SCOPE Work Package 4
ADR Collection

Identification, Management and Raising Awareness of ADR Reports for Drugs Subject to Additional Monitoring

SCOPE

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Contents

Acknowledgments

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide an overview of main aspects of additional monitoring process, summarise Member States' (MS) experiences with regard to additional monitoring and provide an overview of examples of good practice.

1.2 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support operations of pharmacovigilance in the European Union (EU) following the requirements introduced by the 2012 European pharmacovigilance legislation[1,2,3], which came into force in June 2012. Information and expertise on how regulators in EU Member States (MSs) run their national pharmacovigilance systems was gained in order to develop and deliver guidance and training in key aspects of pharmacovigilance, with tools, templates and recommendations. The aim of the SCOPE Joint Action was to support the development of consistent approach across the EU network for all pharmacovigilance operations, in order to benefit medicines safety monitoring and communications to safeguard public health.

SCOPE was divided into eight separate work packages, with five work packages focusing on pharmacovigilance topics to deliver specific and measurable objectives, ranging from improvements in Adverse Drug Reaction (ADR) reporting to assessment of quality management systems.

Work Package 4 ADR Collection focused on national schemes for the spontaneous reporting of adverse drug reactions and aimed to provide National Competent Authorities (NCAs) with a full understanding of and good practices within national systems for collecting adverse drug reactions. Information was gathered from MS institutions[4] to understand their national ADR system and pharmacovigilance IT system capabilities, as well as implementation of patient reporting, types of reporting forms developed, and electronic reporting developments, including those from clinical healthcare systems. This information was used to create best practice guidelines and performance indicators and a media toolkit for raising awareness of ADR reporting systems, which will be supported through the delivery of a training course for institutions.

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[1] Directive 2010/84/EU of the European Parliament and of the Council

[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[3] Commission Implementing Regulation (EU) No 520/2012

[4] The term Member State (MS) institution refers to the institution responsible for Adverse Drug Reaction (ADR) reporting, collection, processing and analysis within the particular Member State. Therefore, wherever the term 'Institution' is mentioned it does not necessarily refer to the National Competent Authority (NCA), although it will be synonymous in the majority of MSs.

Within WP4 there are five topics. Within the topic area Audit of National Reporting Systems, the information about MSs' practices in ADR reporting was collected through a questionnaire completed by MSs. The questionnaire focused on national ADR reporting systems for medicinal products, vaccines and biologics, covering specific issues, such as additional monitoring. In-depth analysis of the retrieved data, as well as subsequent follow-up with relevant stakeholders within the SCOPE project, revealed certain points of interest within the community, bringing out the main problems, as well as examples of good practice.

One of the issues of special interest related to ADR management is additional monitoring. Namely, the results of the SCOPE questionnaire indicate that almost 60% (15/26[5]) of the MSs do not identify ADR reports for drugs subject to additional monitoring in their databases. The MSs that do identify ADR reports for drugs under additional monitoring in their databases usually do it manually, with only a few MSs having implemented technical tracking solutions.

With regards to the management of those ADRs, 75% (21/28) MSs do not differentiate between the management of ADR reports for drugs on the additional monitoring list and ADR reports for drugs that are not.

As a result of this, it was decided to follow-up with the MSs that were considered to have good practices with regard to additional monitoring. This mainly refers to MSs that were able to provide specific data on ADR reports for drugs subject to additional monitoring in their national database, e.g. percentage of this type of ADRs, or to share relevant and useful information regarding their management. Also, information on MS size and ADR number per year, technical resources and data about the organisation of the institutions' PV systems was taken into account in order to choose a practice that can be useful for most MSs. During the follow-up, detailed information on additional monitoring was gathered, identifying key points of the process: identification of ADR reports for drugs subject to additional monitoring in the database, management of those ADR reports, measuring the effectiveness of the additional monitoring and raising awareness of the issue.

There are significant differences between MSs regarding additional monitoring management, although practices are based on the same applicable legislation. The aim of this document is to summarise MSs' experiences with regard to additional monitoring and provide an overview of examples of good practice. These examples and ideas might be used by other MSs for the optimisation of their national additional monitoring process and help achieve its initial purpose of ensuring patient safety by strengthening the monitoring of medicinal products containing a new active substance, biological medicinal products or medicinal products that are subject to specific obligations.

[5] Number of respondents

1.3 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé, the French Medicines Agency
DEC	Drug Event Combinations
DKMA	Danish Medicines Agency
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional
GVP	Good Vigilance Practice
ICSR	Individual Case Safety Report
LAREB	The Netherlands Pharmacovigilance Centre
MAH	Market Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NCA	National Competent Authority
PRAC	Pharmacovigilance Risk Assessment Committee
PT	MedDRA Preferred Term
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SUKL	Státní ústav pro kontrolu léčiv, the Czech Republic Medicines Agency
UMC	Uppsala Monitoring Centre
WP	Work Package
WHO	World Health Organization

2. Additional monitoring

A medicinal product is authorised 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 the initial authorisation and some risks associated with medicinal product usage emerge or are further characterised in the post-authorisation phase of the product's lifecycle.

To strengthen the safety monitoring of medicinal products, the 2010 EU Pharmacovigilance legislation, further amended in 2012, has introduced a framework for enhanced risk-proportionate post-authorisation data collection for medicinal products, including the concept of additional monitoring. The concept of additional monitoring originates primarily from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns that also need to be better characterised. The main goals are to collect additional information as early as possible to further elucidate the risk profile of the products when used in clinical practice, thereby informing the safe and effective use of medicinal products[6].

The additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorisation or, in some cases, at later stages of the product lifecycle, when a new safety concern has been identified. As defined in Article 23 of Regulation (EC) 726/2004 and Article 11 of Directive 2001/83/EC, the European Medicines Agency (EMA), in collaboration with the Member States, set up, maintains and makes public a list of medicinal products that are subject to additional monitoring. Implementing Regulation (EU) No 198/2013 additionally stipulates that those products need to be marked by an inverted equilateral black triangle and followed by an explanatory statement in the summary of product characteristics (SmPC) as follows: *"This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions."* Information is also provided for patients in the package leaflet: *"This medicine is subject to additional monitoring. This 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."*

Information on additional monitoring status for medicinal products registered by the centralised procedure in the EEA, along with European Public Assessment Reports (EPAR), can be retrieved from the EMA webpage (browsing by 'Type').

[6] Guideline on good pharmacovigilance practices (GVP). Module X – Additional monitoring, EMA/169546/2012, 19 April 2013

General principles for assigning additional monitoring status to medicinal products, communication and transparency aspects, and a description of the operation of the EU network regarding the supervision of additional monitoring, are provided in the Guideline on good pharmacovigilance practices (GVP): Module X – Additional monitoring. NCA responsibilities for additional monitoring are specified in section C.3.3. NCAs in the GVP module X. Other aspects of the process, including management of ADRs for these products by the institution at a national level and possible methods for measuring the impact of additional monitoring and the validity of the introduction of additional monitoring process, are not tackled in GVP module X or by other available documents. This is despite the fact that significant resources have been employed in support of the additional monitoring process in the EU (e.g. setting and maintaining the list of products subject to additional monitoring, handling PI changes with regards of black triangle updates at a national level, promotion of the concept).

In order to provide MSs with extended practical information on these aspects of the process, case studies have been provided in this document describing additional monitoring processes in two MSs with different settings regarding the ADR management process in general, number of ADR reports per year/assessor, available technical solutions, baseline reporters' knowledge of the additional monitoring concept, etc.

2.1 Identification of ADR reports for drugs subject to additional monitoring in the national ADR database

Analyses of the SCOPE results indicate that almost 60% (15/26) of MSs do not identify ADR reports for drugs subject to additional monitoring in their national ADR databases. This is probably the reason why more than 50% (15/28) of MSs were not able to provide information on the percentage of ADR reports that include drugs on the additional monitoring list in their national database.

In order to be able to accurately detect those ADR reports in the national database, an up-to-date list of the products subject to additional monitoring published by the EMA (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/04/WC500142453.pdf) should be used for reference. The EMA is responsible for updating the list every month following review by the Pharmacovigilance Risk Assessment Committee (PRAC).

MSs use different ADR databases requiring different amounts of manual work to identify ADRs for the products on the additional monitoring list. Data on the suspect product from the ADR report in the database should be checked against the valid list of products subject to additional monitoring. This step will, in most instances, be a manual process. When the ADR report is being imported into the database it might be flagged if it contains a suspect product from the additional monitoring list. If it is not possible to have a specific flag, then maybe the information on the additional monitoring status can be captured in a searchable way within the case itself, in order to allow for subsequent searching or filtering. This might be something as simple as the addition of a key word or a symbol in the ADR report title, or in another searchable field within the database.

For MSs without these options in the national database, another method could be chosen based on the existing system, for example, adding information on the additional monitoring status as a column in an Excel table used for tracking ADR reports.

For MSs with a large number of received ADR reports, the best solution is to have an automatic flagging of the ADRs by comparison of the suspect drug in the received ADR report and the status of the product with regard to additional monitoring.

The status of the product might change over time and it is therefore important to keep the list of the products subject to additional monitoring up to date. It might be worth considering whether, even after removing the products from the additional monitoring list, previously received ADRs for that product should remain marked in the database for future analysis. In this way, it might be possible to correlate the number of ADRs per particular drug through time with additional monitoring status.

The ability to identify the reports of ADRs for products subject to additional monitoring in the national database is the first prerequisite for further actions, including the measurement of the effect of additional monitoring. Taking all of the above into account, it might be worth considering whether to implement a tracking system for ADRs for products subject to additional monitoring on the national level, according to the existing technical options and applicable process.

2.2 Management of ADR reports for drugs subject to additional monitoring

Responses to the SCOPE survey regarding the management of ADRs for drugs that are subject to additional monitoring indicate that 75% of MSs do not differentiate between the management of ADRs for drugs on the additional monitoring list and ADRs for drugs that are not. The exact reasons for this finding cannot be detected from the available data, but it could be that these MSs do not see the additional value of this specific approach to this type of ADR report, and that the current setup of their ADR reporting system allows them to perform satisfactory national signal detection. The lack of reliable information about the value of additional monitoring can only add to this perception. Another reason for this finding might be that MSs do not have the available resources (technical, human) to support a specific approach for ADR report management for these products.

MSs' differences in the management of ADR reports for the drugs on additional monitoring might be related to the type of assessor responsible for the assessment, additional assessment steps, more stringent procedures, timelines, etc. For example, one MS reported that only assessors reviewing ADR reports for drugs on the additional monitoring list are organised according to therapeutic category, while the others are not. In another MS, ADRs are routed to the senior assessors in order to use their experience and knowledge in the analysis of ADR data and subsequent interpretation of their importance. In addition, these ADRs are reviewed at team and departmental meetings. The benefit of this approach is a better understanding of the issue as a result of approaching the problem from different perspectives. This approach allows the group to think more broadly and make a better decision. One MS uses a national PV committee to enhance the assessment of ADR reports for drugs subject to additional monitoring. National PV committees can include experts from clinical practice, which can add to the assessment by evaluating the real life clinical aspects and the relevance of the ADR.

In order to get a better description of ADRs for drugs requiring additional monitoring, the introduction of a mandatory follow-up action might be considered. In this way, the additional data obtained will help better characterise the reported ADRs and decide on the appropriate actions to take. Also, to add to the sensitivity and assure earlier signal detection and processing, the threshold of the ADR reports needed for triggering an internal signal detection process can be lowered. In this case, the impact on the reduced specificity should be taken into account. Additionally, in case the MS is not sending non-serious ADRs in general to EudraVigilance, it can do so if the suspect drug is subject to additional monitoring. This can lead to enhanced signal detection at the EU level.

Whatever the specificities of the ADR report management procedure are, for the purpose of applying consistent standards and practices within the MS, it would be useful for the MS to apply work instructions or standard operating procedures describing the management of ADR reports for drugs on additional monitoring.

2.3 Raising awareness on additional monitoring

Because there is less information available about the products on the additional monitoring list, compared with other medicinal products, 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.

According to the legislation, healthcare professionals and patients should be enabled to easily identify those products through their product labelling. Information on the additional monitoring status needs to be added to the summary of product characteristics and package leaflet, educational materials, as well as promotional materials for a medicine under additional monitoring.

As defined in Article 106 of Directive 2001/83/EC, each Member State shall make publicly available on their national web-portal the list of medicinal product authorised in their territory that are subject to additional monitoring, and take all appropriate measures to encourage patients and healthcare professional to report any suspected adverse drug reactions.[7] Today's practice shows that most MSs publish only the link directing to the EMA additional monitoring list, instead of their own list containing products under additional monitoring.

The webpage should also contain information on the general principles of additional monitoring, highlighting the need to better characterise the safety profile of a new medicinal product by identifying additional risks, but those potential risks should be placed in the context of the known benefits for this product. MSs should clearly communicate to the public that additional monitoring does not mean that the medicine is unsafe.

Raising awareness can be done through simple actions such as inclusion of the black triangle symbol in the product-related information, which is visible during product search on NCAs' webpages or in national product compendiums. Also, information on additional monitoring can be promoted through annual ADR reports in order to enhance the additional monitoring. One MS provided example of poster with information on additional monitoring aimed at patients, which was distributed to pharmacies and hospitals (http://www.legemiddelverket.no/Bivirkninger/legemiddelovervaaking/svart_trekant/Documents/Svart%20trekant%20plakat.pdf)[8].

[7] Guideline on good pharmacovigilance practices (GVP). Module X – Additional monitoring, EMA/169546/2012, 19 April 2013

[8] Translation of the poster is provided at the end of this document

2.4 Measuring the impact of additional monitoring

According to the currently available information, no systemic efforts have been made so far at EU level to assess the impact of the additional monitoring elements introduced by the 2010 EU PV legislation.

Measuring the impact of additional monitoring is a complex issue mostly due to methodological challenges and the lack of defined measurable outcomes. Currently, there are no broadly accepted methods for measuring how pharmacovigilance activities are translated into health outcomes. This has been recognised by the EMA resulting in the PRAC strategy on measuring the impact of Pharmacovigilance activities. Based on the PRAC strategy, further method identification and development for impact studies is expected. This might help obtain relevant data on the impact of additional monitoring.

The impact of additional monitoring may potentially be measured by quantitative analysis of the number of ADR reports for drugs on additional monitoring or by the analysis of subsequently detected signals. One of the prerequisites for the quantitative analysis, especially for a large number of cases in the database and/or a large number of drugs that are subject to additional monitoring present on the market, is an introduction of technical solutions to identify these ADRs within the database. One of the options might be use of a flag to mark these cases. In some instances, quantitative analysis can be done on data manually extracted from the database, which is more applicable for smaller amount of data.

It should be noted that there are sporadic initiatives for measuring the success of promoting certain aspects of the additional monitoring process, such as promoting an understanding of the concept of additional monitoring by HCPs and patients. The impact of such initiatives can be measured by, e.g. the number of website hits, the number of stakeholders the messages were communicated to, further dissemination of the information cascade, etc.

3. Conclusions

The concept of additional monitoring originates from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns. Since the introduction of additional monitoring in the EU, only certain segments of the process have been adequately described and communicated by applicable guidelines at EU level. However, while the initial steps of the process can be considered successfully implemented, the management of ADRs for products subject to additional monitoring by the institution at national level, and the methods for measuring the impact of additional monitoring, have not been defined or described.

Within the last few years, experience of the management of those ADRs has been gained by MSs. As part of the SCOPE project, these experiences were collected and presented in this document. MSs considered to have good practice were chosen based on their responses to the SCOPE questionnaire and subsequent follow-up. Information on the MS size and the ADR reports number per year, technical resources, and data about the organisation of the institutions' PV system, was taken into account in order to get the most applicable recommendations. Analysis of the data gathered in WP4 identified key points of the additional monitoring process: identification of ADR reports for drugs subject to additional monitoring in the national database, management of those ADRs at a national level, measuring the effectiveness of the additional monitoring and raising awareness on the issue. Information and insights provided might be used for the MSs' process optimisation, however no distinctive recommendation on the additional monitoring process can be provided due to inherent differences between MSs.

The EU regulation requirements regarding additional monitoring necessitates allocation of resources for this purpose from different stakeholders within the community (regulatory authority, MAHs), but the information on the benefits and the impact of the additional monitoring concept is rather scarce at the moment. To determine the full validity of the concept itself and its impact on health outcomes, more emphasis should be given to the measurement of the effect of additional monitoring, which is a complex issue mostly due to methodological challenges and the lack of defined, measurable outcomes. This has been recognised by the EMA resulting in the PRAC strategy on measuring the impact of Pharmacovigilance activities. Based on the PRAC strategy, further method identification and development for impact studies is expected, which will help to provide relevant data on the impact of additional monitoring.

The process of additional monitoring should be handled in such a way as to allow subsequent analysis and optimisation. Only with that approach will additional monitoring achieve its initial purpose of ensuring patient safety by strengthening of the monitoring of medicinal products.

Annex 1. Case study: UK MHRA

The UK has a long tradition of ADR collection through the Yellow Card Scheme (YCS). Yellow Card reports are submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the cases are entered into a custom built national ADR database, holding spontaneous ADR reports dating back to 1963. Reports are received from all types of healthcare professionals, Marketing Authorisation Holders and members of the public). Reports can be received on paper, electronically, directly from healthcare clinical systems and via the telephone. At the moment the database contains over 800,000 UK spontaneous cases.

As soon as a report is received it is entered into the ADR database within strict deadlines by a multidisciplinary team of life science graduates and pharmacists. The reports go through four stages of processing: the first step, 'input verification', confirms the case is valid and assigns a priority (based upon the seriousness of the case). The second step, 'data capture', is where all the details of the case are entered onto the database, the third step is a quality assurance step to confirm the coding of the case is correct and the fourth is an assessment step to determine the completeness of the information and whether a request for further information from the reporter is required. Signal detection is carried out on these reports on a weekly basis using software called Empirica, which generates Drug Event Combinations (DECs) to be manually reviewed. All DECs (serious and non-serious) are reviewed for additional monitoring drugs; however, for established UK reports there are thresholds in place to determine which DECs are reviewed. The thresholds for established UK reports are:

- Non-listed DECs with a raised statistical disproportionality score (using EBGM)
- All fatal, paediatric, parent-child reports, and all Alert Terms (a predefined list of reactions)
- When the DEC is reported more frequently than normal (≥8% reports received in last quarter).

The processing of ADRs for drugs on the additional monitoring list differs from the processing of ADRs for 'established' products. A dedicated team in the MHRA reviews the monthly e-mail from the EMA with updates to the EMA additional monitoring list, including reasons for addition or deletion of products from the list. Newly added products on the list are then assigned an MHRA Assessor and this is recorded in the MHRA drugs dictionary, as well as in the related product licence case folders. This step is to assure that for all products on the additional monitoring list there is a dedicated MHRA Assessor who is responsible for the assessment of ADRs received for that product.

Established and additional monitoring drugs follow the same initial three workflow steps; however, for additional monitoring drugs, the assigned assessor evaluates the report (the fourth step in case processing procedures) for completeness and whether a request for further information is required. The same assessor is also assigned the particular product in the Empirica Signalling software for signal detection activities. The timelines for the case management are the same as ADRs for 'established' products.

With regard to communication of additional monitoring to the public, the UK is in a unique situation, since the concept of the 'black triangle' was in place from the 1970s – a long time before the introduction of EU-wide additional monitoring. The black triangle associated with a product indicated that it was under intensive monitoring by the MHRA. It was also intended to highlight this intensive monitoring and encourage HCPs to report all suspected ADRs to such new medicinal products and vaccines. This included novel products that had new: delivery routes, combination of drug substances, indications, products targeted at special populations such as the paediatric population, novel formulations or due to a new emerging safety issue that was deemed necessary by the MHRA to monitor intensively. Previous communications for such products were always coupled with a statement highlighting that any product that displayed a black triangle did not mean it was unsafe.

The promotion of the same concept and shift to additional monitoring was done at the time of the introduction of the additional monitoring concept across the EU. The aim was to communicate information via a special campaign; messages included the new specific wording added within the Patient Information Leaflets and SmPCs on reporting and the black triangle, information about the change in definition of the black triangle, and the importance of reporting all suspected ADRs.

The information was communicated to various stakeholders through two planned phases. Some patient groups were targeted based on the products on the additional monitoring list. Information was provided to NHS patient-facing websites, added to the MHRA website in the form of a guidance document, and a video of the Chair of PRAC explaining additional monitoring was also provided. The main focus of the campaign was HCPs as the medium to reach patients and to ensure that HCPs had the correct information to be able to explain additional monitoring to them. The campaign was measured by website hits, the number of stakeholders the messages were communicated with and further dissemination of the information cascade. The information guide on the additional monitoring concept for the public and healthcare professionals is available on the MHRA webpage. For transparency, it also contains requirements for the pharmaceutical industry on how to display the black triangle: Black Triangle Scheme – new medicines and vaccines subject to EU-wide additional monitoring.

Additional monitoring is also highlighted within the reporting guidance for HCPs. An example of this is provided on the MHRA website.

Annex 2. Case study: The Czech Republic – Státní ústav pro kontrolu léčiv

The Czech Republic introduced ADR collection in 1970, but their current database contains data from 2004 with roughly 2200 ADR reports per year.

The ADR reports received by SUKL from various sources are entered into the national database. The list of weekly received ADRs is prepared by using a business intelligence (BI) analysis tool for processing data from the Czech national pharmacovigilance database and shared in the form of a table to assessors for the assessment. The ADRs are allocated to the assessors according to the ATC groups of the suspect drug. Within a week, assessors have to go through the ICSR list and during their assessment they can make a comment in the special Comment field in the list table, indicating that the case is related to the drug under additional monitoring. Currently there is no possibility to flag the ADR report for drugs on additional monitoring in the database (but it is designed for the new R3 database, which is in progress). By using the abovementioned BI analysis tool it is also possible to prepare the list of ICSRs with suspect drugs under additional monitoring by restricting the filter to only include drugs on the additional monitoring list and by specifying the time period for the search. The filter has to be set manually and there is no special query developed.

Within the PV department, there is a dedicated person responsible for tracking the changes in the list of drugs under additional monitoring. Information on the updates is shared with other colleagues within a department during the bi-weekly meetings. The same person is also responsible for communication with the EMA on all questions regarding additional monitoring issues.

ADRs are discussed at the department meetings. Assessors are aware of medicinal products included in the list of additional monitoring and reported ADRs associated these products are emphasized during the discussion.

As the review of received ADRs is done weekly and in detail, it seems to be sufficient for the additional monitoring and it is carried out within the same timelines as other ADRs. At the moment, there are also no special time deadlines for follow-up requests for ADRs related to drugs on the additional monitoring list. With regard to prioritisation, only three well-described ICSRs with a causal relation between the ADR and suspect drug (under additional monitoring) are sufficient for triggering internal signal analysis, instead of the 5 cases necessary for ‘established drugs’. In addition, special priority is given to e-RMRs for active substances related to drugs under additional monitoring. They should be assessed within a 14-day timeline.

The announcement and general information on additional monitoring was published at SUKL’s website in the Czech language containing the link to the EMA additional monitoring list; however, the link is not easily accessible for website visitors (Léčivé přípravky podléhající dalšímu sledování), though this is to be changed in the near future.

Annex 3. Translation of the NOMA black triangle poster

The European Medicines Agency has introduced labelling of drugs to be monitored especially carefully. These drugs are marked with a black triangle in the SmPC and PIL, together with a brief explanation:

- "This medicine is subject to additional monitoring to detect new safety information as early as possible. You can contribute by reporting any side effects."
- These medicines will be labelled with a black triangle:
- New active substances approved in EU/EEA after 1 January 2011
- Biological medicines, such as vaccines and medicines created from blood plasma, approved after 1 January 2011
- When special requirements or obligations are linked to the approval of the medicine.

All medicines are carefully monitored after they are placed on the EU market. However, medicines with the black triangle are being monitored even more closely than others. This is generally because there is less information available about them compared with other medicines, for example, because they are new on the market or because the knowledge of long-term use is limited. It does not mean that the medicine is unsafe.

European additional monitoring list

The black triangle will be used in all EU/EEA countries and introduced gradually from autumn 2013. The medicines are recorded on a joint European additional monitoring list, where they will be kept for a minimum of five years. It may take some time from when a drug is listed to when the black triangle can be found in the package information leaflet. This is because the stock of packs with old package information leaflet will be gradually replaced.

The box in the bottom right-hand corner contains links to reporting forms and information about the additional monitoring list.