Zorginstituut Nederland

Obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

Package advice of *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 18 July 2018

Zorginstituut Nederland has carried out an assessment of the pharmaceutical product obeticholic acid (Ocaliva®), which resulted in the following conclusion.

In a letter dated 10 April 2017 (CIBG-17-04265), the Minister of Health, Welfare and Sport asked *Zorginstituut Nederland* to carry out an assessment of whether obeticholic acid (Ocaliva®) is interchangeable with a drug currently included in the Medicine Reimbursement System (GVS). The *Zorginstituut* has now completed its assessment, after being advised by the Scientific Advisory Board (WAR).

Obeticholic acid (Ocaliva®) is registered (in the form of film-coated tablets with 5 mg active substance) for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

This assessment started in 2017 as a joint assessment with our Belgian colleagues from RIZIV, within the framework of a BeNeLuxA pilot project. RIZIV wrote the pharmacotherapeutic report. The contents of the report have the full support of the *Zorginstituut*.

Timeline of the assessment

The joint assessment ended on 24 July 2017 at the request of Intercept. Intercept opted for its completion as a stand-alone assessment in the Netherlands. The company subsequently needed a very long clock-stop, which the *Zorginstituut* extended beyond the normal period. There were two reasons for this. First, we felt it was important to round off the process as it provided useful experience within the framework of BeNeLuxA for assessments that ultimately became stand-alone assessments. Second, the manufacturer indicated that a publication would appear (within the near future) that would play an important role in the assessment of the effectiveness of the drug. That publication, however, took much longer than the parties initially expected. In the end the manufacturer's response was not available until 17 April 2018.

Short summary of the parties' responses to the pharmacotherapeutic report

The manufacturer, the professional group and the patients' association are in favour of including obeticholic acid in the insured package. They refer to recommendations in the (recently published) guidelines of the European Association for Study of the Liver (EASL) as one of the reasons why the drug should be included in the insured package.

Zorginstituut's advice

The *Zorginstituut* feels that obeticholic acid has no demonstrated added value, because of the following reasons:

- The *Zorginstituut* feels that there are better cut-off points than those used in the clinical trial. As a consequence, the effect of treatment on mortality and morbidity is uncertain;
- The published clinical study (the POISE study) involved mainly patients with

a good prognosis;
- The POISE study's short follow-up of the placebo-arm;
- The insufficient quality of the two new, ad-hoc, surrogate outcome measures that the manufacturer presented in second instance. Unknown is, partly due to the lack of statistical analyses between the study arms, whether 12 months of treatment with obeticholic acid leads to significantly lower risk scores in comparison to placebo.

The *Zorginstituut* therefore advises the Minister of VWS against including this drug in the insured package because of inadequate evidence regarding the drug's performance in daily practice. The available data, though sufficient for conditional market registration, do not warrant a positive assessment for inclusion in the insured package.

Possible candidate for the conditional reimbursement program?
Since 1 January 2012, the Minister of Health, Welfare and Sport can decide to accept into the insured package - for a specific period – care that does not comply with the (legal) definition of 'established medical science and medical practice'. This is on the condition that, within this period of conditional reimbursement, data are collected on the effectiveness and cost-effectiveness of the treatment. Based on the collected data, a decision is made on whether the treatment can remain (without conditions) in the insured package.

We checked, based on the criteria for conditional reimbursement – insofar as they can be assessed based on currently available data –, whether this drug is a possible candidate for the program.[1] In principle, obeticholic acid can be eligible for conditional reimbursement. However, for the moment we cannot issue a statement on the matter. This is because a study was recently published showing that an existing drug (bezafibrate) seems to have similar effects on surrogate outcome measures in the population for which obeticholic acid is intended. Bezafibrate is, however, considerably cheaper.
The *Zorginstituut* will only be prepared to recommend Ocaliva® as a candidate for the conditional reimbursement program if two preconditions are fulfilled. These are:
1. the manufacturer, the professional group(s) and the patients' association state which objectifiable data will illustrate the expected added value (both in terms of efficacy and cost-effectiveness) in comparison with the possible alternative treatment with bezafibrate, including the threshold value of the performance to be realised,
2. the parties indicate a willingness to enter into – and comply with – agreements about a covenant.

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The original text of this excerpt from 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.

[1] The criteria can be found in the most recent version of the letter on procedures for the conditional inclusion of medical care. The letter can be found on our website www.zorginstituutnederland.nl.

Furthermore, Zorginstituut Nederland points out that only a 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.