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On 8 April 2017, the CPME Board adopted the 'CPME policy on off-label use of medicinal products' (CPME 2017/006 FINAL).

CPME policy on off-label use of medicinal products

The Standing Committee of European Doctors (CPME) represents national medical associations across Europe. We are committed to contributing the medical profession's point of view to EU and European policy-making through pro-active cooperation on a wide range of health and healthcare related issues[1].

Good medical practice in the patient's best interest requires that physicians use available medicinal treatments according to their best knowledge and judgment. This can include, in some clinical situations, the off-label use of a medicinal product when it is judged by the doctor to be in the best interest of the patient on the basis of current medical knowledge.

Such practice is particularly common in certain areas of medicine, such as in paediatrics, where there is a lack of medicinal products which have been adequately tested and authorised for use in children.

To ensure a responsible use of medicinal products, CPME considers the following points as particularly important to be considered.

What is the off-label use of a medicinal product?

Before being made available to patients across the EU, a medicinal product must obtain a marketing authorisation, granted by an EU or national regulatory authority, for one or more specific indication(s) based on extensive clinical and non-clinical data on safety and efficacy. The objectives of the authorisation process are to ensure the pharmaceutical quality, effectiveness and patients´ safety. Moreover, a rational pharmacotherapy requires the collection of valid study data.

The 'Off-label' use refers to the use of an authorised medicinal product which is not in accordance with the product information included in the Summary of Product characteristics (SPC). Examples include the use of a medicinal product for a different indication, in another age range, dose or route compared to what is approved by the regulatory authority.

This should not be confused with 'compassionate use', which is the regulatory tool for an early patient access to an unauthorised medicinal product, coordinated and implemented by EU member states and recommended by the EMA´s Committee for Medicinal Products for Human Use (CHMP). ´Compassionate use` allows groups of patients with a chronic, seriously debilitating, or life-threatening

[1] CPME is registered in the Transparency Register with the ID number 9276943405-41. More information about CPME's activities can be found under www.cpme.eu

disease, without a satisfactory authorised treatment available and who cannot take part in a clinical trial, access to an unauthorised medicinal product.

Consequences of the off-label prescribing, including responsibility issues

The responsibility that falls on the doctor when prescribing a medicinal product off-label is greater than when prescribing an authorised medicinal product within the terms of its marketing authorisation. If the off-label prescribing may sometimes be clinically beneficial, it may also be associated with a number of clinical, safety, legal and ethical issues. For instance, the physician may expose her/his patient to an ineffective therapy or to unknown risks of severe adverse reactions. Moreover, the patient may not benefit from the strict liability of the producer for adverse effects where medicinal products are used off-label.

This is why the doctor has the responsibility to be well informed about the medicinal product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. In particular, the doctor should be very careful with regard to observations, keeping records and pay particular attention to the risks associated with using a medicinal product off-label, in particular adverse reactions. Finally, the doctor must always consider if an off-label prescription should be part of a clinical trial.

Guidelines

Bearing in mind that the divergence in drug laws, social laws and professional rules across Member States (see the EU Study on off-label use of medicinal products in the EU, published in February 2017) may complicate a uniform approach or guidance, strict guidelines should be followed to reduce inappropriate use, unnecessary risks and, ultimately, enhance patient safety:

- Off-label use should only take place when there is no alternative authorised treatment that would better serve patient's needs. Consequently, the physician should be able to check if there is an at least equally effective authorised medicinal product available for the same indication before she/he decides to prescribe a medicinal product outside its terms of use.
- As for any treatment, available efficacy and safety data should be weighed against the seriousness of the underlying condition. The physician should systematically weigh whether the expected benefits outweigh the possible side effects and risks for the specific condition.
- Decision to prescribe a medicinal product off-label should be evidence-based. The physician shall ensure that there is sufficient evidence and/or experience of using the medicinal product under the same circumstances to show its safety and efficacy (ie. professional clinical guidelines, peer-reviewed articles or other documented information available to support her/his decision).
- Informed consent should be required. The physician must inform the patient before a medicinal product is being used off-label, except in emergency cases, and provide sufficient information about the proposed treatment, including the reason(s) for using the medicine off-label, possible adverse reactions and, whenever needed, additional information about any uncertainties associated with such use, in order to enable her/him to make an informed decision.
- Appropriate monitoring of the patient should be ensured. The physician must take responsibility for overseeing the patient's care, including the monitoring and follow-up of the

patient. This should include recording the prescribed medicinal product, the reason(s) for prescribing this medicinal product off-label and the fact that the risks have been discussed with the patient.

- Reporting of adverse events is equally important whether the use of a medicinal product occurs within or outside the terms of the marketing authorisation. In this respect, the directive 2010/84/EU on pharmacovigilance provides that the pharmacovigilance system, established by Member states, shall also be used to collect adverse events arising from use outside the terms of the marketing authorisation.

Policy recommendations

In order to diminish the insecurity and risks related to such practice, CPME recommends the following actions to be taken on a national or preferably at a European level:

- As a general rule, routine off-label use of a medicinal product should not be recommended before there is sufficient clinical evidence or at least broad consensus that such use is beneficial. This is meant to prevent widespread off-label use without necessary supporting data.
- Where the off-label use of a medicine is common and evidence-based, it should be the responsibility of both the marketing authorization holder and the responsible regulatory authority to take appropriate measures to address legal uncertainty and safety concerns.
- While mainly the positive results of an off-label use are reported in academic literature, the level of evidence published on the adverse events arising from such use is scarce. Consequently, measures must be taken to encourage the notification of adverse reactions related to off-label use at national or even at a European level, through the EUDRAVIGILANCE database, in order to obtain objective data on the risks and benefits.