Report

Off-label use of innovative medicines: from the perspective of health insurance

Summary

What is off-label use?

Off-label use is the practice of prescribing medications for a disorder/disease (indication) for which it was not approved by registration. Registration authorizes the manufacturer to trade the pharmaceutical on the national market, based on the Medicines Act (Geneesmiddelenwet).The registration can only take place at the request of the manufacturer as he is liable when the medication is used in its registered, therapeutic areas. If a pharmaceutical is used off-label, the manufacturer is not liable for the consequences of this off-label use and the responsibility of the doctor plays an important role.
A doctor may decide, based on his medical profession and duty, that it is necessary and justified to prescribe a pharmaceutical outside its registered indication.
This may occur when there is sufficient evidence for the safety and efficacy of a specific pharmaceutical used off-label, even though it is not registered for that off-label use. In these situations we often see that the evidence was gathered by others than the manufacturer, and is of a lesser quality as it was not based on an RCT, since registration was not the objective of its use in clinical practice."

Off-label use of innovative medicines

CVZ has carried out research into the off-label use of a number of (bio)technological, oncolytic and immunomodulating medicines. These are innovative medicines which often involve enormous expenses per treatment. The growing use of these medicines has had substantial consequences for pharmacy expenditure. The inappropriate use of this group of medicines is therefore undesirable. On the other hand, the appropriate use of these innovative medicines may well lead to improvements in health.
CVZ has set itself the goal of ensuring that insured clients receive the care they need and not care they do not need. To this end, this report addresses the following questions:

- For which disorders, under what circumstances and where is off-label usage taking place for a selection of these medicines?
- What level of evidence exists for these off-label applications?
- What are the possibilities for obtaining more evidence?

Good scientific

CVZ research shows that although these medicines are often

evidence often lacking

used off-label, the doctors are not always aware of this fact. WIth regard to the scientific substantiation of off-label usage, although there are many individual reports and case studies, solid scientific evidence of efficacy is rare or the existing evidence is inaccessible. Furthermore, it seems that doctors and health insurers are not always familiar with the regulations in the Health Insurance Act [*Zorgverzekeringswet*] and the Medicines Act [*Geneesmiddelenwet*] in relation to the right to these medicines for off-label usage. This sometimes leads to limitations and inequality among insured clients with respect to access to treatments.

Short cycle of development of (bio)technological medicines

The nature of the new generation of oncolytic and immunomodulating medicines leads to research into new (off-label) applications. Most of them have a (bio)technological origin and their cycle of development is shorter than that of traditional medicines. This is evident from the repeated alterations in their registered indication(s), and the addition of new indications soon after being granted marketing permission. Using these medicines for other indications than the registered ones is to be expected due to the fact that their effect is exerted via new modes of action that also play a role for other indications. In practice, it seems that doctors and patients encounter problems regarding the reimbursement of medicines used off-label. A lack of clarity about rights and funding can result in an insured client not obtaining what he needs or actually being given what he does not need.

Difficulty in obtaining evidence on rare disorders

These medicines are often used off-label for rare disorders, which makes it difficult to collect scientific evidence on efficacy of the off-label use due to the small numbers of patients. This means that CVZ has to issue a statement on whether an off-label treatment is an insured form of care on the basis of very limited data. The manufacturers of medicines have no economic interest in research into new applications of existing medicines for rare disorders. Such research should nevertheless take place. The scarce and scattered knowledge and experience regarding off-label use must be made available in the form of scientific publications. This requires the development of treatment protocols and the capture and dissemination of data and results.

New research methods required

CVZ research shows relatively frequent off-label use of these (bio)technological medicines for rare disorders for which there is no alternative treatment. These are disorders with a high disease burden, whereby it is difficult to collect evidence of treatment efficacy based on an RCT. New methods and forms of research are needed in order to be able to issue reliable statements on these treatments within the framework of the insured package.

Transparency of

Although an informal assessment framework already exists for the use of non-randomised studies, officially adopting the notion that the disease should determine the assessment of

the assessment framework for necessary care	the available evidence will require adjustments in current procedures. When only limited scientific publications are available, CVZ will consider its assessment framework for the care which is essential to be ensured . The present levels of evidence will have to be replaced by a weighted assessment of the available evidence. What is also needed is a detailed elaboration of the characteristics that are important for the outcome of weighing up the evidence, e.g., a rare, serious disorder.
Possible price negotiations for off-label use?	The manufacturer fixes the market price of a medicine based on its use for the registered indication. This enables him to recover the costs of his investments. Therefore, off-label use provides unexpected income. CVZ advises the Minister to examine possibilities for negotiating the prices of innovative medicines when used for non-registered indications.
Conditional finance is a suitable instrument	With reference to CVZ's advice 'Conditional finance within the framework of a justifiable package', issued on 1st December 2009, CVZ confirms that such an instrument would be useful for examining the off-label use of medicines within the framework of substantiated inclusion in – or exclusion from - the insured package.