# 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 October 2017 to December 2017. More information can be found on the Agency's website: http://www.ema.europa.eu/


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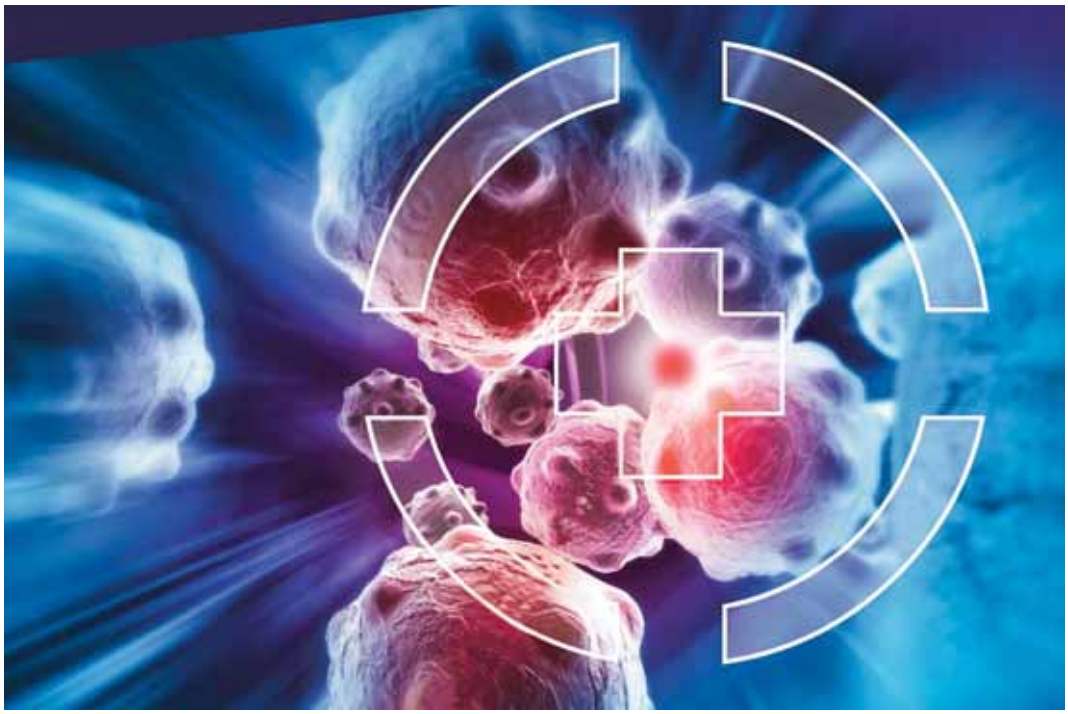
## New action plan to foster development of advanced therapies



**October 20, 2017** — The European Commission's Directorate-General for Health and Food Safety (DG SANTE) and the European Medicines Agency (EMA) have published today a joint action plan to foster the development of advanced therapy medicinal products (ATMPs). The main aim is to streamline procedures and better address the specific requirements of ATMP developers.

ATMPs are medicines for human use that are based on genes or cells. These therapies offer ground-breaking new opportunities for the treatment of disease and injury. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate. ATMPs can be classified into four main groups: gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered medicinal products and combined ATMPs. EMA has received 18 marketing authorisation applications since the ATMP regulation came into force in 2009. Nine products have been approved.

The Agency's Committee for Advanced Therapies (CAT) plays a central role in the scientific assessment of ATMPs, as it provides the expertise needed to evaluate these medicines. Other initiatives include European Commission research programmes, the innovation offices in the national competent authorities and EMA's PRIME scheme.

At international level, a regular forum for dialogue has been set up with the United States Food and Drug Administration (FDA), Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) to share experience on ATMPs. EMA and the CAT also contribute to the cell therapy group and gene therapy group of the International Pharmaceutical Regulators' Forum (IPRF).

DG SANTE and EMA, in collaboration with the Member States' competent authorities, are working on some initiatives to support the development and authorisation of high quality, safe and effective ATMPs. The plan published today contains 19 actions in different key areas. Some of the actions are already in place, others are new. Actions were also informed by the ideas collected during a multi-stakeholder workshop hosted by EMA on May 27, 2016. The workshop aimed to explore solutions to identified challenges in the development of ATMPs. Topics discussed ranged from the need for early interaction and guidance from regulators, to more transparency and information sharing, greater harmonisation between Member States in various aspects of ATMP regulation and measures to tackle inequalities in patient access to ATMP treatments.

Examples of forthcoming actions in the plan include:

- European Commission guideline on good manufacturing practice for ATMPs, to reduce the administrative burden and adapt the manufacturing requirements to the specific characteristics of ATMPs;
- Initiation of dialogue with national competent authorities to address the interplay between the legislation on genetically modified organisms (GMO) and on medicines, to reduce discrepancies across the European Union (EU) regarding the application of GMO rules;
- New EMA scientific guidelines on ATMPs, including investigational ATMPs, to clarify regulatory expectations;
- Continuous awareness and training sessions organised by EMA for the EU network on ATMP-related topics.

DG SANTE and EMA will continue monitoring the field and propose further initiatives as appropriate.

## How to develop vaccines and medicines that prevent and treat respiratory syncytial virus infection

**October 30, 2017** – Respiratory syncytial virus (RSV) is a common respiratory virus that usually causes mild, cold-like symptoms. Most people recover within one to two weeks, but RSV can be serious, especially in infants and older adults. It is the most common cause of lower respiratory tract infections, such as bronchiolitis (inflammation of the small airways in the lungs) and pneumonia (infection of the lungs), in newborn babies and young infants. RSV is also a significant cause of respiratory illness in the elderly. Several medicines are currently under development for RSV disease, for which there is no specific vaccine and only a few treatments available.

The EMA has released a new guideline to support and facilitate the development of vaccines and medicines to prevent and treat infections caused by RSV for a six-month public consultation. Stakeholders are invited to send their comments by April 30, 2018, to vwp@ema.europa.eu using the template provided in the guideline.

EMA's new draft guideline provides advice for medicine developers on how they can best develop safe and effective vaccines and monoclonal antibodies to prevent RSV disease, and direct-acting antiviral agents (DAAs) to treat it. The guideline focuses on assessment of safety and efficacy of vaccines and medicines in people most likely to develop RSV lower respiratory tract infection and severe RSV disease, including newborn babies (0 to 27 days), infants (28 days to 11 months), toddlers (12 to 23 months), older children who are likely to develop severe RSV disease and people aged over 65 years. It also addresses the vaccination of pregnant women with the aim of preventing RSV disease in their babies, once they are born.

Other areas for which guidance is provided include diverse aspects such as study design, how to assess the efficacy of a vaccine in different scenarios, and the selection of the recommended dose regimen for medicines.

## New medicine for multiple sclerosis

**November 10, 2017** – The EMA has recommended granting a marketing authorisation in the EU for Ocrevus (ocrelizumab) for the treatment of adult patients with relapsing multiple sclerosis (RMS) and early primary progressive multiple sclerosis (PPMS). There are currently no disease-modifying therapies available for this particular form of multiple sclerosis (MS) so there is a great medical need for treatment of such a relentless, seriously debilitating disease. Ocrevus is first medicine to receive positive opinion for treatment of patients with early stage of PPMS.

MS is a condition that affects the brain and/or spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation or balance. It occurs more frequently in women than men and is among the most common causes of neurological disability in young adults. In the majority of patients (around 85%), MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery. For the approximately 10% of patients with PPMS the disease is characterised by worsening neurologic function from the onset of symptoms, without early relapses or remissions.

The recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) is based on data from three pivotal Phase III clinical trials in 1423 patients with MS (two in RMS and one in PPMS patients). Treatment with Ocrevus significantly reduced the annualised relapse rate by 46.4% at 96 weeks compared with interferon beta-1a treatment in patients with RMS. For patients with PPMS, treatment with Ocrevus led to a 24% reduction in the risk of 12-week confirmed disability progression compared with placebo. Data from the clinical trial in PPMS indicate that patients in the early stage of disease benefit more from the medicine. More investigation is needed to better understand how beneficial Ocrevus might be in the more advanced stages of the disease.

The most common adverse reactions observed with Ocrevus are infusion-related reactions and infections. The CHMP therefore recommended that Ocrevus treatment should be initiated and supervised by an experienced healthcare professional with access to appropriate medical support to manage severe reactions.

The opinion adopted by the CHMP at its November 2017 meeting is an intermediary step on Ocrevus' 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.

The applicant for Ocrevus is Roche Registration Limited.

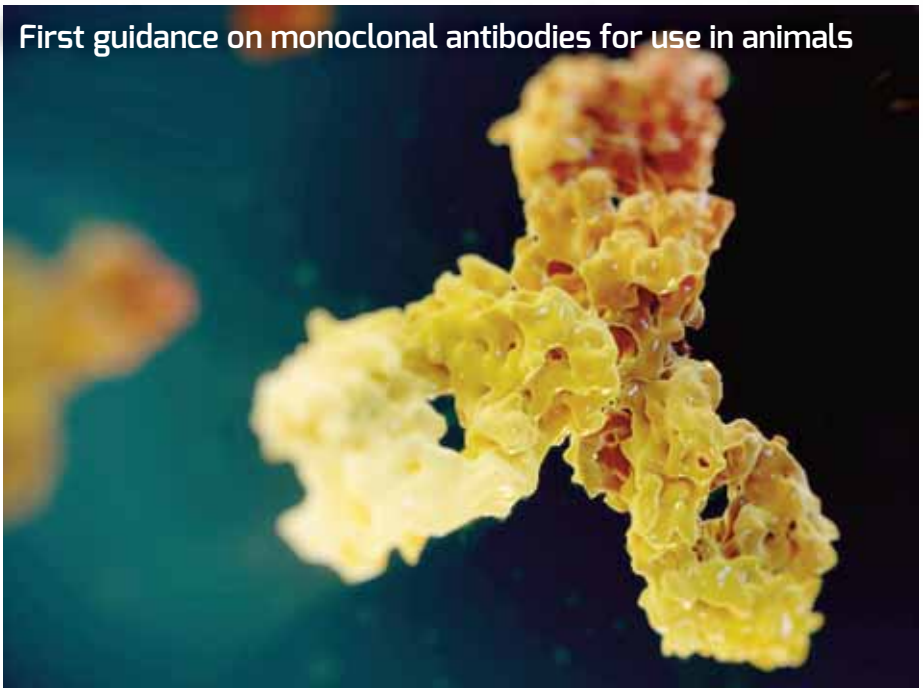
## EMA to relocate to Amsterdam

**November 20, 2017** – The EMA will relocate to Amsterdam. This decision was taken today by the EU 27 Member States in the margins of the General Affairs Council (Art. 50). The EMA has been based in London, since it was established in 1995. It currently employs nearly 900 staff members at its headquarters in Canary Wharf, London. The Agency now has to prepare for the move and take up its operations in Amsterdam on March 30, 2019, at the latest.

EMA's relocation is due to the UK's decision to withdraw from the EU. Amsterdam was one of 19 offers to host EMA submitted by the Member States at the end of July 2017. The decision on EMA's new location follows an assessment of the bids by the European Commission and EMA.

Effective collaboration between EMA and the Netherlands on the basis of the commitments made in its offer to host EMA is essential to ensure a successful move and the continuation of EMA's operations with minimal disruption. EMA and the Netherlands will kick start their collaboration by establishing a joint governance structure to steer and oversee the relocation project. Because of its important role to safeguard public and animal health in the EU, EMA is committed to giving stakeholders and the public full visibility of the relocation project. In early December 2017, the Agency made available a monitoring chart on its website that allows tracking the progress made.

## First guidance on monoclonal antibodies for use in animals



**December 11, 2017** – The EMA's Committee for Medicinal Products for Veterinary Use (CVMP) has approved the first ever guidance at EU level for monoclonal antibody therapies for veterinary use. The guidance was prepared by the CVMP's Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) in the form of a question-and-answer document.

The guidance relates to particularities of monoclonal antibodies for veterinary use, quality control for potential contaminants, stability testing, reproductive safety studies and data to address potential for indirect adverse effects.

Monoclonal antibodies are immune proteins that recognise and bind to a specific target protein, and have not been used in veterinary medicines until recently. In human medicine, these therapies have been authorised for many years for use against cancer and diseases affecting the immune system, such as rheumatoid arthritis. Therapies that are new to veterinary medicine face particular challenges due to a lack of regulatory guidance. Despite these challenges, the first veterinary medicine containing a monoclonal antibody was recommended for approval by the CVMP in February 2017.

Veterinary novel therapies refer to therapies that are either genuinely new, or new only to the veterinary domain, although well known in the context of human medicines. Interest and research activities into veterinary novel therapies have increased over the last few years. The CVMP identified monoclonal antibodies as one of the priority areas that would benefit from specific guidance, following a review of relevant scientific evidence, such as published literature, available guidance on such medicines for human use, experience gained by the CVMP through scientific advice and public consultations.

ADVENT brings together broad knowledge and expertise on the scientific aspects of veterinary medicines and their regulation. The group makes use of additional expertise from across the European network. It was set up by the CVMP to prepare general guidance on the requirements for authorisation of novel veterinary medicines. In this context, the group also prepares guidance on other types of novel therapies. For example, guidance on three different aspects of veterinary stem cell therapies was published earlier this year.

## Modified-release paracetamol-containing products to be suspended from EU market: Recommendation endorsed due to the difficulty in managing overdose

**December 15, 2017** – The CMDh, which is a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein, and Norway, has endorsed an EMA recommendation to suspend marketing of modified- or prolonged-release products containing paracetamol (designed to release paracetamol slowly over a longer period than the usual immediate-release products). The recommendation was made by the Agency's experts in medicines safety, the Pharmacovigilance Risk Assessment Committee (PRAC). As the CMDh position was adopted by majority vote, the CMDh position will now be sent to the European Commission, which will take an EU-wide legally binding decision.

CMDh agreed with the Agency's advice that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine, since the treatment procedures for immediate-release products are not appropriate for modified-release paracetamol. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified-release products, making it difficult to decide how the overdose should be managed.

CMDh noted the PRAC conclusion that practical measures to sufficiently reduce the risk to patients had not been identified. Furthermore, it had not proved possible to agree a feasible and standardised way to adapt the management of overdose across the EU to cover both immediate- and modified-release paracetamol products. The CMDh therefore endorsed the PRAC recommendation that the marketing authorisations for medicines containing modified-release paracetamol, alone or combined with the opioid medicine, tramadol, should be suspended.

The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks. Immediate-release paracetamol products, which are not affected by this review, will continue to be available as before.

The Agency's recommendations are based on a review of available data including a retrospective pharmacokinetic and clinical analysis of 53 cases of acute overdose with modified-release paracetamol by the Swedish Poison Information Centre, which found that the standard treatment protocol utilising solely the Rumack-Matthew nomogram (or variations thereof) based on conventional paracetamol formulations may not be effective for overdoses with modified-release paracetamol formulations. The maximum plasma concentration may occur later, and high concentrations, in particular after large doses, may persist for several days. The usual protocols of sampling and treatment regimens used in the management of overdose with immediate-release formulations are therefore not adequate.

These results confirm a similar Australian case series.

## A new medicine for the treatment of X-linked hypophosphataemia, a rare bone disease: Recommended for conditional approval

**December 15, 2017** – The EMA's CHMP has recommended granting a conditional marketing authorisation in the EU for Crysvita (burosumab), a medicine for the treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

XLH is an inherited disorder characterised by low levels of phosphate in the blood. The phosphate is abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). In most cases, the signs and symptoms of hereditary hypophosphataemic rickets begin in early childhood. Characteristic features include bowed or bent legs, short stature, bone pain, and severe dental pain.

The CHMP recommended conditional approval for the medicine. This is one of EU's regulatory mechanisms to facilitate early access to medicines that fulfil unmet medical need. Conditional approval allows the Agency to recommend a medicine for marketing authorisation in the interest of public health where the benefit of its immediate availability to patients outweighs the risk inherent in the fact that additional data are still required.

There is currently no authorised medicine available to treat this rare, serious, chronic and debilitating disease. Most children with XLH receive conventional therapy consisting of multiple daily doses of oral phosphate and active vitamin D analogues. The benefits of Crysvita are its ability to reduce the loss of phosphate, improve abnormally low serum phosphate concentrations and other metabolic changes, and to reduce the severity of rickets as shown in X-rays.

The CHMP's recommendation is based on two phase II studies. The main study was conducted on 53 children aged 5-12 years. Children treated with Crysvita experienced an improvement in their phosphate level and in the reabsorption of phosphate in their kidneys as well as radiographic improvement of rickets. In the second study of 13 patients age 1 to 4 years old receiving Crysvita, the response was similar than in children in the main study. On this basis, the CHMP considered that efficacy results from age group 5-12 years can be extrapolated to ages 1 to 4 years old. The most common adverse reactions observed with Crysvita were injection site reactions, headache, and pain in extremities.

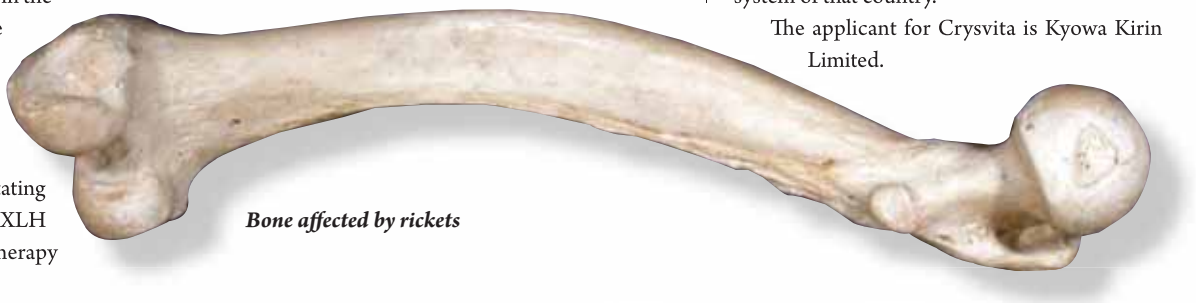
As part of the conditional marketing authorisation, the applicant is required to complete three ongoing studies to further investigate the safety and efficacy of the medicine. The data from all three studies are planned to be submitted by 2020.

The CHMP recommended that Crysvita will be prescribed by physicians experienced in the management of patients with metabolic bone diseases.

Because XLH is rare, Crysvita received an orphan designation from the Committee for Orphan Medicinal Products (COMP) in October 2015. As always at time of approval, this orphan designation will now be reviewed to determine whether the information available to date allows maintaining burosumab's orphan status and granting this medicine ten years of market exclusivity.

The opinion adopted by the CHMP at its December 2017 meeting is an intermediary step on Crysvita'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.

The applicant for Crysvita is Kyowa Kirin Limited.



*Bone affected by rickets*