Zorginstituut Nederland

Tranylcypromine (Tracydal®)

Summary of recommendations by *Zorginstituut Nederland* dated 15 June 2016

Zorginstituut Nederland carried out a budget impact analysis for the medicine tranylcypromine (Tracydal®). They reached the following conclusion.
Based on the currently applicable criteria of the Medicines Reimbursement System (GVS), tranylcypromine is not mutually replaceable with any product in the GVS. For this reason the Zorginstituut advises that tranylcypromine (Tracydal®), 20-mg (film-coated) tablet, is placed on List 1B of the GVS.

In a letter dated 13 June 2016 (CIBG-16-02410), the Minister of Health, Public Welfare and Sport asked *Zorginstituut Nederland* to assess whether tranylcypromine (Tracydal®), 20-mg (film-coated) tablet, is mutually replaceable with a drug that is included in the GVS system. *Zorginstituut Nederland*, advised by the Scientific Advisory Board (WAR), has now completed this assessment.

Registered indication

The full registered indication for tranylcypromine 20 mg is as follows:
"For the treatment of severe depressive episodes in patients with a severe multi-resistant depressive disorder, whereby adequate treatment with 2 standard antidepressants (including tricyclic antidepressants) and augmentation with, e.g., lithium, was insufficiently effective".

Background

Tranylcypromine is an irreversible, non-selective MAO-inhibitor that has been used since the nineteen-fifties for the treatment of severe, therapy-resistant depression. Until recently, tranylcypromine was only available in the Netherlands as unregistered pharmaceutical product (Parnate®) and as a pharmacy preparation.

In the past, the use of imported products that are not registered in the Netherlands, such as tranylcypromine (and fenelzine) for the treatment of severe therapy-resistant depression was assessed by the *College voor Zorgverzekeringen* (the predecessor of *Zorginstituut Nederland)* as rational. In June 2015, however, the Zorginstituut noted that these imported products no longer fulfilled the requirement for reimbursement, namely that the indication for such products may not exceed 1 per 150,000 residents. Based on this fact, tranylcypromine (and fenelzine) were no longer eligible for reimbursement. This requirement regarding the prevalence of the disorder does not apply, however, to pharmacy preparations. Nevertheless, with the arrival of the registered product, Tradydal®, the use of pharmacy preparations is no longer permitted.

The standard medicinal treatment of depression is based on the Dutch Multidisciplinary Guidelines on Depression. Classical MAO-inhibitors, such as tranylcypromine (and to a lesser degree fenelzine), have a place as the fourth step in treatment, before electroconvulsive therapy. According to the guidelines, its use can be considered as long as treatment based on steps 1, 2 and 3 was unsuccessful. This means that its place in the treatment guidelines agrees with the registered indication for tranylcypromine.

Drug rediscovery trajectory

Tranylcypromine (Tracydal®) is registered, via a *drug rediscovery project*, based on well-established use. This means the registration authority has assessed its efficacy based on an intensive examination of the literature and current European treatment guidelines. The applicant does not have to submit new clinical research for an assessment involving well-established use. If there is no new clinical research, the registration authority carries out an assessment based on the available scientific literature.

In its assessment report, the EMA concluded that tranylcypromine has a place in the treatment of patients with severe depression who are resistant to several medicinal treatment options even though the available studies do not irrefutably substantiate the efficacy of tranylcypromine on this group of patients. This makes it an alternative to electroconvulsive therapy, a treatment with various unfavourable effects, such as amnesia. This place, as last medicinal treatment option, is partly based on the risks involved in the use of tranylcypromine. Apart from orthostatic hypotension, agitation, insomnia and a small risk of agranulocytosis, there is another serious adverse effect that can occur when using tranylcypromine: hypertension as an aspect of the serotonin syndrome during simultaneous use with some medicines or foods containing a large quantity of tyramine (the so-called cheese reaction). This can sometimes provoke a fatal hypertensive crisis. Now that we know much more about how to prevent these reactions to tyramine, the risk is limited to patients who do not comply with the dietary restrictions.

Based on this well-established use assessment, the EMA has granted a marketing permit for tranylcypromine (Tracydal®). This marketing permit is, however, subject to conditions. The manufacturer has been asked for a Risk Management Plan mapping out both observed and potential risks of tranylcypromine. In addition, partly due to the said risks, the indication for tranylcypromine has been limited to prescribed use and the medical supervision of a psychiatrist. Furthermore, agreement has been reached with the Medicines Evaluation Board (MEB) that post-registration research has to take place. The efficacy and safety of tranylcypromine will be studied over a 2-3 year period in a study set-up that was recently approved by the MEB.

GVS assessment

In May 2016 the manufacturer of tranylcypromine (Tracydal®) submitted an application for its placement on List 1B of the Health Insurance Regulation (*Regeling zorgverzekeringen,* Rzv).

The Zorginstituut feels that a scientific discussion within the WAR is not possible due to the lack of studies on the effects of tranylcypromine for the registered indication. Furthermore, as no new clinical study was available and placebo-controlled research was deemed unethical, tranylcypromine could only be assessed by the EMA on the basis of well-established use. As a result, the WAR is unable to issue advice on the therapeutic value according to current standards.

Considerations of Zorginstituut Nederland

* Tranylcypromine is an old product that has been used for many years in the Netherlands, as a non-registered product and a pharmacy-preparation, for severe therapy-resistant depression. Health insurers have reimbursed these products for a long time, and various parties (professional group, patients) support the existing practice of using tranylcypromine as final medicinal option. Tranylcypromine (Tracydal®) has recently been registered for this indication.
* The Multidisciplinary Guidelines on Depression refer to tranylcypromine as final medicinal treatment option for severe, therapy-resistant depression. This agrees with the registered indication.
* The EMA states that tranylcypromine has a place in the treatment of patients with severe depression who are resistant to several medicinal treatment options. This makes it an alternative to electroconvulsive therapy.
* Conditions have been attached to the marketing permit for tranylcypromine (Tracydal®) in order to minimize risks due to adverse effects.
* As indicated in our letter dated 21 December 2015 about 6-tioguanine (Thiosix®), the MEB wants to minimize off-label usage, so the initiative in getting medicines registered for the indication concerned is appreciated. The question is whether it is realistic to demand 'full-blown' controlled research for an application such as this, which arose in clinical practice. On the other hand, by approving this usage based on relatively limited clinical studies, the MEB could be setting a precedent, which would be undesirable. The MEB still emphatically prefers full-blown, controlled clinical research. The Zorginstituut agrees with these points of departure.
* Last but not least: making this product accessible means the prescriber is given/retains an extra treatment option for patients for whom standard medicinal treatment options have failed.

Zorginstituut Nederland's advice

Based on the current criteria, tranylcypromine is not mutually replaceable with any product in the GVS. In principle, this means it is eligible for placing on List 1B. On the grounds of the above, Zorginstituut Nederland advises the Minister of Public Health, Welfare and Sport to include tranylcypromine (Tracydal®) film-coated 20-mg tablets on List 1B of the Rzv. Including it on List 1B will reduce the pharmacy budget by about €2.5 million, as the total costs per year for treatment with tranylcypromine are lower than those of the alternative products (Parnate®/pharmacy preparation).

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The original text of this advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.