HEALTHCARE & LIFE SCIENCES - SWEDEN

Off-label use: a comparator in health technology assessments

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Introduction

It is becoming more difficult to demonstrate that new treatments are cost efficient and should be included in the reimbursement scheme. A pharmaceutical company's application to the Dental and Pharmaceutical Benefits Agency (TLV) for a pricing and reimbursement decision regarding a medicinal product with orphan drug status has been rejected. The decision to deny reimbursement for the orphan drug for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) was based on a health technology assessment which took into account off-label use of treatments for pulmonary arterial hypertension (PAH) (for further details please see "Orphan drug denied reimbursement in health technology assessment").

The Stockholm Administrative Court has since upheld the TLV decision.(1)

After the judgment was given, the TLV published a report proposing amendments to the authority's recommendations on economic assessments (formally non-binding).(2) The amendments codify the authority's existing practice and clearly state the possibility for the TLV to take into account off-label use when assessing the cost effectiveness of new treatments.

Decision

The court agreed with the TLV's reasoning that the orphan drug should be compared with available PAH treatments, as it had been shown that PAH treatments are used for the off-label treatment of CTEPH in clinical practice. The fact that the off-label use was due to CTEPH being fatal if left untreated and that there were no previously approved CTEPH treatments did not alter this assessment.

The court noted that the company had not provided material for a comparison between the orphan drug and no treatment. A study between the orphan drug and placebo was considered insufficient. A further indirect study between one of the comparators which the TLV had chosen was submitted; however, it was considered to be uncertain and therefore insufficient. No further indirect comparisons were submitted.

The company had argued that the comparison should be made with a specific PAH treatment (bosentan), as this was the only PAH treatment for which there was some data on the treatment of CTEPH. However, the court focused on the European Society for Cardiology's guidelines, which did not differentiate between specific PAH treatments. The court therefore compared the orphan drug to PAH treatments as a whole.

The decision has been appealed to the Stockholm Administrative Court of Appeal. A judgment is not expected before 2017.

TLV report

The proposed changes to the TLV's recommendations relate to the choice of comparator in the health technology assessment and the analytical method used in that assessment.

The wording in the recommendation for the choice of comparator is that the comparison should be made with the "most relevant treatments in Sweden (eg, the most commonly used ones)" (author's translation).

The proposed change entails that the chosen comparator should be:

> *"the most cost-efficient treatment available in Sweden. Only treatments which are clinically relevant can be used as comparators. 'Clinically relevant' means that the treatment is used in Swedish clinical practice and that the treatment is in accordance with science and proven experience [*lege artis*].*
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> *Also other treatments than medicinal products, medicinal products which do not have the same indications as the medicinal product at issue and medicinal products which are not included in the reimbursement scheme may be used as a comparator. When there are no treatment alternatives which are clinically relevant and cost efficient, the comparator can be 'no treatment'.*
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> *Primarily, direct comparisons between the medicinal product at issue and the relevant comparator should be used. When direct comparisons are lacking or not available, indirect comparisons can be accepted. If possible, adjusted indirect comparisons should be used. Indirect comparisons should be based on systematic reviews of literature and should be presented so that assumptions and methods are clear."* (Author's translation.)

Further, the proposed changes to the recommendation on the analytical method clarifies that analyses based on quality-adjusted life years (QALYs) are the preferred measurement of cost effectiveness. It is also stated that:

> *"As an exception, when it is difficult to use QALYs (eg, in the case of severe pain during a short period of time in connection with treatment), a so-called willingness to pay study could for example be an alternative to measuring health related benefits with QALYs. Studies which measure willingness to pay are however considered to have a lower value as evidence than studies which measure a direct health effect, but can under special circumstances be relevant."* (Author's translation.)

The proposed amendments are on referral until September 30 2016.

Comment

The line of reasoning from the reimbursement authorities and the courts undermines the EU Regulation on Orphan Medicinal Products (141/2000). One of the main incentives of the orphan drug system is market exclusivity, which is intended to encourage investment in the research, development and marketing of orphan medicinal products. The court did not discuss this aspect of the case. Instead, it focused on the material submitted for the health technology assessment and found that it was insufficient. It is possible that the Court of Appeal will discuss the market exclusivity issue, as the appeal has focused on this question.

It is clear from the TLV's proposed amendments that it wishes to clarify that it may take into account off-label use and will require comparisons between the new treatment and the relevant comparator.

A part of the report which is likely to be criticised is an argumentative passage stating that science and proven experience (*lege artis*) is "superior to the regulatory status of a medicinal product", based on the interpretation of existing healthcare ordinances for healthcare malpractice (which is outside the scope of the TLV's supervision). While there is no clear definition presented regarding the proposed formal requirements for science and proven evidence, it is presumed by the TLV that a

comparator has a medical effect if healthcare professionals deem its use to be in accordance with science and proven experience.

Critics of the TLV's proposed amendments claim that accepting off-label use in health technology assessments undermines the regulatory aspects of approved indications in general. The TLV argues in its report that a regulatory approval for an indication is not merely medical and that there may be many reasons for not obtaining or maintaining authorisations, and that choosing off-label use as a comparator does not undermine the regulatory approval process. The TLV states that "off-label use does not take place without good reasons, and is the result of a previously unmet medical need".

Unless the court of appeal takes a different position on this issue, it appears clear that substantial indirect studies between a new approved treatment and off-label treatment may be necessary to obtain reimbursement for certain orphan drugs, and indeed for other new approved treatments. It is also clear from the TLV's report that companies should, where possible, provide studies demonstrating the health economic benefit in QALYs.

These developments appear to be part of a trend in Sweden where the authorities are focused on lowering the costs of medicinal products through various regulatory methods. It remains to be seen what long-term effect this will have for the introduction of new medicinal treatments on the Swedish market.

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Endnotes

(1) Stockholm Administrative Court, Case 30191-14, May 4 2016.

(2) TLV Case 1904/2016, report dated June 28 2016.
