The off-label use of medication in South Africa – what about some information for medical practitioners?

The Medicines and Related Substances Act[1] (the Act) provides for the registration of medicine by the Medicines Control Council (MCC). In terms of the Medicines and Related Substances Amendment Bill, signed but not yet proclaimed, the MCC will shortly be replaced by the South African Health Products Regulatory Authority (SAPHRA). Despite major changes in the administrative structure, SAPHRA will probably have the same functions as the MCC. Section 14 of the Act forbids the sale of unregistered medicine.

Compared with the USA, for example, issues surrounding the off-label use of medication have received little attention in South Africa. The term 'off-label' means that the medicine is used in another way or for an indication other than those specified in the conditions of registration of the medicine and as reflected in its labelling.[2] It does, however, not necessarily imply that the medication is not effective or is unsafe to be used in this way.[3] Off-label use has become an important part of mainstream, legitimate medical practice worldwide[4] and is especially common in oncology, obstetrics, paediatrics, infectious diseases (notably HIV) and rare diseases.[5] Depending on the circumstances, off-label use of medication can vary from being experimental or controversial to standard practice and even state-of-the-art treatment.[4]

The off-label use of any medication obviously carries a higher risk for the patient and the medical practitioner than its registered use, and therefore extra care should be taken. From a legal/ethical point of view the off-label use of medication represents a delicate balance between the statutory regulation of medication (which aims at safeguarding patients against unsafe and ineffective medications) and the prerogative of a physician to prescribe medication that, in his or her medical opinion, will be beneficial to the patient.[6] Legal implications such as when the off-label use of medication will be negligent and when not, and whether the patient must be informed that the medicine is used off-label, are dealt with in a separate contribution in this journal.[7]

Regulatory framework

In a further article in this journal, health care professionals highlight a situation where a life-sustaining drug, Prostin, which is in daily (off-label) use as an emergency treatment for infants to maintain the patency of the ductus arteriosus, unexpectedly became in short supply.[8] The question arises as to whether the dilemma occasioned by unawareness of the shortage was created by the regulatory framework.

In South Africa various stipulations of the Act and regulation 45(3)[9] prohibit the dissemination of information regarding the off-label use of medication. Regulation 45(3) stipulates that no advertisement for medicine may contain a statement regarding its safety, quality or efficacy that deviates from the purpose for which and the manner in which it was registered. Section 20(1)(b) forbids any advertisement from making any claim regarding the therapeutic efficacy and effect other than that for which it is registered (and as indicated in the labelling thereof). The definitions of 'advertisement' and 'public' as contained in section 1 of the Act are very wide and the latter is defined so as to include medical health professionals. In effect no written or oral information regarding the safety, quality or efficacy of off-label use of medicine may be disseminated to the public or to medical practitioners by the manufacturer or distributor.

It is submitted that, according to the ordinary meaning of the words in these stipulations, a general notification to medical practitioners that the medication will be in short supply, whether it is used off-label or not, does not fall thereunder and is therefore not prohibited thereby. On common law grounds a strong argument can even be made out that there is a legal duty on the pharmaceutical company in these circumstances to warn medical practitioners in time of any shortage of this medication. The following factors serve as indicators of the existence of such a duty: when used in this way, Prostin is an emergency, life-sustaining drug; a very vulnerable group is involved; no similar drug is available; the pharmaceutical company gains financially in the selling of this product; the information that the medicine will be in short supply is in the exclusive possession of the pharmaceutical company; and the pharmaceutical company is aware of the off-label use of the medication (a children's hospital is hardly likely to use a drug registered to induce labour other than in an off-label way!). To these factors the constitutional imperative as contained in section 28(2) of the Constitution of the Republic of South Africa,[10] namely that a child's best interests are of paramount importance in every matter concerning the child, can be added.

Whether a legal duty to notify (of shortages) exists will depend on the circumstances of each case. It would for example make a difference if the medication is for chronic use in the treatment of ulcers and other similar medication is also readily available. It would however be good business practice to send out this type of notice in any event.

It is true that pharmaceutical companies are obliged to adhere to the Act and its regulations strictly and that there can in some instances be a very thin line between promotion and mere notification. There is also a draft SA Code of Practice for the Marketing of Medicines in existence which is yet to be published. The wording thereof is in accordance with the Act and its regulations. Lastly, it is important to note that pharmaceutical companies should, in their contracts with

suppliers (for example of packaging material), make provision for timeous notification of inability to supply.

Dissemination of information on off-label use

Physicians become acquainted with off-label uses of medication through professional medical literature, presentations and peer lectures at conferences, medical research and advice from colleagues. There are two diverging views, both with pros and cons, on whether pharmaceutical companies should be allowed to distribute medical journal articles and scientific reference publications on off-label uses for approved drugs.

The main argument against allowing dissemination of this kind of information by pharmaceutical companies is that it significantly reduces the medicines regulatory authority's ability to protect the public against unsafe and ineffective medicines. Anecdotal data are not the equivalent of clinical tests.[6]

On the other hand it is of the utmost importance that medical practitioners have the latest accurate and non-misleading medical and scientific information on medication, including off-label uses, when deciding on a patient's treatment.[11] By missing one or two important articles, the practitioner may be unable to choose the best option.

In the USA section 401 of the FDA Modernization Act of 1997 (FDAMA) greatly eased restrictions on drug promotions. Although section 401 expired in 2006, current policy carries forward many of its provisions. FDA policy currently prohibits the direct promotion of products for off-label uses, but the FDA recently published guidelines for the distribution of medical journal articles and scientific reference publications on unapproved new uses for approved drugs.[11,12] The distribution of this type of information is prohibited in South Africa and the position is therefore more comparable with that existing in European countries.

Testifying before the American Congress, senator Bill Frist, himself a medical practitioner and one of the authors of section 401 of the FDAMA, said: 'If a conscientious doctor were to read two articles before retiring every night, he would have fallen 550 years behind in his reading at the end of the first year.'[13]

Many aspects surrounding the off-label use of medication should be debated in South Africa in order to decide whether a *via media* cannot be found. Attention should be given to the systematic collection of post-marketing data on the prevalence of the off-label use of medicines and its harms and benefits. Medical associations and institutions should also provide medical practitioners with guidelines on the lawful and ethical off-label use of medication.

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