EURORDIS RARE DISEASES EUROPE

EURORDIS
THERAPEUTIC REPORT

June 2019

ISSUE 6

UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

EMA and EU payer community meeting

Last 18th June took place the second meeting between the EMA and EU healthcare payers in the Zorginstituut Nederland (Diemen). The objective of this meeting was to explore synergies and foster mutual understanding and cooperation to help improve timely and affordable access of patients to new medicinal products. This complements EMA's existing cooperation with Health technology assessment (HTA) bodies and especially with EUnetHTA.

For more information, please visit *EMA website*.

Apply to the EURORDIS Winter School on Scientific Innovation & Translational Research 2020

The *EURORDIS Winter School on Scientific Innovation and Translational Research* consists of one week face-to-face training, that will take place on 9-13 March 2020 at the Imagine Institute in Paris.

The Winter School equips participants with knowledge and skills so they are empowered to effectively participate in discussions with the researchers, policymakers, and companies responsible for research or research infrastructures.

To apply for this training, please fill in this *application form*. The **deadline** for applications is **30 August 2019**. The results will be announced by mid-November.

For more information, please visit *EURORDIS website*.

IN THIS ISSUE

EURORDIS article on data sharing/protection published in the OJRD

EURORDIS colleagues, Virginie Bros-Facer and Sandra Courbier, have published an article entitled: *"Share and protect our health data: an evidence based approach to rare disease patients' perspectives on data sharing and data protection - quantitative survey and recommendations"* in the Orphanet Journal of Rare Diseases (OJRD).

This article includes results from a Rare Barometer survey on rare disease patients' perspective on data sharing & protection. It also includes recommendations for policymakers and researchers.

For more information, please read the *article*.

Nominations for the ***EURORDIS Black Pearl Awards 2020*** are now open until **13 September 2019**.

Nominate now!

EU network takes steps to improve reporting and communication on medicine supply

Since 2016, *a task force* set up by the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) looks at availability issues, including medicines that are authorised but not marketed and supply chain disruptions, to improve continuity of supply of human and veterinary medicines across Europe.

This July, this task force has published two documents to better address potential problems with medicines' supply and to develop and coordinate actions to facilitate the prevention, identification, management of and communication about shortages:

- The first document '*guidance for marketing authorisation holders on reporting of shortages*' provides guidance to the pharmaceutical industry, a key player in addressing shortages, to facilitate the detection and early notification to competent authorities.

- The second one '*good practice guidance for communication to the public on medicines' availability issues*' is addressed to EU national competent authorities and EMA. This guidance includes examples of good practices for communication on shortages to the public**, including patients and healthcare professionals**. These groups require timely, accurate and up-to-date information on availability issues to ensure continuity of care.

Both documents lay the foundations for an improved and harmonised EU approach in reporting of and communication on medicines' shortages and availability issues, a key public health priority for the EU network.

The *European medicines regulatory network* aims to **minimise the impact of medicine shortages on patients by**:

- working with pharmaceutical companies to resolve manufacturing and distribution issues
- sharing information with international partners about alternative sources of supply
- seeking input from patients and healthcare professionals on the impact of medicine shortages, to support decision-making
- taking measures to allow alternative medicines or suppliers to be used

For more information, please visit *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

Pharmacovigilance Risk Assessment Committee (PRAC) June 2019

Minutes March 2019
Agenda June 2019
Meeting Highlights June 2019

PRAC starts review of leuprorelin medicines

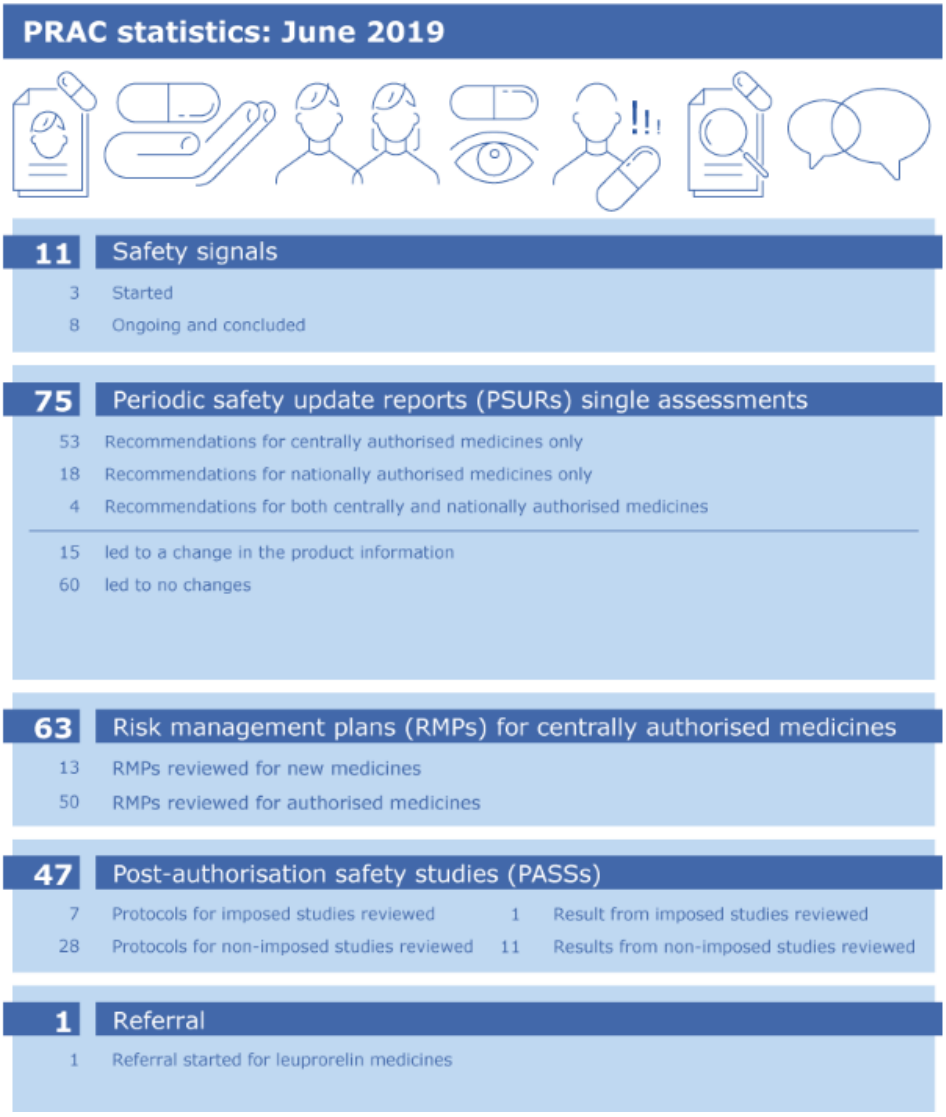
EMA's safety committee (*PRAC*) has started a review of *leuprorelin* containing depot medicines. This review covers formulations called depot formulations which are given by injection under the skin or into a muscle and release the active substance slowly over 1 to 6 months. These include implants as well as powders and solvents for the preparation of injections. These formulations are used to treat prostate cancer, breast cancer and conditions that affect the female reproductive system.

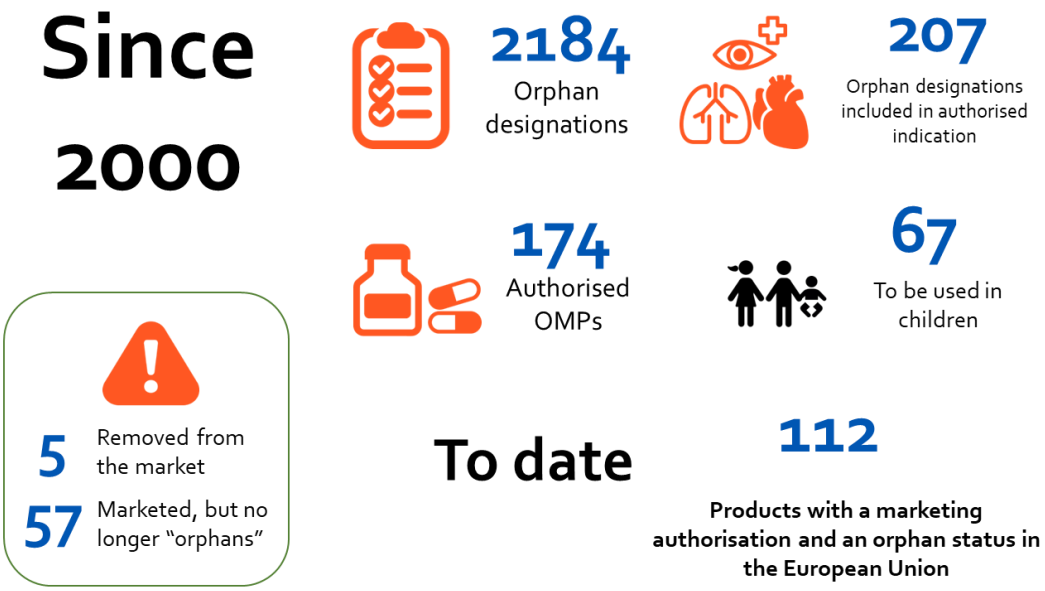
Some reports indicated that errors during preparation and administration of these formulations can cause some patients to receive insufficient amounts of their medicine, thus reducing the benefits of treatment.

The *PRAC* will now evaluate all available data and determine whether measures are needed to ensure that the medicines are prepared and administered appropriately.

While the review is ongoing, healthcare professionals should carefully follow the handling instructions for leuprorelin medicines. Patients prescribed these medicines who have any concerns should discuss them with their doctor.

For more information, please see *EMA website.*





18 July 2019

ORPHAN MEDICINAL PRODUCTS AUTHORISED IN 2019

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Palynziq® (pegvaliase)	BioMarin International Limited	Phenylketonuria (PKU)	03/05/2019
Waylivra® (volanesorsen)	Akcea Therapeutics Ireland Limited	Familial chylomicronaemia syndrome (FCS)	03/05/2019
Zynteglo® (Autologous $CD34+$ cells encoding βA-T87Q-globin gene)	bluebird bio (Netherlands) B.V.	beta-Thalassemia	29/05/2019

Please click also on the following links to see:

Orphan medicinal products authorised during 2019

Orphan medicinal products authorised since 2000

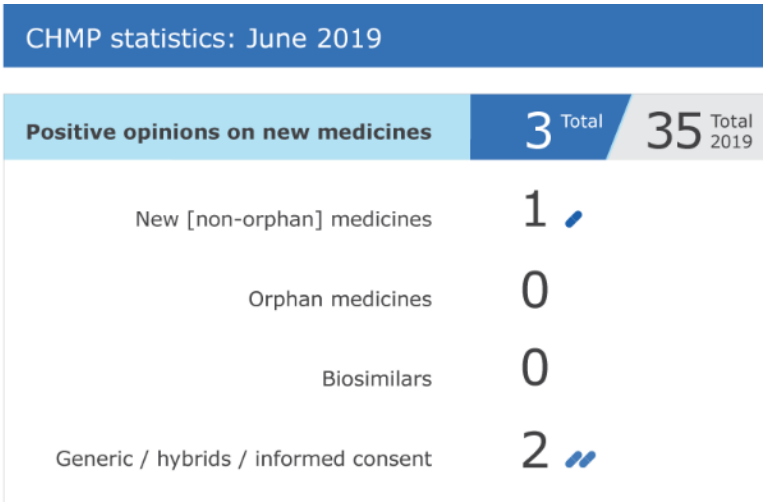
Minutes April 2019
Agenda June 2019
Meeting Highlights June 2019

CHMP Meeting Highlights June 2019

In June, the CHMP recommended **3 medicines for approval**:

- *Giapreza (angiotensin II),* for the treatment of refractory hypotension in adults with septic or other distributive shock
- *Azacitidine Celgene (azacitidine),* for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukemia
- *Lacosamide UCB (lacosamide),* for the treatment of partial-onset seizures with or without secondary generalisation

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 March 2019
Agenda June 2019
Meeting Report June 2019

COMP June 2019 meeting update

During the June plenary, the COMP adopted **8 positive opinions** on the designation of medicines as orphan medicinal products to the European Commission (EC). For further information, please see the *meeting report.* For further information on the work of the COMP see the *2019 work plan*

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

- 7-ethyl-10-hydroxycamptothecin for treatment of **soft tissue sarcoma,** Cebiotex S.L.
- Recombinant mutated extracellular domain of the human acetylcholine receptor subunit alpha1 for treatment of **myasthenia gravis,** Toleranzia AB
- 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one for treatment of **myelodysplastic syndromes,** Aprea Therapeutics AB
- Elafibranor for treatment of **primary biliary cholangitis,** Genfit
- Mavorixafor for treatment of **WHIM syndrome,** Voisin Consulting S.A.R.L.
- N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide for treatment of **neurofibromatosis type 1,** Voisin Consulting S.A.R.L.
- Parsaclisib for treatment of **marginal zone lymphoma,** Incyte Biosciences Distribution B.V.
- Pevonedistat for treatment of **acute myeloid leukaemia,** Takeda Pharma A/S.

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

PDCO June 2019 meeting update

In June, the PDCO adopted **7 positive opinions** agreeing *paediatric investigation plans (PIPs)* for the medicine 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.

- *Recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic Lamino acid decarboxylase protein,* from PTC Therapeutic International Limited, for the treatment of aromatic L-amino acid decarboxylase deficiency
- *6-cyclopropaneamido-4-{[2-methoxy-3-(1-methyl-1H-1,2,4 triazol-3-yl)phenyl]amino}-N- (2H3)methylpyridazine-3-carboxamide*, from Bristol-Myers Squibb International Corporation, for the treatment of psoriasis
- *Human immunoglobulin (Ig) G4-variant monoclonal antibody that binds and neutralizes soluble human interleukin- (IL-) 33,* from Eli Lilly and Company, for the treatment of atopic dermatitis
- *Bulevirtide*, from MYR GmbH, for the treatment of chronic hepatitis D infection
- *Vedolizumab,* from Takeda Pharma A/S, for the prevention of acute graft versus-host disease
- *Oxalobacter formigenes Strain HC-1,* from OxThera AB, for the treatment of hyperoxaluria
- *Humanized anti-CD19, Fc engineered, monoclonal antibody,* from Xencor Inc., for the treatment of immunoglobulin G4-related disease.

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

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CAT June 2019 meeting update

In June 2019, the Committee for Advanced Therapies (CAT) finalised **a total of 3 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 product was classified as a **tissue engineered product**:

• Allogeneic neonatal human cardiac progenitor cells, intended for the treatment of cardiac failure

The following product was classified as a **somatic cell therapy medicinal product**:

• Human embryonic stem-cell derived Müller cells, intended for the treatment of primary open angle glaucoma

The following product was classified as **non-ATMP**:

• Allogeneic human enucleated red cells expressing *Anabaena variabilis phenylalanine ammonialyase*, intended for the treatment of phenylketonuria

CAT May 2019 meeting update

In May 2019, the Committee for Advanced Therapies (CAT) finalised **a total of 4 scientific recommendations on the classification of advanced therapy medicinal products** (ATMPs) depicted below.

The following product was classified as a **gene therapy medicinal product**:

• Autologous dendritic cells, electroporated with messenger ribonucleic acid encoding tumour antigen Wilms tumour-1, intended for the treatment of lung cancer

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

• Allogeneic haematopoietic stem and progenitor cells treated ex vivo with the protein transduction domain of the human immunodeficiency virus-1 transactivation protein fused to MYC transcription factor, intended for the treatment of acute myelogenous leukaemia

• Allogeneic haematopoietic stem and progenitor cells treated ex vivo with the protein transduction domain of the human immunodeficiency virus-1 transactivation protein fused to MYC transcription factor, intended for the treatment of myelofibrosis

The following product was classified as **non-ATMP:**

• Autologous adipose tissue/micronised adipose tissue, intended for autologous skin wound healing

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.*

PCWP 2018-2019 Work Plan

At the last *Plenary with all eligible organisations* held on 22 November 2017, the draft joint work programme for PCWP and HCPWP for 2018 and 2019 was presented. This draft was sent for consultation during December to the drafting group and in it in the final review process by both working. For more information please see the *meeting summary* and the *draft joint work programme 2018-2019 presentation*

PCWP 2018 meetings

The first *PCWP – HCPWP joint meeting* of the year was held at the EMA on 17-18 April 2018. See *agenda* and *summary report.* All presentations are available in the *PCWP-HCPWP joint meeting event page*.

The second *PCWP – HCPWP joint meeting* of the year was held at the EMA on 25 September 2018. They discussed topics such as the results of the 2017 EMA perception survey, also the agency regulatory science initiative to 2025 and an update on Good Pharmacovigilance Practices (GVP). A feedback on the ongoing work on electronic product information and on availability of authorised medicines was given to the working parties' members.

EMA is also **supporting public health campaigns** with the aim to engage more with patients and HCPs. During this meeting a *case study* was presented where EMA has shared EURORDIS #RareDiseaseDay campaign.

For more information, see the *agenda.*

All presentations are available in the *PCWP-HCPWP joint meeting event page*.

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

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GLOSSARY

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.

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.

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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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