Guideline on Good Pharmacovigilance Practices

Module II - Additional Monitoring

Turkish Medicines and Medical Devices Agency

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Chapter I

Introduction

1.1 Introduction

Pharmacovigilance is a vital public health service with the aim of rapidly detecting and responding to potential safety hazards associated with the use of medicinal products.

A medicinal product is authorized on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication s. However, not all risks can be identified at the time of initial authorization and some of the risks associated with the use of a medicinal product emerge or are further characterized in the post-authorization phase of the product's lifecycle. To strengthen the safety monitoring of medicinal products, the "Regulation on the Safety of Medicinal Products," issued on April 15, 2014, has introduced a framework for enhanced risk proportionate post-authorization data collection for medicinal products, including the concept of additional monitoring for certain medicinal products.

As defined in the eighth paragraph of Article 8 of the Regulation on the Safety of Medicinal Products, the Agency will set up, maintain and make public a list of medicinal products that are subject to additional monitoring (hereafter referred to as "the List"). These medicinal products will be readily identifiable by an inverted equilateral black triangle ▼as stipulated in the Regulation on the Safety of Medicinal Products. That triangle will be followed by an explanatory statement in the summary of product characteristics (SmPC) as follows: "This medicinal product is subject to additional monitoring. This triangle will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to TÜFAM. See section 4.8 for how to report adverse reactions."

A similar statement will also be included in the package leaflet. This explanatory statement is intended to encourage healthcare professionals and patients to report all suspected adverse reactions.

Post-authorization spontaneous adverse reaction reports remain a cornerstone of pharmacovigilance. Data from adverse reaction reports is a key source of information for signal detection activities. Increasing the awareness of healthcare professionals and patients of the need to report suspected adverse reactions and encouraging their reporting is therefore an important means of monitoring the safety profile of a medicinal product.

The concept of additional monitoring originates primarily from the need to enhance the adverse reaction reporting rates for newly authorized products for which the safety profile might not be fully characterized or for products with newly emerging safety concerns that also need to be better characterized. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of medicinal products.

Chapter II

Structures and Processes

2.1 Principles for assigning additional monitoring status to a medicinal product

All medicines are authorized on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorization, data from clinical trials conducted during the development of a medicine are assessed. However,

adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from everyday practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. Marketing authorization holders and the Agency continuously monitor medicinal products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the medicinal product. However, for certain medicinal products enhanced post-authorization data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain medicinal products and in particular to encourage the spontaneous reporting of adverse reactions, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorization or in some cases at later stages of the product life cycle when a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorization for medicinal products containing a new active substance and for all biological medicinal products, which are priorities for pharmacovigilance. The Agency may also require additional monitoring status for a medicinal product which is subject to specific obligations imposed on the marketing authorization holder e.g. the conduct of a post-authorization safety study or restrictions with regards to the safe and effective use of the medicinal product.

2.2 Communication and transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. A publicly available list of medicinal products with additional monitoring status will be kept up to date by the Agency. In addition, healthcare professionals and patients should be enabled to easily identify those products through the summary of product characteristics/package leaflet. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected adverse drug reactions for all medicinal products subject to additional monitoring.

Chapter III

Operation of the System

3.1 Criteria for including a medicinal product in the additional monitoring list

3.1.1 Scope

According to the eighth paragraph of Article 8 of the Regulation, it is mandatory to include the following categories of medicinal products in the list:

- medicinal products included in an additional monitoring list in the international practice;
- biosimilar medicinal products, authorized or pending authorization;
- medicinal products monitored in Turkey using special monitoring systems (e.g. drug safety monitoring form, web-based monitoring system, drugs subjected to restricted distribution);
- medicinal products authorized/pending authorization under exceptional circumstances, as provided in the Regulation on the Registration of Human Medicinal Products;

- medicinal products authorized conditional on the performance of post-authorization safety studies;
- medicinal products for which marketing authorization application was submitted after 15.04.2014, which contain a new active substance not contained in any other medicinal product previously authorized in Turkey;
- any biotechnological medicinal products for which marketing authorization application was submitted after 15.04.2014;
- any blood products authorized after 01.01.2011;
- medicinal products designated by the Agency.

3.2 Criteria for defining the initial time period of maintenance in the additional monitoring list

The Agency will remove a medicinal product from the list after five years from the authorization date in Turkey, or may extend this time period. A product may be added to the list again if new safety concerns arise during the product's life cycle.

3.3 Roles and responsibilities

3.3.1 Agency's responsibilities

The Agency will:

- decide if a medicinal product should be subjected to additional monitoring, and hence included in the list;
- publish a publicly available list of medicinal products that are subject to additional monitoring;
- remove medicinal products from the list after a pre-determined time period.

3.3.2 Marketing authorization's responsibilities

The marketing authorization holder will:

- continuously monitor the list of medicinal products subject to additional monitoring, including in the SmPC and PL of their medicinal products the symbol ▼and the standardized explanatory statement on additional monitoring;
- include information on the status of additional monitoring in any material to be distributed to healthcare professionals and patients, and encourage reporting of adverse reactions, as agreed with national competent authorities;
- submit the relevant variation application to include or remove the black symbol and the standardized explanatory sentence from the SmPC and PL.

3.4 Black symbol and explanatory statement

The length of each side of the inverted black triangle should be at least 5 mm and compatible with the size of the standardized sentence that follows the triangle.

For medicinal products included in the list, the top section of the SmPC will include the following statement above the medicinal product's commercial name, immediately preceded by an inverted equilateral black triangle: " ▼ This medicinal product is subject to additional monitoring. This triangle will allow quick identification of new safety information. Healthcare professionals are expected to report any suspected adverse reactions to TÜFAM. See section 4.8 for how to report adverse reactions."

A similar statement will also be included in the package leaflet as follows, immediately after the statement of active substance(s) and excipients: " ▼This medicine is subject to additional monitoring. This triangle will allow quick identification of new safety

information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects."

Once the medicinal product is included or removed from the list, the marketing authorization holder will update the SmPC and the package leaflet to include or remove, as appropriate, the black symbol and the standardized explanatory statement.

If the decision to include or remove a medicinal product from the list is done during the regulatory procedure (e.g. marketing authorization application, extension of indication, extension of validity, etc.) the SmPC and the PL should be updated before finalization of the procedure in order to include or remove the black triangle symbol and explanatory statement from the product information.

If the decision to include or remove a medicinal product from the list is done outside a regulatory procedure, then the marketing authorization holder is requested to submit a variation to update the product information of that product accordingly.

3.5 Transitional period for authorized medicinal products to be included in the additional monitoring list

Authorized medicinal products that are included in the additional monitoring list according to the eighth paragraph of Article 8 of the Regulation on the Safety of Medicinal Products will ensure compliance with the ninth paragraph of Article 5 of the same Regulation within six months after the announcement of the list by the Agency.