EURORDIS
RARE DISEASES EUROPE

EURORDIS
THERAPEUTIC REPORT

January 2021

ISSUE 1

UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

EMA recommended third COVID-19 vaccine for authorization in the EU

EMA recommended granting a *conditional marketing authorisation* for the *COVID-19 Vaccine AstraZeneca*, developed by Astrazeneca, to prevent coronavirus disease 2019 (COVID-19) in people from 18 years of age.

EMA's human medicines committee (CHMP) has completed its rigorous evaluation of the vaccine concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available to recommend a formal conditional marketing authorisation.

For more information, please see the *EMA website.*

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Rare Disease Day 2021

Next 28 February will take place the 14th *Rare Disease Day*! Thousands of people in all parts of the world will connect virtually to advocate and raise awareness for people living with a rare disease.

The central message of this year's campaign **"Rare is many. Rare is strong. Rare is proud"** focuses on reframing the word 'rare', representing over 6000 rare diseases, as well as the different aspects of people's lives and experiences of living with a rare disease. It seeks to remind us that we are more than our disease and that our potential is not limited by what we alone can achieve!

To relay patient stories across diseases and borders, EURORDIS and the 62 National Alliance partners have developed with the marketing agency Shape History multilingual, high-quality *promotional materials* and the Rare Disease Day 2021 animated *video*, translated in thirty-seven languages. *Tell your story* and show your support by sharing the video with a hashtag #RareDiseaseDay!

Collectively we can bring about change and create a better world for all! Get involved by promoting the *Rare Disease Day campaign* and amplifying the voice of people living with a rare disease!

For more information, please visit the *Rare Disease Day website!*

Register now for the upcoming *Rare 2030 Final Policy Conference* and the *EURORDIS Black Pearl Awards 2021*! **Online and free of charge!**

Medicines for Rare Diseases

Authorisation of new medicines is essential to advancing public health as they bring new opportunities to treat certain diseases. During 2020, the EMA recommended 97 new medicines for marketing authorisation in 2020, approval, **22 of which were orphan medicines!**

The EU framework for orphan medicines aims to encourage the development and marketing of medicines for patients with rare diseases by providing incentives for developers. Orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) at the time of approval to determine whether the information available to date allows maintaining the medicine's orphan status and granting the medicine ten years of market exclusivity. Among the 97 medicines recommended, 22 had their orphan designation confirmed by the end of the year. **New orphan medicines with the potential to significantly benefit patients for which there are no other approved products included.**

For more information, see the *EMA highlights 2020.*

Image adapted from *EMA highlights 2020*

Workshop on regulatory support for development of orphan medicines

Last 30th November the EMA's Committee for Orphan Medicinal Products (COMP) hosted a virtual *workshop* to discuss the benefits and impact of early regulatory interactions and incentives for the development of medicines for rare diseases. Treating patients with rare diseases is often difficult because there are often none or only few treatment options available. This represents a huge unmet medical need and a significant public health challenge.

The purpose of the workshop was to encourage early dialogue between developers and regulators in order to facilitate the development of innovative medicines in neglected disease areas. The workshop was targeted at small and medium-sized enterprises (SMEs), academia, patients, healthcare professionals and European Reference Networks (ERNs) who are often at the forefront of medicine development in rare and neglected diseases.

EMA offers incentives to encourage companies to research and develop medicines for rare diseases that otherwise would not be developed. Through *orphan designation*, *protocol assistance* and the *PRIority MEdicines (PRIME) scheme*, EMA provides early and enhanced scientific and regulatory support to medicines that have a particular potential to address patients' unmet medical needs. Early interaction with regulators also helps medicine developers understand regulatory requirements and generate the robust data needed to draw conclusions on the medicines' benefits and risks.

Virginie Hivert, EURORDIS Therapeutic Development Director, presented the *International rare diseases research consortium (IRDiRC) drug development guidebook*. The *agenda*, all *presentations* and the *recording* are now available, please have a look!

For more information, please read *EMA website.*

Pharmacovigilance Risk Assessment Committee (PRAC) January 2021

Minutes November 2020
Agenda January 2021
Meeting Highlights January

Precautionary marketing suspension of thalassaemia medicine Zynteglo

The company, bluebird bio, that markets the gene therapy medicine *Zynteglo*, , for treating the rare blood condition beta thalassaemia has suspended sales pending investigation of a safety concern. The company is developing a related medicine, bb1111, which uses the same technology as Zynteglo, which may have been associated with a case of cancer.

Cancer caused by this type of treatment (insertional oncogenesis) was already identified as a potential risk with Zynteglo, so patients who receive the medicine are followed up and monitored in a registry. So far no cases of cancer have been reported with Zynteglo treatment. Currently, Zynteglo, is only marketed in Germany, and because of limited availability and the rarity of the condition it is intended to treat, only a very small number of patients have received or would have been eligible to receive treatment. However**, if treated patients do have any concerns they should contact the specialist supervising their Zynteglo treatment.**

EMA is liaising closely with the company and experts within the regulatory network, and will now examine the evidence at EU level and decide on any relevant regulatory action for Zynteglo or any similar medicines under evaluation. No other authorised medicines use the same viral vector so no direct implications are foreseen for other licensed 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

2394 Orphan designations

230 Orphan designations included in authorised indication

197 Authorised OMPs

77 To be used in children

5 Removed from the market

66 Marketed, but no longer "orphans"

To date

126

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

19 Feb 2021

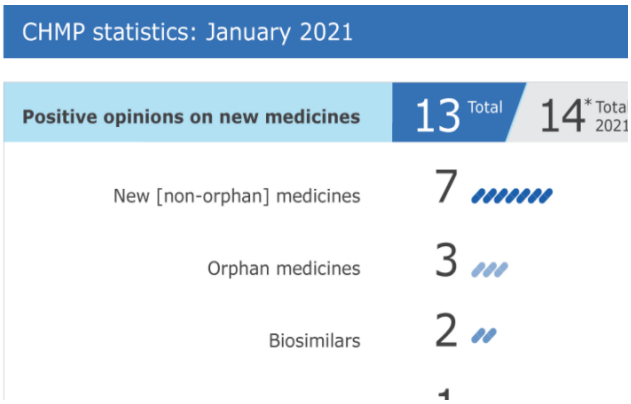
CHMP Meeting Highlights January 2021

Minutes November 2020
Agenda January 2021
Meeting Highlights January 2021

In January, the CHMP recommended **13 medicines for approval, 3 orphan medicines**:

- *Conditional marketing authorisation* for COVID-19 Vaccine AstraZeneca (COVID-19 Vaccine (ChAdOx1-S [recombinant])) to prevent coronavirus disease 2019 (COVID-19) in people from 18 years of age. This is the third COVID-19 vaccine that EMA has recommended for authorization.
- *Conditional marketing authorisation* for Nexpovio (selinexor) for the treatment of relapsed and refractory multiple myeloma.
- *Conditional marketing authorisation* for Pemazyre (pemigatinib) for the second-line treatment of advanced or metastatic cholangiocarcinoma (bile duct cancer) characterized by fusion or rearrangements of fibroblast growth factor receptor 2.
- Sogroya (somapacitan) received a positive opinion from the CHMP for the treatment of growth hormone deficiency in adults.
- Kesimpta (ofatumumab) received a positive opinion from the Committee for the treatment of adult patients with active relapsing forms of multiple sclerosis.
- Ontozry (cenobamate) received a positive opinion for the treatment of adults with epilepsy whose disease is not adequately controlled despite a history of treatment with at least 2 anti-epileptic medicinal products.
- Vazkepa (icosapent ethyl) to reduce the risk of cardiovascular events in patients at high cardiovascular risk.
- Byfavo (remimazolam) for procedural sedation.
- Seffalair Spiromax (salmeterol / fluticasone) and its duplicate BroPair Spiromax (salmeterol / fluticasone) received a positive opinion for the treatment of asthma in adults and adolescents aged 12 years and older.

The CHMP also recommended granting marketing authorisations for two biosimilar medicines, one generic medicines and three 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.

Minutes November 2020
Agenda January 2021
Meeting Report January 2021

COMP January 2021 meeting update

During the January plenary, the COMP adopted **16 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:

- Paroxysmal nocturnal haemoglobinuria Idiopathic, , Alexion Europe S.A.S.;
- Leishmaniasis, Biopharma Excellence GmbH;
- Sickle cell disease, Vifor France S.A.;
- Spinocerebellar ataxia, Vico Therapeutics B.V.;
- Eosinophilic gastroenteritis, Turnkey Pharmaconsulting Ireland Limited;
- Cystinosis, Clinical Technology Centre (Ireland) Limited;
- Sickle cell disease, Genzyme Europe B.V.;
- Gastric cancer, ICON Clinical Research Limited;
- Pancreatic cancer, Hemispherx Biopharma Europe;
- Lymphoplasmacytic lymphoma, Scendea (NL) B.V.;
- Medullary thyroid carcinoma, Southwood Research Limited;
- Gaucher disease, PPD Bulgaria EOOD;
- Retinitis pigmentosa, Ocugen Limited;
- Leber's congenital amaurosis, Ocugen Limited;
- Creatine deficiency syndromes, Ceres Brain Therapeutics S.A.S.;
- Spinal cord injury, Raremoon Consulting Esp S.L.

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

- *INREBIC* (fedratinib), Celgene Europe BV, for the treatment of:
  - post-essential thrombocythaemia myelofibrosis
  - post-polycythaemia vera myelofibrosis
  - primary myelofibrosis

- *Lumoxiti* (moxetumomab pasudotox) for treatment of hairy cell leukaemia, AstraZeneca AB. The opinion was adopted by written procedure after the December meeting.

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

Please click also on the following links to see:

Orphan medicinal products authorised during 2021

Orphan medicinal products authorised since 2000

PDCO January meeting to be updated next issue

PDCO December 2020 meeting update

Minutes November 2020
Agenda December 2020
Meeting Report December 2020

In December, the PDCO adopted **14 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.

- Arimoclomol (citrate), from Orphazyme A/S, for the treatment of amyotrophic lateral sclerosis;
- Autologous peripheral blood T cells CD_4- and CD8-selected and CD_3- and CD28-activated transduced with retroviral vector expressing anti-CD19 CD28/CD_3-zeta chimeric antigen receptor and cultured (KTE-X19), from Kite Pharma EU B.V., for the treatment of mature B-cell neoplasms;
- Lenacapavir, from Gilead Sciences International Ltd., for the treatment of human immunodeficiency virus (HIV-1) infection;
- Allopurinol / verinurad, from AstraZeneca AB, for the treatment of chronic kidney disease;
- Esketamine (hydrochloride), from Celon Pharma S.A., for the treatment of bipolar depression and treatment of major depressive disorder;
- Retinol (Vitamin A), from orphanix GmbH, for the prevention of bronchopulmonary dysplasia;
- Carfilzomib, from Amgen Europe BV, for the treatment of acute lymphoblastic leukaemia;
- Autologous tumour-infiltrating lymphocytes (LN-144/LN-145), from Iovance Biotherapeutics, Inc., for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms);
- (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (KH176), from Khondrion BV, for the treatment of mitochondrial respiratory chain/oxidative phosphorylation defects;
- Obinutuzumab, from Roche Registration GmbH, for the treatment of systemic lupus erythemathosus;
- Sparsentan, from Travere Therapeutics Ireland Ltd., for the treatment of IgA nephropathy;
- Dexmedetomidine (hydrochloride), from BioXcel Therapeutics, Inc., for the treatment of bipolar disorder and treatment of schizophrenia;
- Sparsentan, from Travere Therapeutics Ireland Ltd., for the treatment of focal segmental glomerular sclerosis;
- 3-((1R,3s,5S)-3-((7-((5-methyl-1H-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile (TD-1473), EMEA-002757-PIP01-19, from Theravance Biopharma Ireland Limited, for the treatment of ulcerative colitis.

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.*

CAT January 2021 meeting update

Minutes November 2020
Agenda January 2021
Meeting Report January 2021

In January 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 products were classified as **gene therapy medicinal products:**

- Autologous anti-CD19 chimeric antigen receptor T cells, intended for the treatment of B- cell malignancies;
- Messenger ribonucleic acid (mRNA) encoding the human glucose debranching enzyme, intended for the treatment of glycogen storage disease III;
- Messenger ribonucleic acid (mRNA) encoding human interleukin 2 (IL-2), linked to interfering RNA targeting vascular endothelial growth factor A, intended for the treatment of solid tumours;

The following products were classified as **not an advanced therapy medicinal product**:

- Autologous omental adipose tissue and biodegradable fibrin glue, intended for the treatment of renal traumatic/disease conditions.

CAT noted the **withdrawal** of the marketing authorisation application of autologous human chondrocytes, in vitro expanded, which was intended for the repair of cartilage defects of the knee joint.

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 November meeting

Last 16th November took place a virtual meeting update on *COVID-19 pandemic* 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 focused on the following:

- Update on Agency's response to the COVID-19 pandemic
- Patient / Healthcare Professionals' participation in EMA Covid-19 Taskforce (ETF)
- Pharmacovigilance aspects on COVID therapeutics & vaccines
- Information materials on COVID-19 vaccines

For more information, please see the *agenda*.

EMA second public stakeholder meeting on COVID-19 vaccines

Last 8th January the EMA organised a second virtual *meeting* to explain the processes for the *development, evaluation, approval and safety* monitoring of COVID-19 vaccines in the EU, including EMA's specific role. It gave the opportunity to the public and stakeholder groups to speak and share their needs, expectations and any concerns.

The *event* was broadcasted live, please see the *agenda*, *presentations* and *recording here*.

EURORDIS and the European Patients Forum (EPF) signed a jointly letter asking the EMA to organise a multi-stakeholder meetings open to the public on vaccines to prevent SARS-CoV-2 infection, please read the *letter 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

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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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