National Council of Ethics for the Life Sciences

123/CNECV/2023

OPINION ON OFF-LABEL USE OF MEDICINAL PRODUCTS - ETHICAL IMPLICATIONS

May 2023

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INTRODUCTION

The off-label use of medicinal products is a common therapeutic practice in any healthcare system. The CNECV's opinion provides an analysis of the technical reasons justifying the off-label use of medicinal products, as well as the ethical and legal implications thereof, and makes the corresponding recommendations.

According to the European Medicines Agency (EMA), the off-label use of a medicine refers to situations in which the medicine is used intentionally for a medical purpose, under conditions that do not comply with the terms of the marketing authorisation. More specifically, off-label use is the use of the medicine in conditions other than those expressly stated in the Summary of Product Characteristics (SmPC), the content of which is approved by a regulatory authority when the marketing authorisation is granted.

In most countries, the process for approving medicines for use in clinical practice requires prior demonstration of their quality, safety and efficacy, thus requiring pharmaceutical companies to submit scientific evidence to regulatory authorities. For safety and efficacy, the evidence is derived from the results obtained in clinical trials conducted during the drug development phase, where the drug is compared with a placebo or with another existing drug under a set of well-defined conditions. These include the pathology in question, the patient population included in the study, the route of administration adopted, the administered dose of the active substance present in the medicine in a given pharmaceutical form and the dosage. The granting of a marketing authorisation by a regulatory authority implies that the medicinal product presents a favourable benefit/risk ratio under the specific conditions of the clinical trials conducted, and that the therapeutic indications and conditions of use of the medicinal product in clinical practice are expressly approved.

After medicinal products are made available on the market and in the course of their regular use in clinical practice, often involving millions of patients in different parts of the world, scientific evidence concerning their safety and effectiveness is often

produced in situations which were not approved when the marketing authorisation was granted, namely regarding the therapeutic indication, the patient's age, the dose administered, the posology, the route of administration and the pharmaceutical form. It must be emphasised that the level of this scientific evidence, which as a rule does not derive from clinical trials, is therefore often lower than that submitted when the marketing authorisation is granted, which is the basis for the approval of therapeutic indications and the conditions for use of the medicinal product in clinical practice.

However, despite the lower level of scientific evidence, in certain situations and in the belief that there are benefits for patients, doctors prescribe and pharmacists dispense medicines for use in unapproved conditions, which constitutes off-label use.

As a rule, the off-label use of medicines is accepted in specific situations, with the patient having to give written informed, informed and free consent in advance, in accordance with Rule no. 015/2013, of 03/10/2013, of the Directorate-General for Health (DGS), updated on 04/11/2015 , provided that certain requirements are met, namely: i) there is no medicinal product approved for the patient's clinical condition in the set of medicinal products with MA available on the market; ii) the off-label use of the medicinal product is supported by scientifically convincing results; iii) the off-label use of the medicinal product provides therapeutic results with a favourable benefit/risk ratio for the patient; iv) adequate patient monitoring is in place. In the context of this last requirement, it is particularly important to also institute active pharmacovigilance, since the off-label use of the medicinal product, not having been previously evaluated by a regulatory authority, has an increased potential for the occurrence of un-described and unexpected adverse drug reactions (ADRs).

OPINION

Considering that:

a) the off-label use of medicines constitutes a frequent practice in therapeutics, the recourse to which is justified by beneficent values, with a view to providing specific patients with the most appropriate treatment for their clinical situation, in the light of the best available scientific evidence;

b) the system for the approval of medicines, namely the granting of a Marketing Authorisation (MA) by the regulatory authorities, requires the submission of scientific

evidence of their safety and efficacy under the specific conditions of the clinical trials conducted, and the therapeutic indications and conditions of use of the medicine in clinical practice are expressly approved and set out in the respective Summary of Product Characteristics (SmPC)

c) after the medicines are made available in the market and in the course of their regular use in clinical practice, scientific evidence is often produced concerning their safety and effectiveness in situations that were not approved when the MAA was granted

d) under the regulatory system in force, only the holder of the marketing authorisation for a medicine may request the regulatory agencies to add new therapeutic indications or new conditions of use for the medicine, which rarely happens;

e) it is not the legal competence of Infarmed, I.P. to pronounce on the off-label use of medicines;

f) off-label use may be justified when there is no approved off-label medicine for a specific clinical condition of a specific patient and there is sufficient scientific proof of the benefit of off-label use provided that the risk-benefit evaluation is positive and that it is significantly more cost-effective

g) it is possible to identify in clinical practice three distinct situations of off-label use of medicines, which differ in terms of the clinical evidence available, thus configuring distinct levels of risk, with ethical contours that are also distinct, dictated by different degrees of (in)certainty

h) there is a clear diversity of procedures in Portugal as regards the pronouncement of Pharmacy and Therapeutics Committees (CFT) and Hospital Ethics Committees (EC) on the off-label use of medicines and that, in outpatient clinics, whether in primary healthcare units or in private medical practices, the off-label prescription is not preceded by any technical-scientific or ethical assessment by CFT and EC

i) there are also significant differences between the procedures adopted in hospital in terms of obtaining the patient's informed consent and that in outpatient clinics this is not frequent;

j) obtaining the patient's informed consent is a fundamental ethical process that arises from respect for the person and the expression of his or her autonomy to the extent of his or her capacity

k) the validity of the patient's informed consent is based on the adequate transmission of information and on the proven understanding of its premises, including the anticipated benefits and inherent risks, leading to a free and informed decision, which is especially relevant in situations of off-label use of medication;

The CNECV is of the opinion that:

1. the off-label use of medicines should be restricted to situations in which i) in the set of medicines with a MA, there is no one approved for the patient's clinical situation; ii) off-label use is supported by credible scientific evidence; iii) off-label use produces therapeutic results with a favourable benefit/risk ratio for the patient; iv) off-label use is significantly more cost-effective; v) adequate patient monitoring is instituted, in particular active pharmacovigilance;
2. the National Pharmacy and Therapeutics Commission should play an active role in matters of off-label use of medicines, pronouncing on the different off-label uses covered in each of the three situations identified in clinical practice and which are practised daily in Portugal, not only at hospital level but also in outpatient clinics;
3. within the scope of their mission to regulate good professional practice, the professional associations for doctors and pharmacists should play a more active role with regard to the off-label use of medicines, namely by pronouncing and issuing recommendations, on a technical-scientific, deontological and ethical level, on the off-label use of medicines practised in Portugal;
4. the off-label use of medicines shall be ruled by procedures standardized at a national level, both as regards their previous evaluation on a technical-scientific and ethical level, and as regards the obtaining of the patient's informed consent
5. the off-label use of medicines in hospitals shall be subject to analysis and pronouncement by the institution's CFT and EC beforehand, under the terms foreseen in point 6, and a similar mechanism shall be created for the off-label use in outpatient clinics, under the terms of points 11. and 12;
6. in hospital settings, three situations of off-label use of medication identified in clinical practice justify the adoption of differentiated approaches and procedures, with ethical requirements proportional to their growing degree of uncertainty and risk:

i) when the off-label use of a medicine is supported by recognised clinical evidence and is fully established in clinical practice, often integrating therapeutic guidelines/guidelines, it is justified that the off-label use and the therapeutic protocols that provide for it, after prior assessment at the technical-scientific level by the CFT and at the ethical level by the EC, Approval should be given for use in a given hospital facility in all patients who meet the respective clinical criteria. Periodic reassessments should be made at each renewal of the mandates of the TWC and EC and whenever justified by the evolution of scientific knowledge. The duty to permanently update therapeutic protocols assumes, in the case of off-label use of medicines, an added ethical requirement. As regards the informed consent of the patient, in these cases, the adoption of a simplified procedure is justified, with information to the person or his/her legal representative or health care proxy on the need for the off-label use of the medicine, explaining the advantages and possible underlying risks, dispensing as a rule the written form, but always making a note in the respective clinical file;

ii) when the off-label use refers to a medicine that has been in the market for several years (at least three years) and is occasionally used to treat specific patients, sometimes constituting a new use, involving a new therapeutic indication or new conditions of use that have not been approved, in which there is little scientific evidence of safety and potential benefit, prior assessment by the SFC and EC should be carried out on a case-by-case basis, with due regard for the scientific evidence available and the patient's clinical condition. Responses from CTFs and ECs should be provided in a timely manner. Informed consent should always be given in writing;

iii) When off-label use involves innovative medicines for the treatment of specific patients, which may entail significant complexity due to the scarcity of data on safety and effectiveness under the specific conditions of use, prior assessment by the OTC and EC should be conducted on a case-by-case basis, taking due account of the available scientific evidence and the patient's clinical condition. In addition, as innovative medicines are usually costly, it is necessary that the OTC perform not only a

pharmacotherapeutic assessment, in order to determine the added therapeutic value in relation to the currently available treatment, but also an economic assessment, in order to determine the corresponding cost-effectiveness profile. These issues assume particular relevance in the case of innovative medicines used in patients with particularly serious pathologies, such as cancer. Responses from CTFs and ECs should be provided in a timely manner. Informed consent should always be given in writing;

7. the medical prescription in a hospital context shall clearly indicate that it is an off-label use, and the information shall also be registered in the patient's clinical file;

8. when validating the prescription, the hospital pharmacist shall pay attention to the appropriateness of the off-label use of the medicine and its conformity with the protocols approved by the CFT and EC and in force in the hospital or with the specific authorizations of these committees for the patient in question;

9. at the moment the medicine is administered, the health professional who administers it should be aware that it is an off-label use;

10. in cases where a medicine is dispensed in the hospital pharmacy in off-label use to outpatients, the pharmacist, at the time of dispensing, shall duly inform the patient as to the correct use of the medicine and contribute towards promoting the safety and effectiveness of the therapeutic;

11. the principles formulated above for the prior evaluation of the off-label use of medicines, both technical-scientific and ethical, at the hospital level, should, in essence, also be adopted in outpatient clinics, whether in primary health care units or in private medical practices, for each of the three identified typologies of off-label use of medicines;

12. CFTs and ECs of the Regional Health Administrations (ARS), or equivalent structures, should assume, at a regional level, the responsibilities of evaluating the off-label use of medicines in conditions comparable to the hospital setting (referred to in 6.), in order to guarantee the necessary technical-scientific and ethical support for the off-label prescription of medicines in outpatient clinics, justifying the adoption of differentiated approaches and procedures, with ethical

requirements proportional to their growing degree of uncertainty and risk, for the different situations of off-label use of medicines:

i) when the off-label use of a medicine is supported by recognized clinical evidence [as described in 6. i)], it is justified that the off-label use and the therapeutic protocols that foresee it receive approval for outpatient use in all patients who meet the respective clinical criteria. Informed consent shall adopt a simplified procedure, with the person or his/her legal representative or health care proxy being informed of the need for off-label use of the medicine, explaining the advantages and possible underlying risks. The written form may be dispensed with, always noting it in the respective clinical file;

ii) when the off-label use refers to a medicine that has been on the market for several years (at least three years) and is occasionally used in the treatment of specific patients [as described in 6. ii)], prior assessment by the CFT and the EC of the Regional Health Authorities should be carried out on a case-by-case basis and in due time, with due regard for the scientific evidence available and the patient's clinical condition. Informed consent should always be given in writing;

iii) where off-label use involves innovative medicines for the treatment of specific patients [as described in 6. iii)], prior assessment by the FCT and the NRAs' EC should occur on a case-by-case basis, with due regard to the available scientific evidence and the patient's clinical condition. An economic assessment should also be carried out in order to determine the corresponding cost-effectiveness profile. Responses from CTFs and ECs should be given in a timely manner. Informed consent should always be given in writing;

13. the outpatient prescription shall also clearly indicate that it is an off-label use, and the information shall also be recorded in the patient's clinical record;

14. when dispensing a medicine which is prescribed off-label, the community pharmacist must have the necessary conditions in place to adequately inform the patient or his/her caregiver about the correct use of the medicine and contribute towards promoting the safety and effectiveness of the therapeutic, namely by accessing the patient's relevant clinical information

15. as regards the informed consent of patients, whether in an inpatient or outpatient setting, the physician shall ensure that the information on the off-label use of the drug has been adequately conveyed and its premises understood, so that the decision of the patient or his/her legal representative is truly informed

16. the undertaking of clinical research with the purpose of producing evidence to support the safety and effectiveness of medicines constitutes an ethical imperative, particularly in those cases where the available scientific evidence is scarce

17. experimental studies, amongst which those clinical trials known as "investigator-initiated", in the context of the off-label use of medicines, due to their relevance, shall be strongly promoted and encouraged, from the outset by the entities that finance scientific research in Portugal, namely the Foundation for Science and Technology;

18. it is also important to motivate health professionals and researchers in the area of health, as well as their institutions (e.g. universities, hospitals, clinical academic centres), to establish partnerships that continuously promote the strengthening of the link between scientific research and clinical practice in the context of off-label use of medication, and consequently the carrying out of clinical (translational) research;

19. sharing the clinical experience of health professionals as to the off-label use of medicines should be strongly encouraged, namely by promoting, in health establishments and units, a culture of presenting this topic in congresses and other scientific meetings and publishing it in peer-reviewed scientific journals;

20. it is necessary to perfect the incentives that already exist at the European level and develop other, complementary ones, as well as to appeal to the social responsibility of pharmaceutical companies, encouraging them to i) include in their pre- and/or post-marketing clinical trials patient populations that are not usually covered and ii) regularly study other therapeutic indications and/or other conditions of use that are justified for the medicines developed, different to those already approved;

21. pharmaceutical companies should be strongly discouraged from adopting commercial strategies of market segmentation by introducing a new and usually

more expensive medicine onto the market, rather than requesting that regulatory agencies add new therapeutic indications or new conditions of use to the MAA of a medicine already available on the market.

22. an electronic platform dedicated to the off-label use of medicines must be created, in which the off-label use of medicines is registered, as well as the respective positive and negative effects, and with interoperability with the other health information systems.

Lisbon, 21 April 2023.

The President of the CNECV, *Maria do Céu Patrão Neves*.
Rapporteurs: *Carlos Maurício Barbosa, André Dias Pereira, Miguel Guimarães*.

The present opinion was adopted unanimously on 21 April 2023, at the 276th plenary meeting of the CNECV, which was attended by the councillors:

Maria do Céu Patrão Neves (Presidente); André Dias Pereira (Vice-Presidente); Carlos Maurício Barbosa; Helder Mota Filipe; Inês Fronteira; Inês Godinho; João Queiroz e Melo; João Ramalho-Santos; José Manuel Pereira de Almeida; Luís Madeira; Margarida Silvestre (por meios telemáticos); Maria de Lurdes Martins; Miguel Guimarães; Miguel Oliveira da Silva; Miguel Ricou; Paula Pinto de Freitas; Pedro Fevereiro; Rosalvo Almeida.

Hearings held within the framework of Opinion No. 123/CNECV/2023
25 January 2022 - Hearings:

- President of INFARMED, Dr. Rui Santos Ivo
- Vice-President of INFARMED, Dr. António Faria Vaz

INFARMED technical team:

- Dr. Marta Marcelino, Director of the Directorate for Drug Evaluation
- Dr. Cláudia Furtado, Director of Health Technologies Evaluation
- Dr. Joana Castro, Director of the Legal Office.

9 March 2022 - Working meeting:

- Dr. Marta Soares, Clinical Director and President of the Pharmacy and Therapeutics Committee of the Portuguese Oncology Institute of Porto (IPO-Porto).
- Dr. Artur Lima Bastos, President of the Ethics Committee of IPO-Porto.