EURORDIS
RARE DISEASES EUROPE

EURORDIS THERAPEUTIC REPORT

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ISSUE 1

UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study

The EMA just published a *paper* where shows that **patients' contributions have a tangible impact** on the recommendations provided to developers and in over half of the cases, this led to further discussion on relevant patient perspectives. The paper provides data with quantitative evidence of the value of patient input in medicines development and supports EMA's continued inclusion of their voice throughout the medicine's lifecycle.
The paper concludes that there is a need to further expand patient input to real-world evidence, patient reported outcomes, patient preferences and patient experience data, which can only be to the benefit of public health in the EU.

For more information, please *read the paper here!*

IN THIS ISSUE

EMA highlights of 2021

In 2021, the EMA recommended **92 new positives opinions** for new medicines, **19 are medicines which had orphan designation**.

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.

The following picture includes **5 orphan medicines** with the potential to significantly benefit patients for which there are **no other approved products** included. For more information, please read *here the EMA highlights 2021.*

Cancer

Pemazyre
for the second-line treatment of advanced or metastatic cholangiocarcinoma (bile duct cancer).

Immunology/ Rheumatology/ Transplantation

Voxzogo
to treat achondroplasia in patients two years of age and above whose epiphyses are not closed.

Gastroenterology/ Hepatology

Bylvay
for the treatment of progressive familial intrahepatic cholestasis in patients aged 6 months or older.

Metabolism

Imcivree
to treat obesity and control hunger associated with genetic deficiencies of the melanocortin 4 receptor pathway.

Neurology

Koselugo
to treatment of paediatric patients with neurofibromatosis type 1 plexiform neurofibromas.

Image from EMA Report 2021

Register now!
Deadline 7th March!

Initiation of DARWIN EU® Coordination Centre

What is DARWIN EU®?

The European Medicines Agency (EMA) is establishing a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the European Union (EU).

This initiative is called the *Data Analysis and Real World Interrogation Network (DARWIN EU®)* and will deliver real-world evidence from across Europe on diseases, populations and the uses and performance of medicines.

Objectives of the DARWIN EU®

The vision of *DARWIN EU®* is to give EMA and national competent authorities in EU Member States access to valid and trustworthy real-world evidence, for example on diseases, patient populations, and the use, safety and effectiveness of medicines, including vaccines, throughout the lifecycle of a medicinal product. *DARWIN EU®* will support regulatory decision-making by:

- establishing and expanding a catalogue of observational data sources for use in medicines regulation;
- providing a source of high-quality, validated real world data on the uses, safety and efficacy of medicines;
- addressing specific questions by carrying out high-quality, non-interventional studies, including developing scientific protocols, interrogating relevant data sources and interpreting and reporting study results.

By supporting decision-making on the development, authorisation and surveillance of medicines, a wide range of stakeholders will benefit, from patients and healthcare professionals to health technology assessment bodies and the pharmaceutical industry. Additionally, DARWIN EU® will provide an invaluable resource to prepare for and respond to future healthcare crises and pandemics.

Timelines

The first *DARWIN EU®* pilot studies will be delivered in 2022. EMA will oversee the Coordination Centre, connect it to the work of the EMA medicines committees and monitor its performance. A multi-stakeholder information webinar to introduce the establishment of *DARWIN EU®*, highlight opportunities for collaboration and answer questions will be organised by EMA on 24 February 2022.

Between 2022 and 2023 the EMA will be working with Erasmus University Medical Center Rotterdam to set up DARWIN EU®'s operational processes and governance structures and to run pilot studies with data from DARWIN EU®, to support EMA scientific committees and down-stream decision-makers in their decision-making and support the establishment of the *European Commission's European Health Data Space (EHDS)*.

In 2024, EMA expects DARWIN EU® to be fully operational and will routinely support the evaluation work of EMA's scientific committees and the national competent authorities.

For further information, *please read here*.

Pharmacovigilance Risk Assessment Committee (PRAC) January 2022

Minutes April 2021
Agenda January 2022
Meeting Highlights Jan 2022

Review of terlipressin medicines started

EMA has started a review of medicines that contain *terlipressin*. These medicines are authorised in several EU countries to treat increased pressure in central veins causing kidney problems in people with advanced liver disease (hepatorenal syndrome; HRS), as well as bleeding from enlarged veins in the passage between the mouth and the stomach (the oesophagus) and certain forms of bleeding associated with surgery.

EMA's safety committee (PRAC) started this review due to safety concerns about results from a large clinical trial involving patients with a form of HRS where kidney function declines rapidly.

As a result of these concerns, the Danish medicines agency requested a review of the safety of *terlipressin* medicines in the context of their benefits when used to treat HRS. At present, this review does not cover the use of *terlipressin* for the treatment of bleeding, since no new information on safety concerns has emerged for these uses.

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

2480 Orphan designations

249 Orphan designations included in authorised indication

216 Authorised OMPs

87 To be used in children

6 Removed from the market

71 Marketed, but no longer "orphans"

To date

139

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

21 February 2021

CHMP Meeting Highlights January 2022

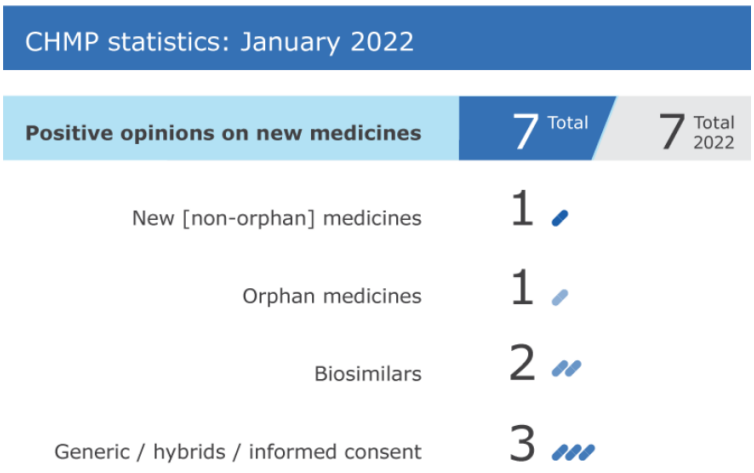
Minutes December 2021
Agenda January 2022
Meeting Highlights January 2022

In January, the CHMP recommended **7 medicines for approval, 1 orphan medicine**:

- *Breyanzi* (lisocabtagene maraleucel)* for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after at least two previous lines of treatment.
- Conditional marketing authorisation for the antiviral *Paxlovid* (PF-07321332 / ritonavir) for the treatment of COVID-19.
- Two biosimilar medicines were recommended for approval: *Sondelbay* (teriparatide) to treat osteoporosis and *Stimufend* (pegfilgrastim) to reduce the duration of neutropenia and the incidence of febrile neutropenia after cytotoxic chemotherapy.

The CHMP also recommended **8 extensions of therapeutic indication,** and recommended granting marketing authorisations for **3 generic medicines**.

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 January 2022 meeting update

During the January plenary, the COMP adopted **12 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:

- Hypoparathyroidism, Amolyt Pharma;
- Amyotrophic lateral sclerosis, Iltoo Pharma;
- Pyruvate kinase deficiency, Consorcio Centro de Investigación Biomédica en Red, M.P.;
- Respiratory distress syndrome, Aerogen Pharma Limited;
- Fragile X syndrome, EUDRAC GmbH;
- Ehlers-Danlos syndrome, Dlrc Pharma Services Limited;
- Diffuse large B-cell lymphoma, AbbVie Deutschland GmbH & Co. KG;
- Pancreatic cancer, Nh Theraguix;
- Pyridoxamine 5'-phosphate oxidase deficiency, Amsterdam UMC;
- Dravet syndrome, Insidereg Limited;
- Peripheral T-cell lymphoma, Daiichi Sankyo Europe GmbH;
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, 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 **2 positive opinions at time of CHMP opinion**:

- *Ngenla (somatrogon)* for treatment of growth hormone deficiency, Pfizer Europe MA EEIG.
- *Oxbryta* (2-hydroxy-6-((2-(1-isopropyl-1h-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde) for treatment of sickle cell disease, Global Blood Therapeutics Netherlands B.V.

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

Please click also on the following links to see:

Orphan medicinal products authorised during 2022

Orphan medicinal products authorised since 2000

PDCO November to January meetings to be updated when info available

Minutes June 2021
Agenda October 2021
Meeting Report October 2021

PDCO October 2021 meeting update

In October, the PDCO adopted **9 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.

- 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 nonalcoholic steatohepatitis;
- Marzeptacog alfa (activated), from Catalyst Biosciences, Inc., for the treatment of haemophilia A and haemophilia B;
- Satralizumab, from Roche Registration GmbH, for the treatment of myasthenia gravis;
- Ravulizumab, from Alexion Europe SAS, for the treatment of neuromyelitis optica spectrum disorders;
- Magrolimab, from Gilead Sciences International Ltd, for the treatment of acute myeloid leukaemia and treatment of myelodysplastic syndromes (including juvenile myelomonocytic leukaemia);
- Lutetium (177Lu) oxodotreotide, from Advanced Accelerator Applications, for the treatment of gastroenteropancreatic neuroendocrine tumours;
- 2'-O-(2-methoxyethyl) phosphorothioate antisense oligonucleotide targeting CD49d RNA (ATL1102), from Antisense Therapeutics Limited, for the treatment of Duchenne muscular dystrophy;
- Evenamide, from Newron Pharmaceuticals SpA, for the treatment of schizophrenia;
- Neisseria meningitidis serogroup B Protein-based active substance / Recombinant Neisseria meningitidis serogroup B protein 1 / Recombinant Neisseria meningitidis serogroup B protein 3 / Recombinant Neisseria meningitidis serogroup B protein 2, from Sanofi Pasteur, for the prevention of meningococcal disease.

The PDCO also adopted opinions on **product-specific waivers, modifications to an agreed PIP and compliance check** that can be consulted in the *meeting report.*

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

Minutes October 2021
Agenda December 2021
Meeting Report December 2021

CAT January meeting to be updated next issue

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.*

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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