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Date 21 July 2022
Subject GVS reassessment report on testosterone undecanoate (Nebido®)

Our reference
2022024660

Dear Mr Kuipers,

In your letter of 31 May 2022, you asked the National Health Care Institute to advise on a reassessment of the medicinal product testosterone undecanoate (Nebido®) in the context of interchangeability within the current cluster.

Background
Since 2012, the testosterone preparation Nebido® for intramuscular injection has been included in the Medicine Reimbursement System (GVS) on List 1A of the Healthcare Insurance Regulation. It is part of the same cluster as Sustanon® '250' for intramuscular injection.
Nebido® consists of testosterone undecanoate 1000 mg/4 ml.
Sustanon® '250' 1 ml ampoule consists of testosterone propionate (30 mg), testosterone phenylpropionate (60 mg), testosterone isocaproate (60 mg) and testosterone decanoate (100 mg).
Both medicinal products are registered as supplement therapy for hypogonadism in men, when testosterone deficiency has been confirmed based on clinical characteristics and biochemical tests.

Previous assessment
Nebido®'s current place in the GVS was established on the basis of a previous advisory report from the National Health Care Institute[1], which concluded that Nebido®'s desirable effects (based on achieving a physiological concentration of testosterone in the blood, as confirmed by pharmacokinetic testing) could be considered equivalent to Sustanon® and the other testosterone preparations (testosterone gel, oral testosterone undecanoate).
It also concluded that fluctuating testosterone concentrations could trigger undesirable effects shortly after administration, for example, or just before a new administration. However, it found no evidence to indicate any differences between the preparations in this regard. Finally, it was concluded that, in terms of ease of use, Nebido® is superior to Sustanon®, as administration is less frequent. However, the report stated that there was no evidence that this actually leads to improved patient compliance and, as a result, to more favourable outcomes for patients.

1. CFH Report 12/18: testosterone undecanoate (Nebido®). 2012.

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Reasons for reassessment
Administration of the short-acting testosterone ester Sustanon® results in fluctuating testosterone concentrations, due to its pharmacokinetic profile with two to three weekly doses.
The administration of 10 to 14 weekly doses of the long-acting testosterone ester Nebido® results in a stable physiological testosterone concentration (12.0 – 35.0 nmol/l). These values reflect the normal concentrations of testosterone in the bodies of eugonadal men. Here, values below 12 nmol/l can be regarded as sub-physiological and values above 35 nmol/l as supra-physiological.
According to practitioners and patient organisations, as well as the guidelines used by the physicians' association, the fluctuating testosterone concentrations caused by administration of the short-acting testosterone ester Sustanon® result in fluctuations in mood and energy. This, therefore, creates a clinically relevant higher risk of undesirable effects than when patients are treated with the long-acting testosterone preparation Nebido®.

Based on newly available data, Nebido®'s marketing authorisation holder, as well as physicians' associations and patient associations, have requested that Nebido® be placed on List 1B of the Healthcare Insurance Regulations.

Conclusion of substantive assessment (see GVS reassessment report in annex)
Assessment of interchangeability
The effects of Nebido® and of short-acting intramuscular (i.m.) testosterone esters (with similar pharmacokinetics to Sustanon®) were described in a network meta-analysis (NMA) of placebo-controlled randomised studies in hypogonadal men.
When compared to placebo, Nebido® (1000 mg/12 wks) was found to be the only testosterone preparation that had a significant effect on these patients' quality of life.
In addition, indirect comparisons indicate that treatment with short-acting i.m. testosterone has a clinically relevant, higher risk of treatment discontinuation due to undesirable effects than Nebido®. A pooled analysis carried out by the National Health Care Institute found that short-acting i.m. testosterone had a clinically relevant, higher (by a factor of 2.6) risk of treatment discontinuation compared to placebo. For Nebido® users, the risk of treatment discontinuation is no higher than for individuals using a placebo.

The difference in the risk of treatment discontinuation due to undesirable effects in randomized studies is supported by observational studies. In a controlled observational study, 42% of patients treated with short-acting i.m. testosterone discontinued this treatment within 12 months, compared to only 9% of those treated with Nebido®.
Several non-controlled observational studies also indicate a difference in the risk of erythrocytosis (1% with Nebido® and around 40% for short-acting i.m. testosterone). Erythrocytosis is a disorder in which the haematocrit (the red blood cell [erythrocyte] count in the blood), is too high. It is associated with the excessive testosterone concentrations that develop during the use of short-acting i.m. testosterone esters. According to Dutch guidelines, erythrocytosis is an indication for the interruption of testosterone treatment. Due to the risk of erythrocytosis, the Dutch guidelines caution against prescribing short-acting i.m. testosterone to patients with type 2 diabetes mellitus (DM2), to smokers, and to

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patients with thrombogenic co-morbidity.

Users of the short-acting i.m. testosterone preparation Sustanon® quite often experience undesirable effects. In this context, data from the scientific literature is supported by the results of a published user study of Dutch testosterone users. Nebido® has a higher rating than Sustanon®, in terms of its mode/ease of administration.

Conclusion: All things considered, newly available data confirms that there are clinically relevant differences between the properties of Nebido® and Sustanon®. At the present time, both of these medicinal products are included in the GVS cluster 0G03BAAP. As a result, Nebido® is no longer interchangeable with Sustanon®.

Nebido® complies with established medical science and medical practice and has an added therapeutic value in comparison with Sustanon®. It is, therefore, eligible for inclusion on List 1B of the Healthcare Insurance Regulations.

Budget impact analysis
The number of patients using Nebido® is expected to rise from 2,000 to approximately 5,400. This is expected to be accompanied by an annual cost increase of €0.6 million. This cost increase is partly due to the increasing number of patients and partly to the increasing annual reimbursement per patient.

Advice
Testosterone undecanoate (Nebido®) is no longer interchangeable with Sustanon®. The National Health Care Institute recommends that Nebido® be placed on List 1B. The inclusion of Nebido® on List 1B will involve additional costs of €0.6 million.

Yours sincerely,

Peter Siebers
Acting Chairperson of the Executive Board

Annex: GVS report on testosterone undecanoate (Nebido®) and budget impact analysis

Annex

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Budget impact analysis Nebido®
This report estimates the costs (additional costs) to the pharmaceutical budget that would be incurred if Nebido® were to be removed from its present cluster and if this medicinal product were to be placed on List 1B of the Healthcare Insurance Regulation. At the present time, Nebido® is clustered with Sustanon® in cluster 0G03bAAP on List 1A of the Healthcare Insurance Regulation. Both medicinal products are registered for the following indication: "as testosterone supplement therapy for hypogonadism in men, when testosterone deficiency has been confirmed based on clinical characteristics and biochemical tests". Both medicinal products can also be used off-label in the hormone treatment of gender incongruity.

Number of patients and cost per patient.
Based on the Genees- en hulpmiddelen Informatie Project (GIP; Medicines and medical devices information project) database (G03BA03), it appears that, in 2021, approximately 22,000 Dutch people were treated with a form of testosterone [1]. It is important to note that these can include patients with hypogonadism or Klinefelter syndrome. It can also involve treatment in the context of Transgender Care.

The National Health Care Institute's access to the GIP database provides insight into the number of users of individual medicinal products with this ATC code. In 2021, the approximate user figures for Nebido®, Sustanon®, and the various gels were 2,000, 5,000 and 15,000 respectively.

The number of Nebido® users is expected to rise when this medicinal product is placed on List 1B. This is because, at the present time, there is a reimbursement limit, which presents an obstacle for some patients. Based on a study entitled "Gebruik, ervaringen en keuzegrondslag testosteronsuppletie" (Use, experiences and basis for choice of testosterone supplementation) by various patient associations, the marketing authorisation holder has estimated the increase in the number of patients who will ultimately use Nebido®. Half of the current Sustanon® users are expected to switch to Nebido®, while 6% of current users are expected to switch to testosterone gels. Based on the above GIP figures, 3,400 patients are expected to switch. As a result, the total number of patients using Nebido® is expected to reach 2,000 + 3,400 = 5,400.

Placing Nebido® on List 1B of the Healthcare Insurance Regulation will trigger an increase in the costs of Nebido®. This is partly because more patients are expected to use Nebido® and partly because the cost per patient will be higher if this medicinal product were to be removed from its present cluster.

The GIP database provides insight into the average annual costs per patient for the various testosterone medications. For Nebido®, Sustanon® and the testosterone gels, the annual costs average out to about €270, €110, and €330 respectively. When the cluster limit expires, the annual costs for Nebido® will increase.

Nebido® has a pharmacy purchase price of €107.62 per vial. Nebido® is intended for 10 to 14 weekly treatments. Patients need an average of 4.3 vials per year,

based on an average of 12 weeks per treatment [2]. Thus the treatment costs per patient per year amount to €466.35. However, patient compliance is not expected to be 100%. The GIP database shows that Nebido® has a DDD of approximately 220 per patient per year. Thus, the National Health Care Institute has decided to multiply the annual treatment costs of Nebido® by 2/3, to arrive at a more realistic estimate of the annual costs. The resulting amount is €310.90. This amount is approximately equal to the current annual cost for the use of testosterone gel. Thus, no further consideration is given to those patients who switch from a gel to Nebido®. These patients will not incur any additional costs.

In summary:

- The costs incurred by the 2,000 current Nebido® users will increase from €270 to €310.90 per patient per year, which amounts to an additional €40.90 per patient per year.
- The costs incurred by the 2,500 Sustanon® users who switch to Nebido® will increase from €110 to €310.90 per patient per year, which amounts to an additional €200.90 per patient per year.
- For the 900 current testosterone gel users, the annual costs will remain about the same.

Table 1: Annual additional costs if Nebido® is placed on List 1B.

	Number of patients	Additional costs per patient	Total additional costs
Current Nebido® users	2,000	€40.90	€81,804.44
Patients switching from Sustanon® to Nebido®	2,500	€200.90	€502,255.56
Total			**€584,060.00**

Budget impact and conclusion

The number of patients using Nebido® is expected to rise from 2,000 to approximately 5,400. This is expected to be accompanied by an annual cost increase of €0.6 million. This cost increase is partly due to the increasing number of patients and partly to the increasing annual reimbursement per patient.
It is uncertain how many patients will actually switch to Nebido®.

References

1. GIP databank. Aantal gebruikers 2017-2021 voor ATC-subgroep G03BA03 : Testosteron 2022 [Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&tabel_h_00-totaal=B_01-basis&geg=gebr&spec=&item=G03BA03.
2. Hall SA, Esche GR, Araujo AB, Travison TG, Clark RV, Williams RE, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. The Journal of Clinical Endocrinology & Metabolism. 2008;93(10):3870-7.