

News from the EMA

The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from July 2018 to September 2018. More information can be found on the agency's website: www.ema.europa.eu

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EMA identifies gaps in industry preparedness for Brexit



July 10, 2018 – A recent European Medicines Agency (EMA) survey shows that marketing authorisation holders for more than half (58%) of the 694 centrally authorised products (CAP) with an important step in their regulatory processes in the United Kingdom (UK), are on track with their regulatory planning to ensure that their marketing authorisation remains valid once the UK leaves the European Union (EU).

Regulatory authorities and marketing authorisation holders both play an important part in preparing for the consequences of Brexit to safeguard the continuous supply of human and veterinary medicines after the withdrawal of the UK from EU. Since May 2017, the European Commission and EMA have informed companies and raised their awareness of the need to put the necessary measures in motion. Information notices on legal issues and guidance on practical and simplified requirements for companies have been published and regularly updated.

For marketing authorisation holders of CAPs, this may imply changes to the marketing

authorisation itself, including, for example, a transfer of the marketing authorisation to a legal entity established in the European Economic Area (EEA), or a change of the qualified person for pharmacovigilance (QPPV) or pharmacovigilance system master file (PSMF) to a location in the EEA, as well as adaptations to their logistics, manufacturing sites, supply chains and contracts.

However, for 108 (88 human products and 20 veterinary products), or 16%, of these medicines with manufacturing sites located in the UK only, there are serious concerns that the necessary actions will not be carried out in time.

For 10% of the products included in the survey, EMA received no feedback from companies.

The aim of the survey, which was launched in January 2018, was to identify CAPs that are potentially at risk of supply shortages and to obtain information on the timelines for submission of the necessary regulatory changes. The survey was sent to marketing authorisation

holders of the 694 CAPs (661 human and 33 veterinary products) who are located in the UK or who have quality control, batch release and/or import or manufacturing sites, or a QPPV or PSMF in the UK.

According to EU law, the marketing authorisation holder, the QPPV, the PSMF and certain manufacturing sites need to be based in the EEA for a company to be able to market a medicine in the EU.

EMA is liaising directly with the marketing authorisation holders who either did not reply to the survey or have indicated in the survey that they do not plan to submit the changes required by 30 March 2019 and have manufacturing sites in the UK only, as this could potentially lead to supply disruptions.

EMA has analysed feedback from the survey and is now looking in detail at those medicines where there are risks of supply shortages and will assess how critical these are. As a regulator, EMA's role is to ensure that it has a complete overview of the potential risks, and to work together with the relevant marketing authorisation holders to address these risks as early as possible and discuss relevant mitigation measures.

EMA will also regularly monitor the submission of changes to marketing authorisations for all 694 products to check if the relevant variations/notifications are being submitted. Figures are likely to change as regulatory changes are submitted.

EMA urges those companies who have not yet informed EMA of their Brexit preparedness plans to do so as soon as possible to mitigate any risks to the continuous supply of medicines for human and veterinary use within the EU.

Companies are reminded to plan for the UK's withdrawal from the EU on 29 March 2019 and are advised to regularly check EMA's dedicated webpage on the consequences of the UK's withdrawal from the EU. In particular, EMA encourages companies to refer to the updated questions and answers and practical guidance for industry published on June 19, 2018.

New medicine to treat infections caused by resistant bacteria

September 21, 2018 – The EMA's CHMP has recommended granting a marketing authorisation for Vabomere (meropenem trihydrate/vaborbactam), a new treatment option against the following infections in adults:

- Complicated urinary tract infection, including pyelonephritis, a sudden and severe infection causing the kidneys to swell and which may permanently damage them,
- Complicated intra-abdominal infection,
- Hospital-acquired pneumonia, including ventilator associated pneumonia,
- Bacteria in the blood associated with any of the infections listed above,
- Infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The lack of availability of medicines to treat patients with infections caused by resistant bacteria has become a major problem in recent years. It is estimated that at least 25,000 patients in the EU die each year from infections due to bacteria that are resistant to many medicines.



Vabomere is a fixed combination of vaborbactam, a new beta-lactamase inhibitor and meropenem, a broad-spectrum antibiotic belonging to the class of carbapenems that is already approved for use in the EU. It is a powder for concentrate for solution for infusion (drip into a vein).

Resistance to carbapenems has been increasing lately, in particular in Gram-negative bacteria, and is of major concern. Beta-lactamases are enzymes involved in bacterial resistance to these antibiotics. By inhibiting the action of beta-

lactamases, vaborbactam protects meropenem from being inactivated and restores its activity against many, but not all, carbapenem-resistant pathogens.

In the clinical development programme, the exposure to vaborbactam at the recommended dose was shown to be sufficient to protect the activity of meropenem against carbapenem-resistant Enterobacteriaceae. The CHMP also agreed that the studies did not indicate any major concerns regarding the safety profile of meropenem-vaborbactam.

Gene therapy for rare inherited disorder causing vision loss recommended for approval

September 21, 2018 – The EMA's CHMP has recommended granting a marketing authorisation for the gene therapy Luxturna (voretigene neparvovec), for the treatment of adults and children suffering from inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness.

The mutations of the RPE65 gene, which encodes one of the enzymes involved in the biochemistry of light capture by the cells of the retina, hinder the patient's ability to detect light. It is a severely debilitating disease, characterised by a progressive loss of vision. Most patients will be blind by the time they are young adults. There is currently no treatment for this disease; support to patients is limited to measures

allowing the management of the disease such as aids for low vision.

Luxturna is meant for patients with confirmed biallelic mutations of the RPE65 gene (i.e., patients who have inherited the mutation from both parents) and who have sufficient viable retinal cells. It is the first gene therapy to be recommended for approval for a retinal disease. Luxturna works by delivering a functional

RPE65 gene into the cells of the retina through a single retinal injection, which restores the production pathway for the required enzyme thereby improving the patient's ability to detect light.

Luxturna was studied in 41 patients. In the main clinical trial supporting the approval of Luxturna, patients treated with the medicine showed a significant improvement of night vision,

one of the typical symptoms of the disease, after one year, while no improvement was seen in the control group. The most common side effects were conjunctival hyperaemia (eye redness), cataracts and increased intraocular pressure.

Given the novelty of the treatment and the limited number of treated patients, the CHMP requires the company to ensure the long-term follow-up of patients to confirm Luxturna's continuing efficacy and safety. Follow-up studies were agreed, including a post-authorisation safety study based on a disease registry in patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations, as well as a 15-year follow-up programme of efficacy and safety outcomes for all patients treated in the clinical programme.

The CHMP's opinion is based on the assessment by EMA's expert committee on Advanced Therapy Medicinal Products (ATMPs), the Committee for Advanced Therapies. Luxturna was designated as an orphan medicine and an ATMP and EMA provided protocol assistance to the applicant during the development of the medicine.



EMA's proactive publication of clinical data: First report on transparency policy shows high user satisfaction

July 16, 2018 – The EMA has published the first report on the implementation of its flagship policy on the publication of clinical data (Policy 0070). Under this policy citizens, including researchers and academics, can directly access thousands of pages from clinical reports submitted by pharmaceutical companies to EMA in the context of marketing authorisation applications for new medicines as of January 1, 2015. Clinical reports give information on the methods used and results of clinical trials conducted to demonstrate the safety and efficacy of medicines.

The report covers one year from the launch of EMA's clinical data website on October 20, 2016, and lists the 50 medicines for which clinical data were published, including orphan, paediatric, biosimilar and generic medicines, as well as the corresponding 54 regulatory dossiers. These data have attracted a total of 3,641 users, resulting in 22,164 document "views" and 80,537 "downloads" for non-commercial research purposes.

The report sheds light on the total number of documents published, the amount of commercially confidential information (CCI) redacted and the anonymisation techniques used. EMA accepted 24% of CCI redactions proposed by pharmaceutical companies, with the result that only 0.01% of 1.3 million pages published contained CCI redactions. The report also details the various anonymisation techniques used to protect personal data. It also suggests conducting a proper assessment of the impact of the anonymisation technique on data utility and improving the quality of the anonymisation reports.

The results of a user survey of the clinical data

website are also included in the report. Of the total respondents, 62% were affiliated to the pharmaceutical industry, 14% to academia, 8% were patients and 8% healthcare professionals. The report summarises the reasons of the different user groups for accessing the data and their views on its usability. Importantly, it shows that very few respondents disagree with EMA's rationale for developing the policy. In addition, most respondents strongly agree that publishing clinical data increases public trust in EMA's decision-making and that it allows the reassessment of clinical data.

To implement the policy successfully, EMA made sure that the pharmaceutical industry received regularly updated guidance. The Agency also provided one-on-one assistance to individual companies to prepare them for the publication of clinical data. As a result, EMA published an average of six dossiers a month in the period from October 2017 to May 2018, reaching the hundredth published dossier milestone on May 29, 2018.

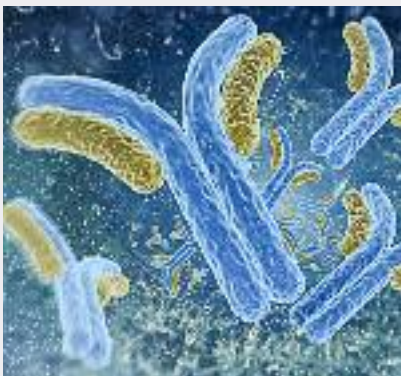
EMA is the first regulatory authority worldwide to provide open access to clinical data submitted by companies in support of their marketing authorisation applications. This is a cornerstone of EMA's commitment to openness and transparency, which was recently endorsed by the EU's General Court rulings on the limited scope of commercial confidentiality with regard to authorised medicines. Moreover, EMA's



proactive publication of clinical data has shaped the global debate towards more transparency, as other regulators, such as the US Food and Drug Administration and Health Canada, have subsequently implemented – or are considering implementing – similar transparency measures.

EMA is currently preparing for its relocation to the Netherlands, its new host Member State, and is implementing the next phase of its business continuity plan to facilitate the relocation. This will also impact the publication of clinical data as of the second half of 2018 and in 2019. EMA will liaise with pharmaceutical companies currently preparing their submissions. The Agency will do its utmost to resume this activity to the level outlined at the start of the policy once the relocation is complete.

A monoclonal antibody for the prevention of migraine recommended for marketing authorisation



September 21, 2018 – The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for Emgality (galcanezumab), a monoclonal antibody for the prevention of migraine. Emgality belongs to a new class of medicines that work by blocking the activity of calcitonin gene-related peptide (CGRP), a molecule that is involved in migraine attacks.

It is estimated that approximately 15% of the population in the EU suffers from migraine. Patients experience recurrent episodes of intense,

throbbing headache, most often only on one side of the head. Sometimes, the pain is preceded by visual or sensory disturbances known as an 'aura'. Many people also experience nausea, vomiting and increased sensitivity to light or sound. Migraine can substantially impair a patient's ability to function physically, at work or school, and socially.

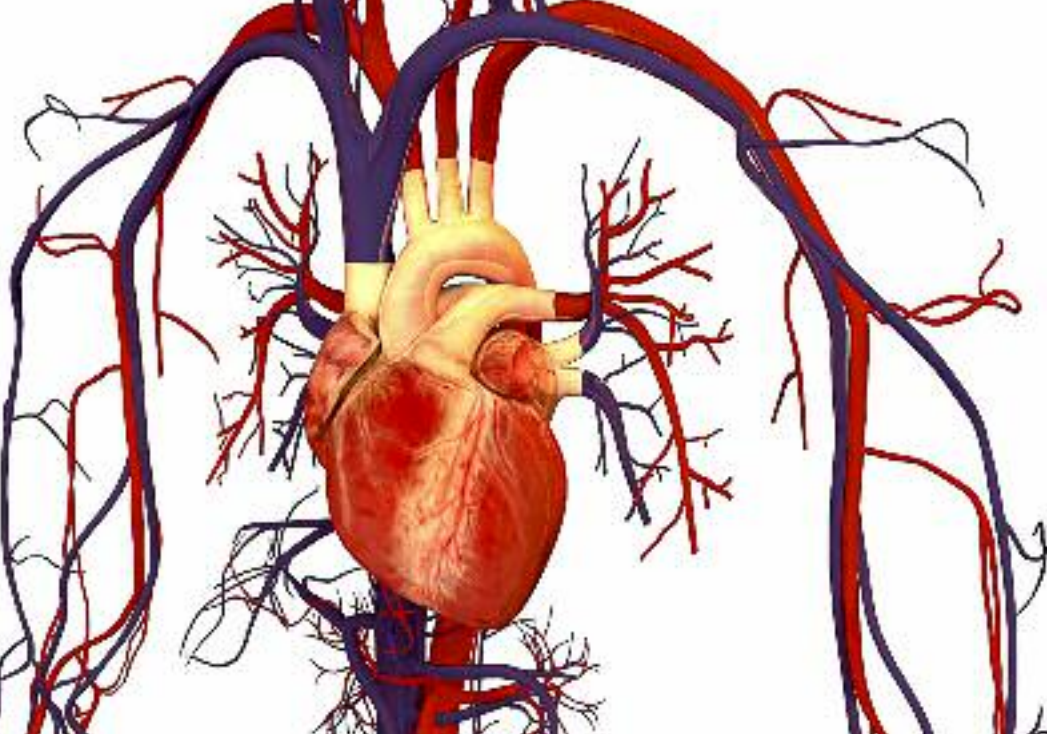
The exact cause of migraine is unknown, but it is believed to be a neurovascular disorder with disease mechanisms both within the brain and the blood vessels of the head. It is most frequent

Valsartan and sartan medicines: Review and risk assessment of impurities

September 13, 21, and 28, 2018 – Valsartan is an angiotensin-II-receptor antagonist used to treat hypertension (high blood pressure), recent heart attack and heart failure. It is available on its own or in combination with other active substances. A review of valsartan medicines was triggered by the European Commission on 5 July 2018 to test the presence of certain carcinogenic impurities.

Initially, the review focussed on medicines containing the active substance manufactured by Zhejiang Huahai and Zhejiang Tianyu where unacceptable levels of Nnitrosodimethylamine (NDMA) were confirmed. A related impurity, Nnitrosodiethylamine (NDEA), was also detected in valsartan made by Zhejiang Huahai using its previous manufacturing process prior to 2012. Medicines containing valsartan from Zhejiang Huahai and Zhejiang Tianyu have been recalled and are no longer being distributed in the EU. An inspection by EU authorities in collaboration with European Directorate for the Quality of Medicines found that Zhejiang Huahai did not comply with good manufacturing practice in the manufacture of valsartan at the Chuannan site in Linhai, China. Consequently, this site is no longer authorised to produce valsartan (and its intermediates) for EU medicines. Marketing authorisation holders in the EU are prohibited from using valsartan from this site for the production of medicines. The inspection found several weaknesses at Zhejiang Huahai, including deficiencies in the way the company investigated the presence of NDMA and NDEA in its valsartan products.

Both NDMA and NDEA belong to the class of nitrosamines and are classified as probable



human carcinogens (substances that could cause cancer). How these impurities came to be present during the manufacture of sartans is yet to be fully established and is being evaluated in the ongoing review.

The EMA has now expanded its review of impurities in valsartan following the detection of very low levels of NDEA in another active substance, losartan, made by Hetero Labs in India. As a result of the detection of this impurity by German authorities, the review will now include medicines containing four other 'sartans' (angiotensin-II-receptor antagonists), namely candesartan, irbesartan, losartan and olmesartan. Like valsartan, these active substances have a specific ring structure (tetrazole) whose synthesis could potentially lead to the formation of impurities such as NDEA. The extension of the review to other sartans is precautionary.

EMA's risk assessment is based on the average levels of NDMA in the active substance produced by Zhejiang Huahai since 2012 (when the company changed its manufacturing process)

and on the assumption that all the NDMA is transferred to the final product. The life-time risk of cancer is considered low and is estimated to be in the order of 1 in 5,000 for an adult patient who had taken an affected valsartan medicine at the highest dose (320 mg) every day from July 2012 to July 2018. Patients who have taken treatments with lower doses or for shorter lengths of time will be at a lower risk. The risk will also be lower for patients who have taken valsartan produced by Zhejiang Tianyu, which had smaller amounts of NDMA than valsartan produced by Zhejiang Huahai.

Based on the trace amounts of NDEA seen so far in one batch of losartan from Hetero Labs, there is no immediate risk to patients. Patients are therefore advised not to stop taking losartan or other sartan medicines without speaking to their doctor.

Further tests are required to determine the extent of the contamination and whether impurities are present in sartan medicines above levels that can be considered acceptable.

in women and has a strong genetic component.

Emgality will be available as a solution for injection intended only for patients who have at least four migraine days per month. The benefits and safety of Emgality were studied in three pivotal trials involving 1,780 patients with episodic migraine and 1,117 with chronic migraine. After six months of treatment, patients with episodic migraine showed a reduction of 1.9 monthly migraine days on average compared to placebo. For patients with chronic migraine the reduction was 2 days. The most

common side effects are pain and reactions at the injection site, vertigo and constipation.

Emgality is the second monoclonal antibody therapy for the prevention of migraine to be recommended for authorisation, following the positive opinion for Aimovig (erenumab) in May 2018. There is no cure for migraine and these two medicines widen the therapeutic options for this disease. There are other available treatments to tackle the symptoms and reduce the frequency of migraine days. However, existing preventative treatments do not always

work well and may have unpleasant side effects.

The opinion adopted by the CHMP is an intermediary step on Emgality's path to patient access. The CHMP 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/use of this medicine in the context of the national health system of that country.