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European Federation of Pharmaceutical Industries and Associations

POSITION PAPER

Promotion of off-label use of medicines by European healthcare bodies in indications where authorised medicines are available

EFPIA represents the pharmaceutical industry operating in Europe. Through its direct membership of 31 national associations and 38 leading pharmaceutical companies, EFPIA provides the voice of 2,000 companies committed to researching, developing and bringing new medicines to improve health and quality of life around the world.

The pharmaceutical sector directly employs some 640,000 people in Europe including 115,000 working in research and development.

BACKGROUND

Any medicine intended for market approval in Europe must undergo a rigorous analysis of its safety and efficacy in the disease population in question. Approval of a medicine comes about after an extensive analysis of the benefit versus the potential risks posed by that medicine in that patient population. The robust European regulations in force are there to safeguard patient safety.

More recently, healthcare bodies[1] in some European countries have begun promoting off-label use[2] of medicines in indications where there are already approved medicines available.

In the UK, the National Institute for Health and Clinical Excellence (NICE) has included off-label recommendations in some of its clinical guidelines and has used an off-label medicine as a relevant comparator in the scope of a cost-effectiveness assessment[3]. In Germany, several sickness funds have entered into agreements with doctors' associations which provide financial incentives to use off-label medicines[4].

In addition, clinical trials sponsored by healthcare bodies comparing approved medicines with off-label medicines are currently being held in five European countries.[5] The aim of these trials is to investigate the safety and efficacy of the cheaper off-label medicine against the approved treatment.

KEY ISSUES

1. Decisions on off-label medicine use should remain in the hands of the treating physician and be taken on the basis of the medical need of the individual patient.

- EU law provides that medicinal products must receive a Marketing Authorisation (MA) before being marketed and used to treat a specific

[1] For the purpose of this paper *healthcare bodies* include national healthcare administrations, HTA/ cost-effectiveness bodies, social insurance bodies and other governmental agencies, excluding regulatory authorities.

[2] *Off-label use* for the purpose of this position paper is defined as any use of an authorised medicinal product not covered by the terms of the marketing authorisation, including the use of the product for a different indication, different dose or dosage or for a patient group not specified on the summary of the product characteristics (SPC).

[3] NICE has included an off-label recommendation for sertraline in its Anxiety (GAD) guideline (CG 113). In addition, NICE has included off-label Avastin as a comparator in the scope of the assessment of the clinical and cost-effectiveness of Ozurdex (Allergan) for the treatment of macular oedema caused by retinal vein occlusion (guidance TA 229). Furthermore, NICE has recently stated that it can appraise the cost-effectiveness of Avastin in wet-age-related macular degeneration (AMD), although the drug has only been licensed for oncology indications (so-called 'Exploratory work of bevacizumab in eye conditions').

[4] Frankfurter Allgemeine Zeitung, 24th of February, page N1.

[5] Currently trials are being sponsored by government agencies in the UK, France, Germany, Austria, and Norway to evaluate the safety and efficacy of two anti-VEGF drugs, Lucentis (ranibizumab) and off-label Avastin (bevacizumab) in the treatment of wet age-related macular degeneration (AMD). For more information, see: www.agingresearch.org/section/repository/amd

condition. The MA is granted after establishment of benefit vs. risk following an assessment of quality, safety and efficacy by the competent regulatory authority. This is based on the fundamental principle of public health protection.

- Under EU law, the supply of medicines for unauthorised uses is an exception to the requirement that a medicinal product should either have an MA or be used in the context of a clinical trial. Other uses may, at the option of the Member State, be permitted in order to fulfil special needs, in response to a bona fide unsolicited order from a physician for use in treating their individual patient's special needs (Art. 5.1 of Directive 2001/83/EC)[6].
- Under EU law, medicines may not be promoted for unlicensed uses (Art. 87 of Directive 2001/83/EC).
- The cost of treating a patient with a medicine authorised for a given disease is not a relevant criterion to promote off-label use and is contrary to the principle that protection of public health should be given precedence over economic considerations[7].

2. Promotion of off-label use by healthcare bodies may compromise patient safety and creates legal uncertainty with regard to product liability

- Promotion of off-label use by healthcare bodies bypasses and indeed undermines the rigorous regulatory approval process, which is designed to ensure patient safety. It raises serious concerns over patient safety as it is promoting the use of medicines in indications for which the competent regulatory authorities have not performed a risk-benefit analysis following established safety and efficacy criteria.
- Promotion of off-label use by healthcare bodies also creates legal uncertainty associated with product liability, in particular the question of who would be accountable for safety issues associated with the off-label use.
- There are additional practical concerns as to how the new information generated by non-industry funded clinical trials would be disseminated (if not in the summary of the product characteristics (SPC) or patient information leaflet (PIL)) or updated (e.g. reacting to adverse event reporting). In many countries other information sources, e.g., websites, derive patient information from the official PILs.
- If non-regulatory authorities, governmental agencies and HTA/ cost-effectiveness bodies such as NICE, promote off-label use of medicinal products, the position and authority of the competent regulatory authorities at EU and national level is undermined. Ultimately, it could lead to double

[6] In some instances off-label use can be medically appropriate and an important element of high-quality patient care, but only in the context of existing, stringent statutory requirements. Physician decisions whether to prescribe a drug off-label should be guided by evidence-based medicine and the best interest of patients.

[7] EU Directive 2001/83 is underpinned by the principle that public health prevails over economic considerations and the system of medicines licensing is fundamental to this. The Court of Justice of the EU (CJEU) has also stated that public health must override any budgetary concerns [Case C-180/96R UK v Commission (BSE)]

standards for medicines and thus compromise patient safety and public health.

3. Promotion of off-label use by healthcare bodies sets double standards

- Promotion of off-label use by healthcare bodies gives rise to the impression that these bodies may have the discretion to override the regulatory approval process.
- On the other hand companies that try to expand use of an approved medicine through off-label use promotion are rightly threatened with heavy sanctions.
- Government agencies have the right to assess the value of new and existing medicines and to fund clinical trials where companies have not carried out direct comparisons. In order to maintain the same regulatory standards and not to compromise patient safety, clinical trials on off-label uses should meet the same criteria as those sponsored by companies, including trial design and statistical plans. The results must be analysed under the same regulatory standards that review submissions from companies.

CONCLUSIONS AND RECOMMENDATIONS

EFPIA considers that it is not appropriate for healthcare bodies in Europe to promote the use of a medicine for an indication for which it has not been approved as it may compromise patient safety, lead to legal uncertainty with regard to product liability, set double standards and create disincentives for continued research.

The decision to prescribe a medicine off-label should be left to a physician based on the concrete medical needs of the individual patient and with his/her consent.

Off-label use of medicines is acceptable in certain circumstances. The *promotion* of off-label use, regardless if by companies or governments, is never acceptable.

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