EURORDIS
THERAPEUTIC REPORT
April 2022
ISSUE 4
UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

New Rare Barometer survey out!

EURORDIS Rare Barometer survey on diagnosis is out, make your voice heard and *answer it now, here!*! This survey should take you around 20 minutes to complete and it is available in 26 different languages! Your invaluable input will help us understand and improve the diagnosis journey of those who live with a rare disease.

The aim of the survey is to understand the journey people living with a rare disease go through when seeking a diagnosis for their rare disease, for example by measuring the time taken to obtain a diagnosis, or the consequences of being undiagnosed or misdiagnosed. The survey is open to all people living with a rare disease and their family members.

For more information, please *read here!*

IN THIS ISSUE

Join the 11th European Conference on Rare Diseases & Orphan Products

From the 27th June to the 1st July (from 14.00-18.00 CEST) will take place online *the 11th European Conference on Rare Diseases & Orphan Products.*

The event will be spread over 5 half days, being the first one an opening plenary session and the last one a closing one, and the other three days will target the following main topics:

- *Ensuring healthy lives and promoting well-being for all people living with a rare disease at all ages* (Tuesday 28th)
- *Reduce inequality within and among countries by focusing on equity for people living with a rare disease* (Wednesday 29th)
- *Building resilient infrastructure, promoting inclusive and sustainable industry and fostering innovation for people living with a rare disease* (Thursday 30th)

This 11th ECRD has been designated as an official event of the 2022 French Presidency of the Council of the European Union and follows a pivotal two-year *Rare 2030 Foresight Study*.

Although online, ECRD 2022 will also be among our most interactive, inclusive and sustainably responsible conferences to date!

For more information, please see the *programme here* and *register here*.

Register now!

What are the European Reference Networks (ERNs)?

European Reference Networks are networks for clinicians and researchers to share expertise, knowledge and resources across the EU. The first 24 ERNs were launched in 2017, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 Member States.

This joint initiative of the European Commission and Member States with support from the European Parliament, aims to address common challenges faced by professionals when diagnosing and providing highly specialised healthcare in complex, rare or low prevalence diseases. It does not interfere with already existing networks. ERN are part of the legal framework of the EU Directive on Patients' Rights in Cross-Border Healthcare Directive adopted in 2011. Since 2006 EURORDIS has advocated for centres of expertise and European Reference Networks for rare diseases and is highly engaged in the implementation of this Directive.

For more information about the ERNs, please *read here.*

What are the European Patient Advocacy Groups (ePAGs)

It is unfeasible to create a separate ERN for every one of the over 6000 rare diseases that exist, therefore, the clinical community organised ERN according to disease groupings. This grouping of diseases does not prevent a patient from being able to go to a disease-specific centre of expertise. EURORDIS wants patient organisations to participate in European Reference Network (ERN) decision-making processes and is supporting its membership to ensure a democratic process of patient representation.

EURORDIS has developed a European Patient Advocacy Group (ePAG) for each ERN disease grouping. ePAGs bring together elected patient advocates and affiliated organisations who will ensure that the patient voice is heard throughout the ERN development process. It is important that patient advocates and clinicians evolve how they work together in the new system of ERNs.

The European Reference Networks (ERNs) are now recruiting new European Patient Advocacy Group (ePAG) advocates. ePAGs are open to all rare disease patient organisations (EURORDIS members and non-members based in the European Union.

For more information on ERNs and the role of ePAG advocates you may watch this *video* and *read this short guide*.

If you want to apply or need further information on the specific requirements for Patients Organisations to apply, the required skills and experience for candidates and the application process, **please contact lenja.wiehe@eurordis.org**

This is your chance to make the voice of your patient community heard at the European level. **Don't miss it! Deadline to apply 31st July 2022.**

Pharmacovigilance Risk Assessment Committee (PRAC) April 2022

Minutes August 2021
Agenda April 2022
Meeting Highlights April 20222

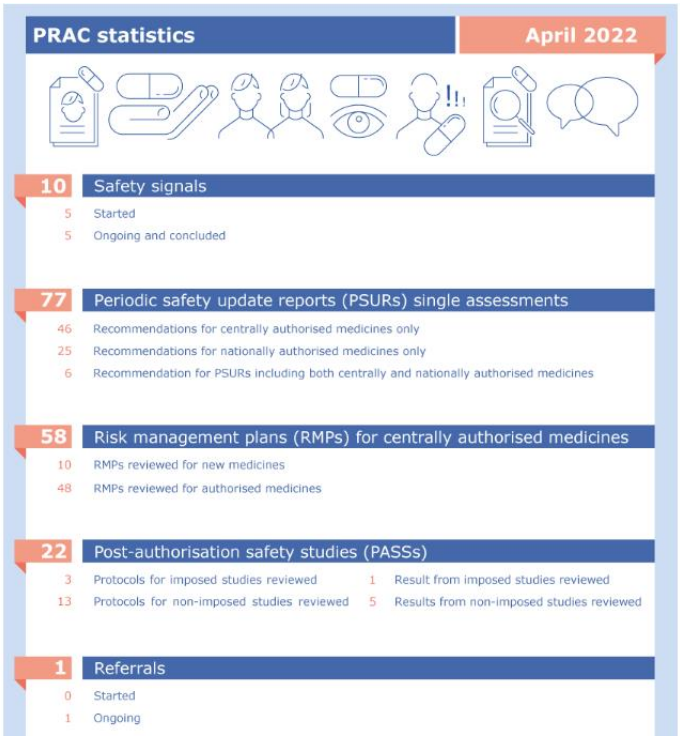
New safety information for healthcare professionals

EMA's safety committee (PRAC) discussed a direct healthcare professional communication (DHPC) containing important information for *Defitelio* (defibrotide), a medicine used to treat severe veno-occlusive disease (VOD) in patients undergoing haematopoietic (blood) stem cell transplantation. VOD is a condition in which the veins in the liver become blocked and stop the liver working properly. VOD is usually a complication resulting from a treatment known as myeloablative chemotherapy given before HSCT.

This communication follows the result of a study which compared Defitelio in combination with best supportive care (BSC) with BSC alone, when used for prophylaxis (prevention of) veno-occlusive disease (VOD) after hematopoietic stem-cell transplantation (HSCT). The study was stopped after interim analysis as it showed that there is **no benefit in using Defitelio for prevention of severe VOD after HSCT.** Defitelio increases the risk of bleeding and should be withheld or stopped if significant bleeding occurs.

In view of the findings of the study and taking the safety profile of defibrotide into account, the PRAC considers it useful to inform health care professionals that Defitelio should not be used for prophylactic treatment of VOD.

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

2577 Orphan designations

253 Orphan designations included in authorised indication

220 Authorised OMPs

89 To be used in children

6 Removed from the market

74 Marketed, but no longer "orphans"

To date

140

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

24 May 2022

CHMP Meeting Highlights
April 2022

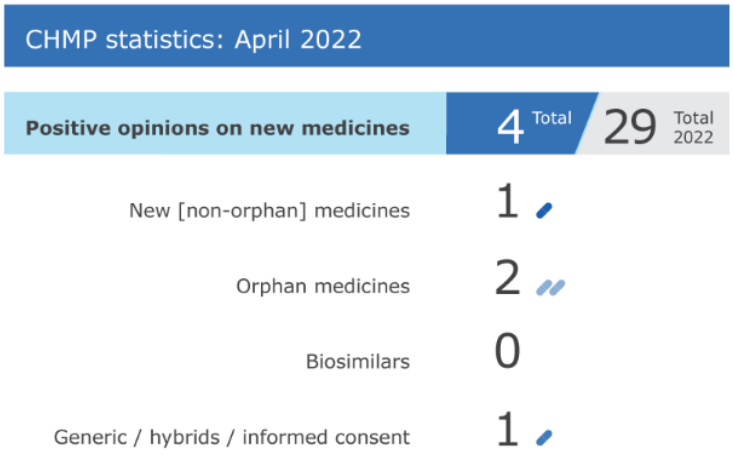
Minutes February 2022
Agenda April 2022
Meeting Highlights April 2022

In April, the CHMP recommended **5 medicines for approval, 1 orphan medicine**:

- *Filsuvez (birch bark extract)* for the treatment of epidermolysis bullosa.
- *Lunsumio (mosunetuzumab)* conditional marketing authorisation for the treatment of relapsed or refractory (when treatment does not work) follicular lymphoma.
- *Tabrecta (capmatinib)* for the treatment of advanced non-small cell lung cancer.

The CHMP also recommended **7 extensions of therapeutic indication,** and recommended granting marketing authorisations for **1 generic medicine** for the treatment of idiopathic pulmonary fibrosis.

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 February 2022
Agenda April 2022
Meeting April 2022

COMP April 2022 meeting update

During the April plenary, the COMP adopted **13 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:

- Limb-girdle muscular dystrophy, Atamyo Therapeutics;
- Inherited retinal dystrophies due to defects in the RPGR gene, Pharma Gateway AB;
- Blastic plasmacytoid dendritic cell neoplasm, INSERM UMR 1098;
- Hyper IgM syndromes, Fondazione Telethon;
- Epidermolysis bullosa, Tetra Bio-Pharma Europe Limited;
- Idiopathic pulmonary fibrosis, JVM Europe B.V.;
- Spinal cord injury, AbbVie Deutschland GmbH & Co. KG;
- Myopathic mitochondrial DNA depletion syndrome, Scendea (NL) B.V.;
- Focal segmental glomerulosclerosis., Pfizer Europe MA EEIG;
- Fragile X syndrome, Healx Technology Limited;
- Amyotrophic lateral sclerosis, Inflectis Bioscience S.A.S;
- Noninsulinoma pancreatogenous hypoglycemia syndrome, Recordati Rare Disease;
- Primary lymphatic malformations, Pharma Gateway AB

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 **three positive opinions at time of CHMP opinion**:

- **Polivy** (*polatuzumab vedotin*) for treatment of diffuse large B-cell lymphoma, Roche Registration GmbH.
- **Lunsumio** (*mosunetuzumab*) for treatment of follicular lymphoma, Roche Registration GmbH.
- **Filsuvez** *(betulae cortex dry extract (DER 5-10: 1)*, extraction solvent n-heptane 95% (w/w)) for treatment of epidermolysis bullosa, Amryt Pharmaceuticals Designated Activity Company.

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

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Tavneos ® (avacopan)	Vifor Fresenius Medical Care Renal Pharma France	Adult patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)	11/01/2022
Voraxaze ® (glucarpidase)	SERB SAS	Adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity	11/01/2022
Lonapegsomatropin Ascendis Pharma® (lonapegsomatropin)	Ascendis Pharma Endocrinology Division A/S	Children who do not produce enough growth hormone (GHD)	11/01/2022
Oxbryta® (voxelotor)	Global Blood Therapeutics Netherlands B. V.	Haemolytic anaemia, and +12 years old sickle cell disease	14/02/2022
Ngenla® (somatrogon)	Pfizer Europe MA EEIG	Children and adolescents with growth hormone deficiency	14/02/2022
Kimmtrak® (tebentafusp)	Immunocore Ireland Limited	Adult patients with unresectable or metastatic uveal melanoma	01/04/2022
Uplizna® (inebilizumab)	Viela Bio	Adults with neuromyelitis optica spectrum disorders (NMOSD)	25/04/2022

Please click also on the following links to see:

Orphan medicinal products authorised during 2022

Orphan medicinal products authorised since 2000

PDCO April meeting to be updated when info available

Minutes February 2022
Agenda March 2022
Meeting Report March 2022

PDCO March 2022 meeting update

In March, the PDCO adopted **11 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.

- Ibutamoren mesylate, from Lumos Pharma, Inc., for the treatment of growth hormone deficiency;
- Zinc gluconate / alisitol / retinyl palmitate, from Vanessa Research Magyarorszag Kft, for the treatment of microvillus inclusion disease;
- Peptide derivative of glucagon-like-peptide 1 and glucagon with fatty acid side chain (BI 456906), from Boehringer Ingelheim International GmbH, for the treatment of obesity;
- Mitapivat, from Agios Netherlands B.V., for the treatment of thalassaemia;
- Deucravacitinib, from Bristol-Myers Squibb International Corporation, for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis);
- Adeno-associated viral vector serotype rh.10 expressing beta-galactosidase, from Lysogene, for the treatment of GM1 gangliosidosis;
- Virus-like particle of SARS-CoV-2 spike protein (recombinant, adjuvant) (CoVLP), from Medicago Inc., for the prevention of coronavirus disease 2019 (COVID-19);ç
- SARS-CoV-2 virus, beta-propiolactone inactivated, from Valneva Austria GmbH, for the prevention of coronavirus disease 2019 (COVID-19);

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*.

Minutes October 2021
Agenda December 2021
Meeting Report December 2021

CAT from January to April meeting to be updated when info available

CAT December 2021 meeting update

In December the Committee for Advanced Therapies (CAT) finalised **4 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 **fulfil the definition of a gene therapy medicinal product:**

- CD 19 CAR T-cells transduced with lentiviral vector, intended for the treatment of adults and children with B-cell non-Hodgkin's lymphoma and acute lymphoblastic leukaemia;
- Recombinant adeno-associated virus, serotype 2, containing human ND4 codon-optimised gene, intended for the treatment of Leber's hereditary optic neuropathy.

The following products fulfil the definition of a somatic cell therapy medicinal product:

- Allogeneic adipose-derived mesenchymal stromal cells, ex-vivo expanded, intended for the treatment of osteoarthritis of the knee;
- Allogeneic T-cell precursors, mobilised peripheral blood-derived, ex vivo cultured, intended for the treatment of paediatric and adult patients undergoing partially human leucocyte antigen (HLA) compatible allogeneic haematopoietic stem cell transplantation to accelerate adaptive immunological reconstitution.

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.*

First EMA PCWP & HCPWP meeting with all eligible organisations of 2022!

Last 2nd and 3th of March took place *the first annual meeting of 2022* 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 first day of the meeting provided an update on EMA projects and initiatives, including:

- *accelerating clinical trials in the EU (ACT EU),*
- *big data;*
- *electronic product information (ePI);*
- *the Agency's extended mandate.*

The second day of the meeting enabled discussion on *advanced therapy medicinal products (ATMPs)* and sharing members' voices. The meeting closed with looking ahead to 2022 to 2025.

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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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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