

News from the EMA

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Facilitating global access to diabetes treatments for non-EU patients

April 22, 2022

EMA human medicines committee (CHMP) has given a recommendation for two diabetes mellitus treatments, Actrapid and Insulatard, for use outside the European Union (EU).

EMA is committed to supporting global regulatory capacity building and contributing to the protection and promotion of public health beyond the EU by assessing medicines for countries with limited regulatory resources. The two diabetes medicines were submitted to EMA under a regulatory procedure (Article 58 of Regulation (EC) No 726/2004) known as EU Medicines for all (EU-M4All).

This allows the Agency to assess the quality, safety and efficacy of medicines that address unmet medical needs or are of major public health interest for use outside the EU and give an opinion on their benefit-risk balance, taking into

account the context of their use in target populations and any specific requirement in certain low- and middle-income countries outside the EU. Medicines submitted under this programme are assessed by EMA in collaboration with experts from the World Health Organisation (WHO) and the target countries. Any medicine assessed under this procedure must meet the same standards as medicines intended for EU citizens.

Actrapid and Insulatard are human insulins that have been centrally authorised in the EU since 2002. According to the EU marketing authorisation, unopened insulin products must be stored in a refrigerator (2–8°C). These strict storage conditions are difficult to adhere to when temperature conditions are challenging and access to refrigeration is limited, for example in countries experiencing conflict or a humanitarian

emergency situation. This adds an extra burden to the care of diabetes patients who live under these conditions.

The company applied for an assessment of these two medicines with changed storage time, to include storage without refrigeration when used in countries outside the EU. Following the evaluation of stability data submitted by the company in support of their request, the CHMP concluded to allow storing the two insulin products at temperatures up to 30°C for a maximum of four weeks before they are taken into use or carried as a spare. This positive opinion by the CHMP paves the way towards increased access to treatment for diabetes patients worldwide.

Diabetes is a chronic disease in which the body does not produce enough insulin to control the blood glucose (type-1 diabetes) or when the body is unable to use insulin effectively (type-2 diabetes). Insulin is a hormone that regulates blood sugar. Raised blood sugar is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, causing blindness, kidney failure, heart attacks, stroke and lower limb amputation. Left untreated, type-1 diabetes can be a life-threatening condition. According to the WHO, in 2019 diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly caused by this disease. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.

Actrapid and Insulatard are the thirteenth and fourteenth medicines to receive an EMA recommendation under EU Medicines for all (EU-M4All). Experts from the WHO and regulators from Bangladesh, India, Iraq and Zambia were invited to follow the evaluation as observers. This helps to ensure that specific disease expertise and local knowledge are taken into account.

National regulators can use the CHMP's scientific assessment to decide on the use of these medicines in their countries.



Synchron Research Service: suspension of medicines over flawed studies

May 20, 2022



EMA's CHMP has recommended the suspension of the marketing authorisations of several generic medicines tested by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, India.

The recommendation comes after irregularities were found in how the CRO carried out bioequivalence studies, which raised serious concerns about the company's quality management system and the reliability of data from that site. Bioequivalence studies are conducted to show that a generic medicine releases the same amount of active substance in the body as the reference medicine.

The CHMP looked at all medicines tested by Synchron Research Services on behalf of EU companies and found that for the majority (around 100 medicines) no adequate bioequivalence data were available from other sources. The Committee recommended that

these medicines be suspended. To lift the suspension, companies relying on data from Synchron Research Services must provide alternative data demonstrating bioequivalence. For a small number of authorised generic medicines (around 20), adequate bioequivalence data were available from other sources, and these medicines are allowed to remain on the EU market.

With just a couple of exceptions for which data from other sources are available, the majority of medicines that were being evaluated for authorisation on the basis of data from Synchron Research Services will not be granted authorisation in the EU. The list of concerned medicines can be found on the EMA website.

Some of the medicines that have been recommended for suspension may be of critical importance (e.g., due to lack of available alternatives) in a given EU Member State. Therefore, national authorities can temporarily

postpone the suspension in the interest of patients. Member States should also decide whether recalls of the affected medicines are needed in their territories.

EMA and national authorities will continue working closely together to ensure that studies on EU medicines are carried out to the highest standards and that companies comply with all aspects of good clinical practice (GCP). If companies do not meet required standards, authorities will take whatever measures necessary to ensure the integrity of data used to approve EU medicines.

The CHMP's recommendation will now be sent to the European Commission which will issue a legally binding decision in due course.

Information for patients and healthcare professionals:

- Several generic medicines have been suspended from the EU market because the company that tested them is considered unreliable.
- There is no evidence of harm or lack of effectiveness with any of the affected medicines. However, the medicines have been suspended until supporting data from more reliable sources are available.
- Several alternative medicines are available. Patients taking the affected medicines can contact their doctor or pharmacist for more information.
- National authorities in the EU will consider how critical individual medicines are in their countries and make final decisions on whether to suspend or allow them to remain available while new data are generated.

The CHMP review covered generic medicines authorised or being evaluated via national procedures on the basis of studies conducted by Synchron Research Services on behalf of marketing authorisation holders. The medicines were authorised or being evaluated for approval in several EU Member States.

The review was initiated at the request of national medicines regulatory authorities in several EU countries (Belgium, Denmark, Finland, the Netherlands and Sweden), under Article 31 of Directive 2001/83/EC. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.



First therapy to treat rare genetic nervous system disorder, AADC enzyme deficiency

May 20, 2022

EMA has recommended granting a marketing authorisation in the EU for Upstaza (eladocagene exuparvovec; from PTC Therapeutics International Limited), a therapy for the treatment of adult and paediatric patients with severe aromatic L-amino acid decarboxylase (AADC) deficiency with a genetically confirmed diagnosis.

AADC deficiency is an ultra-rare, inherited genetic disease which typically manifests within the first year of life. It is caused by changes in the gene that produces the AADC enzyme which is needed to produce certain substances vital for the normal functioning of the brain and nerves, including dopamine and serotonin. These substances are used by cells in the brain and the nervous system to send signals and are crucial for the development of motor functions.

Patients with AADC typically experience developmental delays, weak muscle tone, and inability to control the movement of the limbs. AADC deficiency is a long-term, debilitating, and life-threatening condition because it can lead to multiple organ failure. Patients also experience intellectual disability, show irritability, and are at risk of death in the first decade of life.

According to recent estimates, this condition affects 1 in 118,000 people in the EU. Currently, there are no approved therapies for the treatment of AADC deficiency. Patients are offered supportive treatments to manage the symptoms without addressing the underlying cause of the disease. Therefore, there is an unmet medical need for these patients.

Upstaza consists of a modified virus (adeno-associated viral vector) that contains a functional version of the AADC gene. When given to the

patient by infusion into the brain, it is expected that the virus will carry the AADC gene into nerve cells enabling them to produce the missing enzyme. This in turn is expected to enable the cells to produce the substances they need to function properly (such as dopamine and serotonin), thus improving symptoms of the condition. The virus used in this medicine does not cause disease in humans.

EMA's recommendation is based on the results of three trials including 28 children between the ages of 18 months and 8 years and 6 months with severe AADC deficiency confirmed by a genetic diagnosis. All trials were conducted with an unblinded single arm and historic control data from published studies was used as a comparator.

The main favourable effects attained by the participants were head control and the ability to sit unassisted. An ad-hoc expert group was consulted to discuss the clinical relevance of the motor benefits of treatment and concluded that efficacy had been demonstrated and is clinically meaningful.

The most commonly reported side effects were raised body temperature (pyrexia) and involuntary, erratic movements (dyskinesia). The majority of side effects reported were mild or moderate.

In its overall assessment of the available data, the Committee for Advanced Therapies (CAT), EMA's expert committee for cell- and gene-based medicines, found that the benefits of Upstaza outweighed the possible risks in patients with AADC deficiency.

Upstaza was designated as an orphan medicinal product for the treatment of AADC

deficiency on November 18, 2016. The applicant for Upstaza received scientific advice from the Agency at various stages prior to submission of a marketing authorisation application.

The CHMP, EMA's human medicines committee, agreed with the CAT's assessment and positive opinion, and recommended approval of this medicine under exceptional circumstances.

A marketing authorisation under exceptional circumstances allows patients access to medicines that cannot be approved using a standard authorisation route as comprehensive data cannot be obtained under normal conditions of use, 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.

The CHMP requested the applicant to submit data to further characterise the long-term efficacy and safety of patients enrolled in the clinical trials, on the basis of a 10-year follow-up, and a registry-based safety study on patients treated globally with the medicine. The studies will be conducted according to agreed protocols.

The opinion adopted by the CHMP is an intermediary step on Upstaza's path to patient access. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on the EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

EMA guidance supports development of new antibiotics

May 24, 2022

As part of its efforts to support a global approach to the development of new antimicrobial medicines, EMA has published the final revised guideline on the evaluation of human medicines for the treatment of bacterial infections.

Antimicrobial resistance (AMR), which is the ability of microorganisms to resist antimicrobial treatments, especially antibiotics, has a direct impact on the health of people and animals and carries a heavy economic burden worldwide. In the EU alone, it is responsible for an estimated

33,000 deaths per year. It is also estimated that AMR costs the EU €1.5 billion per year in healthcare costs and productivity losses.

EMA plays an important role in the fight against AMR by guiding and supporting the development of new medicines and treatment approaches, especially for patients with infections caused by multidrug-resistant bacteria, who currently have very few therapeutic options.

As AMR is a global threat, regulators in the EU, the United States and Japan have agreed to align as much as possible their respective data

requirements so that medicine developers can design clinical trials that meet the evidence needs of multiple regulatory agencies. The revised document reflects the outcome of these discussions, and also includes:

- clarifications on recommended clinical development programmes for antimicrobials intended to address an unmet need;
- guidance on clinical trials to support treatment of uncomplicated urinary tract infections and uncomplicated gonorrhoea;
- updated guidance on displaying microbiological and clinical efficacy data in the summary of product characteristics.

The revised guideline is published together with an addendum aiming to steer clinical development programmes required to support the authorisation of medicines for treatment of bacterial infections in children.

For the treatment of some infections, efficacy results can be extrapolated in certain children age groups by looking at efficacy data from adults. The addendum mentions that companies developing new antibiotics need to develop an extrapolation concept and provide details about it in an extrapolation plan.

For some infections that occur only or mostly in children below a certain age, extrapolating efficacy data from adults is not possible. The addendum includes guidance on trials that may be conducted in these exceptional cases.

The revised guideline was under public consultation for 6 months in 2019. The final document with all the updates implemented was adopted by EMA's CHMP at its May 2022 meeting.



Big Data strategy for veterinary medicines in the EU

June 13, 2022

EMA and the Heads of Medicines Agencies (HMA) have adopted a Veterinary Big Data strategy to 2027 outlining their vision for fostering data-driven, digital innovations in the veterinary medicines' domain in the EU.

Building upon key objectives of the recently implemented Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6), the strategy aims to converge traditional regulatory

practice with innovative digital solutions. The strategy proposes to identify relevant use cases, existing and additional data sources, critical infrastructure, and methods to enable an environment that encourages innovation in the development of new veterinary medicines for the benefit of animal and human health and welfare.

As part of the implementation of the veterinary legislation, EMA and the whole EU veterinary medicines regulatory network have

made significant investments to implement new IT systems that generate and centrally collect increased amounts of data. The strategy sets up a framework for managing and using these data to support key regulatory activities. This will enhance consistency, transparency, and responsiveness across the network by providing accurate and reliable information to promote public and animal health.

The Veterinary Big Data strategy proposes implementation in phases:

- Up to 2023: strengthen collection of key data

First gene therapy to treat severe haemophilia A

June 06, 2022

EMA has recommended granting a conditional marketing authorisation in the EU for Roctavian (from BioMarin International Limited) for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies produced by the immune system which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5).

Patients with haemophilia A cannot produce factor VIII (an essential protein required for blood to clot and stop bleeding); they are more prone to bleeding and have prolonged bleeding, e.g. after injury or surgery. Haemophilia A is a rare debilitating disease affecting approximately 0.7 in 10,000 people in the EU. It is life long and may be life-threatening when bleeding occurs in the brain, the spinal cord or the gut.

Medicines currently authorised for treating haemophilia A mostly contain factor VIII, to replace the missing protein. Available treatments require one or more injections per week or per month and are lifelong. Therefore, there is an unmet medical need for new therapeutic approaches that might free patients from frequent injections.

Roctavian is the first gene therapy to treat haemophilia A. The active substance in Roctavian, valoctocogene roxaparvovec, is based on a virus (adeno-associated virus or AAV) which has been modified to not cause disease in humans. The virus contains the gene for factor VIII; once given to a patient as a one-off infusion, it is expected to carry the factor VIII gene into the liver cells, enabling them to produce the

missing factor VIII. This helps the blood to clot more easily and prevents bleeding or reduces bleeding episodes. It is yet unknown how long the treatment effect from this single infusion will last in an individual patient. A sustained positive treatment effect of up to two years following a single infusion has been reported in approximately one hundred patients in the main study and up to five years in a few patients in a supportive trial conducted by the applicant. Longer-term follow-up tests may be required to verify a continued safe and effective response to the medicine.

EMA's recommendation is based on the results of a Phase 3 single arm (main study), non-randomised study in 134 male patients with haemophilia A without a history of factor VIII inhibitor and without detectable pre-existing antibodies to AAV5. Two years after the administration, efficacy data showed that the therapy significantly increased factor VIII activity levels in the majority of patients. Bleeding rates were reduced by 85% and most patients (128) no longer needed factor VIII replacement therapy.

Hepatotoxicity (liver damage), a common side effect due to immune reaction induced by these AAV-based gene therapies and characterised so far by an increase in the levels of a liver enzyme called alanine aminotransferase (ALT), has been reported with Roctavian. The condition can be treated successfully with corticosteroids. Other common side effects include headache, joint pain, and nausea.

Patients treated with Roctavian will be monitored for 15 years, to ensure the long-term



efficacy and safety of this gene therapy.

Roctavian was supported through EMA's PRIority Medicines (PRIME) scheme, which provides early and enhanced scientific and regulatory support to medicines that have a particular potential to address patients' unmet medical needs.

In its overall assessment of the available data, the CAT, EMA's expert committee for cell- and gene-based medicines, found that the benefits of Roctavian outweighed the possible risks in patients with haemophilia A.

The CHMP, EMA's human medicines committee, agreed with the CAT's assessment and positive opinion, and recommended approval of this medicine.

The opinion adopted by the CHMP is an intermediary step on Roctavian's path to patient access. The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role or use of this medicine in the context of the national health system of that country.

and identification of additional data sources to better support regulatory activities in subsequent implementation phases

- 2023-2025: integrate key data in targeted regulatory processes and start analytics solutions
- 2024-2027: connect data to power information sharing and dissemination and expand analytic capabilities. This phase will be aligned with the Big Data strategy for human medicines.

The new strategy impacts different business areas, such as pharmacovigilance, the fight against AMR, environmental risk assessment, regulatory submission, innovation of veterinary medicinal products development, and demonstration of efficacy/effectiveness.

A first Veterinary Big Data stakeholder forum bringing together regulators, the pharmaceutical industry, farm management system providers, academia, consumers and practitioners, took place in June 2021. A follow-up forum will be held on November 23, 2022.



EMA launches pilot project on analysis of raw data from clinical trials

July 12, 2022

EMA has launched a pilot project to assess whether the analysis of “raw data” from clinical trials by regulatory authorities improves the evaluation of marketing authorisation applications (MAAs) for new medicines as well as post-authorisation applications and to explore the practical aspects of the submission and analysis of such data.

Raw data constitutes individual patient data from clinical studies (including clinical trials as well as non-interventional studies) in electronic structured format that is directly accessible for analysis and visualisation. Examples of raw data include records of original observations and measurements of clinical study participants, such as clinical laboratory results, imaging data, and patient medical charts. Currently, the European medicines regulatory system does not routinely require the submission of raw data in the context of a marketing authorisation or post-authorisation application.

EMA’s CHMP receives data submitted by the applicant or marketing authorisation holder (MAH) after statistical processing in aggregated format as clinical summaries, as well as in PDF listings. The CHMP scrutinises these summaries as part of the scientific evaluation of the benefits and risks of medicinal products. This process typically results in several rounds of questions in which the Committee may ask the applicants/MAHs for methodological clarifications, re-analysis of data, or additional data. However, according to EU regulation, the CHMP can request the applicant/MAH at any time to provide the raw data to perform further analyses to support the benefit risk assessment of

medicines. Raw data have been requested by the CHMP on several occasions in the past when it was considered that it would be helpful in the evaluation of a medicinal product.

The pilot project is open to applicants or MAHs that are about to submit MAAs or post-authorisation applications. If selected, they will include raw data already as part of their submissions. More information on the pilot’s objectives and on the terms of participation is available in the description of the pilot to industry on EMA website. The pilot is expected to last up to two years and will include approximately ten regulatory procedures submitted to EMA from September 2022. The pilot will fully comply with data protection legislation requirements.

Applicants and MAHs can contact EMA via

rawdatapilot@ema.europa.eu to express their interest in participating in the pilot or to gather more information.

This pilot stems from one of the ten priority recommendations issued by the joint Big Data Task Force of EMA and the HMA in 2020 which highlighted the need to strengthen the network’s capability to analyse data collected at individual patient level to better inform regulatory decision making. There are several potential benefits the analysis of raw data might bring including faster evaluation through fewer questions being put to applicants and a better definition of the target treatment population. Thus, raw data analysis may enable faster and better access to new medicines for patients.

Upon the completion of the pilot, EMA will organise a workshop with relevant stakeholders to discuss the learnings and will also publish a summary report.



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This is called the hash, pound, or number character. A hashtag is a keyword or set of keywords that is preceded by the # character. It is used in social media to create a thread of conversations around a specific theme or topic conveyed in short texts or microblogs. It is commonly used in Twitter, Instagram, YouTube, Pinterest, etc.

A dictionary of most common hashtags can be found at <https://www.hashtags.org/definition/~h/>.

For your info, EMWA is compiling a list of standardised hashtags for our social media use.

@

This is called the “at” sign or symbol. The @ sign is part of email addresses and social media user names (“handles”). Our EMWA handles are as follows: @Official_EMWA (Twitter), @EMWA (LinkedIn), and @europeanmedicalwritersassociation (Facebook)

The two most important keys on your keyboard

Towards better prevention of medicine shortages in the EU

July 15, 2022

European Medicines Agency (EMA) has published a guidance for patients' and healthcare professionals' organisations with key principles and examples of good practices to support them in preventing and managing shortages of human medicines.

Medicine shortages and reduced availability of medicines represent an increasing issue across the EU and the globe, and it has been amplified by the COVID-19 pandemic. It may have a significant impact on patient care by causing medicine rationing and delay of critical treatments. Due to medicine shortages, patients may need to use less effective alternatives and they could risk using medication incorrectly.

The causes of shortages can include manufacturing problems leading to delays or interruption in the production, shortages of raw materials, increased demand of medicines, distribution problems, labour disruptions, and natural disasters.

Patients and healthcare professionals are the main actors at the end of the supply chain, therefore their activities in preventing shortages are usually limited to managing the demand for medicines at risk of shortages. The EMA guidance also looks at measures that help to improve preparedness, planning and rationed use for medicines that are either in short supply or expected to be so in the near future.



Some of the key recommendations included in the EMA guidance apply only to patients' organisations, some only to healthcare professionals' organisations, and some to both. For example, both types of organisations are encouraged to:

- develop observatories in collaboration with national authorities to collect and analyse information from patients and healthcare professionals on shortages and their early signs;
- work with national authorities on criteria and ways to develop registries of essential and critical medicines;
- set up campaigns across the EU to raise awareness of shortages, where to find information on ongoing shortages, risks of stockpiling and safe use of alternative medicines.

The key recommendations have been prepared based on consultations with member organisations of the EMA Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP). They draw on existing practices and initiatives in individual EU Member States where the recommendations have been implemented often in isolation, some of which are described in the annex of the guidance.

The full set of guidelines can be consulted in the good practice guidance, but also in an info-sheet developed by EMA for patients and healthcare professionals.

A collection of info-cards presents what patients can do when it comes to shortages of medicines.

New Special Interest Groups

Welcome to our new special interest groups!

