

# News from the EMA

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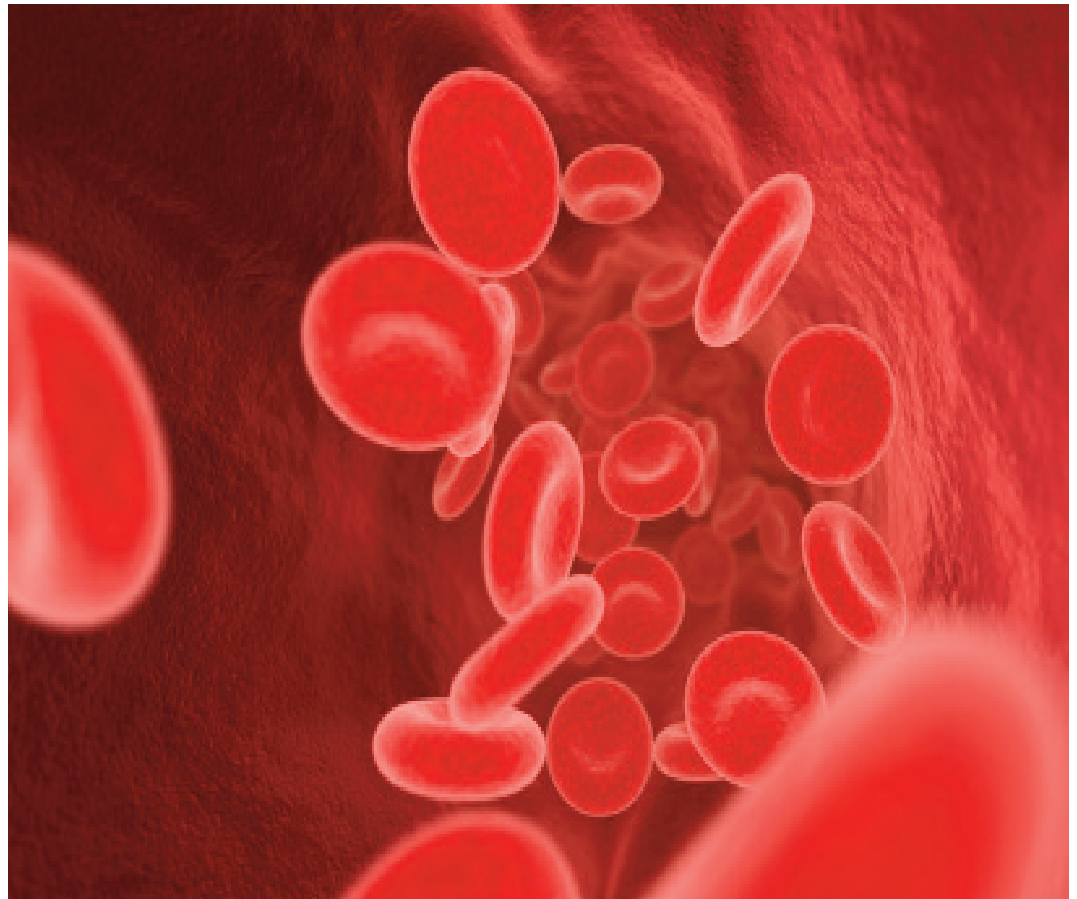
The articles included in this section are a selection from the European Medicines Agency's News and Press Release archive from January 2018 to March 2018. More information can be found on the agency's website: [www.ema.europa.eu](http://www.ema.europa.eu)

## First-in-class medicine to prevent bleeding in haemophilia A patients with inhibitors

**January 26, 2018** – The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation for Hemlibra (emicizumab), a first-in-class medicine to prevent bleeding or reduce the frequency of bleeding episodes in patients with haemophilia A with factor VIII inhibitors, in patients of all ages.

Haemophilia A is an inherited bleeding disorder caused by lack of a clotting protein called factor VIII, and affects mainly males. Patients with haemophilia A are usually treated with factor VIII medicines, which replace the missing factor VIII and help control and prevent bleeding. However the body may develop inhibitors (antibodies) as a reaction to these medicines. The inhibitors reduce the medicines' effect, so bleeding is no longer controlled. The development of inhibitors is the most severe treatment-related complication of haemophilia A because it makes it difficult to manage the disease. Current treatment alternatives in patients with haemophilia A who develop inhibitors are time-consuming and often burdensome, particularly for children, and they are not effective in all patients. There is therefore an unmet medical need for more convenient and effective treatment options.

Hemlibra is the first monoclonal antibody to be recommended for use in patients with haemophilia A with inhibitors, an area of medicine where no new medicines have been made available in 20 years. It works by mimicking the coagulation function of factor VIII. The treatment is given weekly via a subcutaneous injection, making it more convenient than bypassing agents (medicines that bypass



factor VIII) which are the current standard of care but which require frequent, prolonged administration by infusion (drip). The Committee for Medicinal Products for Human Use reviewed the application for Hemlibra under its accelerated assessment procedure, which allows the speeding up of patients' access to medicines that address unmet medical needs.

The safety and efficacy of the medicine was evaluated in two phase III clinical trials: a randomised, open-label study conducted in 109 patients aged 12 years or older, and an ongoing single-arm, open-label study in children under 12 years of age, for which results in 60 patients were included in the application. Overall, the prophylactic use of emicizumab in

haemophilia A patients with inhibitors reduced bleeding episodes that needed treatment with coagulation factors by around 80% to 90% compared to on-demand use of bypassing agents without prophylactic treatment.

The most common adverse events observed were reactions at the site of injection, headache, thrombotic microangiopathy (damage to small blood vessels supplying organs such as the kidney), fever, diarrhoea, and joint and muscle pain.

The opinion adopted by the CHMP is an intermediary step on Hemlibra'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.

## General Court confirms EMA approach to transparency

**February 6, 2018** – The General Court delivered today three landmark rulings for the EMA, upholding EMA's decisions to release documents requested in accordance with Regulation (EC) No 1049/2001, the so-called "Transparency Regulation". This is the first time that the Court of Justice of the European Union (EU) has had the opportunity to pronounce itself on the application of the Transparency Regulation to documents held by EMA.

The judgments concern Case T-235/15, *Pari Pharma v EMA*, in relation to the disclosure of similarity and superiority reports on an orphan medicine, prepared by the CHMP; Case T-718/15, *PTC Therapeutics*

*International v EMA*, on the disclosure of a clinical study report; and Case T-729/15, *MSD Animal Health Innovation and Intervet international*, regarding five toxicology study reports for a veterinary medicine. In all three cases, the pharmaceutical companies challenged EMA's decision to release the concerned documents in accordance with the Transparency Regulation and EMA's 2010 policy on access to documents (Policy 0043).

The General Court noted that the companies failed to give any concrete evidence of how the release of the contested documents would undermine their commercial interests, and therefore it rejected their claims.



Based on the guidance issued today by the General Court, the Agency will continue to diligently assess each individual request for access to documents submitted under the Transparency Regulation and in accordance with its policy on access to documents.

## First medicine to treat neonatal diabetes

**February 23, 2018** – The EMA's CHMP has recommended granting a marketing authorisation in the EU for Amglicia (glibenclamide), a medicine indicated for the treatment of neonatal diabetes mellitus, for use in newborns, infants, and children.

Neonatal diabetes is an extremely rare form of diabetes that is diagnosed in the first six months of life. It is life-threatening and debilitating because of the symptoms caused by high blood sugar levels and the risk of ketoacidosis, a serious problem that can occur in people with diabetes if their body starts to run out of insulin and ketones build up in the body. Different gene mutations have been identified causing this type of diabetes.

Amglicia is a new oral formulation of glibenclamide, a medicine which is already authorised for treating type 2 diabetes, specifically developed for use in newborns, toddlers, and

children with neonatal diabetes. It works on insulin-producing cells in the pancreas by attaching to an ATP-sensitive potassium (KATP) channel, which controls the release of insulin. In many newborn babies with neonatal diabetes, the cells in the pancreas produce insulin but they are not able to release it into the blood because their gene mutations lead to dysfunctional KATP channels. The lack of insulin in the blood causes symptoms of diabetes. Glibenclamide's effect on the KATP channel restores the cells' ability to release insulin into the blood. These effects are expected to reduce the symptoms of neonatal diabetes.

Currently, to treat neonatal diabetes, nursing staff under medical prescription, or the parents at home, administer insulin or off-label commercially-available glibenclamide tablets licensed for adults only. To make the products suitable for

newborns and children, the tablets are crushed into small pieces that are mixed with a small amount of water, and then administered with an oral syringe. This practice can cause errors in the administration, potentially leading to a risk of under- or over-dosing. Amglicia's formulation is meant to allow a more accurate dosing of glibenclamide. Moreover, patients treated with Amglicia may not need to be treated with insulin or may need a smaller dosage.

Amglicia is a hybrid medicine of Daonil which has been authorised in the EU since January 1969. Hybrid applications rely in part on the results of pre-clinical tests and clinical trials for a reference product, and in part on new data. The benefits of Amglicia are supported by data published in literature as well as data from a bio-availability study and the NEOGLI study. Due to the extreme rarity of the disease, there were only 10 patients included in the NEOGLI study. It showed that glycaemic control remained stable after switching from crushed tablets to oral suspension.

Because neonatal diabetes mellitus is a very rare disease, Amglicia was granted an orphan designation in January 2016. As always at time of approval, this orphan designation will now be reviewed by EMA's Committee for Orphan Medicinal Products (COMP) to determine whether the information available to date allows maintaining Amglicia's orphan status and granting this medicine ten years of market exclusivity. The CHMP opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation.





## Revised guideline on clinical studies for Alzheimer's disease medicines

**February 28, 2018** – The EMA's CHMP has adopted a revised guideline on clinical studies for medicines that target Alzheimer's disease. This document aims to provide guidance for the development of medicines across all stages of Alzheimer's disease.

Alzheimer's disease, a condition that destroys brain cells and nerves, disrupting the transmitters which carry messages in the brain, is the most common cause of dementia in the elderly. According to the World Health Organization

(WHO), 35.6 million people have dementia worldwide and this number is expected to double by 2030. It affects more than 5 million people in the EU.

Recent progress in understanding the pathophysiology of Alzheimer's disease suggests that the biological changes associated with the disease start to occur as early as 10 to 20 years before clinical symptoms start to appear. Many of the experimental medicines are therefore investigated in earlier disease stages as certain treatments may be more effective at that stage than later in the illness.

Currently available medicines for Alzheimer's disease only treat its symptoms. However, a number of therapies under development are targeting the biological mechanism of the condition to try and modify the course of the disease.

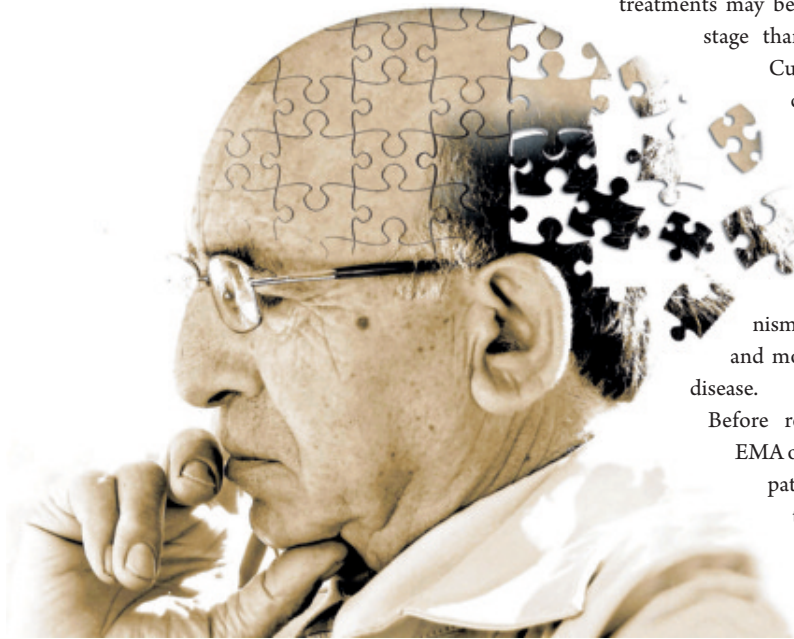
Before revising the guideline, EMA organised a workshop for patients, academia, regulators, representatives from the pharma-

ceutical industry and independent experts to ensure that it was informed of the most up-to-date scientific developments in understanding and treating Alzheimer's disease. This effort was complemented by a series of meetings between EMA and developers of medicines intended to slow down the disease progression, to discuss the issues encountered in their clinical trials. The guideline also builds on scientific advice provided by the Agency to medicine developers on specific products and methodologies, such as the qualification of biomarkers for use in clinical trials and a longitudinal model describing changes in cognition in patients with mild or moderate Alzheimer's disease.

EMA's new guideline addresses, among others:

- impact of new diagnostic criteria for Alzheimer's disease, including early and even asymptomatic disease stages, on clinical trial design.
- factors to be considered when selecting parameters to measure trial outcomes at the different disease stages in Alzheimer's.
- potential use of biomarkers in the various stages of medicine development.
- design and analysis of efficacy and safety studies.

The guideline will become effective from September 1, 2018.



## New tracking tool for EMA's relocation to Amsterdam

**March 6, 2018** – The EMA has published a new tool showing the main milestones and deliverables for the Agency's move to Amsterdam. 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. The tracking tool will allow all interested parties to follow the progress made.

EMA will move from London to Amsterdam before March 29, 2019, when the United Kingdom withdraws from the EU. The Dutch authorities have committed to building completely new, tailor-made premises for EMA in the Zuidas business district which are expected to be available from November 15, 2019. For an interim period until the new building is complete, EMA will occupy temporary premises in the Sloterdijk area of Amsterdam. The success of EMA's relocation is

dependent on a number of activities which need to take place in the context of these two consecutive moves.

Following the EU27 decision to relocate EMA to Amsterdam, a joint governance structure was agreed between EMA and the Netherlands with five work streams relating to the temporary and permanent premises, staff relocation, financial and legal aspects, and external communication.

The tracking tool first gives a general overview of the main milestones agreed for each of the work streams, with the exception of external communication, which is an ad-hoc activity dependent on the progress made with the other work streams. It then outlines in more detail the deliverables for each work stream, highlighting clearly if these are on track. The tracking tool is an interactive, living document that will be updated every month.



## EMA recommends immediate suspension and recall of multiple sclerosis medicine Zinbryta

**March 7, 2018** – The EMA has recommended the immediate suspension and recall of the multiple sclerosis medicine Zinbryta (daclizumab beta) following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningo-encephalitis. Three of the cases were fatal. A preliminary review of the available evidence indicated that immune reactions observed in the reported cases may be linked to the use of Zinbryta.

To protect patients' health, EMA is recommending the immediate suspension of the medicine's marketing authorisation in the EU and a recall of batches from pharmacies and hospitals. Healthcare professionals should immediately contact patients currently being treated with Zinbryta and should stop their treatment and consider alternatives. Patients stopping treatment must be followed up for at least 6 months.

Zinbryta was authorised in 2016 for treating relapsing forms of multiple sclerosis. Following a 2017 review of the medicine's effects on the liver, the use of the medicine was restricted to



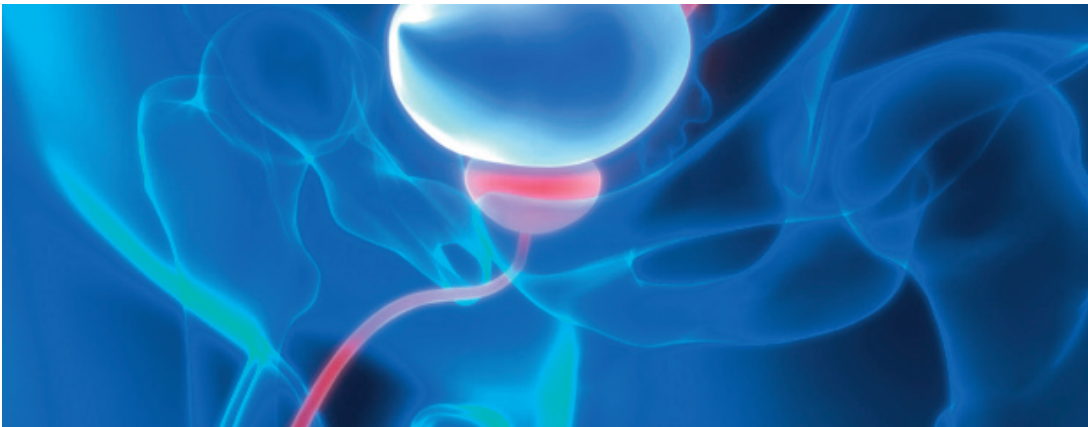
patients who have tried at least two other disease-modifying treatments and cannot be treated with any other multiple sclerosis treatments. To date over 8,000 patients have been treated with Zinbryta worldwide. The majority of EU patients have been treated in Germany.

To date EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed 12 cases of immune-mediated inflammatory disorders, including encephalitis. Most cases occurred within 8 months of starting treatment. A previous PRAC review in 2017 found that unpredictable and potentially fatal immune-mediated liver injury can occur with Zinbryta for up to 6 months after stopping treatment and concluded that patients stopping treatment should be followed up. Available evidence also

indicates that Zinbryta could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis or glomerulonephritis.

The review of Zinbryta was initiated following a request from the European Commission on February 26, 2018, under Article 20 of Regulation (EC) No 726/2004. EMA's recommendation to suspend Zinbryta and recall the product is being sent to the European Commission for a legally binding decision. The company that markets Zinbryta (Biogen Idec Ltd) has already voluntarily requested a withdrawal of the medicine's marketing authorisation and informed EMA of its intention to stop clinical studies. The initial review is being carried out by the PRAC, which will make a set of recommendations.

## Prostate cancer medicine Xofigo must not be used with Zytiga and prednisone/prednisolone



**March 9, 2018** – The EMA has recommended contraindicating the use of the prostate cancer medicine Xofigo (radium-223 dichloride) with Zytiga (abiraterone acetate) and prednisone/prednisolone, due to an increased risk of death and fractures with this combination.

EMA's PRAC has reviewed the preliminary data from an ongoing clinical study in metastatic prostate cancer patients. In this study 34.7% of patients treated with Xofigo, Zytiga and

prednisone/prednisolone have died so far, compared with 28.2% of patients given placebo, Zytiga and prednisone/prednisolone. Fractures have also occurred more frequently with the Xofigo combination than the placebo combination (26% versus 8.1%).

Xofigo is currently authorised for use in men whose prostate cancer has spread to the bones and is causing symptoms. The ongoing clinical study includes metastatic prostate cancer patients

who have not previously received chemotherapy and who have no symptoms or only mild symptoms, such as pain. Patients have completed the Xofigo part of the study, and the combination is no longer being used; all the patients involved are being monitored closely.

Healthcare professionals in the EU must not use a combination of Xofigo with the anti-androgen Zytiga and prednisone/prednisolone, and should stop this combination in

men currently treated with it and review the treatment for these patients. Healthcare professionals are also warned that the safety and efficacy of Xofigo in combination with a class of medicines called second generation androgen receptor antagonists, such as Xtandi (enzalutamide), have not been established.

These are temporary measures until the ongoing in-depth review of the benefits and risks of Xofigo is complete.