EURORDIS
RARE DISEASES EUROPE

EURORDIS
THERAPEUTIC REPORT

September 2020

ISSUE 8

UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

Executive Summary for ECRD 2020 now available!

The *Executive Summary for ECRD 2020* is now available! The European Conference on Rare Diseases & Orphan Products (ECRD) took place last May with +1500 participants, and is recognised globally as the largest, patient-led rare disease event in which collaborative dialogue, learning and conversation takes place, forming the groundwork to shape future rare disease policies.

Within the interactive summary you will find the **key figures, priorities and outcomes from the conference themes,** as well as a snapshot of all keynote speakers and poster winners. The document outlines the conference participants' preferred policy options from among the four scenarios presented within the *Rare 2030 foresight project*.

For further information please read the *Executive summary!*

IN THIS ISSUE

PARADIGM Q&A for the patient community

PARADIGM is organising four ***Q&A sessions for the patient community on the Patient Engagement Toolbox & tools*** developed during the project. The objective of the sessions is to allow participants to ask questions, and facilitate an active interaction between the audience and the lead authors of the tools, with the aim of clarifying concepts and discuss how to best use the tools. The sessions will cover the following topics and tools:

- **27th October (3-4 pm, CET):** *Raising awareness on managing competing interests in a multi-stakeholder environment: Guidance to patients and engaging stakeholders*
- **9th November (3 -4 pm CET):**
  - *Recommendations on required capabilities for patient engagement and*
  - *Patient engagement in medicines development: Recommendations on how to find the right match for the right patient engagement activity*
- **16th November (3 -4 pm CET):** *Patient Engagement Monitoring and Evaluation Framework*
- **20th November (3 -4 pm CET):**
  - *Working with Community Advisory Boards: Guidance and tools for patient communities and pharmaceutical companies*
  - *Guidance for reporting and dissemination of patient engagement activities*

If you would like to join the mentioned webinars, please **register *here***: *https://www.surveymonkey.com/r/KD7KZTW*.

For more information, please visit *PARADIGM website*.

IMI-conect4children (c4c)

EURORDIS is a member of the project consortium for *c4c (conect4children)*, a European network that aims to facilitate the development of new drugs and other therapies for the entire paediatric population.

First c4c 'Train the Trainers' Workshop

The *c4c project* was launched in 2018 and after two years, many initiatives have been carried out, such as the development of specific training courses for clinical experts and patients and the promotion of specific paediatric clinical trials. In all its activities c4c places patients at the centre, ensuring children and young people participate in all aspects of clinical trials.

Last 16 & 17 September was held the first c4c virtual '*Train the Trainers*' workshop with +30 patients and patient representatives in attendance. It was a successful event where we shared experience and expertise in the lifecycle of medicines and *how to get involved with the c4c project*. The topics covered included clinical trials methodology, clinical research, ethics in medicines development, regulatory affairs and marketing authorisation. The objectives of the workshop were:

- Building capacity on the life cycle of medicines (e.g. ethics, regulatory and clinical trial sessions
- Educate participants to support patients'/parents involvement at the European level for paediatric clinical trials.
- Describe and demonstrate the different ways patients can be engaged within the c4c project.

The recording of the workshop will be upload it soon at *the c4c website*. In the meantime, please check all the already available *educational resources* for patients! **Congratulations to all the participants**!

Join the pool of expert patients for c4c

The voices of children, young people and their families are a pivotal part of the innovative approach of c4c project. In order to guarantee patients' involvement in the project, c4c has setup a database to gather information on patients, caregivers, patient organisations and/or young person's advisory boards of rare/paediatric diseases.

Join the *c4c pool of expert patients* or spread the word among your members to join!

For more information, please see *c4c website.*

Pharmacovigilance Risk Assessment Committee (PRAC) September 2020

Minutes April 2020
Agenda September 2020
Meeting Highlights Sept 2020

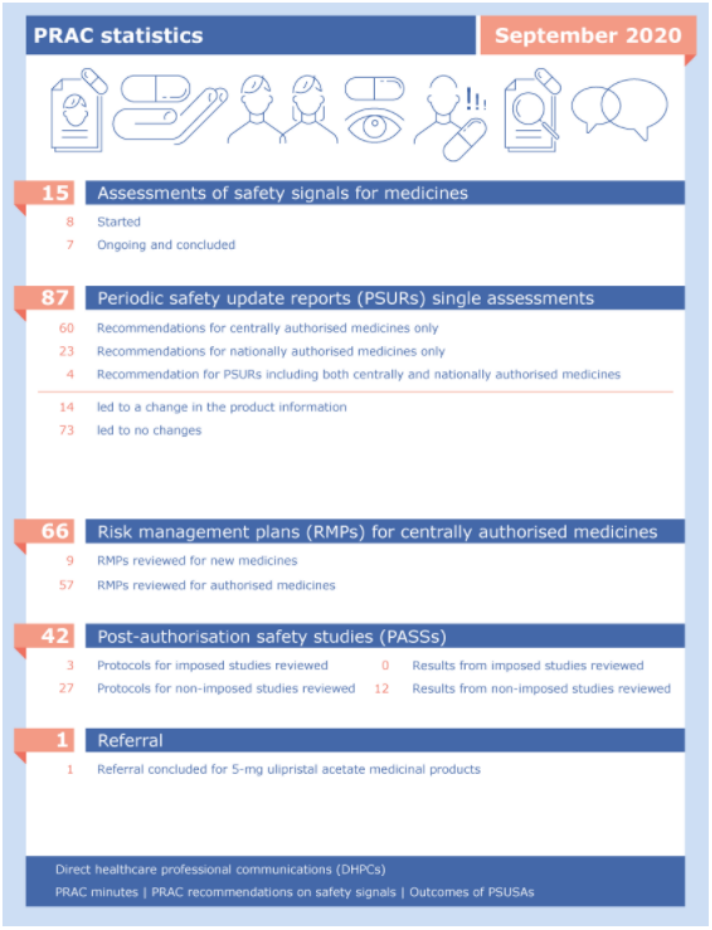
PRAC recommends revoking marketing authorisation of ulipristal acetate

EMA's safety committee (PRAC) recommended the revocation of the marketing authorisations of 5-mg ulipristal acetate (Esmya and generic medicines) used for the treatment of symptoms of uterine fibroids, as a review carried out by the Committee confirmed liver injury, including the need for liver transplantation, caused by these medicines.

PRAC concluded that the risks of these medicines outweighed their benefits and that they should not be marketed in the EU.

This recommendation does not affect the single-dose ulipristal acetate emergency contraceptive (ellaOne and other trade names) as there is no concern about liver injury with these medicines.

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

2327 Orphan designations

222 Orphan designations included in authorised indication

189 Authorised OMPs

72 To be used in children

5 Removed from the market

65 Marketed, but no longer "orphans"

To date

119

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

23 Sept 2020

CHMP Meeting Highlights September 2020

Minutes June 2020
Agenda September 2020
Meeting Highlights Sept 2020

In September, the CHMP recommended **7 medicines for approval, one orphan medicine**:

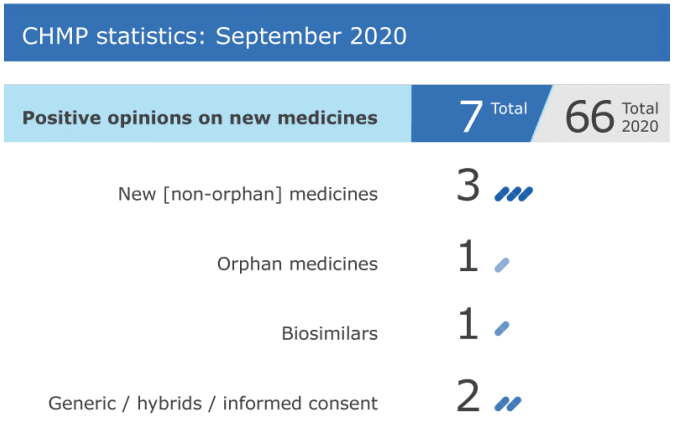
- Marketing authorisation under exceptional circumstances for *Obiltoxaximab SFL* (obiltoxaximab), for the treatment or post-exposure prophylaxis of inhalational anthrax.
- *Exparel* (bupivacaine), for the treatment of post-operative pain.
- *MenQuadfi* (meningococcal group A, C, W and Y conjugate vaccine), a vaccine for prophylaxis against invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W and Y.
- *Supemtek* (Quadrivalent Influenza Vaccine (recombinant, prepared in cell culture)), a vaccine for prophylaxis against influenza.

The CHMP also recommended granting marketing authorisation for **one hybrid medicine, one generic medicine**, and **one biosimilar medicine**:

- *Phelinun* (melphalan), a hybrid medicine for the treatment of certain haematological and other cancers and as reduced intensity conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in haematological diseases in adults and children. *Hybrid applications rely in part on the results of pre-clinical tests and clinical trials of an already authorised reference product and in part on new data.*
- *Nyvepria* (pegfilgrastim), a biosimilar medicine for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy.
- *Rivaroxaban Accord* (rivaroxaban), an anticoagulant generic medicine intended for the treatment and prevention of venous thromboembolism, pulmonary embolism and the prevention of atherothrombotic events in adults with various risk factors for such events.

Fifteen recommendations on extensions of therapeutic indication were also granted.

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.

COMP September 2020 meeting update

Minutes July 2020
Agenda September 2020
Meeting Report Sept 2020

During the September plenary, the COMP adopted **22 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:

- Primary IgA nephropathy, Novartis Europharm Limited
- Sickle cell disease, Clinipace GmbH
- Polycythaemia vera, Scendea (NL) B.V.
- Diagnosis of corticobasal degeneration, Life Molecular Imaging GmbH
- Fabry disease, ICON Clinical Research Limited
- Acute lymphoblastic leukaemia, Kite Pharma EU B.V.
- Sickle cell disease, Novo Nordisk A/S
- Anal cancer, Incyte Biosciences Distribution B.V.
- KCNQ2 developmental and epileptic encephalopathy, FGK Representative Service GmbH
- Multiple myeloma, Janssen-Cilag International N.V
- Aspartylglucosaminuria, Real Regulatory Limited
- RDH12 mutation associated retinal dystrophy, MeiraGTx B.V.
- GM1 gangliosidosis, Pharma Gateway AB
- Epidermolysis bullosa, Amryt Genetics Limited
- Activated phosphoinositide 3-kinase delta syndrome, Pharming Group N.V.
- Neuronal ceroid lipofuscinosis, Theranexus S.A.S.
- Homocystinuria, Aeglea Biotherapeutics UK Limited
- Hypoparathyroidism, Ascendis Pharma Bone Diseases A/S
- Limb-girdle muscular dystrophy, Premier Research Group S.L.
- Primary IgA nephropathy, Retrophin Europe Limited
- Peripheral T-cell lymphoma, TMC Pharma (EU) Limited
- Neuronal ceroid lipofuscinosis, Theranexus S.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. During the June plenary, the COMP adopted **5 positive opinion at time of CHMP opinion**:

- *Adakveo* (crizanlizumab) for treatment of sickle cell disease, Novartis Europharm Limited
- *Arikayce liposomal* (amikacin) for treatment of nontuberculous mycobacterial lung disease, Insmed Netherlands B.V.
- *Ayvakit* (avapritinib) for treatment of gastrointestinal stromal tumours, Blueprint Medicines (Netherlands).
- *Blenrep* (belantamab mafodotin) for the treatment of multiple myeloma, GlaxoSmithKline (Ireland) Limited
- *Kalydeco* (ivacaftor) - Type II variation, for the treatment of cystic fibrosis, Vertex Pharmaceuticals (Ireland)

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

ORPHAN MEDICINAL PRODUCTS AUTHORISED IN 2020

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Isturisa® (*osilodrostat*)	Novartis Europharm Limited	Cushing Syndrome	09/01/2020
Polivy® *(polatuzumab vedotin)*	Roche Registration GmbH	Diffuse large B-cell lymphoma (DLBCL)	16/01/2020
Givlaari® *(Givosiran)*	Alnylam Netherlands B.V.	Acute hepatic porphyria	02/03/2020
Trepulmix® *(Treprostinil)*	SciPharm Sàrl	Chronic thromboembolic pulmonary hypertension (CTEPH)	03/04/2020
Zolgensma® *(onasemnogene abeparvovec)*	AveXis EU Limited	Spinal muscular atrophy (SMA)	18/05/2020
Reblozyl® *(luspatercept)*	Celgene Europe B.V.	Beta thalassaemia & Myelodysplastic syndromes	25/06/2020
Daurismo® *(glasdegib)*	Pfizer Europe MA EEIG	Newly-diagnosed acute myeloid leukaemia (AML)	26/06/2020
Pretomanid FGK *(pretomanid)*	FGK Representative Service GmbH	Adults with drug-resistant tuberculosis	31/07/2020
Hepcludex *(bulevirtide)*	MYR GmbH	Chronic (long-term) hepatitis delta virus (HDV) infection in adults	31/07/2020
Idefirix *(imlifidase)*	Hansa Biopharma AB	Prevent the body from rejecting a newly transplanted kidney	25/08/2020
Kaftrio *(ivacaftor / tezacaftor / elexacaftor)*	Vertex Pharmaceuticals (Ireland) Limited	Cystic fibrosis	21/08/2020
Blenrep (belantamab mafodotin)	GlaxoSmithKline (Ireland) Limited	Multiple Myeloma	25/08/2020
Ayvakyt (avapritinib)	Blueprint Medicines (Netherlands) B.V.	Gastrointestinal stromal tumour (GIST)	24/09/2020

Please click also on the following links to see:

Orphan medicinal products authorised during 2020

Orphan medicinal products authorised since 2000

PDCO September 2020 meeting update

Minutes June 2020
Agenda September 2020
Meeting Report Sept 2020

In September, 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.

- Danicopan, from Alexion Europe SAS, for the treatment of paroxysmal nocturnal haemoglobinuria
- rAAVrh74.MHCK7.microdystrophin (SRP-9001), from Sarepta Therapeutics Ireland, for the Duchenne muscular dystrophy
- Doravirine / Islatravir, from Merck Sharp & Dohme (Europe), Inc., for the treatment of human immunodeficiencyvirus-1 (HIV-1) infection
- Plasma kallikrein inhibitor, from KalVista Pharmaceuticals Ltd, for the treatment of hereditary angioedema
- Glycopyrronium bromide, EMEA-002383-PIP01-18, from Dr. August Wolff GmbH & Co. KG - Arzneimittel, for the treatment of hyperhidrosis
- The whole range of unmanipulated autologous mononuclear cells derived from human umbilical cord blood (Hau-UCB-mnc), from BrainRepair UG (haftungsbeschränkt), for the treatment of periventricular leukomalacia
- N-(3-cyano-4-fluorophenyl)-1-methyl-4-[[(2S)-1,1,1-trifluoro-2-propanyl]sulfamoyl]-1H-pyrrole-2-carboxamide, from Janssen-Cilag International NV, for the treatment of chronic viral hepatitis B
- (2S,4S)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-1-ium chloride—water (1/1), from Novartis Europharm Limited, for the treatment of IgA Nephropathy
- Mixture of 2 synthetic double-stranded N-acetyl-galactosamine conjugated siRNA oligonucleotides that are directed against the hepatitis B virus, from Janssen-Cilag International NV, for the treatment of chronic viral hepatitis B
- (2S,4S)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-1-ium chloride—water (1/1), from Novartis Europharm Limited, for the treatment of C_3 Glomerulopathy
- Recombinant human granulocyte colony-stimulating factor – human immunoglobulin Fc fusion protein (rhG-CSF-Fc), from Generon (Shanghai) Corporation, for the prevention of chemotherapy-induced febrile neutropenia and treatment of chemotherapy-induced neutropenia
- Dabrafenib, from Novartis Europharm Limited, for the treatment of glioma
- Trametinib, from Novartis Europharm Limited for the treatment of glioma

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.*

PDCO July 2020 meeting update

In July, the PDCO adopted **14 positive opinions** agreeing *paediatric investigation plans (PIPs)*. 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*, *and agenda.* For a comprehensive list of opinions and decisions on PIPs, please check the *EMA website.*

CAT September 2020 meeting update

Minutes July 2020
Agenda September 2020
Meeting Report Sept 2020

In September the Committee for Advanced Therapies (CAT) finalised **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 **gene therapy medicinal products:**

- Recombinant adeno-associated viral vector (serotype 8) carrying an optimised gene for human cyclic nucleotide gated channel subunit alpha 3 (CNGA3) protein, intended for the treatment of achromatopsia caused by mutations in the CNGA3 gene

- Autologous naïve regulatory T cells transduced with a lentiviral vector encoding for a Chimeric Antigen Receptor (CAR) to recognize the HLA-A*02 antigen, intended for the prevention of immune-mediated graft rejection in HLA-A*02 mismatched renal transplantation

- Live-attenuated, genetically modified Mycobacterium bovis expressing the gene coding for listeriolysin from Listeria monocytogenes, intended for treatment of non-muscle invasive bladder cancer.

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.*

PCWP and HCPWP September meetings

During 22&23 September *two virtual meetings* took place 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).

A *workshop on benefit-risk of medicines used during pregnancy and breastfeeding* took place the 22nd September with the following objectives:

- Share experiences and expectations from real life and clinical practice
- Provide input into the draft EMA strategy on drug safety in pregnancy and breastfeeding
- Discuss how to progress with implementing the 'EMA strategy towards obtaining evidence on medicine utilisation and safety for pregnant and breastfeeding women' report.

For more information, please see the *agenda*.

The 23rd September *a workshop on the application of the General Data Protection Regulation (GDPR) in the area of health and Secondary Use of Data for Medicines and Public Health Purposes* with the following objectives:

- Discuss with patients, consumers and healthcare professionals the development of an EU-wide governance framework and a future code of conduct on the processing of personal data in the health sector
- For stakeholders who submitted feedback as part of EMA's targeted stakeholder consultation on the application of GDPR in the health sector and the secondary use of health data for medicines and public health purposes, provide a platform to discuss their key questions
- Provide an overview of the European Commission's (EC) work on the creation of the European Health Data Space for the use and re-use of health data for better healthcare, informed health policy-making and the development of new treatments, medicines, medical devices and services. The initiative aims to provide a clear legal and governance framework, interoperable technical infrastructure, quality health data and semantic interoperability and support capacity building in the Member States
- Enable EMA to present an update on the drafting status of Questions and Answers (Q&As) on secondary use of data for medicines and public health purposes and next steps.

For more information, please see the *agenda*.

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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