Summary minutes of the Pharmacovigilance Expert Advisory Group meeting held on 1st June 2022

Background

The Pharmacovigilance Expert Advisory Group meets once a month to discuss and give independent advice on pharmacovigilance issues, including those relating to the balance of risk and benefits of licensed medicines in the UK. The Group's advice is used to make sure that medicines are prescribed and used safely. It can also be taken forward for discussion at the UK Commission on Human Medicines of which the Pharmacovigilance Expert Advisory Group is a subcommittee.

Please note that regulatory terms in this document are hyperlinked to a glossary at the end of the document. Click on the underlined term to be taken to the definition. This publication summarises the discussions of the meeting held on 1st June 2022.

Risk assessments

Nitrofurantoin and risk of serious lung side effects

The Group was informed that the MHRA had been sent a Coroner's Regulation 28 Report concerning the death of a patient from lung damage, after taking nitrofurantoin to treat a urinary tract infection.

Nitrofurantoin may cause lung side effects in some people and the current UK product information for healthcare professionals and patients includes warnings about the risk of possible acute, subacute and chronic lung side effects including pulmonary fibrosis (damage and scarring of the lungs causing difficulty breathing) with its use.

The Group was presented with an assessment of safety data for nitrofurantoin, including details of the case provided by the Coroner, data from the Yellow Card Scheme, and from the published scientific literature. The Group's view was sought on whether the evidence was sufficient to warrant changes to the product information for nitrofurantoin, and communication about the risk to healthcare professionals in the UK.

The Group's recommendations will be taken forward.

Paternal metformin exposure and genital birth defects in male offspring

The Group considered an assessment of a recently published pharmacoepidemiology study which reports an association between preconception paternal metformin exposure and birth defects in offspring, particularly genital birth defects in male offspring.[1]

The Group discussed the strengths and limitations of the study and noted significant limitations. The Group considered the study in the context of other safety information about pregnancy outcomes following paternal exposure to metformin.

[1] Wensink MJ, Lu Y, Tian L et al. Preconception Antidiabetic Drugs in Men and Birth Defects in Offspring – a nationwide cohort study. Annals of Internal Medicine. https://www.acpjournals.org/doi/10.7326/M21-4389

The Group agreed that there was insufficient evidence of an association between preconception paternal exposure to metformin and birth defects and that no regulatory action was required.

Signal Detection Methodology

Signal detection methodology and disproportionality analysis at the MHRA

The Group received a slide presentation on how the MHRA conducts signal detection activities using the UK Yellow Card database, including the use of disproportionality analysis. The UK Yellow Card database contains all the Yellow Card reports of suspected side effects to medicines and vaccines sent to the MHRA by UK healthcare professionals and members of the public.

The Group was presented with the results of an investigation into the impact of the large proportion of COVID-19 vaccine reports in the Yellow Card database on disproportionality analyses and signal detection for COVID-19 vaccines and other vaccines.

The EAG agreed that overall, the impact of COVID-19 vaccines reports on disproportionality analyses for other vaccines appeared to be limited and noted that already planned changes to the MHRA's signal detection methodology would address any potential issues.

The Group's recommendations will be taken forward.

Pharmacovigilance

Pharmacovigilance statistics: trends and themes in UK reporting

The Group was presented with statistics on suspected adverse drug reactions (ADRs) reported to the MHRA via the Yellow Card Scheme. The report analysed trends and themes in UK ADR reports received for all medicines and vaccines between 1 January 2022 and 30 April 2022, excluding the COVID-19 vaccines.

The total number of spontaneous reports received between 1 January 2022 and 30 April 2022 was approximately 3% lower than for the same period in 2021 but was 55% higher than for the same period in 2020.
The Group noted that the increase in reporting seen in 2021 compared to 2020 was likely due to changes in reporting requirements for pharmaceutical companies following the UK's exit from the EU as well as the impact of increased public awareness of the MHRA and the Yellow Card scheme due to the COVID-19 pandemic. The subsequent decrease in reporting in 2022 compared to 2021 may represent a slight reduction in the previously seen positive effects of the COVID-19 pandemic on ADR reporting in general.

Pharmacovigilance statistics: COVID-19 vaccines

The Group was also presented with a report on the trends and themes in reports of suspected adverse reactions for the COVID-19 vaccines. A summary of these reports is also published online.

Suspected side effects of any medicine or vaccine should be reported to the MHRA through the Yellow Card Scheme. Suspected side effects to medicines and vaccines or adverse incidents associated with medical devices and diagnostics used in coronavirus (COVID-19) should be reported using the dedicated Coronavirus Yellow Card reporting site or the Yellow Card app.

Procedural notes

- The Group completed its usual procedural business including the need to observe the confidentiality of the meeting and to declare interests, announcements, apologies, and approval of minutes
- Apologies were received from Professor Douglas, Drs Hawcutt, McGettigan, and Miller and Mrs Wang for the meeting.
- A list of members and invited experts who attended the meeting is in **Annex A**
- The Chair welcomed Professor Sofat to her first meeting as a new member of the EAG.
- Professor Ashcroft declared interests in two agenda items; the nature of these interests did not prevent him from taking part in the discussion
- The meeting was held via videoconference
- The meeting started at 10:33 and finished at 12:25
- The next meeting of the Pharmacovigilance Expert Advisory Group is scheduled to take place on 29th June 2022

To note:
Information can be withheld, under Section 43 of the Freedom of Information (FOI) Act 2000. Information regarding the issue under consideration and advice from the Pharmacovigilance Expert Advisory Group remain confidential at the date of this summary and will remain so until a final decision has been taken. There is normally no overriding public interest in releasing such information in advance of the regulatory process being completed. Any request for future information should be made direct to the MHRA (via info@mhra.gov.uk) and will be considered in accordance with the FOI Act.

Glossary of regulatory terms

Commission on Human Medicines (CHM)
The Commission gives advice on the safety, efficacy and quality of medicinal products. For further information, see: https://www.gov.uk/government/organisations/commission-on-human-medicines

Declaration of interests
The Chairman and Members are required to declare any interests that they hold in the pharmaceutical companies concerned with any of the agenda items.

Direct Healthcare Professional Communication (DHPC)
Letters sent to healthcare professionals to inform them of new safety information for medicines.

Disproportionality analysis
A statistical method of signal detection in a database of suspected adverse drug reaction reports. Measures the extent to which the adverse reaction of interest is associated with the drug of interest compared with all other drugs in the database.

Drug Safety Update
The MHRA and CHM's monthly bulletin to healthcare professionals on medicines safety. Drug Safety Update is published every month on the MHRA's website and on the Yellow Card App. https://www.gov.uk/drug-safety-update

Freedom of Information (FOI) Act
An act to make provision for the disclosure of information held by public authorities or by persons providing services for them. For further information, see: http://www.legislation.gov.uk/ukpga/2000/36/contents#pt2-l1g43

Marketing authorisation holder (MAH)
Holder of a marketing authorisation (licence) for a medicine. A marketing authorisation allows a company to make the medicine available to patients.

Regulation 28 Report (Preventing Future Deaths)
Coroner Regulation 28 Reports are sent to organisations when a Coroner believes that action should be taken to prevent future deaths.

Pharmacoepidemiology
The study of the therapeutic effect(s), risks and use of health products, in large populations, in the real-world setting

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of side effects to medicines or any other medicine-related problem

Product information
The product information for a medicine is made up of a Summary of Product Characteristics (SPC or SmPC) and a Patient Information Leaflet (PIL). SPCs advise healthcare professionals, such as doctors or pharmacists, how to prescribe and prepare a medicine correctly. A PIL is the paper leaflet that is included in the box with a medicine and advises patients how to use the medicine safely. SPCs and PILs for products licenced in the UK can be found on the MHRA's website https://www.gov.uk/guidance/find-product-information-about-medicines

Risk Management Plan
It is recognised that at the time of authorisation (licensing), information about the safety of a medicine is relatively limited. A Risk Management Plan documents what is and what is not known about the safety of the medicine at the time of authorisation, provides a plan to show how safety knowledge will be extended post-authorisation (e.g., through further studies) and, where necessary, defines the measures required to minimise the known risks and monitor the success of these measures.

Safety signal
A safety signal is information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation.

Yellow Card Scheme
A UK scheme for healthcare professionals and members of the public to report suspected side effects for a medicine or vaccine, or an adverse incident with a medical device. See https://yellowcard.mhra.gov.uk/

ANNEX A - Attendees of the Pharmacovigilance Expert Advisory Group meeting held on 2 March 2022

Chair

Professor Jamie Coleman MD MA (Med Ed) FRCP FBPhS
Professor in Medical Education / Consultant Clinical Pharmacologist, University of Birmingham

Members

Mrs Alana Adams BPharm (Hons) MSc MRPharmS IP
Principal Pharmacist, Welsh Medicine Information Service and advice, University Hospital of Wales, Cardiff

Professor Darren Ashcroft BPharm, MSc, PhD, FRPharmS
Professor of Pharmacoepidemiology, University of Manchester

Professor Ann Daly BA PhD FBPhS
Professor of Pharmacogenetics, Faculty of Medical Sciences, Newcastle University

Professor Ian J Douglas BSc MSc PhD
Professor of Pharmacoepidemiology, London School of Hygiene & Tropical Medicine

Dr Richard Fitzgerald MD MBChB PhD FRCP
CRF Director - NIHR Royal Liverpool and Broadgreen Clinical Research Facility; Consultant Physician, Clinical Pharmacology & Therapeutics/General Medicine; Honorary Senior Lecturer, University of Liverpool

Dr Mark Glover BA MA MB BChir MRCP PhD
Associate Professor and Honorary Consultant Physician, Clinical Pharmacology and General Medicine, University of Nottingham

Ms Susan Hunneyball BSc (Hons)
Lay Member

Dr Patricia McGettigan MD, BSc, MB, BCh, BAO, BA
Reader in Clinical Pharmacology and Medical Education and Consultant Physician, Barts Health Trust, London

Dr Rupert Payne MB ChB MRCP PhD MRCGP FRCP
Consultant Senior Lecturer in Primary Care, University of Bristol

Professor Reecha Sofat
Breckenridge Chair in Clinical Pharmacology and Therapeutics; Head of Department, Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology (ISMIB), University of Liverpool; Vice President (Clinical), British Pharmacological Society

Dr Ruben Thanacoody MD FRCP (Edin)
Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust; Honorary Clinical Senior Lecturer in Clinical Pharmacology, Newcastle University; Honorary Consultant Clinical Toxicologist, Public Health England; Director National Poisons Information Service (Newcastle unit)

Mrs Madeleine Wang BA (Hons)
Lay Representative and Patient Advocate

Invited experts

N/A