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Off-label Prescriptions: how to Identify Them, Frame Them, Announce Them and Monitor Them in Practice?

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Abstract – Following the Mediator crisis and the passage of the Health and Safety Law of December 2011, off-label prescriptions are a real concern shared by all those involved in healthcare system. Off-label, in the strictest sense of the term, is defined as all prescriptions that do not correspond to the summary of product characteristics (SPC), particularly those that fail to comply with the indications and dosage regimens defined by the marketing authorization (MA) for clear safety reasons. There are various rasons for off-label prescriptions, both conscious and unconscious. They are intended to respond to unmet medical needs, the needs of poorly studied populations or not studied at all in trials, but in relation to whom it is reasonable to extrapolate that MA would be given (common-sense prescriptions) and, additionally, to urgent public health needs (such as baclofen, pregnant women, and HIV drugs). All these prescriptions would deserve to be studied for a potential MA. However, there are off-label prescriptions that need to be restricted or even penalized in the case of compassionate prescriptions or unjustified prescriptions or prescriptions not based on any scientific grounds.
Off-label prescriptions are not easy to track down because if the prescriber has to write "off-label" on his prescription, then clearly, in practice, he will only do so in exceptional cases. Neither the pharmacists who dispense the drug nor the Social Security that reimburses it, have access to the diagnosis (or targeted indication). Thus, in order to identify the off-label prescription, we must be able to cross reference the available databases (such as pharmacovigilance database, medicalized information

† Articles, analyzes and proposals from the Giens workshops are those of the authors and do not prejudice the position of their parent organization.

system program [*programme de médicalisation des systèmes d'information*, PMSI], hospital drug formularies, general sample of beneficiaries [*échantillon généraliste de bénéficiaires*, EGB] or national inter-regional Health Insurance Information System *[système national d'informations inter-régions d'Assurance maladie*, SNIIRAM], sales data, and data from market surveys). The shared computerized patient file may resolve this problem. The temporary use recommendation (TUR) proposed by the Drug Safety Law will only partially deal with this problem for recently marketed molecules.
This temporary and exceptional mechanism will authorize a recognized off-label prescription, which may be reimbursed and monitored for 3 years. These TURs will only concern a small portion of "off-label" drugs having yet a positive risk/benefit ratio (conditional MA) but this is far from matching with majority of off-label prescriptions. As such, and in order to improve the use of drugs, it is important to propose a control system for all "off-label" prescriptions with a dedicated committee: **the "off-label" committee** which would determine the frame of the "off-label" prescriptions.

Abbreviations: see end of article.

1. Introduction

In 2010, the Mediator crisis highlighted the risks by using the drug out of the scope of its marketing organization (MA). Such a use is a widespread practice and has become a concern shared by all the stakeholders involved in the healthcare system. During the *Assises du médicament* (drug conference), a group has been specifically assigned for providing some recommendations on the off-label prescriptions.[1]

The recommendations of this group were:

1. To track and to monitor the "off-label" prescriptions.

2. To track the risks of "off-label" prescriptions from clinical trials and consequently to reinforce the public research.

3. To improve the reliability of the "off-label" prescription recommendations issued by the health authorities (such as High Health Authority [*Haute autorité de santé*, HAS], National Insitute against Cancer [*Institut national contre le cancer*, INCA]), and French Agency for the Safety and Health Products [*Agence française de sécurité sanitaire des produits de santé*, Afssaps]).

4. To report more frequently the unjustified "off-label" prescriptions, particularly those that are safety concerns.

5. To reinforce the exemption mechanisms: temporary use (*autorisation temporaire d'utilisation,* ATU), temporary treatment protocol (*protocole thérapeutique temporaire*, PTT) or "article 56"[2] by strongly monitoring the patient follow-up and by scheduling the end of such systems.

6. To gradually extend the article 56 model to all off-label prescription recommendations issued by the health authorities.

7. To mobilize all the Health Authorities like the HAS, the National Security Agency of Medicines and Health Products (*Agence nationale de sécurité du médicament et des produits de santé*, ANSM), the INCA and the Economic Committee for Health Products (*Comité économique des produits de santé*, CEPS) and to ensure their coordination under the responsibility of the Health Ministry.

8. To inform patients and healthcare professionals.

9. To give greater responsibility to in the healthcare system stakeholders.

These mostly common-sense recommendations were the basis of the health and safety law of December 2011, which specifies in the Public health code (*Code de la santé publique*, CSP) the acceptable conditions for off-label prescriptions and the creation of a new control mechanism for medically justified off-label prescriptions: temporary use recommendations decided and centralized by the ANSM.[3]

Currently, all the needed regulatory texts for the implementation of this mechanism have been published.[4-6] The responsibilities of each stakeholder are defined although some practical points need to be clarified. In this context, it is important to consider the off-label prescription management by taking this new mechanism into account as well as those situations that this mechanism might not cover. In September 2012, this question was dealt with at one of the workgroups of the Giens pharmacological meeting. The purpose of this article is to present the proposition of this group in order to identify, to control, to announce and to monitor the off-label prescriptions.

2. Methods

During the first session, the group adopted a consensual definition. Then all the situations in which the off-label prescriptions were done and the identification means have been listed.

Finally, the needed mechanisms to be implemented by the health authorities for monitoring the off-label prescriptions and for validating certain common-sense situations have been raised.

2.1. Definition of the off-label prescription

The group agreed on the simplest and broadest definition. The off-label prescriptions gathered all the prescriptions out of the scope defined by the summary of the product characteristics (SPC). These situations especially address the indication and dosage headings of the SPC, but also specific population for which the usage is limited, often due to a lack of exploratory data.

The need of care is clearly important in populations such as children, pregnant women, elderly patients, patients with a body mass index >25, patients suffering from kidney or liver failure.