice on the clustering of combination preparations and the ghost clusters in the Medicine Reimbursement System (GVS; your reference 1681288-204715-GMT). Because these involve a large number of medicinal products, we have to give our advice in phases and in parts.

The first part of our advice was delivered to you on 4 May 2021 (our reference 2021012702).[1] This advice also indicated that we would be planning the assessment of the remaining (groups) of medicinal products in the course of 2021. In consultation with your GMT Directorate, we have agreed on a step-by-step approach. Products that can be classified in the GVS for technical reasons will be processed first. Medicinal products that require a pharmaco-therapeutic assessment will be discussed later, preferably in a group assessment. Finally, there may be one or more remaining products that cannot be dealt with by us for different reasons, for example because of ongoing legal procedures. In that case, we shall also indicate that.

The present advisory report is related to part 2. As requested by your ministry, we will treat the remaining combination preparations in part 3 (scheduled around summer 2022). Discussion of the other ghost clusters will follow in 2023 and later.

In your request of May 2020, a summary of ghost clusters was provided by CIBG/Farmatec (based on the G standard of September 2020; *Annex 17 of part 1*).[1] Ghost clusters are clusters on List 1A of the Health Insurance Regulation (Rzv) with only one remaining product. The ghost products that have not yet been discussed are listed in subsection 6.3 of that advisory report. Furthermore, our advisory report of 4 May 2021 did not discuss a number of combination preparations. As indicated above, we will deal with them in part 3. These are Augmentin®, Cofact® and combination preparations of which one of the substances in the combination preparation is not included in the GVS as a mono

[1] https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/04/advies-clustering-van-combinatiepreparaten-en-spookclusters-in-gvs-deel-1

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preparation (see *Annex 15 of part 1*). In addition, we did not discuss the immunoglobulins because these were to be transferred to intramural by 2022. However, the Minister recently decided not to continue this transfer due to the pandemic.[2]

In this advisory report (part 2), we are advising on nine ghost clusters. These are seven injections: Zantac®, Etalpha®, Solu Cortef®, Pneumovax®, Tramal®, Diazepam®, Temgesic®. In addition, we will discuss the De-Nol® tablet and Tramadol® suppository.

The substantive discussion of these ghost products is set out in Annex 1. Reactions from the different parties are included in Annex 2.

Based on our assessments, the National Health Care Institute has completed the following advice:

Advice by the National Health Care Institute (part 2):

- Zantac® injection and De-Nol® tablet can be removed from the GVS.
- Etalpha®, Solu Cortef®, Pneumovax®, Tramal® and Temgesic® injections: these products can be placed on List 1B of the Rzv.
- Tramadol® suppository can be moved to the 0N02AXAO V cluster of List 1A of the Rzv.
- Diazepam® injection (DDD 10 mg parenteral) may remained in List 1A. This product, together with Temesta® injection (lorazepam; DDD 2.5 mg parenteral) can be placed together in a newly formed cluster.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

[2] https://www.rijksoverheid.nl/documenten/kamerstukken/2021/04/21/kamerbrief-over-overheveling-geneesmiddelen-per-2022

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ANNEX 1. Substantive discussion

Ghost cluster	Name of article	Explanation	Advice
0A02BAAPV	ZANTAC INJ FLD 25MG/ML AMPOULE 2ML	Ranitidine injection. This product is no longer registered as a medicinal product in the Netherlands. It is also no longer available on the market (technical withdrawal).	Remove from the GVS
0A02BXBOV	DE NOL TABLET FILM-COATED 120MG	De-Nol film-coated tablets contain the active ingredient dried colloidal solution of bismuth subcitrate, corresponding to 120 mg bismuth oxide (ATC code A02BX05; categorized under other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)). Registered indication: Gastro- and duodenal ulcers. Gastritis accompanied by dyspepsia symptoms, when elimination of Helicobacter pylori is required.[3] De-Nol tablet has not been included in the G-standard since September 2003, nor is it available on the Dutch market. According to the marketing authorization holder, in exceptional cases, De-Nol® is imported from abroad via the international pharmacy, and the costs are declared to the health care insurer at the expense of the GVS. In 2020, 107 users received reimbursement for De-Nol tablets and the total cost was €2,684 (Source: GIP database). For reflux symptoms during eradication of Helicobacter pylori, several medicinal products (or product groups) are included in the GVS, such as H_2 antagonists and proton pump inhibitors.	Remove from the GVS
0A11CCAPV	ETALPHA INJ FLD 2MCG/ML AMPOULE 0.5ML	Alfacalcidol (A11CC03) is a vitamin D analogue. This product has been registered for the treatment and prevention of renal osteodystrophy and hypoparathyroidism. The oral forms of alfacalcidol are included in the 0A11CCA cluster without any other substances. ETHALPHA INJ FLD is the only product with alfacalcidol via injection (technical 1B).	Placement on List 1B

[3] https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,10721

0H02ABAP V	SOLU CORTEF INJECTION POWDER PHIAL 100MG SOLU CORTEF INJ PWDR 100MG + 2ML SOLV IN ACT O PHIAL	Hydrocortisone, powder for injection liquid for intramuscular and intravenous administration, with and without solvent ('Act-O-Vial'). There are 2 products available, both from the same manufacturer, which is why it is categorized as a ghost product. Hydrocortisone in oral form is clustered with cortisone acetate. No injections of cortisone acetate are available. Solu Cortef® is the only product with hydrocortisone via injection (technical 1B).	Placement on List 1B
0J07ALAP V	PNEUROVAX 23 INJ FLD WWSP 0.5ML	Pneumococcal vaccine (23-valent) is the only product in this cluster. Pneumovax 23® is not interchangeable with the other pneumococcal vaccine included in the GVS (13-valent pneumococcal conjugate vaccine; see our assessment of Prevenar 13®).[4] Since there is no other product to cluster with Pneumovax 23®, this product is eligible for a placement on List 1B. This will eliminate the unwanted additional payment (€12.70 per item). This measure will be accompanied by additional health insurance costs (€ 12.70 x 5,833 users in 2020 = € 74,079 per year). The reimbursement for pneumococcal vaccine shall be subject to further conditions, which will apply without prejudice.	Placement on List 1B (and maintaining List 2 conditions)
0N02AXAP V	TRAMAL INJ FLD 50MG/ML AMPOULE 2ML	Tramadol injection. The oral forms of tramadol are included in the (ON02AXAO V) cluster. This is the only tramadol-containing product that is administered via injection (technical 1B).	Placement on List 1B
0N02AXAR V	TRAMADOL HCL CF SUPPOSITORY 100MG	Tramadol suppository. Article 2.40 of the Health Insurance Regulation (Rzv) states the following about the assessment of interchangeability. Medicinal products are considered to be interchangeable if they are administered […] via a similar route of administration. As with capsules and tablets, suppositories have an administration route not by means of an injection that is intended to have a systemic effect. From the GVS system point of view, tramadol suppository can be assigned	Placement on List 1A in the 0N02AXAO V cluster

[4] https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/03/03/gvs-advies-13-valent-pneumokokkenconjugaat-vaccin-prevenar13

<table>
<tr><td></td><td></td><td>to the cluster with the oral forms with tramadol. In other words: Tramadol suppository can be moved from cluster 0N02AXAR V to cluster 0N02AXAO V.</td><td></td></tr>
<tr><td>0N05BABP V</td><td>DIAZEPAM CF INJ FLD 5MG/ML AMP 2ML</td><td>Diazepam injection.
The oral cluster that includes diazepam tablets (0N05BAAO), also includes lorazepam tablets.

Lorazepam injection (TEMESTA INJ FLD 4MG/ML AMPOULE 1ML) is currently included in List 1B. Diazepam injection and lorazepam injection can be considered interchangeable.
<table>
<tr><th colspan="2">Therapeutic indications:</th></tr>
<tr><th>Diazepam injection</th><th>Lorazepam injection (Temesta®)</th></tr>
<tr><td>-Sedation in local anaesthesia (conscious sedation)
-Premedication and induction of anaesthesia
-Occasional/initial use for pathological anxiety and stress, if the condition is serious, or if the patient is suffering severely or their performance is impaired
-Acute withdrawal symptoms when alcohol is discontinued
-Epileptic convulsions, status epilepticus
-To reduce muscle spasms in case of tetanus
-(Pre-)eclampsia</td><td>Symptomatic treatment of pathological anxiety and stress if oral medication is not possible.

Premedication before surgery.

Off-label: status epilepticus.</td></tr>
</table></td><td>Diazepam injection can be combined with Temesta® injection in a new cluster.</td></tr>
<tr><td>1N02AEAP V</td><td>TEMGESIC INJ FLD 0.3MG/ML AMPOULE 1ML</td><td>Buprenorphine injection.
The buprenorphine patches are included in the 0N02AEADP cluster, which only contains substances with ATC code N02AE01 (buprenorphine). Injections (and oromucosal tablets) with buprenorphine are used for postoperative pain in non-ambulatory patients. In 2020, there were only 5 users of Temgesic® injection, total reimbursement €1,886.
Temgesic® injection is the only product with buprenorphine via injection (technical 1B).</td><td>Placement on List 1B</td></tr>
</table>

ANNEX 2. Results of the open consultation (input from parties who sent a response)

Who	Comment description	Reaction of the National Health Care Institute
Patiëntenfederatie Nederland (Netherlands Patients Federation, PfN) 2022010171	The draft advisory report does not give PfN any reason for a further reaction.	PfN has no comments on the concept.
Vereniging Innovatieve Geneesmiddelen (Association Innovative Medicines, VIG) 2022011445	As an association, VIG decided not to use the opportunity to respond. VIG members can send in their own reactions about individual products.	As an umbrella organisation, VIG has no comments on the concept.
Zorgverzekeraars Nederland (Association of Dutch Healthcare Insurers, ZN)	Health care insurers agree with the advisory report.	ZN agrees with the advisory report.
Nederlands Huisartsen Genootschap (Dutch College of General Practitioners, NHG) 2022011964	NHG does not agree with the advice to move Tramadol® suppository to the 0N02AXAO V. cluster The NHG believes that the suppositories are not interchangeable with tablets. Patients who are very sick and are vomiting can often use suppositories. NHG does not consider rectal administration as a similar route of administration to oral. Therefore, NHG considers moving tramadol suppositories to the cluster with tramadol oral forms of administration undesirable. The general practitioner uses the different forms of administration depending on patient characteristics and	In the GVS, the designated drugs are classified whenever possible in groups of interchangeable medicinal products. Rules have been established for the clustering of interchangeable medicinal products and for the calculation of the reimbursement limit for each group of interchangeable medicinal products (Article 2.8 (5) of the Rzv). The GVS concept 'interchangeable' is a legal instrument to regulate the reimbursement of extramural medicinal products, which is not intended as a tool for the treatment of individual patients.

	conditions. NHG wants to be able to continue to use the various options from reimbursed basic care and has requested the National Health Care Institute to modify this advice for the tramadol suppository.	If the proposal of the National Health Care Institute is accepted by the Minister (move to cluster 0N02AXAO V), the Tramadol suppository is still fully reimbursed. The National Health Care Institute sees no reason not to maintain the applicable GVS criteria.
Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (The Royal Dutch Pharmacists Association, KNMP) 2022012249	KNMP does not agree with the draft advisory report to move Tramadol® suppository to the 0N02AXAO V cluster There are circumstances when patients are unable to take tramadol orally in tablet form, but where a suppository is a suitable treatment (for instance in case of nausea and vomiting). From the point of view of good pharmaceutical care, the KNMP says that the suppositories are not interchangeable with tablets because the route of administration is not similar. Therefore, KNMP considers moving tramadol suppositories to the cluster with tramadol in oral forms as undesirable. The KNMP wants to be able to provide the various options of good pharmaceutical care after a prescription as reimbursed care and asks the National Health Care Institute to amend this advice on the tramadol suppository.	See above. The reimbursement status of Tramadol suppository will not be cancelled by this advisory report. This product will still be reimbursed.

NHG and KNMP	Both organisations do agree with the other draft advisory reports on: -Zantac® injections, De-Nol tablet (both for withdrawal from GVS); -Etalpha®, Solu Cortef®, Pneumovax®, Tramal® and Temgesic® injections (all placement on 1B); -diazepam injection: forming a new cluster together with lorazepam injection.	The NHG and the KNMP agree with the above-mentioned advisory reports.

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