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Off-label use: application and reimbursement

Stosowanie leków poza wskazaniami — przesłanki oraz refundacja

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Abstract

The off-label use of drugs is one of the most important elements of medical practice and, unfortunately, one that is still shrouded in a great deal of controversy and doubt. This is because of a lack of explicit, detailed legal regulations. On the one hand, physicians should follow the dosage regimen and indications for use specified in the summary of product characteristics (SPC), while on the other hand, for some patients, in particular regarding paediatrics and oncology, there may be a lack of therapy that would be characterised for such use as in the SPC. When prescribing off-label therapy, doctors must primarily be guided by current medical knowledge and due diligence. Despite the lack of legal regulations, several criteria can be distinguished that justify the off-label use of drugs, e.g. the need to save the patient's life or the unsatisfactory result of the therapy recommended to date. Before prescribing a particular drug, the patient should be informed, for instance, about the risk of the unregistered use of the medicine. Only after the patient has been properly informed can informed consent for treatment be given. A doctor's failure to satisfy these obligations could expose him or her to civil, criminal or disciplinary liability. Polish law also allows for therapy conducted in indications other than those arising from the SPC to be publicly financed. Although this requires compliance with the statutory requirements, this often constitutes the patient's key opportunity to actually undergo treatment.

Key words: off-label use of drugs, off-label, patient consent, drug reimbursement

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How to define off-label use

Off-label use in everyday medical practice is a relatively common phenomenon. It most frequently arises from the experience of doctors. There is no legal definition of off-label use. The legal doctrine assumes that it is the use of medicinal products in a manner that differs from the use specified in the Summary of Product Characteristics (SPC) [1]. The SPC is one of the documents required for registering a medicinal product so that it can be authorised. The information provided in the SPC is presented by the Marketing Authorisation Holder (MAH) in the registration dossier, and then accepted by the competent authority (*i.e.* in Poland by the Polish Registration Office, URPL).

According to Article 4 of the Act on the Professions of Doctor and Dentist [2], a doctor is required to practice the profession in accordance with current medical knowledge, using methods and measures available to him or her to prevent, diagnose and treat diseases, in accordance with the principles of professional ethics, and with due care.

As the Supreme Court pointed out in one of its judgments: "The Summary of Product Characteristics (...) is not, however, normative, but informative, defining the state of knowledge about this agent at a given moment. (...) Due to the continuous advancement of medical knowledge, a physician must have adequate freedom enabling him to use medicines in a manner that is adapted to current medical achievements and the needs of the given patient"

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[3]. This indicates that the doctor should comply with the SPC when prescribing a specific therapy, although it must also be based on the requirements of current medical knowledge. Therefore, in some cases, most often in paediatrics and oncology, in the absence of regulations arising from the SPC, the doctor may decide to use the medicine in a manner that differs from that specified in the SPC.

Experiment or established practice?

It is worth mentioning that, in the light of the provisions of the Act on the Professions of Doctor and Dentist, the justified off-label use of medicines is not so much the doctor's right as his or her duty. This is because the lawmakers do not allow the doctor to withdraw from treatment because of inconsistency between current medical knowledge and the drug's registration status. However, this differs from a therapeutic experiment [4]. On the one hand, the said act on the medical professions requires the doctor to act on the basis of the available measures, while on the other, Article 21, para. 2 indicates that a therapeutic experiment is the introduction by the doctor of new or only partially tried diagnostic, therapeutic or prophylactic methods in order to achieve a direct health benefit for the person being treated. Conducting an experiment involves increased requirements, such as the need to obtain the consent of the Ethics Committee. The automatic qualification of the off-label use of a medicine as a therapeutic experiment is controversial, although this view was once shared by the National Health Fund in the financing of medicines [5]. From the definition of a medical experiment, it can be deduced that not every use of an off-label drug will have its novel nature, so the position that any use of the drug other than one characterized in SPC is a medical experiment, should be rejected.

However, in its judgment of 24 November 2011, the Supreme Court clearly held that, when making therapeutic decisions, the doctor is responsible for them, so he or she cannot be bound by the dosage method expressed in the SPC. The selection of the appropriate dosage regimen must address the individual needs of the patient [6]. Otherwise, the ability of the doctor issuing the prescription, as expressed in the Regulation of the Minister of Health on prescriptions, to specify the dosage, would not make sense [7].

Criteria for off-label use and the doctor's responsibility

In the absence of clear limits on off-label use, several criteria can be applied if the indication is not contained in the SPC. These include [8]:

- the need to save the patient's life or health;
- the use of all available medicinal products registered in a given indication during the treatment process;
- the lack of efficacy of the current therapy;
- the unsatisfactory result of treatment.

If off-label treatment is recommended, the patient should be informed of all the necessary components, in detail, before consent is obtained. According to Article 9 of the Act on Patient Rights and the Patient Rights Ombudsman (UPP) [9], the patient has the right to be informed about his or her health, as well as to obtain information on the proposed and possible methods of treatment. The patient only has the right to agree to the provision of health services after obtaining the relevant information. The form of consent depends on the nature of the health service being provided. Written consent is required in the case of a health service posing an increased risk to the patient.

In other cases, consent may be provided orally or comprehensively, *i.e.* through such behaviour of the patient that sufficiently expresses his or her intention to undergo a specific therapeutic activity. Whether or not the off-label treatment of a patient with a medication poses an increased risk to the patient cannot be clearly stated. The level of risk of a given procedure can only be assessed subjectively, *i.e.* with respect to a given case, taking into account the level of technical complexity of the treatment, the patient's physical and mental condition, and the experience of the medical staff. The scope and manner of providing information should depend on the result of this assessment [10]. The off-label use of drugs by a doctor should be based on current medical knowledge enabling the assessment of the risks related to such treatment. Simultaneously, appropriate standards of health services should be maintained, because, according to Article 6, para. 1 and Article 8 of UPP, the patient has the right to health services that meet the requirements of current medical knowledge and the assurance that the health services are provided with due care.

The mere consent of the patient for off-label treatment is not equivalent to releasing the doctor from liability for the prescribed medications. The limits of liability are defined by the previously mentioned criteria of current medical knowledge and due care. If the doctor does not act on the basis of these criteria, or fails to meet the information obligation and does not receive the appropriate consent for treatment, he or she exposes themselves to civil, criminal and disciplinary liability. Some consequences are also associated with the financing of off-label indications in drug programmes [11].

Therefore, care must be taken with the off-label use of drugs, which must be based on reliable scientific sources. In the case of legal proceedings, it is the doctor's responsibility to present evidence that proves that the use of drugs outside the indications in the SPC was in compliance with current medical knowledge.

Reimbursement of off-label use

The legal issues related to the reimbursement of medicines in Poland are contained in the Polish Reimbursement Act [12]. The general rule is that the reimbursement indications arise from the indications specified during the marketing authorisation procedure. The prerequisite for reimbursement is that the medicinal product in question is authorised on the Polish market [13]. However, there may be derogations from this rule. According to the teleological interpretation, the scope of reimbursement should be in line with the state of current medical knowledge, which does not necessarily have to be identical with registered indications. Therefore, many products are currently publicly financed on an off-label basis, which is often due to the fact that these products were reimbursed before the Polish Reimbursement Act came into force, and their reimbursement status from before 1 January 2012 was transferred to the new system unchanged. Also, the practice of reimbursing drugs available in pharmacies, or in a catalogue of chemotherapy, or in drug programmes, does not always correspond to the registration indications.

In addition to the above practical examples of off-label reimbursement, the Polish Reimbursement Act provides for a formal procedure for the general (non-individual) public financing of medicines in indications other than those arising from the marketing authorisation, if it is necessary to save the lives or health of patients, where there are no other appropriate medical procedures financed with public funds.

The Polish Reimbursement Act explicitly specifies the ability to finance a medicinal product which has clinical data on its indications for use or dosage, or method of administration, which differ from those specified in the SPC. Such an exceptional procedure only applies under certain circumstances, which are strictly defined in Article 40 of the Polish Reimbursement Act. According to this provision, the Minister of Health may issue a positive administrative reimbursement decision for a medicinal product with clinical data, indications, dosage or means of administration other than those defined in the SPC should it be necessary to save the lives or health of patients, in the absence of other medical procedures financed with public funds which can be applied in a given clinical condition, after consulting the Transparency Council and the national consultant in the relevant field of medicine.

Therefore, a reimbursement decision issued for off-label indications may only differ from sections 4.1 and 4.2 of the SPC. Most frequently, off-label reimbursement will apply to the extension of the population to include paediatrics or the addition of an indication justified by current medical knowledge [14].

This unique procedure is not only an exception to this rule regarding binding registration and reimbursement indications, but is also an exception to the general principle of issuing reimbursement decisions on request. While the regular reimbursement procedure is initiated by the MAH or its representative, the off-label procedure may take place *ex officio* [8]. Furthermore, the procedure of issuing an off-label reimbursement decision does not include a stage of negotiations with the Economic Commission. However, the key element is the opinion of the Transparency Council and of the national consultant in the relevant field of medicine. Although these positions are not legally binding on the Minister of Health, in practice the opinion of the consultant seems to be of crucial importance in the justification — in the light of the principles of evidence-based medicine — of the use of a given product in a specific off-label indication.

Additionally, the medicine in question should be cost-effective and should meet the so-called reimbursement criteria referred to in Article 12, items 4–6, 9, 10, 12 and 13 of the Polish Reimbursement Act (clinical and practical efficacy; safety of administration; relationship between health benefits and risks of administration; impact on expenditures of the entity responsible for financing benefits with public funds and the beneficiaries; existence of alternative medical technology in the meaning of the Act on Benefits and its clinical efficacy and safety of administration; health priorities; and the cost of obtaining an additional year of life).

The need to introduce this unique procedure into the Polish healthcare system, namely off-label reimbursement, primarily arises from therapeutic practice in paediatrics and oncology, which, to a significant extent, is based on off-label treatment [14].

Off-label reimbursement will also play a particularly important role in the cases of rare and extremely rare diseases, where the population is so small that conducting clinical trials for a given disease unit would be cost-inefficient.

Summary

The use of off-label medicines is important in practice, because, in many areas, such as paediatrics and oncology, there is a shortage of medicines that can be used in accordance with the SPC. Following the principle of current medical knowledge, a doctor often goes outside the scope of the SPC. Therefore, it appears to be necessary to precisely define the limits of off-label use. The regulation itself arising from Article 40 of the Polish Reimbursement Act is exceptional, and strictly applies to the financing process. The whole issue of using off-label drugs is definitely of a broader scope. Nevertheless, doctors should primarily consider the patient's life and health, meaning that they should be guided by current medical knowledge and due care when recommending treatment.

Streszczenie

Pozarejestracyjne zastosowania leków (*off-label*) jest jednym z ważniejszych elementów pracy lekarzy, a niestety wciąż budzi wiele kontrowersji i wątpliwości. Wynika to z braku jednoznacznych, szczegółowych regulacji prawnych w tym zakresie. Z jednej strony lekarze powinni się kierować sposobem dawkowania i wskazaniami do stosowania określonymi w charakterystyce produktu leczniczego (ChPL), zaś z drugiej strony w przypadku niektórych pacjentów, w szczególności w dziedzinie pediatrii i onkologii, może brakować terapii, które byłyby scharakteryzowane pod kątem takiego zastosowania w ChPL. Podczas przepisywania terapii *off-label* lekarze muszą się przede wszystkim kierować wskazaniami aktualnej wiedzy medycznej oraz należytą starannością. Mimo braku regulacji prawnych można wyróżnić kilka kryteriów, które uzasadniają zastosowanie leków *off-label*, na przykład konieczność ratowania życia pacjenta czy niesatysfakcjonujący wynik zaleconej dotychczas terapii. Przed przepisaniem określonego leku należy poinformować pacjenta między innymi o ryzyku związanym z pozarejestracyjnym zastosowaniem leku. Dopiero po właściwym poinformowaniu pacjenta można od niego odebrać świadomą zgodę na leczenie. Niespełnienie tych obowiązków przez lekarza może go narazić na odpowiedzialność cywilną, karną lub dyscyplinarną. W polskim prawie przewidziano także możliwość publicznego sfinansowania terapii prowadzonej w innych niż wynikające z ChPL wskazaniach. Chociaż wymaga to spełnienia ustawowych przesłanek, często stanowi kluczową szansę dla rzeczywistego rozpoczęcia leczenia pacjenta.

Słowa kluczowe: pozarejestracyjne stosowanie leków, *off-label*, zgoda pacjenta, refundacja leków

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