

News from the EMA

SECTION EDITORS



Section Editor:

Anuradha Alahari

Anuradha.Alahari@parexel.com



EMA contact:

Monika Benstetter

press@ema.europa.eu

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Increasing oversight of API manufacturing through international collaboration

April 12, 2018 – The European Medicines Agency's (EMA) and its European and international partners have successfully strengthened their interactions to improve the oversight of active pharmaceutical ingredient (API) manufacturers worldwide, as highlighted in the International API inspection programme report for 2011-2016, published today. APIs are the substances responsible for the activity of a medicine.

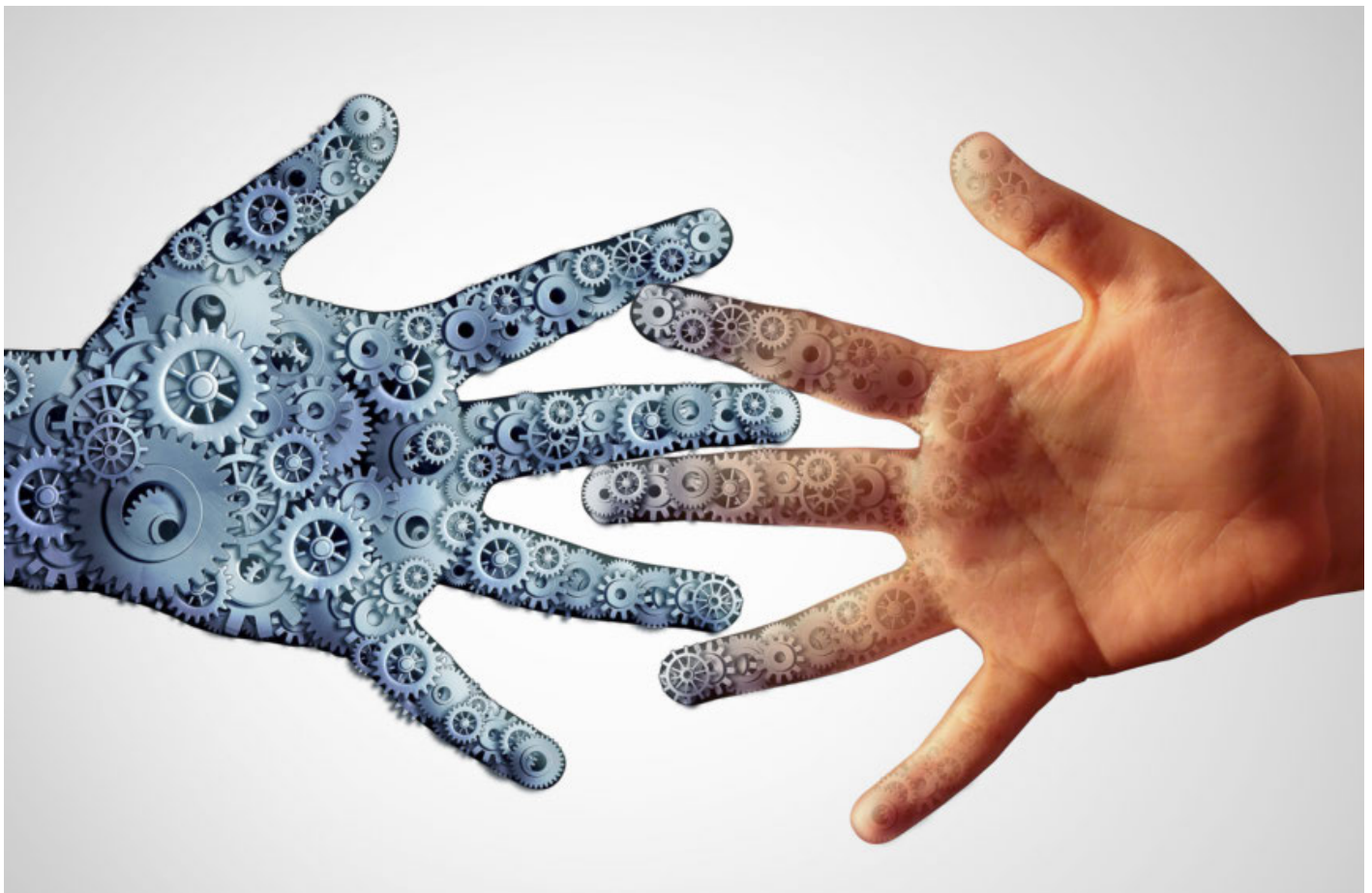
This international collaboration allows EMA, several European Union (EU) national authorities (France, Denmark, Ireland, Italy, and the United Kingdom), the European Directorate for the Quality of Medicines (EDQM), the United States Food and Drug Administration (FDA),

Australia's Therapeutic Goods Administration (TGA), Health Canada, the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), and the World Health Organization (WHO) to share information on good manufacturing practice (GMP) inspections of manufacturers of APIs that are located outside the participating countries.

Nowadays, many pharmaceutical companies outsource the production of APIs to contract manufacturers located all over the world. This has led to an increased need for inspections, to ensure adequate oversight of these facilities. The overall objective of this initiative is to ensure more sites are monitored by making best use of inspection

resources worldwide through increased co-operation, mutual reliance between participating regulatory bodies, reducing duplication of inspections and increasing inspection coverage.

The initiative started with a pilot in 2008–2010, and became a full programme in January 2011. The report published today gives an overview of the activities carried out by European authorities, the FDA, TGA, and WHO between 2011 and 2016. Over 6 years, 1,333 inspections were carried out at 458 manufacturing sites of common interest. These sites were located in 18 different countries, most of them in India (49%) and China (36%). The participating authorities have concluded that this programme is beneficial and agreed to continue their collaboration.





Two years of PRIME

May 7, 2018 – In the 2 years since its launch, the PRiority Medicines scheme (PRIME) of the EMA has succeeded in driving innovation and improved the efficiency of the development process in therapeutic areas with the most pressing unmet medical needs. The goal is to support and optimise medicine development, so that patients whose diseases cannot be treated or who need better treatment options have access to new medicines that enable them to live healthier lives.

Since the launch of PRIME in March 2016, EMA has received and assessed a total of 177 requests for eligibility to the scheme. Of these, 36 (21%) have been accepted. The agency has received requests across a wide range of therapeutic areas; oncology and haematology medicines make up the largest share, but there have also been notable submissions for medicines that cover indications in infectious

diseases, neurology and psychiatric disorders.

An overview of the 36 medicines accepted for PRIME shows the focus of the scheme on therapeutic areas where the availability of new medicines could be particularly beneficial: 83% concern rare diseases and 44% are intended to treat paediatric patients. 40% of the medicines admitted into PRIME are advanced therapy medicinal products (ATMPs), which have the potential to reshape the treatment of a wide range of conditions. A large proportion of these medicines are being developed by small and medium-sized enterprises (SMEs), who often lack experience in the regulatory approval process. 22 (61%) of the medicines accepted for PRIME have received scientific advice from the Agency

Two years on, the agency has already received the first three marketing authorisation applications for medicines that were accepted for

PRIME. They are all currently under evaluation with the first opinion expected later in 2018.

A key feature of the PRIME scheme is “kick-off” meetings – a unique type of meeting for medicines that are eligible for PRIME. The aim of the meetings is to agree on next steps on how best to address any identified issues and/or to identify issues to be discussed normally in the context of scientific advice. These multidisciplinary meetings bring together the rapporteur for the medicine as well as the chairs and experts of relevant EMA committees to ensure that all aspects of a medicine’s life cycle are discussed early, including risk management issues.

EMA has published new guidance for applicants on interactions in the context of PRIME which covers the preparation and conduct of kick-off meetings, questions and answers and the template for applicants’ requests.

Multiple sclerosis medicine Zinbryta no longer authorised as its risks outweigh its benefits

May 18, 2018 – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed that the multiple sclerosis medicine Zinbryta (daclizumab beta) poses a risk of serious and potentially fatal immune reactions affecting the brain, liver, and other organs. Patients could be at risk from the start of treatment and for several months after stopping treatment, and it is not possible to predict which patients will be affected.

Zinbryta was authorised in 2016 for treating relapsing forms of multiple sclerosis. To date over 10,000 patients have been treated with Zinbryta worldwide, of which the majority of EU patients were in Germany.

The review of Zinbryta was initiated following a request from the European Commission on February 26, 2018. On March 6, 2018, while the review was ongoing, EMA’s PRAC recommended suspension of the marketing authorisation of Zinbryta and a recall of the product. The European Commission issued a legally binding decision to suspend the marketing authorisation on March 8, 2018. On March 27, 2018, the European Commission withdrew the marketing



authorisation of the medicine at the request of the marketing authorisation holder (MAH) Biogen Idec Ltd.

Zinbryta is no longer authorised in the EU.

Healthcare professionals are expected to continue monitoring patients who have been treated with Zinbryta, in line with recommendations issued in March 2018.

Antisense oligonucleotide to treat a rare hereditary disease

June 1, 2018 – The EMA’s Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorisation in the EU for Tegsedi (inotersen), a medicine for treatment of stage 1 or stage 2 polyneuropathy (a condition in which the peripheral nerves are damaged) in patients with hereditary transthyretin amyloidosis (hATTR). Latter is a rare disease estimated to be diagnosed in approximately three cases per 10 million people in Europe yearly.

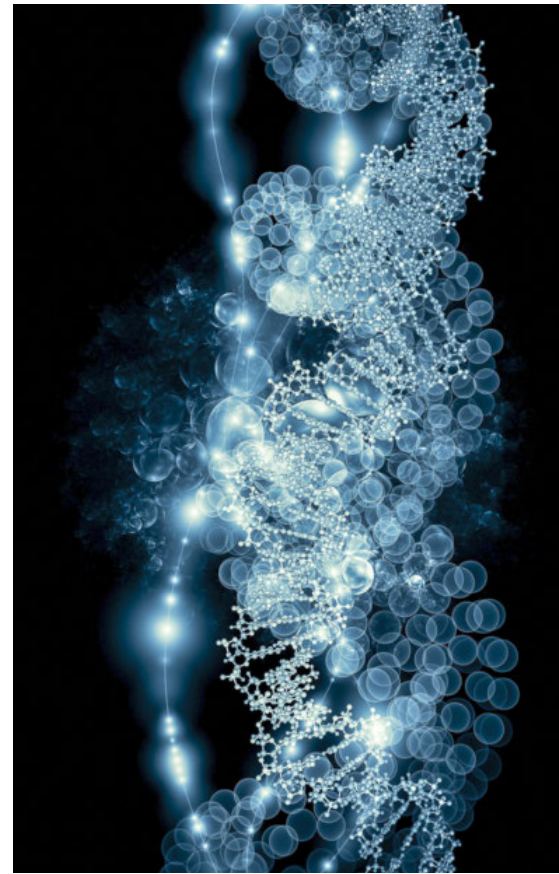
In patients with hATTR, a blood protein called transthyretin is defective and breaks easily. The broken protein forms a fibrous substance called amyloid that builds up in the peripheral nervous system and multiple organs, such as the gastrointestinal tract, kidney and heart, where it interferes with their normal functions.

Tegsedi is an “antisense oligonucleotide”, a very short piece of synthetic DNA designed to attach to the genetic material of the cells responsible for producing the transthyretin

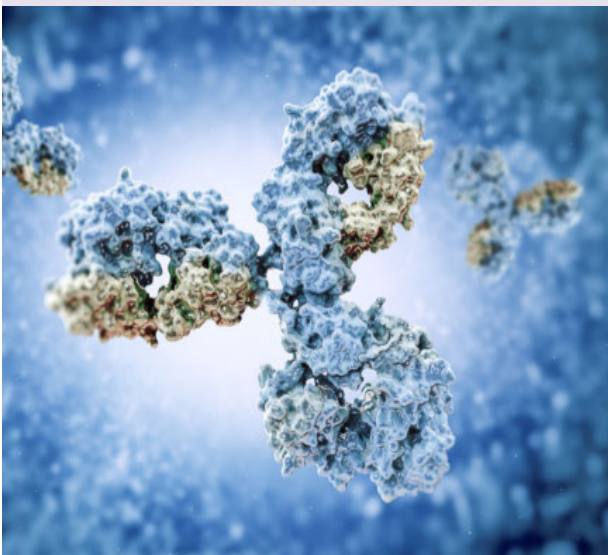
protein. This is expected to decrease transthyretin production, thereby reducing the formation of amyloids and relieving the symptoms of hATTR.

The effects of Tegsedi were evaluated in a study involving hATTR patients with stage 1 or stage 2 polyneuropathy, but not stage 3. The study showed clinically relevant effects on the neurological manifestations of the disease and on patients’ quality of life.

Tegsedi was designated as an orphan medicine in 2014. Current therapeutic options for hATTR are liver transplant, treatment with tafamidis and off-label use of a non-steroidal anti-inflammatory drug (NSAID). All of these have considerable limitations for patients with stage 2 and stage 3 polyneuropathy, meaning there is a clear unmet medical need. Therefore, the CHMP considered that Tegsedi is of major interest for public health and agreed to the applicant’s request for an accelerated assessment of this medicine.



Aimovig: First monoclonal antibody therapy for prevention of migraine recommended for marketing authorisation



June 1, 2018 – The EMA’s CHMP has recommended granting a marketing authorisation for Aimovig (erenumab), the first human monoclonal antibody therapy for prevention of migraine. Aimovig 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 European population 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 in women and has a strong genetic component.

There is no cure for migraine, but there are a number of treatments available both to tackle the symptoms and reduce the frequency of migraine days. However, existing prophylactic treatments

are frequently associated with variable efficacy and poor safety and tolerability. There is therefore an unmet medical need for new treatment options.

The benefits and safety of Aimovig were studied in two pivotal trials involving 667 patients with chronic migraine and 955 with episodic migraine. After 3 months of treatment, patients with chronic migraine showed a reduction of 2.5 monthly migraine days on average compared to placebo. For patients with episodic migraine the reduction was either 1.3 or 1.8 days, depending on the dose taken. The most common adverse events observed were injection site reactions, constipation, muscle spasms and pruritus.

Aimovig should only be taken by patients who have at least 4 migraine days a month. It is a solution for injection that is administered once a month. Patients can inject themselves after appropriate training.

The opinion adopted by the CHMP is an intermediary step on Aimovig’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.

First chimeric antigen receptor T-cells cell medicines recommended for approval in the European Union

June 29, 2018 – The EMA's CHMP has recommended granting a marketing authorisation for Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel), the first two chimeric antigen receptors (CAR) T-cells medicines in the EU. Kymriah and Yescarta are advanced therapies for blood cancer that belong to a new generation of personalised cancer immunotherapies that are based on collecting and modifying patients' own immune cells to treat their cancer.

Kymriah is indicated for the treatment of paediatric and young adult patients (up to 25 years of age) with B-cell acute lymphoblastic leukaemia that is refractory or in second or later relapse, and in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Yescarta is indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.

The main safety concerns related to the administration of CAR-T cells are cytokine release syndrome (CRS), which is a systemic

response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and neurologic toxicities. Both can be life-threatening and in some cases even fatal.

A risk management plan is an integral part of the marketing authorisation. Monitoring and mitigation strategies for these side effects are described in the product information. The CHMP recommended adding the treatment of CAR-T cell induced CRS as an indication for this medicine. Another important risk management measure for Kymriah and Yescarta is the utilisation of a patient registry to monitor the long-term safety and efficacy of these therapies, as a condition for the marketing authorisation. EMA has qualified a registry for collection of post-authorisation safety and efficacy data.

Kymriah and Yescarta are also the first medicines supported through EMA's PRIME scheme to receive positive opinions from the CHMP. Because Kymriah and Yescarta are ATMPs, they were assessed by the CHMP and the CAT, the agency's expert committee for cell, gene- or tissue-based medicines which is responsible for the evaluation of these products.

Hydroxyethyl starch solutions to remain on the market conditionally

June 29, 2018 – Hydroxyethyl starch (HES) solutions for infusion are used to replace plasma volume following acute blood loss, where treatment with alternative products known as 'crystalloids' alone is not considered sufficient. HES belong to the class of medicines known as 'colloids' and are blood volume expanders to prevent a dangerous drop in blood pressure following acute bleeding.

In the EU, HES solutions for infusion have been approved via national procedures and are available in the Member States under various trade names. In January 2018, EMA's safety committee PRAC recommended suspending the marketing authorisations of these medicines because they continued to be used in critically ill patients and patients with sepsis despite restrictions introduced in 2013 due to the risk of kidney injury and death in these patients.

The CMDh, which is a medicines regulatory body representing

Iceland, Liechtenstein and Norway, has now decided that HES solutions for infusion should remain on the market provided that a combination of additional measures to protect patients is implemented. The CMDh agreed with the PRAC's assessment, however, the CMDh gave further consideration to the place of HES in the clinical practice of some countries, noted that previous risk minimisation measures had some

effect, and considered that a combination of new risk minimisation measures would effectively ensure that HES solutions are not used in patients at risk.

The new measures are:

- Implementation of a controlled access programme by MAHs to ensure that only accredited hospitals will be supplied with these medicines. The accreditation would require that relevant healthcare professionals receive training on the safe use of

HES solutions for infusion.

- Warnings in the medicines' packaging and at the top of the summaries of product characteristics (SmPCs) reminding healthcare professionals that these medicines must not be used in patients with sepsis or kidney impairment or in critically ill patients.
- Writing directly to healthcare professionals to ensure that they are fully aware of the conditions of use of the medicines and the groups of patients that must not receive them due to an increased risk of kidney injury and death.

The CMDh also requested MAHs to conduct studies to check that only patients who should be treated with these medicines are receiving them. This is in addition to ongoing studies on the benefits and risks of HES solutions in patients with trauma and those undergoing elective surgery.

The CMDh position was adopted by majority vote and the matter will now be sent to the European Commission, which will take an EU-wide legally binding decision.

