Frequently asked questions

04/11/2010

Q&A ON OFF-LABEL USE OF MEDICINES

Version 3

Information compiled by Eurordis

All drugs need approval for specific indications before they can be sold in that indication. Off-label use is the practice of prescribing pharmaceuticals for an unapproved indication. Off-label use of medications is very common. Up to one-fifth of all drugs are prescribed off label. Off-label use of medicines can help many patients as not all rare diseases benefit from an approved and well evaluated medicinal product.

This document answers some of the questions you may have on off-label use of medicines.

Q&A on off-label use of medicines

CONTACT YOUR NATIONAL REGULATORY AUTHORITY TO LEARN MORE

WHAT IS CALLED THE ON-LABEL OF A MEDICINE? 1 | one

The label of a medicine can be defined as the uses of the medicine, along with the conditions under which the medicine should be used.

The uses of a medicine are defined by the regulatory authorities during the evaluation of its benefits and risks: they clearly mention a disease, a medical condition or health status the medicine is aimed at treating or preventing. Sometimes even the stage of the disease is part of the indication (in rare cancers, e.g. metastatic stage versus non metastatic). The conditions of use are defined in the approved product information leaflet.

For example, the label of PegIntron® is: PegIntron® is used to treat long-term hepatitis C (a disease of the liver due to infection with the hepatitis C virus) in patients aged three years and older. For this condition

(hepatitis C infection), the efficacy (including the dose) and safety of the medicine were evaluated with animal studies followed by clinical trials in human.

WHAT IS CALLED THE OFF-LABEL USE OF A MEDICINE? 2| two

Any use that does not correspond to the conditions of use as defined by regulatory authorities at the time of marketing authorisation is off-label use. By definition, off-label use of a medicine applies for products that benefit from a marketing authorisation.

In the example above, PegIntron® taken by a patient who does not suffer from hepatitis C but from Kaposi Sarcoma, Chronic Myeloid Leukaemia, or Polycythemia Vera (Vaquez disease) is off-label use. This does not mean the product can not help the patient with one of these rare diseases, it means the efficacy and safety of PegIntron® to treat them has not been scientifically evaluated but there are sound scientific reasons to believe it can help patients with these diseases.

The PEG (polyethylene glycol) protects the molecule from proteolytic breakdown and increases the biological half-life of the interferon. PegIntron® or Pegasys® can be used by weekly infusions, whereas IntronA is given three times per week or even more frequently. Else, their characteristics are very similar.

	to treat hepatitis C infection	to treat Kaposi Sarcoma	to treat Polycythemia Vera	to treat Chronic Myeloid Leukaemia
PEGINTRON®	on-label	off-label	off-label	off-label
PEGASYS®	on-label	off-label	off-label	off-label
IntronA®	on-label	off-label	off-label	on-label
Clinical trials for the efficacy and safety of interferon	Completed and evaluated (marketing authorisation)	Interferon only, not the pegylated form	Trials with pegylated interferon in progress	Interferon only, not the pegylated form

IS OFF-LABEL USE LEGAL? 3| three

The fact that a medicine has not been evaluated for all its possible uses does not mean that it cannot be helpful for other uses (indications). Doctors' freedom of prescription exists: with certain limitations sometimes defined by law, they can prescribe a medicinal product without fully respecting the label, if it is reasonable or appropriate.

This possibility benefits both public health and patients. Most medicines prescribed to children are off-label: since the dose and conditions of use were not tested in this population, the use in this age groups ins not part of the label. Moreover, important medical progress is derived from off-label use of a medicine. A striking observation made in the 50s by Dr Jacob Sheskin, Hansen Leper Hospital in Jerusalem, who prescribed thalidomide as a sleeping pill (its approved label by that time) to a patient suffering from leprosy: not only could the patient sleep, but the next morning he woke up with significant improvements in his leprosy scars and pain (this revealed the anti-inflammatory activity of this product). In the USA, the Food and Drug Administration (FDA) approved thalidomide to treat leprosy in 1998.

IS PROMOTION OF OFF-LABEL USE LEGAL? 4| four

Both in the EU[1] and in the US, the promotion of off-label use is banned.

In the US, Food and Drug Administration guidelines enable pharmaceutical companies and their sales representatives to provide information that is complete, accurate and not misleading, such as articles from peer-reviewed journals about off-label uses, to healthcare professionals only.

CAN A PHARMACEUTICAL COMPANY BE SUED FOR THE PROMOTION OF OFF-LABEL USE?

In the fraud case involving the epilepsy drug Neurontin in the US, it was alleged that Parke-Davis promoted the use of Neurontin for patients with bipolar disorder, Lou Gehrig's disease, drug and alcohol withdrawal seizures and attention deficit disorder, and made payments (kickbacks) to encourage the expansive use of the drug. Financial inducements led doctors to prescribe Neurontin to patients who otherwise wouldn't have received the drug. The company, Pfizer, paid US$ 430 million to settle criminal charges and civil liabilities resulting from the qui tam[2] case that exposed the practice.

WHAT ARE THE RISKS RELATED TO OFF-LABEL USE? 5| five

1. A relative lack of readily available information for prescribers, nurses, patients or consumers about the unapproved use of some medications and in particular the higher risk of adverse drug reactions.
2. Inversely, the failure to prescribe off-label medications in patients where it might be appropriate may constitute malpractice (e.g. as indicated by the American Academy of Paediatrics)
3. Expert consensus meetings develop “treatment and care management guidelines for diseases”. There needs to be a balance between these guidelines independent from the influence of pharmaceutical companies whilst still maintaining a good working relationship to obtain maximum knowledge about unlicensed or off-label use of medications. Potential conflicts of interest should be acknowledged.

[1] Article 87, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Official Journal L – 311, 28/11/2004, p. 67–128:

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorisation has not been granted in accordance with Community law.
2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

[2] Whereby a private individual who assists a prosecution can receive all or part of any penalty imposed

WHAT SHOULD BE DONE BEFORE PRESCRIBING? 6 | six

Before prescribing an off-label medicine, the prescribing doctor or nurse should always:

- Analyse the level of evidence supporting the off-label use of the drug
- Consider the risk-benefit ratio
- Consider the clinical impact of use or non-use of the drug
- Inform the patient that the prescription is off-label but could be beneficial based on scientific arguments and medical experience

DO GUIDELINES EXIST ON HOW TO PRESCRIBE OFF-LABEL USE?

Consensus recommendations exist in some countries such as Australia. As shown in the graph below, the recommendations define broad categories of appropriate off-label use:

- Off-label use is justified when high-quality evidence exists;
- Use within the context of a formal research proposal; and
- Exceptional use, justified by individual clinical circumstances.

WHAT CAN BE DONE? 7| seven

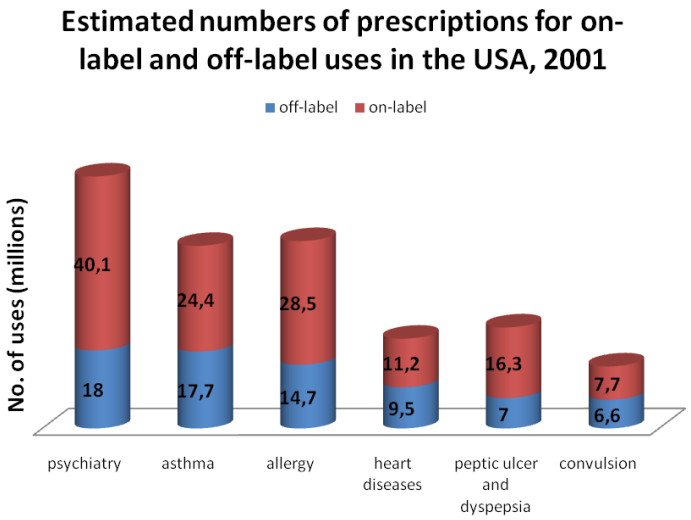
1. One proposal would be that patients or consumers give fully informed consent to the use of off-label drug.
2. When many patients are treated off-label with the same product, it could make sense to validate this use (information on efficacy, safety) with scientific assessment and results from a clinical trial. The marketing authorisation holder could develop a proper programme to validate this use, e.g. a marketing authorisation application for this new indication (so-called marketing authorisation extension), with the involvement of centres of expertise when they exist.
3. For older medicines, there is little incentive to perform additional clinical trials to generate the data needed to support off-label use. In some cases, public funding could commission clinical trials where further evidence is required.

IS OFF-LABEL USE FREQUENT IN COMMON DISEASES? 8| eight

According to a study conducting in the US in 2008[1], off-label use could represent 36.4% of all prescriptions in six major diseases areas (see figure 1 below). In this survey, 31% of psychiatry, 42% of asthma, 34% of allergy, 45.9% of heart disease, 30% of peptic ulcer and 46.2% of convulsion drug prescriptions were found to be used off-label.

These data are corroborated by other studies in Australia and Europe. In particular, up to 42% of children were exposed to at least one off-label prescription in a prospective study of outpatients in France[2].

FIGURE 1: N ENGL J MED 358;14 APRIL 3, 2008



WHY PRESCRIBE OFF-LABEL IN COMMON DISEASES? 9| nine

Off-label prescription has been observed in seven main situations:

- Drug is prescribed although contra-indicated for the patient
- Drug is prescribed for an indication other than the approved one
- Drug is prescribed at a different dose than the approved dose
- Drug is prescribed in a patient of inappropriate age (e.g. no data in elderly)
- Drug is used via a different route of administration
- Drug is prescribed for an inadvisable co-prescription
- Drug is prescribed in a different stage of the disease (often the case in cancer)

In the study by Horen et al., 56% of off-label use was explained by the necessity to use the drug for a different indication than the approved indication.

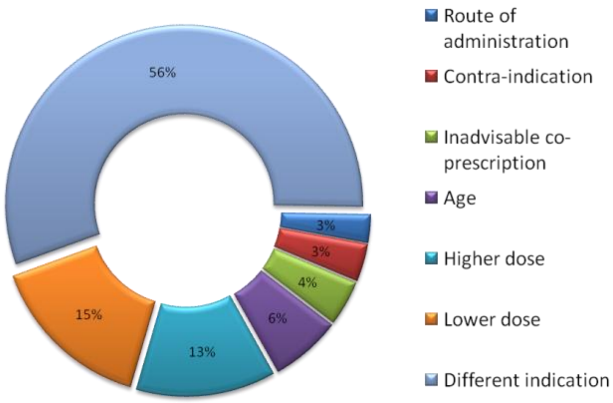


FIGURE 2: FREQUENCY OF OFF-LABEL DESCRIPTION, BY REASON. FROM HOREN AT AL. 2002

IS OFF-LABEL USE FREQUENT IN RARE DISEASES? 10| ten

Rare diseases are by excellence diseases for which a specific treatment does not exist (i.e. with an approved indication). The absence of a specific treatment is the rule; the existence of a specific designated orphan product is still the exception. Since the adoption of the Orphan Drug Regulation in the EU (2000), some 74 orphan drug indications were approved and authorised on the European market[3]. Some cover the same disease, and some others were on the market before this Regulation was adopted. However in all cases only a small proportion of rare diseases benefit from an **on-label** drug: in 2007, 581 orphan drug designations in Europe addressed 343 rare diseases[4]. Among the 5000 to 6000 rare diseases, this represents 6% to 7% of rare diseases that benefit from a designated drug. Considering that 1 out of 13 designations translate into an approved drug, the number of rare diseases with a marketed orphan drug will remain low in the near future.

Medicines authorised for more common diseases are sometimes active in rare diseases. The marketing authorisation holder is not willing to develop the product for the rare indication and because the product is already on the market, the off-label use is an easy solution.

In this context, it is natural that doctors prescribe drugs for which there is a rationale that it could help their patients, even though they are not authorised for the concerned diseases.

Off-label use may be the only means to provide effective treatment. Indeed, up to 90% of drug use for rare conditions is off-label[5].

CAN OFF-LABEL USE BE REIMBURSED? 11 | eleven

Yes, and different schemes for reimbursement exist in different countries.

"Physicians feel pressure from patient advocacy groups and others who are pushing for more off-label prescribing and loosening of reimbursement rules that restrict access to off-label therapies. Such restrictions often exist for patients with rare diseases, which may have no effective approved therapies" according to Prof. Tracy Hampton[5].

There are two situations to be considered: firstly off-label use is supported by clinical studies assessing full or partial efficacy and safety profiles and secondly off-label use is supported by theoretical ideas but in the absence of clinical evidence.

WHAT OFF-LABEL USE SHOULD NOT BE CONFUSED WITH 12| Twelve

- Seeding trials: Pharmaceutical companies use these trials as marketing tools, paying doctors to prescribe certain drugs for off-label uses as part of a "clinical trial." Seeding trials are usually conducted post-marketing. The information collected is typically not for submission to the European Medicines Agency or for publication. Seeding trials are intended primarily to encourage doctors to prescribe the drug more often.
- Compassionate use: compassionate use is to enable the use of a medicine before its marketing authorisations, for patients who are so sick that they have few chances to benefit from the treatment before it is fully evaluated and authorised.

WHAT THE EU LEGISLATION SAYS ABOUT OFF-LABEL USE? 13|Thirteen

In addition to the ban on the promotion of off-label use, a proposal to change the existing EU legislation on pharmacovigilance (provisions in Regulation (EC) No 726/2004 and Directive 2001/83/EC) is being discussed at the European Parliament and Council of Ministers, for a possible adoption before the end of 2010.

In particular, article 101 of the proposal states:

Article 101
The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall particularly refer to adverse reactions in human beings, arising from use of the product within the terms of the marketing authorisation as well as from any other use, including overdose, misuse, abuse, medication errors, and those occurring in the course of studies with the medicinal product or after occupational exposure.

In other words, the proposed legislation provides the legal tools for the European Medicines Agency together with Member States to collect information on the use of medicines, even if this use does not fully correspond to the authorised indication. Information on overdose, misuse, abuse, medication errors or events occurring during studies of after occupational exposure can be collected, after this legislation is adopted.

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[1] Regulating Off-Label Drug Use — Rethinking the Role of the FDA? Randall S. Stafford, M.D., Ph.D. N Engl J Med 358;14 - april 3, 2008
[2] Adverse drug reactions and off-label drug use in paediatric outpatients. Benjamin Horen, Jean-Louis Montastruc & Maryse Lapeyre-Mestre. Br J Clin Pharmacol,54, 665–670 - 2002
[3] As of June 2010
[4] Dr Ségolène Aymé, Orphanet Director, Rare Disease Day 28-02-2010
[5] Experts Weigh in on Promotion, Prescription of Off-label Drugs. Tracy Hampton, PhD - JAMA, February 21, 2007—Vol 297, No. 7