Declaration on Good Off-Label Use Practice

Recent concerning events in Member States following the passing of legislation to promote the off-label use of medicines for economic purposes, highlight the importance of preserving the European regulatory framework to ensure the safery of patients. The following Good Off-Label Use Practices principles stem from decades of research and clinical practice and serve to create a framework for healthcare practicon-ers to ensure that patient safety always prevails over cost considerations. The signatories of this declaration call on the European Medicines Agency to adopt strict guidelines to support healthcare practioners and ensure economic benefit does not prevail over public health.

Off-label Use of medicinal products should only occur if the following criteria are met:

1. **Presence of a severe, life-impairing or life-threatening condition;**
2. **Absence of authorised treatment or repeated treatment failure;**
3. **Absence of alternative treatments authorised for the condition;**
4. **The off-label use is supported by strong evidence in scientific literature;**
5. **The patient has been educated and has given his or her informed consent;**
6. **Presence of established reporting routes for adverse events and linked to off-label use.**

In all instances, off-label prescription should only occur after individual assessment of the treating physician of the needs of the individual patient. Physicians need to be given the freedom to uphold their pledge towards their patients to act ethically and put the patient's interest first. They should be supported by the public bodies and authorities responsible for the approval and usage of medicines whose role is to protect public health.

EFNA European Federation of Neurological Associations
EBC European Brain Council
emsp EUROPEAN MULTIPLE SCLEROSIS PLATFORM
European Alliance for Access to Safe Medicines
EMA European Medical Association
Duchenne Parent Project onlus
Accademia dei Pazienti Conoscere per Decidere
United Parent Projects Muscular Dystrophy

Background

Before reaching the market, medicines need to obtain a marketing authorisation for a specific indication based on the balance of the desired effects or 'benefits' of the medicine against its undesired effects or 'risks'. The information regarding how, and by whom, the medicine should be taken, based on extensive testing of the product's quality, efficacy and safety, is described within its label (packaged insert). This strict procedure is designed to maintain the highest levels of patient safety and minimise adverse events.

Off-label use is the practice of using a medicine outside of its authorised indication, dose, route of administration or patient group. It plays an important part in medical practice, since it may be of benefit to patients when no other authorised treatment option is available. This is often the case with serious or life threatening illnesses (e.g. cancer or rare diseases) where patients and physicans run out of treatment options.

While there is support for off-label use in specific circumstances, a growing trend of promoting the prescription of medicines off-label without a medical rationale but for other motives such as cost-containment and economic reasons compromises patient safety. Member States are passing legislation / guidelines / or establishing practices promoting off-label use mainly to reduce healthcare spending - for instance in Italy, France and Denmark. These practices create unnecessary and avoidable risks for patients, often without their consent. This view is supported by the European Court of Justice, which has ruled that patient safety must always prevail against any economic rationale.

Good Off-label Use Practices – A closer look

1. Presence of a severe or life-threatening condition

The off-label use of a medicinal product entails taking risks with patient safety as the product has not been tested for the particular indication for which it is being used. This risk is only justifiable if a condition is severe or life-threatening and, as a result of it, the risks related to non-treatment are higher than those linked to the off-label use of a medicine.

Sildenafil (Viagra) has been used off-label in the treatment of patients with Pulmonary Arterial Hyperten-sion with very good results. Now it has been recently authorised as an orphan drug under the name of Revatio with a new label that states Pulmonary Arterial Hypertension as an indication.

2. The authorized treatment has failed repeatedly or is not available in a specific country

Physicians may decide to prescribe medicines off-label if the standard treatment has failed or is not available in a particular market. This condition should however not result in Member States delaying entry into market of a particular product so they can justify the use of an off-label alternative for economic reasons.

Indeed, the European Court of Justice has ruled that off-label use cannot be encouraged for economic purposes and that economic considerations should never prevail over patient safety interests.

For example, Fucidin – an antibiotic (tablet or ointment) to treat bacterial infections caused by a specific germ (Staph aureus) – is considered to be standard of care for the treatment of specifc infections in cystic fibrosis patients. However, the treatment is not available in every EU Member State (e.g. Belgium).

3. There is no authorized treatment option for the condition

Many diseases continue to lack any medicinal products to treat them. This is often the case for rare diseases or for paediatric indications. In these cases, physicians may prescribe an off-label product as long as they receive patient consent and there is strong evidence to support the physician's decision.

As an example, Thalidomide is used off-label in dermatology to treat rare diseases where there are no alternative treatments available, such as Prurigo Nodularis, Osler-Weber-Rendu Disease or Jessner-Kanof Disease. Thalidomide had been developed as a sedative agent and was taken off the market in 1961 after it was linked to thousands of birth defects. Despite its teratogenicity, it was reintroduced in 2008 as an authorized treatment for the treatment of multiple myeloma following extensive research and development. Later, it was approved for the treatment of Erythema nodosum leprosum, a skin complica-tion in Lepra patients.

Most medicinal products used in the treatment of cancer in children have a label that mentions "do not use in children." No other authorised treatments exist for children and there is a lot of evidence in the literature about the successful use of specific products in children with cancer.

4. The off-label use is supported by strong scientific evidence in the literature

Even when authorised treatments have failed or there are no other on-label treatments available, medicines should only be used off-label if there is strong scientific evidence in the literature of their potential benefit for a particular condition. Ideally, published reports of well-designed clinical studies will be available or support for the off-label use will be provided in peer-reviewed literature.

While it may not always be possible to gather this evidence, there needs to be an overall positive therapeutic perspective as reflected by clinical evidence, expert opinion, best practices, and/or authorita-tive guidelines. In addition to this, there should be an absence of potential clinically important concerns about the treatment option, such as increased toxicity with no substantial therapeutic gain as compared to the authorized standards of care.

As an example, to date, limited evidence is available regarding outcomes of the treatment of breast cancer during pregnancy as clinical trials with anti-cancer medications are almost impossible to conduct. As strong evidence by clinical trials cannot be obtained, observational studies have been published in peer-reviewed journals and expert opinions in peer-reviewed journals discuss the pros and cons of interrupting treatment in patients with breast cancer during pregnancy or to receive inferior therapy.

5. Patients have been fully educated and have given their informed consent

Signatories agree that off-label treatments should be initiated by a physician in collaboration with the patient based on a medical assessment of the latter's therapeutic needs.

This is an important element of our good off-label use practices for a number of reasons. First of all, given the safety risks involved with the use of an off-label product, it is important that the patient understands the proposed treatment option and is informed of any risks. Secondly, patients should be made aware of the product they are being prescribed so that they can accurately self-report adverse events. This is crucial as the off-label use of medicines creates uncertainty around liability and physicians may be less likely to report adverse events experienced by the patient.

6. Physicians and patients report adverse events and outcomes linked to the use of the off-label product through established routes

Pharmacovigilance activities may be hindered by the off-label use of products because of inaccurate reporting of adverse events and the fact that patients may not always know they are being prescribed off-label.

The EudraVigilance platform, the European data processing network and management system for reporting and evaluating suspected adverse reactions could be used to gather better data on adverse effects but patients still lack all the necessary information about self-reporting as they may not always read the product's label.

Furthermore, in academic literature there is a tendency to report only positive experiences with off-label products rather than recording adverse events. Literature can therefore be unbalanced and an effort should be made to publish articles and reports of adverse events linked to the off-label use of a product.

It is crucial for patients and physicians to report adverse events and outcomes as accurately as possible. Furthermore, the use of patient registries should be encouraged.

About the author

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