EURORDIS
THERAPEUTIC REPORT
October 2021
ISSUE 9
UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

EU Big Data Stakeholder Forum

The European medicines regulatory network is organising the 2nd *multi-stakeholder forum on big data* to foster collaboration and engage different stakeholders. The meeting will be broadcast live on the 7th of December (from 9am to 4pm CET) meeting using this *link*. No registration is required to view the live broadcast. Also, a video recording will be made available afterwards.

The main objectives of the forum are to:

- inform stakeholders about the delivery of the data pillar of the *Network Strategy 2025 via the HMA-EMA joint Big Data Steering Group 2021-2023*;
- listen to stakeholder views and feedback;
- discuss areas for collaboration.

For more information, please see agenda *here*.

IN THIS ISSUE

EMA's guidance on registry-based studies

The EMA has published a *guidance to provide key methods and good regulatory practices to pharmaceutical organisations on the planning and conduct of registry-based studies*.

This guideline aims to help those involved in registry-based studies to better define study populations and design study protocols; it provides further guidance on data collection, data quality management and data analysis to achieve higher quality evidence. This in turn will facilitate EU regulators' assessment of the safety and effectiveness of medicines, for the benefit of public health.

The *guideline* focuses on studies involving disease registries or condition registries to evaluate the benefit-risk of medicines prescribed to or consumed by patients. It explains the methodological differences between these types of studies and registries. It also contains an annex with good practices in the establishment and management of patient registries and their use for other possible regulatory purposes.

For more information, please *read the press release here*!

#ShareYourReason for a new European action plan on rare diseases!
Your voice counts!

What is the EURORDIS Round Table of Companies?

Since its inception 20 years ago, EURORDIS has gained expertise in dealing with the various public and private institutions involved in the rare disease and orphan drug fields. Through the ERTC programme, EURORDIS shares this expertise by bringing together industry, patient advocates, public officials and other experts to address patient needs.

The *EURORDIS Round Table of Companies (ERTC)* holds around two workshops each year, fostering an educational relationship and a constructive dialogue by bringing together different stakeholders to discuss topics relevant to the development of orphan drugs and other treatments for rare diseases.

The topic of the last ERTC workshop that was held online in October was about *the impact of the EU regulatory network strategy 2020-2025 on the development of orphan medicines.* The main objectives of the workshop were to:

- Get insights into the future of the regulatory strategy for data acquisition and analysis
- Learn about the new EMA task forces established to prepare the regulatory network for modern methods
- Understand how all stakeholders can prepare and plan the future, and therefore benefit from the changes
- Learn how clinical trials will be conducted in the next 20 years with the revision of the ICHE6
- Understand how patients will benefit from shorter and more innovative clinical trials, more robust HTA assessments, new digital solutions to measure efficacy and how more real-world evidence data will help to reduce risk and make decisions more certain.

For more information on the different sessions, please *read here.*

European Medicines Agency Task Forces

The EMA has *four mission-critical task forces*, bringing together expertise to drive transformational change in high-priority areas of the Agency's work:

- The *Digital Business Transformation task force* drives complex, digital change initiatives that impact on EMA's strategy, operational structure and operations in relation to the European medicines regulatory network, its partners and stakeholders. This includes adapting EMA operations to fundamental changes brought by legislative initiatives, digital technologies and global trends to meet stakeholders' needs and expectations.
- The *Data Analytics and Methods task force* builds up capability and capacity within EMA and across the European medicines regulatory network to deliver robust evidence for benefit-risk decision-making. This is achieved through expert scientific advice on products under development, strengthened support to marketing authorisation assessments and expert methods advice and data analysis for products on the market.
- The *Regulatory Science and Innovation task force* enables the continuous 'future-proofing' of the Agency and the *European medicines regulatory network*, by addressing key scientific and technological trends and their translation through the development of EMA's *regulatory science strategy*, planning and governance. It seeks to offer an enhanced first point of contact service to developers, in particular, small and medium-sized enterprises (SMEs) and academia.
- The *Clinical Studies and Manufacturing task force* develops and guides EMA's strategy at European Union and global level to support the facilitation of clinical studies and manufacturing.

The EMA is also establishing a coordination centre to provide timely and reliable evidence on the use, safety, and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the EU through a network called the *Data Analysis and Real-World Interrogation Network (DARWIN EU).*

For more information, please read *here*.

Pharmacovigilance Risk Assessment Committee (PRAC) October 2021

Minutes January 2021
Agenda October 2021
Meeting Highlights Oct 2021

Imbruvica risk of cardiac death not linked to the use of ACE inhibitors

The PRAC has concluded the review of a safety signal of sudden or cardiac death with *Imbruvica* (ibrutinib) when used in combination with angiotensin-converting enzyme (ACE) inhibitors. *Imbruvica* is a medicine for treating the blood cancers mantle cell lymphoma, chronic lymphocytic leukaemia (CLL) and Waldenström's macroglobulinaemia (also known as lymphoplasmacytic lymphoma).

After reviewing additional analyses from different sources, the PRAC has concluded that the possible association between treatment with Imbruvica with concomitant use of ACE inhibitors and the risk of sudden or cardiac death does not seem to be plausible.

The committee has therefore decided that although some cardiac adverse reactions are already known for Imbruvica, a further analysis of serious cardiac events is considered necessary in order to determine if these events might be linked to the use of Imbruvica alone and better characterise the risk of cardiotoxicity with the medicine, regardless of ACE inhibitor use.

For more information, please see *EMA website*.

COVID-19 vaccines update

The PRAC has concluded that there is currently insufficient evidence on a possible link between COVID-19 vaccines and very rare cases of multisystem inflammatory syndrome (MIS). MIS is a rare serious inflammatory condition affecting many parts of the body and symptoms can include tiredness, persistent severe fever, diarrhoea, vomiting, stomach pain, headache, chest pain and difficulty breathing. MIS has previously been reported following COVID-19 disease.

The committee's assessment is based on the available spontaneous reports and currently does not warrant an update of the product information.

The PRAC encourages all healthcare professionals to report any cases of MIS that may have occurred after vaccination and other adverse events in people receiving these vaccines.

EMA will continue to closely monitor any new reports of the condition and take appropriate measures if necessary.

For more information, please see *EMA website*.

Medicines safety resources

- List of medicines under additional monitoring
- EudraVigilance
- Shortages catalogue
- Recommendations on medication errors
- Good Pharmacovigilance Practices
- Patient registries
- Rules of procedure on the organisation and conduct of public hearings at the PRAC

Click on the image to get the latest issue of ***QPP Update***, an EMA newsletter with the latest news on EU Pharmacovigilance

Orphan medicines key figures

Since 2000

2449 Orphan designations

244 Orphan designations included in authorised indication

211 Authorised OMPs

84 To be used in children

6 Removed from the market

69 Marketed, but no longer "orphans"

To date

136

Products with a marketing authorisation and an orphan status in the European Union

25 November 2021

CHMP Meeting Highlights October 2021

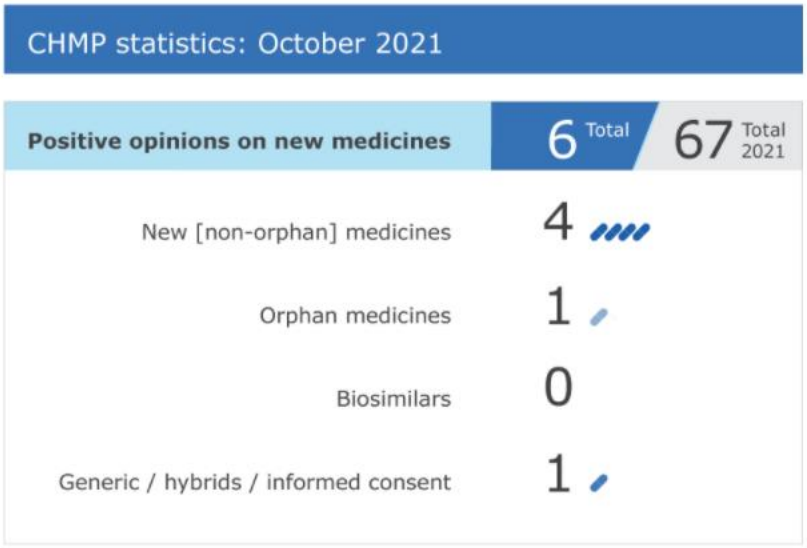
Minutes July 2021
Agenda October 2021
Meeting Highlights Oct 2021

In October, the CHMP recommended **6 medicines for approval, 1 orphan medicine**:

- *Aspaveli (pegcetacoplan)* for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria.
- *Trodelvy (sacituzumab govitecan)* for the treatment of unresectable or metastatic triple-negative breast cancer.
- Conditional marketing authorisation for *Rybrevant (amivantamab)* intended for the treatment of non-small cell lung cancer.
- *Cibinqo (abrocitinib)* for the treatment of atopic dermatitis.
- *Vaxneuvance (pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed))*, intended for prophylaxis against pneumococcal pneumonia and associated invasive disease.

The CHMP also recommended **10 extensions of therapeutic indication,** and recommended granting marketing authorisations for one generic medicine.

For further details, read the full *CHMP meeting highlights*.



Click on the image to get the latest issue of ***Human Medicines Highlights***, a newsletter published by EMA address to organisations representing patients, consumers and healthcare professionals summarising key information on medicines for human use.

Minutes September 2021
Agenda October 2021
Meeting Report Oct 2021

COMP October 2021 meeting update

During the October plenary, the COMP adopted **18 positive opinions** on the designation of medicines as orphan medicinal products to the European Commission (EC). For further information, please see the *meeting report.*

Please find below the list of indications covered in the medicines that were recommended for orphan designation:

- Systemic sclerosis, Topadur Pharma Deutschland GmbH;
- Diffuse large B-cell lymphoma, Vincerx Pharma GmbH;
- Diamond-Blackfan anemia, Consorcio Centro de Investigación Biomédica en Red, M.P.;
- Primary biliary cholangitis, GlaxoSmithKline (Ireland) Limited;
- Follicular lymphoma, Roche Registration GmbH;
- Pancreatic cancer, Cantargia AB;
- Ovarian cancer, Deciphera Pharmaceuticals (Netherlands) B.V.;
- Solid organ transplantation, Mimetech S.r.l.;
- Cystic fibrosis, Vertex Pharmaceuticals (Ireland) Limited;
- Leigh syndrome, Raremoon Consulting Esp S.L.;
- Amyotrophic lateral sclerosis, Encefa;
- Complex regional pain syndrome, Tetra Bio-Pharma Europe Limited;
- Amyotrophic lateral sclerosis, Neurevo GmbH;
- Adrenoleukodystrophy, Consorcio Centro de Investigación Biomédica en Red, M.P.;
- Invasive candidiasis, Dlrc Pharma Services Limited;
- Chronic myeloid leukaemia, Ascentage Pharma Europe Limited.
- Pancreatic cancer, Karma Oncology B.V.;
- Lennox-Gastaut syndrome, Takeda Pharma A/S.

Re-assessment of orphan designation at time of marketing authorisation

When a designated orphan medicinal product receives a positive opinion for marketing authorisation from EMA's Committee for Medicinal Products for Human Use (CHMP), the COMP has the responsibility to review whether or not the medicinal product still fulfils the designation criteria prior to the granting of a marketing authorisation.

The COMP adopted **2 positive opinions at time of CHMP opinion**:

- *Qinlock (ripretinib)* for treatment of gastrointestinal stromal tumours, Deciphera Pharmaceuticals (Netherlands) B.V.
- *Artesunate Amivas (artesunate)* for treatment of achondroplasia, Amivas Ireland Ltd.

Summaries of positive opinions on orphan designations are available on the *EMA website*.

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Elzonris® (tagraxofusp)	Stemline Therapeutics B.V.	Adults with blastic plasmacytoid dendritic cell neoplasm (BPDCN)	07/01/2021
Inrebic® (fedratinib)	Celgene Europe BV	Adults with myelofibrosis (a rare form of blood cancer)	08/02/2021
Lumoxiti® (moxetumomab pasudotox) *(Withdrawn by the company)*	AstraZeneca AB	Adults with hairy cell leukaemia, a cancer of the white blood cells	08/02/2021
Evrysdi® (risdiplam)	Roche Registration GmbH	5q spinal muscular atrophy (SMA) in patients +2 months of age with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies	26/03/2021
Pemazyre® (pemigatinib)	Incyte Biosciences Distribution B.V.	Adults with cholangiocarcinoma	26/03/2021
Sogroya® (somapacitan)	Novo Nordisk A/S	Growth hormone deficiency	31/03/2021
Koselugo® (selumetinib)	AstraZeneca AB	Neurofibromatosis type 1	17/06/2021
Enspryng® (satralizumab)	Roche Registration GmbH	Neuromyelitis Optica Spectrum disorders (NMOSD)	24/06/2021
Bylvay® (odevixibat)	Albireo	+6 months with progressive familial intrahepatic cholestasis (PFIC)	16/07/2021
Skysona® (elivaldogene autotemcel) *(Withdrawn by the company)*	bluebird bio (Netherlands) B.V.	Under 18 years of age with early cerebral adrenoleukodystrophy (CALD)	16/07/2021
Imcivree® (setmelanotide)	Rhythm Pharmaceuticals Limited	+6 years who have pro-opiomelanocortin (POMC) deficiency or leptin receptor (LEPR) deficiency	16/07/2021
Abecma® (idecabtagene vicleucel)	Celgene Europe BV	Adults with multiple myeloma (a cancer of the bone marrow)	18/08/2021
Voxzogo® (vosoritide)	BioMarin International Limited	Achondroplasia in patients aged +2 years	26/08/2021
Minjuvi® (tafasitamab)	Incyte Biosciences Distribution B.V.	Adults with diffuse large B-cell lymphoma (DLBCL)	26/08/2021
Qinlock® (ripretinib)	Deciphera Pharmaceuticals (Netherlands) B.V.	Gastrointestinal Stromal Tumors	18/11/2021

Please click also on the following links to see:

Orphan medicinal products authorised during 2021

Orphan medicinal products authorised since 2000

PDCO July to October meetings to be updated next issue

Minutes November 2021
Agenda October 2021
Meeting Report June 2021

PDCO June 2021 meeting update

In June, the PDCO adopted **13 positive opinions** agreeing *paediatric investigation plans (PIPs)* for the medicines below. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages.

- Human, recombinant, non-fucosylated IgG1k monoclonal antibody targeting OX-40 receptor on activated T cells (KHK4083), from Kyowa Kirin Pharmaceutical Development Limited, for the treatment of atopic dermatitis;
- Infigratinib, from QED Therapeutics Inc., for the treatment of achondroplasia;
- (1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-methyl-2-azabicyclo[3.1.0]hexane-3-carboxamide, from Alexion Europe SAS, for the treatment of paroxysmal nocturnal haemoglobinuria;
- Fenebrutinib, from Roche Registration GmbH, for the treatment of multiple sclerosis;
- Deucravacitinib, from Bristol-Myers Squibb International Corporation, for the treatment of systemic lupus erythematosus;
- Cefepime/zidebactam, from Wockhardt Bio AG, for the treatment of complicated urinary tract infections;
- Vatiquinone, from PTC Therapeutics International Limited, for the treatment of mitochondrial disease;
- Ublituximab, from CambPharma Solutions (CY) Ltd, for the treatment of multiple sclerosis;
- Afamitresgene autoleucel, from Adaptimmune Ltd, for the treatment of soft tissue sarcoma;
- Allogeneic anti-CD19 CAR T cells produced using CRISPR/Cas9 to disrupt the T cell receptor alpha constant (TRAC) and β2-microglobulin (B2M) genomic loci and a recombinant adeno-associated viral vector to deliver donor template for insertion of the anti-CD19 CAR expression cassette into the TRAC locus, from CRISPR Therapeutics AG, for the treatment of Blymphoblastic leukaemia/lymphoma and treatment of mature B cell neoplasms;
- Iptacopan, from Novartis Europharm Limited, for the paroxysmal nocturnal haemoglobinuria;
- Bardoxolone (methyl), from Reata Pharmaceuticals Inc., for the treatment of Alport syndrome;
- Human Immunoglobulin G1 constant region – human ectodysplasin-A1 receptor-binding domain fusion protein (ER004), from EspeRare Foundation, for the treatment of Xlinked hypohidrotic ectodermal dysplasia (XLHED).

The PDCO also adopted opinions on **product-specific waivers, modifications to an agreed PIP and compliance check** that can be consulted in the *meeting report.*

For further information on the work of the PDCO for this 2021, please see the *work plan.*

For a comprehensive list of opinions and decisions on PIPs, please check the *EMA website*.

CAT October meeting to be updated next issue

Minutes May 2021
Agenda September 2021
Meeting Report Sept 2021

CAT September 2021 meeting update

In September the Committee for Advanced Therapies (CAT) finalised **8 scientific recommendations on the classification of advanced therapy medicinal products** (ATMPs) depicted below.

The outcome of these assessments can be found here: *Summaries of scientific recommendations on classification of ATMPs*.

The following products were classified as **gene therapy medicinal products:**

- Recombinant serotype 9 adeno-associated virus encoding a codon-optimised human galactosylceramidase transgene, intended for the treatment of Krabbe disease;
- HEK293 cells transfected with a lentiviral vector to express Wilms' tumour antigen (WT1) and the antigen presenting molecule, cluster of differentiation 1d, intended for the treatment of WT1-expressing tumours.

The following products were classified as somatic cell therapy medicinal products:

- Autologous population of selected renal cells, intended for the treatment of chronic kidney disease;
- Allogeneic natural killer cells armed with anti-CD20 monoclonal antibody, intended for the treatment of B-Cell Non-Hodgkin lymphoma.

The following product was classified as **advanced therapy medicinal product**:

- Autologous adipose mesenchymal stem cells, intended for cartilage defects of degenerative origin and for the treatment of osteoarthritis;
- Wharton's jelly derived mesenchymal stem cells, intended for the treatment of:
    - rheumatoid arthritis;
    - systemic lupus erythematosus;
    - systemic sclerosis.

The following products **do not fulfil the definition of an advanced therapy medicinal product**:

- Minimally manipulated autologous pancreatic islets, intended for the treatment of chronic pancreatitis and recurrent acute pancreatitis immediately following pancreatectomy;
- Ribonucleoprotein (RNP), a complex of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Cas 9 and sgRNA, delivered by a novel synthetic non-viral vector, for the excision of exon 80 of the human COL7A1 gene, intended for the treatment of recessive dystrophic epidermolysis bullosa.

For more information, see also the *EMA meeting report.*

PATIENTS' AND CONSUMERS' WORKING PARTY

The Patients' and Consumers' Working Party (PCWP), established in 2006, serves as a platform for exchange of information and discussion of issues of common interest between EMA and patients and consumers. It provides recommendations to EMA and its human scientific committees on all matters of interest in relation to medicines.

For more information, see also the *PCWP mandate, objectives and rules of procedure.*

EMA PCWP and HCPWP September meeting

Last 21st and 22nd September took place a *2 days virtual meeting* which brought together all eligible patient and consumer and healthcare professionals organisations and members of the Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP).

During the first day of meeting, the Agency introduced the latest updates on COVID-19. EMA also presented on ongoing activities related with the impact of pharmacovigilance activities on healthcare and patient safety. An update on the implementation of the Clinical Trials regulation was also provided.

On the second day, the PCWP/HCPWP discussion focused on communication and stakeholder engagement topics linked with EMA's future extended mandate and Big Data. The final part of the meeting was dedicated to topic prioritisation for 2022, key dates and activities.

For more information, please see the *agenda, the presentations* and the *summary of the meeting here*.

EMA Glossaries

The EMA just published a *medical terms simplifier* that gives plain-language descriptions of medical terms commonly used in information about medicines.

A *glossary of regulatory terms* that gives definitions for the main terms used on the EMA website and in their documents has also been published.

For more information, please check the *glossaries here.*

GLOSSARY

Accelerated assessment
Rapid assessment of medicines in the centralised procedure aimed at facilitating patient access to new medicines that address an unmet medical need. Accelerated assessment usually takes 150 evaluation days, rather than 210.

Advanced therapies or advanced-therapy medicinal products (ATMPs)
ATMPs are new medical products based on genes, cells and tissues, which offer new treatment opportunities for many diseases and injuries. There are four main groups:

Gene-therapy medicines
They are medicines that contain genes leading to a therapeutic effect. They work by inserting 'recombinant' genes into cells, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

Somatic-cell therapy medicines
These contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases;

Tissue-engineered medicines
These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue.

Combined advanced-therapy medicines
These are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

Authorisation under exceptional circumstances
It allows patients access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with the disease, the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Compliance check
It is performed to verify that all the measures agreed in a *Paediatric Investigation Plan* (PIP) and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measured contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Conditional marketing authorisation
It is granted to a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Designation, orphan medicinal product
A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market.

European Public Assessment Report (EPAR)
It is a lay-language document, which provides a summary of the grounds on which the EMA/CHMP based its recommendation for the medicine to receive a marketing authorisation. This happens when a manufacturer develops a generic medicine based on a reference medicine, but with a different strength or given by a different route.

Hybrid application for marketing authorisation
Hybrid applications rely partly on the results of tests on the reference medicine and partly on new data from clinical trials.

Informed consent application for marketing authorisation
An informed consent application makes use of data from the dossier of a previously authorised medicine, with the marketing authorisation holder of that medicine giving consent for the use of their data in the application.

Orphan Legislation
Regulation (EC) No 141/2000 on orphan medicinal products

Paediatric Investigation Plan (PIP)
It sets out a programme for the development of a medicine in the paediatric population. It aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the EMA, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent.

Paediatric Use Marketing Authorisation (PUMA)
It is a dedicated marketing authorisation for medicinal products indicated exclusively for use in the paediatric population, or subsets thereof, with, if necessary, an age-appropriate formulation. It has been designed to promote paediatric development of already authorised products which are no longer covered by a patent. Benefits are 8 years of data protection and 10 years market protection

Patient-reported outcomes (PROs)
Measurements based on data provided directly by patients regarding their health condition without interpretation of the patient's response by a clinician or anyone else.

Patient-reported outcome measures (PROMs)
They are instruments, scales, or single-item measures that have been developed to measure PROs, for example a self-completed questionnaire to assess pain.

Periodic Safety Update Reports (PSURs)
Periodic reports that the evaluate the benefit-risk balance of a medicine as evidence is gathered in clinical use. They are submitted by marketing authorisation holders at defined time points after the authorisation.

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GLOSSARY

Post-authorisation efficacy studies (PAES)
PAES are studies relating to authorised medicinal products conducted within the therapeutic indication with the aim of addressing well-reasoned scientific uncertainties on aspects of the evidence of benefits of a medicine that could not be resolved before authorisation or were identified afterwards.

Post-authorisation safety studies (PASS)
A PASS is carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. The PRAC is responsible for assessing the protocols of imposed PASSs and for assessing their results.

Prevalence
In the context of the Orphan Legislation, the prevalence refers to the number of persons with the condition at the time the application is made, divided by the population of the European Union (EU) at that time. It requires demonstration through authoritative references that the disease or condition for which the medicinal product is intended affects not more than 5 in 10,000 persons in the EU, when the application is made.

Public summaries of PDCO evaluations of PIPs
They describe the applicant's proposal for the development of their medicine in children, the PDCO's conclusion on the potential use of the medicine in the paediatric population, the plan agreed between the committee and the applicant at the completion of the procedure (including any partial waivers or deferrals) and the next steps.

Referral procedures for safety reasons
A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or a class of medicines on behalf of the European Commission or a Member State.

Risk Management Plans (RMPs)
RMPs are regulatory documents submitted by medicine developers when they apply for marketing authorisation and include information on the medicine's safety profile; how its risks will be prevented or minimised in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; risk factors for developing adverse reactions; measuring the effectiveness of risk-minimisation measures.

Scientific advice/protocol assistance
Through scientific advice, companies can ask the EMA for advice on whether they are conducting the appropriate tests and studies during the clinical development of a given product. In the case of orphan medicines for the treatment of rare diseases, it also includes advice on1) the demonstration of significant benefit for the designated orphan indication and on 2) similarity or clinical superiority over other medicines; which are criteria for the authorisation of an orphan medicine.

Significant benefit
Demonstrating a significant benefit, this is demonstrating a "clinically relevant advantage or a major contribution to patients" is one of the criteria that medicines for the treatment of rare diseases must fulfil to benefit from 10 years of market exclusivity once they have been authorised. For further information, read the *workshop report: Demonstrating significant benefit of orphan medicines*, held at the EMA in December 2015.

Safety signal
A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature, but their presence does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of a safety signal is required to establish whether or not there is a causal relationship between the medicine and the adverse event.

Similar active substance
It means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of them) and which acts via the same mechanism.

Scientific Advisory Group (SAG)
SAGs have been established to provide an independent recommendation on scientific/technical matters related to products under evaluation through centralised regulatory procedures and referrals by the CHMP or any other scientific issue relevant to the work of the Committee.

Waiver
A waiver can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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