

News from the EMA

SECTION EDITOR



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Photo: Erik Karits

New vaccine to protect people in the EU and worldwide against dengue

October 14, 2022

European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for Dengue Tetravalent Vaccine (live, attenuated) developed by Takeda GmbH, used to prevent disease caused by dengue virus serotypes 1, 2, 3 and 4 in people from four years of age.

Dengue is a mosquito-borne tropical disease caused by four types of the dengue virus, leading to mild, flu-like symptoms in most people. However, a small number of patients develop severe disease, with potentially fatal bleeding and organ damage. The risk of severe disease is higher in people who have been infected a second time.

According to the World Health Organization, there are approximately 390 million dengue infections per year worldwide, with an estimated death rate of 20,000 to 25,000 per year, primarily in children. Before 1970, only nine countries had experienced severe dengue epidemics, while today the disease is endemic in more than 100 countries, including in Europe. It is the second most-diagnosed cause of fever after malaria among travellers returning from low- and middle-income countries.

This is the first time the CHMP simultaneously reviews a medicinal product meant for the European Union (EU) market, under the centralised procedure, and non-EU countries, under the "EU-Medicines for all" programme – or EU-M4all. EMA's initiative to support parallel applications for the EU-M4all opinion and the centralised procedure aims to make innovative or generic medicines and vaccines that address unmet medical needs or are of major public health interest available in Europe and globally faster, while avoiding duplication of efforts from regulators.

An antiviral therapy for dengue virus infection is not available, and most of the current measures that rely on mosquito control are not very efficient in preventing disease. There is an already approved vaccine, but the dengue tetravalent vaccine shows a wider protection for young children and people older than 45 years old. In light of this, a global unmet public health need is being addressed.

The benefits and safety of the current vaccine have been evaluated in 19 clinical trials that

enrolled more than 27,000 people aged between 15 months and 60 years, from both endemic and non-endemic regions. The results of the studies show that dengue tetravalent vaccine prevents fever, severe disease, and hospitalisation caused by any of the four serotypes of the dengue virus.

The most frequently reported suspected adverse events after any dose of this vaccine were injection site pain, headaches, muscle pain, and feeling generally unwell.

Medicines submitted under the EU-M4all programme are assessed by the CHMP in collaboration with the WHO and the target countries, combining EMA's scientific review capabilities with the epidemiology and local disease expertise of WHO and experts and national regulators in the target countries. The CHMP scientific opinion under the EU-M4all procedure supports global regulatory capacity building and contributes to the protection and promotion of public health beyond the EU by assessing medicines for countries where regulatory capacity may be limited. National regulators can rely on the CHMP's scientific assessment to decide on the use of the medicine in their countries.

First therapy to treat transplant patients with post-transplant lymphoproliferative disease

October 14, 2022

The EMA has recommended a marketing authorisation in the EU for Ebvallo (tabelecleucel), developed by Atara Biotherapeutics Ireland Limited, for the treatment of adult and paediatric patients who experience a serious complication following solid organ transplantation (SOT) or bone marrow transplantation (hematopoietic cell transplant – HCT) called EBV+ PTLD. This is one of the most important malignancies after transplantation. It is a result of the immunosuppression caused by the medication required to reduce the possibility of rejection of the transplanted organ or cells and the most common form of this condition is associated with the Epstein-Barr virus. Ebvallo is indicated in patients after a transplant and who have received at least one prior therapy when the symptoms of the disease come back after treatment (relapsed) or when the treatment does not work (refractory).

A significant unmet need exists for patients who fail first-line therapies as they have only weeks to a few months' survival after treatment failure, and other treatment options are limited. The aim of new treatments is to achieve the disappearance of all signs of cancer after treatment (complete remission) and prolong overall-survival, thereby reducing transplantation-related mortality of patients with EBV+ PTLD.

Tabelecleucel, the active substance of Ebvallo, targets and eliminates infected cells. It is an advanced therapy medicinal product made of cells of the immune system called T-cells that have been taken from a donor (allogeneic). The T-cells

are first mixed with another type of white blood cells in the immune system (B-cells) from the same donor that have been infected with the Epstein-Barr virus so that the T-cells learn to recognise infected B-cells. The T-cells are then grown to increase their numbers. When the medicine is given to the patient, the T-cells are expected to attack and kill the patient's own infected B-cells, thereby helping to control cancers associated with the virus.

Ebvallo 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.

EMA's recommendation is based on the results of an ongoing multicentre, phase 3, single-arm, open-label clinical trial. The study investigated the efficacy and safety of tabelecleucel in 43 patients with relapsed/refractory EBV+ PTLD who had received at least one prior therapy. Approximately half of the treated subjects achieved partial or complete remission. A significant number of patients enrolled in the study responded to the treatment with a durable response of six months or more without disease signs or symptoms after treatment. The most common side effects are fever, diarrhoea, tiredness, feeling sick, low levels of red blood cells, decreased appetite, and low blood sodium levels.

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 Ebvallo outweighed the risks in patients with EBV+ PTLD.

The CHMP 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. Sometimes this is due to the small number of patients with the disease. In other cases, the collection of complete information on the efficacy and safety of the medicine is not possible or would be unethical. The medicines concerned 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, and to conduct a post-authorisation observational safety study in patients treated with the medicine in Europe. The protocol must be submitted within three months of marketing authorisation.

The opinion adopted by the CHMP is an intermediary step on Ebvallo'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 confirms recommendation to withdraw marketing authorisations for amfepramone medicines

November 11, 2022

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed its recommendation to withdraw the marketing authorisations for amfepramone obesity medicines. This follows a re-examination of its previous recommendation of June 2022, which was requested by the companies that market these medicines.

Amfepramone is a sympathomimetic, which means that it acts in the brain and causes effects that are similar to those of adrenaline. Such medicines reduce a feeling of hunger. Amfepramone medicines are currently authorised in Denmark, Germany and Romania as treatment for patients with obesity (body mass index of at least 30 kg/m²) in whom other weight-reduction methods have not worked on their own. Amfepramone medicines were authorised to be used for 4 to

6 weeks and no longer than 3 months.

The recommendation follows a review which found that measures to restrict the use of these medicines for safety reasons have not been sufficiently effective. It found that the medicines were being used for longer than the recommended maximum period of 3 months, thereby potentially increasing the risk of serious side effects such as pulmonary arterial hypertension (high blood pressure in the lungs) and dependency. The medicines were also being used in patients with a history of heart disease or psychiatric disorders, increasing their risk of heart and psychiatric problems. In addition, there was evidence of use during pregnancy, which could pose risks to the unborn baby.

The review considered all available information relating to these concerns, including data

from two studies on the use of amfepramone medicines in Germany and in Denmark. In addition, the PRAC received advice from a group of experts, comprising endocrinologists, cardiologists, and a patient representative.

The PRAC considered introducing further measures to minimise the risk of side effects but could not identify any that would be sufficiently effective. The PRAC therefore concluded that the benefits of amfepramone medicines do not outweigh their risks and recommended that the medicines be removed from the market in the EU.

The PRAC recommendation will now be sent for its consideration to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing or dispensing the medicine and published on a dedicated page on the EMA website.

Save the date!

EMWA Spring Conference
May 9–13, 2023

Prague

EMWA conferences provide a medium for networking, active discussions and extensive cost-effective professional training. It is also an opportunity to benefit from the experiences of other medical writers.

Sales of antibiotics for animal use have almost halved between 2011 and 2021

November 18, 2022

EMA's annual report on the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) shows that, since 2011, European countries have substantially reduced sales of veterinary antibiotics in animals. According to data from 25 countries that continuously provided input for the full 2011–2021 period, overall sales of veterinary antibiotics decreased by 47% in this interval, reaching the lowest value ever reported.

Sales of antibiotic classes considered critically important in human medicine also decreased noticeably between 2011 and 2021 and accounted for only 5.5% of total sales in 2021. Sales of third and fourth generation cephalosporins dropped by 38%, polymyxins by 80%, fluoroquinolones by 14% and sales of other quinolones dropped by 83%. These antibiotics should be used prudently and responsibly to preserve their effectiveness and mitigate the potential risk to public health, as indicated in the Antimicrobial Advice ad hoc

Expert Group (AMEG) categorisation.

This ESVAC report includes, for the first time, information on the progress made towards the European Commission's Farm to Fork Strategy target to reduce the sale of antimicrobials for farmed animals and aquaculture in the EU. In only three years, between 2018 and 2021, the 27 EU Member States have already achieved a 18% reduction, approximately one third of the 50% reduction target set for 2030.

The Farm to Fork Strategy is at the core of the European Green Deal and aims to make food systems fair, healthy, and environmentally friendly. For each country participating in the ESVAC project there is a separate section presenting sales trends by antimicrobial class. Some countries describe their main measures to address antimicrobial resistance and how these activities contribute to the observed changes in sales in their country. The measures include national action plans, national campaigns for prudent use of antimicrobials in animals,

restrictions on the use of certain antimicrobials in food-producing animals, or measures to control prescription of antimicrobials in animals.

The twelfth ESVAC report presents data from 31 European countries (29 EU/EEA countries, Switzerland and the United Kingdom). All participating countries voluntarily provided information on sales of veterinary antimicrobials. The ESVAC project was launched by EMA in September 2009 following a request from the European Commission. Since then, the Agency has coordinated and supported European countries' efforts to establish standardised and harmonised reporting on the volume of sales of veterinary antimicrobial medicinal products. The ESVAC report is published annually and is used as a reference source of information for scientists, veterinarians and other health professionals, risk assessors, and policy makers in the EU Member States.

Under Regulation (EU) 2019/6, reporting data on the sales and use of antimicrobials in animals will become a legal obligation for EU Member States and the Agency. The new requirements will apply to data from 2023 onwards.





DARWIN EU® welcomes first data partners

November 23, 2022

EMA has selected the first set of data partners to collaborate with DARWIN EU®, the Data Analysis and Real-World Interrogation Network. The data available to these partners will be used for studies to generate real-world evidence that will support scientific evaluations and regulatory decision making. Real-world evidence refers to information derived from analysis of real-world data, which is routinely collected data about a patient's health status or delivery of healthcare from a variety of sources other than traditional clinical trials.

The selected partners include both public and private institutions. The common feature is that they all have access to real-world healthcare data from one or more sources such as hospitals, primary care, health insurance, biobanks, or disease-specific patient registries. The data partners will provide the DARWIN EU® Coordination Centre with results of analyses of these data.

With the onboarding of data partners, EMA has initiated the launch of the first three studies to be provided by DARWIN EU®. One study will focus on the epidemiology of rare blood cancers to inform on their prevalence in Europe. The second study is on drug use of valproate and the third one is looking at the use of antibiotics to inform future work on anti-microbial resistance.

EMA will report more details of these studies in due course, including the publication of protocols and reports in the EU Post-Authorisation Studies (PAS) register. These studies mark the start of a rapid ramp-up in the number of studies conducted to support regulatory decision making. The aim is that by 2025 DARWIN EU® will deliver approximately 150 real-world evidence studies per year.

Data partners were selected according to prioritisation criteria after consultation with the DARWIN EU® Advisory Board. According to these criteria:

Sources should have continuous data collection with at least annual data updates, a lag time of less than six months in data availability for analysis and capture of health outcomes and medicines prescribing or dispensing.

The data should be available already converted into the Observational Medical Outcomes Partnership OMOP Common Data Model (CDM), which allows analyses to be performed using the same analytical code.

Data sources should represent different healthcare settings of medicines use (primary, secondary, specialist use) as well as, collectively, the EU population. Non-EU data sources can be considered for inclusion if they add value to real-

world evidence analyses and enrich the results for decision making on medicines.

The number of data partners will increase in the coming years. The target is to add at least ten new data partners every year. In 2023, a call for expressions of interest for potential new data partners will be launched.

DARWIN EU® is a federated network which gives the European medicines regulatory network, composed of national competent authorities in the EU Member States, EMA and the European Commission, access to results from analysis of data from real-world healthcare databases across the EU whenever needed and supporting decision making throughout the lifecycle of a medicine. Thus, DARWIN EU® enables more informed regulatory decision making.

Knowledge of diseases, of medicines use and of how medicines perform in clinical practice can inform regulatory decision making and support the development, authorisation, and safe and effective use of medicines by patients.

EMA manages DARWIN EU® and oversees the Erasmus University Medical Center Rotterdam which was appointed as the DARWIN EU® Coordination Centre in February 2022. The network will act as a pathfinder for the proposed European Health Data Space (EHDS), and will ultimately connect to the EHDS services, enabling the use of the EHDS in medicines regulation in Europe.

Facilitating decentralised clinical trials in the EU

December 19, 2022

The European Commission (EC), the Heads of Medicines Agencies (HMA) and the EMA have published recommendations that aim to facilitate the conduct of decentralised clinical trials (DCTs) while safeguarding the rights and well-being of participants as well as the robustness and reliability of the data collected (https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements-clinical-trials_rec_en.pdf). This is an outcome of their joint initiative to Accelerate Clinical Trials in the European Union (ACT EU).

Traditionally, clinical trials have been conducted at specific clinical trial sites, to which patients had to travel. The aim of DCTs is to make it easier for patients to participate in clinical trials by reducing the need to travel to central trial sites. This approach has the potential to make clinical trials available to a wider demographic of

participants and reduce drop-out rates.

Decentralisation is enabled by the advancement of digital tools, telemedicine, and more mobile and local healthcare. It includes aspects such as home health visits, remote monitoring and diagnostics, direct-to-patient shipment of study drugs, and electronic informed consent.

The recommendations include an overview of national provisions for specific decentralised clinical trial elements to be used in clinical trials. They were put together by the European medicines regulatory network with experts from regulatory bodies responsible for the authorisation of clinical trials, members of ethic committees, good clinical practice inspectors, methodology experts and representatives of patient organisations. Drafting of the paper was coordinated by the clinical trials

coordination group (CTCG).

These recommendations under ACT EU are a first and important step towards clarifying the use of decentralised clinical trials in the EU/EEA by the European medicines regulatory network. They are expected to evolve as knowledge increases and experience is gained. In particular, the overview of national provisions will be updated on a continuous basis.

ACT EU initiative was launched in January 2022 and aims to further develop the EU as a focal point for clinical research, to promote the development of high-quality, safe and effective medicines, and to better integrate clinical research in the European health system. ACT EU will strengthen the European environment for clinical trials, whilst maintaining the high level of protection of trial participants, data robustness, and transparency that EU/EEA citizens expect. ACT EU features ten priority action areas that are the basis for the ACT EU 2022–2026 workplan.

