IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

50th EDITION

50th Edition of Irish Medicines Board's Drug Safety Newsletter

Dear Colleagues,

Welcome to the 50th Edition of the Drug Safety Newsletter (DSN) from the Irish Medicines Board (IMB).

For many people, taking medicines is a regular part of their daily life and these medicines are relied upon to treat disease and improve health. While medicines provide enormous health benefits, no medicine is without risk. As highly regulated healthcare products, medicines are authorised only when it is judged that the product is of high quality and that the benefits outweigh the risks. Once a product is authorised and placed on the market, the monitoring of benefits and risks continues throughout the entire product lifecycle through a system known as pharmacovigilance.

In 1995, when the first edition of the DSN was published, it was intended to be an occasional publication to communicate new and emerging pharmacovigilance issues to physicians and pharmacists. While in the initial years publication continued on that basis, the frequency of production increased steadily over time with some six editions of the DSN published annually over the past few years. During this time, the DSN has also been distributed to an increasing audience of health care professionals and through a variety of formats. This 50th edition of the DSN coincides with the introduction of substantial changes in the legislative framework for pharmacovigilance, and the relevant issues for healthcare professionals in this revised framework are outlined in this edition.

Marking the 50th edition, spanning a seventeen year period in which we have seen many changes in the field of medicines, including the development of new, innovative and targeted treatments, along with developments in the regulatory framework to support and enhance patient safety, is a significant milestone for this publication.

The evolution of the DSN has been in line with both the expanding remit of the Irish Medicines Board and the ongoing feedback and comments from the readers. In a recent survey conducted on behalf of the IMB, 75% of health care professionals cited the DSN as a principal source of information on medicines.

Throughout the 17 years of publication, the intention of the IMB for the DSN has been to provide clear, consistent communication on safety issues with medicinal products directly to healthcare professionals. After seventeen years, it remains a conduit for the provision of this information, ensuring that the latest data and updated recommendations to support safe use of medicines are highlighted in line with our remit to protect public health.

Healthcare professionals play a crucially important role in pharmacovigilance and their willingness to report suspected adverse reactions is and will continue to be the cornerstone of drug safety systems. There are many examples where an observant healthcare professional has alerted regulators to an emerging safety signal. The IMB will continue to work in partnership with healthcare professionals to encourage reporting and some products, particularly newly authorised medicines, will be subject to additional monitoring.

The role of healthcare professionals is however not confined to the reporting of adverse drug reactions but a key aspect is their role in communicating and managing risk at the individual patient level. Through the DSN, healthcare professionals can access information on medicinal products and updates on actions taken as a result of the information they provide.

In this edition

The publication of the DSN over the past seventeen years has involved considerable time and effort and I pay tribute to the editorial team, past and present, and all who have contributed material for their commitment in delivering this publication.

For the foreseeable future, we will continue to print and post the DSN to those who currently receive it in hard copy. In addition, as technology advances we are looking at more efficient and more rapid means of distribution to ensure timely communication of key safety messages. For example, we publish an electronic version of the DSN on our website **www.imb.ie**, which is increasingly accessed by subscribers. Should you wish to receive an email alert notifying you that future editions of the newsletter are available online, please submit your request to **imbpharmacovigilance@imb.ie**. Individual safety and quality alerts are also published directly on our website and subscribers can receive tailored alerts directly to their email or mobile phones.

In closing, colleagues at IMB will strive to ensure that the DSN remains a relevant and trusted source of information on medicinal products and one that meets the needs of healthcare professionals in an increasingly complex communications environment. We are committed to working in partnership with healthcare professionals to achieve our overall objective of promoting and protecting public health and, in this context, we encourage you to continue to provide your comments and feedback on the contents of the publication.

With very best regards,

Pat O'Mahony, Chief Executive, Irish Medicines Board

IMB Chief Executive Mr. Pat O'Mahony is pictured with the DSN editorial team, from left to right, Ms Niamh Arthur – Pharmacovigilance Manager, Dr. Almath Spooner – Pharmacovigilance and Risk Management Lead and Dr. Joan Gilvarry – Director of Human Products Monitoring. Absent from the picture is Ms Anna Marie Coleman – Pharmacovigilance Surveillance Assessor.

Updated Pharmacovigilance Legislation

Background

Medicines save lives and relieve suffering but can also cause side effects. According to an Impact Assessment undertaken by the European Commission, 5% of all hospital admissions are for side effects, 5% of all hospital patients suffer a side effect to a medicine and side effects are the fifth most common cause of hospital death. It is estimated that 197,000 deaths per year in the EU are related to adverse reactions and that the societal cost could be in the order of 79 billion Euros.[1] These figures are a stark reminder that we must always strive to minimise the burden of side effects and indeed evidence has shown that a sizeable proportion of side effects can be prevented.

Up until now pharmacovigilance has consisted of a series of process steps starting with data collection, though signal detection, risk evaluation, action to protect public health and communication. New pharmacovigilance legislation builds on existing systems to strengthen the EU wide network for monitoring the benefits and risks of medicines and for taking action on drug safety issues.

This legislation, which came into effect in July 2012, aims to reduce the burden of adverse reactions through proactive risk management and by optimising the safe and effective use of medicines. It does so by enhancing the current pharmacovigilance system in the EU, increasing the options for reporting of adverse reactions, improving transparency and introducing special provisions for medicines that need additional monitoring. The legislation also aims to increase the opportunities for members of the public to become better informed about the benefits and risks of taking medicines, as well as providing a legal basis for direct reporting of suspected adverse reactions by patients and consumers.

Many of the changes brought about by the new legislation primarily affect Marketing Authorisation Holders (i.e. pharmaceutical companies) and competent authorities such as the IMB; however a core objective of the new legislation is to increase the participation of all stakeholders, particularly patients and healthcare professionals, in the entire range of pharmacovigilance processes right through from adverse reaction reporting to ensuring effective risk minimisation.

Reporting of adverse reactions

What to report?

'Adverse reactions' and 'adverse events' are not always the same. An adverse event is any undesirable event experienced by a patient whilst taking a medicine, regardless of whether or not the medicine is suspected to be related to the event. Whereas an adverse reaction is any undesirable experience that has happened to the patient while taking a drug that is suspected to be caused by the drug or drugs.

Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. Examples include low blood pressure with antihypertensives and low blood sugar with insulin. Type A reactions also include those that are not directly related to the desired pharmacological action of the drug (e.g. dry mouth that is associated with tricyclic antidepressants). Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug e.g. anaphylaxis with penicillin and skin rashes with antibiotics.

Under the new legislation, an adverse reaction is formally defined as 'a response to a medicinal product which is noxious and unintended' thus capturing harms associated with any use of a medicinal product including use outside the terms of the marketing authorisation. This means that if an adverse effect of a medicine occurs following overdose, misuse or error, it is still considered an adverse reaction and should be reported.

As of July 2012 across the EU, patients have a legal right to report adverse reactions directly. Additionally, patients may tell their healthcare professional about symptoms they have experienced since taking a new medicine. However, as some adverse reactions may not be apparent to the patient, healthcare professionals need to be alert to the possible occurrence of adverse reactions. Clinical observations and initiative are vital in this respect, in linking a sign or symptom to either current or previous therapy. It is important to be alert to:

- Abnormal clinical measurements (e.g. temperature, pulse, blood pressure, blood glucose, body weight) while on drug therapy
- Abnormal biochemical or haematological laboratory results while on drug therapy. For example, plasma drug concentrations or liver biopsy where drug-induced hepatitis is suspected
- If new drug therapy is started which may be used to treat the symptoms of an adverse reaction
- Listening to the patient's own concerns regarding drug therapy

The concept of suspected has also been reinforced by the revision to the legislation, to emphasise that the suspicion of a causal relationship between a medicine and an adverse reaction should be sufficient to prompt reporting.

Key message: By submitting an adverse reaction report, you are simply notifying your suspicion. The report will be looked at in the context of any other information that we have about that particular reaction, and can therefore add to our knowledge and understanding of the reaction. Remember, if in doubt, please report.

Who can report?

Healthcare professionals and patients are strongly encouraged to report suspected adverse reactions to the IMB.

While the new legislation provides for direct reporting of suspected adverse reactions by patients throughout the EU, this option already exists in Ireland and will continue to be supported and developed.

The revised legislation also introduces a requirement for State Authorities to promptly report suspected adverse reactions to the IMB and for the sharing of information across national organisations responsible for patient safety.

Emphasising the importance of appropriate confidentiality, in line with the EU Privacy Directive and national data protection requirements, the legislation supports the processing and sharing of adverse reaction reports to facilitate the detection, assessment, understanding and prevention of adverse reactions, which is considered to constitute a substantial public interest. In keeping with these requirements, the IMB reiterates its advice that reporters should only provide anonymised patient identifiers, i.e. initials/record number/sex/age, when submitting adverse reaction reports.

The package leaflet for all products will be updated with guidance for patients on how to report a suspected adverse reaction to the IMB. The Summary of Product Characteristics will also encourage healthcare professionals to report suspected adverse reactions. These updates to the package leaflet and the Summary of Product Characteristics will have an implementation period.

Key Message: Healthcare professionals and patients are strongly encouraged to report suspected adverse reactions, which will continue to be managed and processed in compliance with data protection and privacy requirements.

How to report?

There are several options in place for reporting suspected adverse reactions to the IMB. These are as follows:

- By following the links to the online reporting options accessible from the IMB homepage,
- Using the downloadable report form also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'
- Using the traditional 'yellow card' report, which also utilises a freepost system
- By telephone to the IMB Pharmacovigilance Section (01 – 6764971)

Please note that certain mandatory fields are required to successfully submit an adverse reaction report via the online system. These include reporter details and a contact email address. The latter facilitates return of a unique report identifier number, as a confirmation of a successfully submitted report. Once submitted, a hyperlink is provided, which allows a PDF of the report to be generated as a record. A PDF of the report is also attached to the acknowledgement email.

In addition and in line with international guidance for adverse reaction reporting, the minimum criteria for an adverse reaction report must be provided:

- An identifiable patient (i.e. patient initials/age/sex/record number)
- An identifiable medicinal product (i.e. product name or active substance if brand is unavailable)
- An identifiable reporter
- An identifiable reaction

While these elements reflect the minimum criteria essential for a 'valid' adverse reaction report, additional information regarding the details relating to the reaction and the patient, such as relevant medical history, concomitant treatment(s), action taken with the medicine, patient outcomes and any relevant in-use circumstances are also extremely helpful in the evaluation of a suspected adverse reaction. Provision of this information also helps in reducing the need for subsequent follow up of individual case reports.

Key Message: A variety of options exist to facilitate adverse reaction reporting, Please use the one best suited to your practice and provide as much information as possible to facilitate case report evaluation

Additional Monitoring – reporting of adverse reactions to products under intensive surveillance

All medicines are authorised on the basis that at the time of authorisation the benefit of treatment is judged to outweigh the potential harm in the specified indication(s) for the target population. To come to this conclusion, data from clinical trials conducted during the development of a medicine are assessed. However, not all risks can be identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product can only be discovered or fully characterised in the post authorisation period, when larger populations of people are treated over longer periods of time. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring of any safety and efficacy information that becomes available to assess the impact on the risk-benefit profile of the medicinal product.

However, for certain medicinal products enhanced post-authorisation data collection is needed to support prompt identification of any new safety hazards and to allow appropriate action to be initiated immediately. The revisions to the pharmacovigilance legislation therefore introduce the concept of additional monitoring. This means that some medicines will be intensively monitored to ensure that any new safety hazards are identified promptly. In particular, healthcare professionals will be strongly encouraged to report all adverse reactions to these medicines. These medicines will be identifiable by a standard black symbol accompanied by an explanatory statement in the Summary of Product Characteristics and the Package Leaflet. Details of the exact symbol to be used and the initial list of products subject to additional requirements will be communicated once finalised and approved at EU level (likely to be in the springtime of 2013). When available, this list will be accessible to the public and healthcare professionals via the IMB website and will be updated regularly.

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 to increase awareness about the safe and effective use of certain medicinal products. Additional monitoring status will particularly apply to medicinal products with a new active substance and biological medicinal products (including biosimilars) but can be assigned to a medicinal product at any time during its life cycle.

Key Message: Products subject to additional monitoring will be identifiable by a standard black symbol. Please report all suspected adverse reactions to products which carry this symbol.

Biological traceability

The legislation also requires clear identification of any biological medicinal product which is the subject of a suspected adverse reaction report, indicating that the brand name and batch number of the product should be specified for adverse reaction reports. In accordance with this strengthened requirement, all adverse reaction reports associated with vaccines and other biological products will be followed up by the IMB/Marketing Authorisation Holder to obtain this information if missing.

Key Message: Please include the brand name, batch number and expiry date (where available) when reporting a suspected adverse reaction to a biological medicinal product.

Pharmacovigilance Risk Assessment Committee (PRAC)

A new scientific committee at the European Medicines Agency, the Pharmacovigilance Risk Assessment Committee (PRAC), was established under the new legislation and will meet on a monthly basis. The PRAC replaces the Pharmacovigilance Working Party in the current EU regulatory network and its mandate covers all aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions. The PRAC will issue recommendations for co-ordinated regulatory action across the EU. Regulatory actions to minimise risk and maximises benefits to the patient may include changes to warnings in the product information, restricting the indications for use of a medicine or in rare circumstances, removal of the medicine from the market, if the risks of a medicine are found to outweigh the benefits.

Membership of the PRAC will include a representative from each competent authority across the Member States, as well as from patient organisations, healthcare professionals, and independent experts appointed by the European Commission. The IMB is delighted to announce that the current IMB delegate to the PRAC, Dr. Almath Spooner was recently elected as its Vice-Chair for a three year period.

Key message: There will be strengthened coordination of EU decision making to take action on safety issues. Legally binding outputs for product reviews should lead to fast efficient updates to product information.

New levels of transparency

The new pharmacovigilance legislation includes an explicit commitment to openness and transparency in the European medicines safety-monitoring system. There will result in much more information being made publically available.

Agendas and Minutes of the PRAC meetings will be published. For EU-wide safety reviews, more information than ever before is provided at the beginning of the safety review. The list of products subject to additional monitoring will be made publically available. Extensive information on medicines will be made available on regulatory authority websites.

Users of the IMB website have the option of registering their contact information with the IMB to enable them to receive direct and immediate notification of safety alerts/updates by email or text message. To facilitate prompt access to these updates, users are encouraged to avail of this option by registering on the website at www.imb.ie

Key Message: Healthcare professionals and the public will be able to access much more information on medicinal products and updates on actions taken as a result of the information they provide. The aim is to provide information to support and enhance prescribing decisions in order to optimise benefits and minimize risks for their patients.

Conclusion

The role of healthcare professionals will continue to contribute to pharmacovigilance through reporting suspected adverse reactions seen in patients. In addition, they may be required to implement any advice received on minimising risks, for instance through following updated recommendations in revised product information or other information materials. Over time, the participation of healthcare professionals as well as patients in EU regulatory processes, including those for pharmacovigilance, has steadily increased and the active participation of these stakeholders is now at the core of the new pharmacovigilance legislation in Europe.

The IMB will continue to work with a wide range of stakeholders including the European Medicines Agency and other national regulators to implement the provisions contained in the new legislation.

Further Information

1. Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance Legislation. The European Commission 2008.
   http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf

More detailed information on the new pharmacovigilance legislation can be found in **Directive 2010/84/EU** and **Regulation (EU) No1235/ 2010**.

The legislation is accompanied by the implementing **Regulation (EU) No 520/2012** which was published by the European Commission in June 2012 and a series of modules on Good Pharmacovigilance Practice available on www.ema.europa.eu.

The national legislation transposing the EU pharmacovigilance legislation was signed by the Minister of Health on 25/07/2012 and officially published in the Irish Statute Book:

SI 272 of 2012 (Medicinal Products (Control of Placing on the Market)(Amendment) Regulations2012)

SI 273 of 2012 (Medicinal Products (Control of Manufacture) (Amendment)Regulations 2012)

SI 274 of 2012 (Medicinal Products (Control of Wholesale Distribution)(Amendment) Regulations 2012)

A Q&A document on the new Pharmacovigilance legislation is also available from the **European Medicines Agency (EMA)**. Further information is available on www.imb.ie.