EURORDIS
THERAPEUTIC REPORT
November 2021
ISSUE 10
UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

11th European Conference on Rare Diseases and Orphan Products (ECRD)

The *ECRD* is recognised globally as the largest, patient-led rare disease policy event in which collaborative dialogue, learning and conversation takes place, forming the groundwork to shape goal-driven rare disease policies and allow for important and innovative discussions on a national and an international level to take place.

EURORDIS-Rare Diseases Europe is offering **patient fee waivers** for up to 80 patients' advocates to attend the next ECRD 2022 which will take place fully **online from 27 June to 1 July 2022.** These fee waivers aim at empowering patient advocates by offering a platform for networking opportunities, access to information and sharing experiences. To apply for the *fee waiver programme* please *fill in the application form* by **15 January 2022**.

For more information, please see *here* or contact *anja.helm@eurordis.org*

IN THIS ISSUE

EMA's Public stakeholder meeting on COVID-19 vaccines

Last 25th November took place the fourth EMA's public stakeholder meeting which provided an update on COVID-19 vaccines and therapeutics in the EU, including vaccine effectiveness, and the use of booster and third doses in national vaccination campaigns. It also addressed misinformation and highlighted the current vaccination coverage in the EU and updated on vaccine safety information.

For more information, please see the *agenda, the presentations and the recordings here*.

EMA recommends Nuvaxovid for authorisation in the EU

EMA has recommended granting a conditional marketing authorisation for Novavax's COVID-19 vaccine Nuvaxovid to prevent COVID-19 in people from 18 years of age. Nuvaxovid is the fifth vaccine recommended in the EU for preventing COVID-19. It is a protein-based vaccine and, together with the already authorised vaccines, will support vaccination campaigns in EU Member States during a crucial phase of the pandemic.

For more information, please *see here.*

Patient advocates fee-waiver application!
Apply now!
Deadline 15 January!

Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia

What is drug repurposing?

Drug repurposing is the process of identifying a new use for an existing drug/active substance in an indication outside the scope of the original indication.

What is the aim of this pilot?

The *European Medicines Agency (EMA)* and the *Heads of Medicines Agencies (HMA)* are launching a pilot project to support the repurposing of medicines as a follow-up to the *European Commission's Expert Group on Safe and Timely Access to Medicines for Patients (STAMP)* discussions on a proposal for a medicines repurposing framework.

The **aim** of this initiative is to support not-for-profit organisations and academia (institutions and individuals) who have a particular interest in repurposing an authorised medicine for a new indication in an area of public health interest, have a scientific rationale for their repurposing programme and would like to seek scientific advice with a regulatory authority. This is a way of making new treatment options available to patients. As part of the pilot, EMA and the national medicines agencies will provide regulatory support, primarily scientific advice, to help these stakeholders generate a data package robust enough to support a future application by a pharmaceutical company.

Further information on the pilot project is available in a *question-and-answer document here.*

Which are the criteria?

Candidate medicines for the pilot should fulfil the following criteria:

- contain a well-established active substance;
- be an authorised medicine (containing the concerned active substance) out of data exclusivity and market protection periods and out of basic patent / supplementary protection certificate (SPC) protection;
- target an indication in a condition distinct from the currently authorised indication(s);
- target an indication in an area where important public health benefits are likely to be achieved. Conditions for which no or few medicines are currently authorised or which are associated with high morbidity and / or mortality despite available medicines, will be the focus of the pilot.

Eligible academia sponsors developing orphan medicines will automatically benefit from a fee waiver. Additional fee waivers will be granted to a subset of selected applications considering the extent of the expected public health benefits and the strength of the evidence to substantiate the promise held by the proposal. **Repurposing of medicines for COVID-19 falls outside the scope of this pilot project.**

Sponsors wishing to seek EMA *scientific advice* should complete the *drug repurposing submission form* and submit it to *sarepurposing@ema.europa.eu* by **28 February 2022**. For submissions to *national competent authority* contacts, please refer to the additional information in the annex to the *question and answer document*.

EMA proposes to support the development and implementation of a repurposing framework in its *Regulatory Science Strategy to 2025*, which is its plan for advancing engagement with regulatory science over the next five to ten years.

For further information, please *see here*.

Pharmacovigilance Risk Assessment Committee (PRAC) November 2021

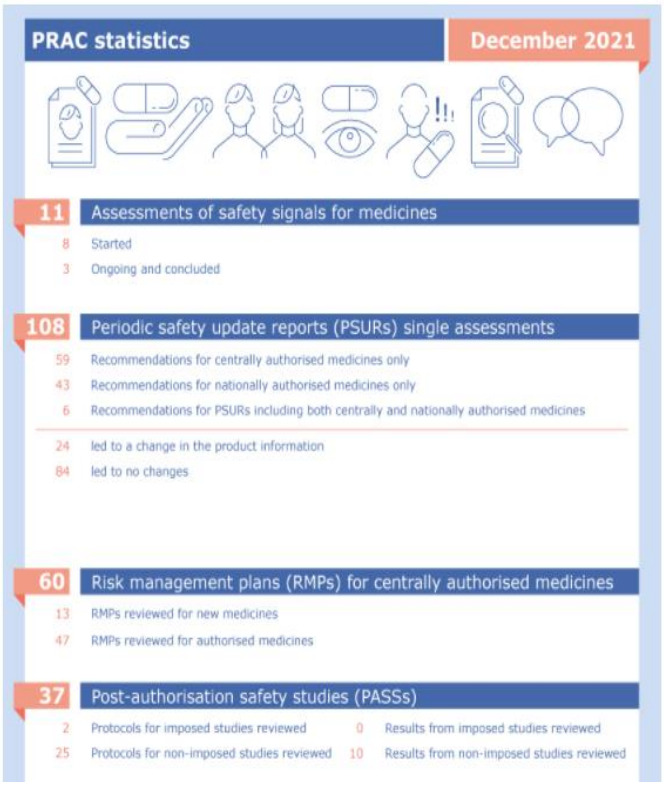
Minutes February 2021
Agenda November 2021
Meeting Highlights Nov 2021

PRAC update on risk of myocarditis and pericarditis with mRNA vaccines

EMA's safety committee (*PRAC*) has assessed recent data on the known risk of myocarditis and pericarditis following vaccination with COVID-19 vaccines Comirnaty and Spikevax (previously COVID-19 Vaccine Moderna). Myocarditis and pericarditis are inflammatory conditions of the heart that present a range of symptoms, often including breathlessness, a forceful heartbeat that may be irregular (palpitations), and chest pain.

Overall, the outcome of the review confirms the risk of myocarditis and pericarditis, which is already reflected in the product information for these two vaccines and provides further details on these two conditions. Based on the reviewed data, **the PRAC has determined that the risk for both conditions is overall "very rare"**, meaning that up to one in 10,000 vaccinated people may be affected. **EMA confirms that the benefits of all authorised COVID-19 vaccines continue to outweigh their risks**, given the risk of COVID-19 illness and related complications, and as scientific evidence shows that they reduce deaths and hospitalisations due to COVID-19.

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

245 Orphan designations included in authorised indication

212 Authorised OMPs

84 To be used in children

6 Removed from the market

71 Marketed, but no longer "orphans"

To date

135

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

20 December 2021

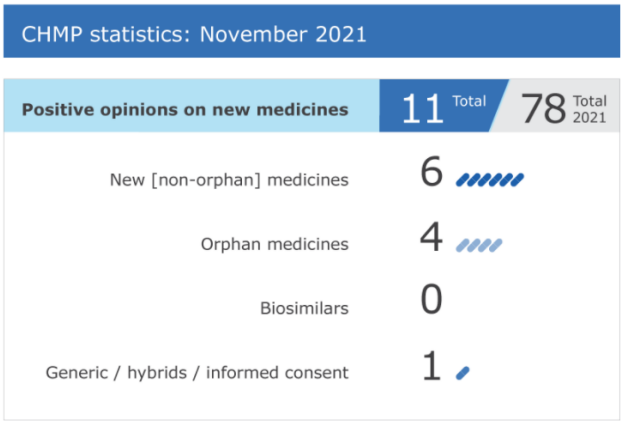
CHMP Meeting Highlights November 2021

Minutes November 2021
Agenda November 2021
Meeting Highlights Nov 2021

In November, the CHMP recommended **11 medicines for approval, 4 orphan medicines**:

- *Tavneos (avacopan)* for the treatment of adult patients with severe, active granulomatosis with polyangiitis or microscopic polyangiitis, a rare type of inflammation of the blood vessels.
- *Lonapegsomatropin Ascendis Pharma (lonapegsomatropin)* for the treatment of growth hormone deficiency in adolescents and children above 3 years of age.
- *Uplizna (inebilizumab)* for the treatment of adult patients with neuromyelitis optica spectrum disorders.
- Recommendation for a marketing authorisation under exceptional circumstances was adopted for *Voraxaze (glucarpidase),* intended to reduce toxic plasma methotrexate concentration in adults and children with delayed methotrexate elimination or at risk of methotrexate toxicity.
- *Regkirona (regdanvimab) and Ronapreve (casirivimab / imdevimab)* are the first monoclonal antibodies to receive a positive opinion by the Committee for the treatment of COVID-19.
- Conditional marketing authorisation for *Lumykras (sotorasib)* intended for the treatment of non-small cell lung cancer in patients with a specific mutation, G12C, in the KRAS protein.
- Recommendation for a marketing authorisation under exceptional circumstances was adopted for *Tecovirimat SIGA (tecovirimat)* for the treatment of orthopoxvirus disease.
- *Vyepti (eptinezumab)* for the prophylaxis of migraine in adult patients who have at least 4 migraine days/month.
- *Wegovy (semaglutide)* was granted a positive opinion for weight management in people with obesity or who are overweight and have other related conditions.

The CHMP also recommended **6 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 October 2021
Agenda November 2021
Meeting Nov Oct 2021

COMP November 2021 meeting update

During the November plenary, the COMP adopted **23 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:

- Cystic fibrosis, AdRes EU B.V.;
- SCN2A developmental and epileptic encephalopathy, Real Regulatory Limited;
- SCN8A developmental and epileptic encephalopathy, Real Regulatory Limited;
- Acute lymphoblastic leukaemia, Yes Pharmaceutical Development Services GmbH;
- Frontotemporal dementia, Scendea (NL) B.V.;
- Osteogenesis imperfecta, Boost Pharma ApS;
- Pulmonary arterial hypertension, Gmax Biopharm Belgium;
- Primary IgA nephropathy, Voisin Consulting Life Sciences;
- Acute lymphoblastic leukaemia, Onechain Immunotherapeutics S.L.;
- Acute myeloid leukaemia, Otsuka Pharmaceutical Netherlands B.V.;
- Primary sclerosing cholangitis, JVM Europe B.V.;
- Glioma, Advanced Center Oncology Macerata - S.r.l.;
- Short bowel syndrome, Napo EU S.p.A.;
- Hereditary angioedema, CSL Behring GmbH;
- Chronic thromboembolic pulmonary hypertension, Janssen-Cilag International N.V.;
- Epileptic encephalopathy with continuous spike-and-wave during sleep, Neurocrine Therapeutics Limited;
- Familial exudative vitreoretinopathy, Maxia Strategies-Europe Limited;
- Idiopathic intracranial hypertension, Granzer Regulatory Consulting & Services;
- Bronchopulmonary dysplasia, Real Regulatory Limited;
- Epidermolysis bullosa, Branca Bunus Limited;
- Spinocerebellar ataxia, Biohaven Pharmaceutical Ireland DAC;
- Soft tissue sarcoma, PTC Therapeutics International Limited;
- Alpers-Huttenlocher syndrome, PTC Therapeutics International Limited.

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 1 **positive opinion at time of CHMP opinion**:

- *Aspaveli (pegcetacoplan)* for treatment of a paroxysmal nocturnal haemoglobinuria, Swedish Orphan Biovitrum AB (publ).

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
Aspaveli® *(pegcetacoplan)*	Swedish Orphan Biovitrum AB (publ)	Adults with paroxysmal nocturnal haemoglobinuria (PNH)	13/12/2021

Please click also on the following links to see:

Orphan medicinal products authorised during 2021

Orphan medicinal products authorised since 2000

PDCO July to November meetings to be updated when info available

Minutes July 2021
Agenda November 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.*

Minutes August 2021
Agenda November 2021
Meeting Report November 2021

CAT November 2021 meeting update

In November the Committee for Advanced Therapies (CAT) finalised **1 scientific recommendation 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 **does not fulfil the definition of an advanced therapy medicinal product**:

- Autologous red blood cells chemically coupled with 12 antigenic peptides, intended for the treatment of multiple sclerosis.

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

CAT October 2021 meeting update

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

The following products were classified as gene therapy medicinal products:

- Optimised DNA encoding the sequence of interest COL7A1, intended for the treatment of dystrophic epidermolysis bullosa;
- Recombinant adeno-associated virus serotype HSC 15 (rAAVHSC15) expressing human iduronate-2-sulfatase, intended for the treatment of mucopolysaccharidosis type II (known as Hunter syndrome).

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

- Isolated CD31+ cells, intended for the treatment of erectile dysfunction.

The following product was classified as a tissue engineered product:

- Extracellular matrix and non-viable osteogenic cells derived from human adipose-derived stem cells, associated with hydroxyapatite/beta-tricalcium phosphate (HA/βTCP) particles, intended to stimulate bone regeneration in pathological hypoxic and/or necrotic bone conditions.

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

- Autologous adipose derived mesenchymal stem/stromal cells, intended for the treatment of amyotropthic lateral sclerosis.

The following product does not fulfil the definition of an advanced therapy medicinal product:

- Point-of-care skin cell isolation kit.

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

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.*

Annual EMA PCWP and HCPWP meeting with all eligible organisations

Last 24th November took place *the annual 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).

The meeting focuses on the following topics:

- Future challenges and key priorities for the European Medicines Agency (EMA) and the European medicines regulatory network
- Beyond business continuity plans and EMA's state of play in 2022
- Future challenges and key priorities for patient and healthcare professionals' organisations
- Update on the *Clinical Trials Regulation*
- Collaboration between EMA and *Health technology assessment bodies*

For more information, please see the *agenda, the presentations and the recordings 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 on 1) 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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