

News from the EMA

SECTION EDITORS



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The articles included in this section are a selection from the European Medicines Agency (EMA)'s News and Press Releases archive from October 2018 to December 2018. More information can be found on the Agency's website: www.ema.europa.eu

Restrictions on the use of fluoroquinolone and quinolone antibiotics recommended



October 5, 2018 and November 16, 2018 – Fluoroquinolones and quinolones are a class of broad-spectrum antibiotics that are active against bacteria of both Gram-negative and Gram-positive classes. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the disabling and potentially permanent side effects with these medicines given by mouth, injection or inhalation, and recommended restricting their use. The review incorporated the views of patients, healthcare professionals and academics presented at EMA's public hearing on fluoroquinolone and quinolone antibiotics in June 2018.

The serious side effects reported with fluoroquinolones and quinolones include inflamed or torn tendon, muscle pain or weakness, and joint

pain or swelling; walking difficulty, feeling pins and needles, burning pain, tiredness, depression, problems with memory, sleeping, vision and hearing, and altered taste and smell. Tendon swelling and injury may occur within 2 days of starting treatment with a fluoroquinolone or may even occur several months after stopping treatment.

The PRAC review covered the following fluoroquinolone antibiotics: ciprofloxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin; and quinolone antibiotics: cinoxacin, nalidixic acid, piperidic acid.

The PRAC recommended that some of the medicines, including all those that contain a quinolone antibiotic, should be removed from

the market. This is because they are authorised only for infections that should no longer be treated with this class of antibiotics. EMA's human medicines committee (CHMP) has now endorsed the PRAC recommendations and concluded that the marketing authorisation of medicines containing flumequine or quinolones should be suspended.

Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Importantly, fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU countries.



First treatment for rare inherited muscle contraction disorders

October 19, 2018 – EMA has recommended granting a marketing authorisation for Namuscla (mexiletine hydrochloride) for the treatment of adult patients with non-dystrophic myotonia, a group of inherited muscle disorders where muscles are slow to relax after contraction. These disorders are chronic life-long debilitating conditions characterised by pain, fatigue, and muscle stiffness, resulting in frequent falls and disability.

This is the first time that a treatment for certain forms of myotonic disorders could be authorised EU-wide. The active substance mexiletine has been approved for treatment of these disorders in France only since 2010. Non-dystrophic myotonia is caused by abnormalities in the ion channels, tiny pores in the muscle cells that control the passage of charged particles (ions) such as sodium or chloride and play a key role in the contraction and relaxation of muscles.

Mexiletine is a known antiarrhythmic medicine (used to restore normal heart rhythm), which was first authorised in Europe in the 1970s. It works by blocking ion channels for sodium ions in

muscle cells. These sodium channels play a role in the contraction and relaxation of muscles and by blocking them, the medicine helps to reduce the rate of contractions as well as the stiffness that occurs when the contractions are prolonged.

The opinion from the Committee for Medicinal Products for Human Use (CHMP) is based on data from one phase 3 clinical trial in patients with non-dystrophic myotonia as well as data from the literature. These data show that treatment with mexiletine allows relieving stiffness in the muscles. The medicine's safety profile is well-established; the most common unfavourable effects with this medicine were gastrointestinal disorders, such as heartburn, nausea, vomiting, diarrhoea and abdominal pain. Another less frequently occurring side effect of mexiletine is that it can also trigger arrhythmia or aggravate an existing arrhythmia; the CHMP therefore agreed on specific measures to minimise this risk such as certain contraindications and cardiac monitoring.



Namuscla was designated as an orphan medicinal product in November 2014. As always at time of approval, EMA's Committee for Orphan Medicinal Products will review the orphan designation to determine whether the information available to date allows maintaining Namuscla's orphan status.

First vaccine for prevention of dengue

October 19, 2018 – EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended granting marketing authorisation for Dengvaxia, a live, attenuated dengue tetravalent vaccine, for the prevention of dengue caused by dengue virus serotypes 1, 2, 3 and 4 in people who are between 9 and 45 years old, live in an endemic area and already had a prior dengue virus infection.

Dengue is by far the most common mosquito-borne viral disease affecting people worldwide (mainly in tropical areas); tens of millions of cases occur each year resulting in approximately 20,000-25,000 deaths, mainly in children. Dengue is caused by a virus which is transmitted by *Aedes* mosquitoes, a type of mosquito that is widely spread in tropical and subtropical regions. Most people who contract the disease experience mild, influenza-like symptoms. However, around 2% of people affected will develop severe dengue, a potentially lethal complication that includes dengue haemorrhagic fever and/or dengue shock syndrome. Main risk factors for severe dengue include young age and chronic diseases. Secondary infection, in the form of two sequential infections by different serotypes, is

also a risk factor for severe disease.

There are four types of dengue virus and people living in a dengue endemic area can have several dengue infections in their lifetime. No specific treatments for dengue exist and prevention is mainly limited to the environmental management of mosquitoes. There is currently no vaccine available for dengue in the EU.

The approved indication excludes the populations of the EU mainland and territories outside tropical areas since dengue is not endemic in these regions. However, a number of EU territories, mainly overseas, are situated in endemic areas, and these territories could benefit from this vaccine.

The benefits and safety of Dengvaxia have been evaluated in 31 clinical studies conducted mostly in dengue endemic areas (Latin America and Asia Pacific). Together, these trials included over 41,000 participants

aged 9 months to 60 years receiving at least one dose of the vaccine. The overall available data demonstrate that for people between 9 and 45 years of age, the vaccine has positive effects in preventing symptomatic and severe dengue disease in people who have had previous dengue infection and live in endemic areas. In people who have never had dengue, there is an increased risk of clinically severe dengue disease leading to hospitalisation when vaccinees are subsequently infected with dengue virus. The CHMP therefore recommends limiting the use of the vaccine to individuals with prior dengue virus infection, for whom laboratory confirmation of the previous infection is available before vaccination. In addition, because there are no safety, immunogenicity or efficacy data to support vaccination of individuals living in non-endemic areas and travelling to endemic areas, vaccination of these individuals is not recommended.

A number of additional risk minimisation measures will be put in place, such as educational material for physicians and a guide for healthcare professionals. Use of the vaccine should be according to official recommendation from Member States.



CHMP recommends first oral-only treatment for sleeping sickness

November 11, 2018 – EMA's human medicines committee (CHMP) has adopted a positive opinion for Fexinidazole Winthrop (fexinidazole), the first oral-only medicine (tablets) for the treatment of human African trypanosomiasis (HAT), commonly known as sleeping sickness, due to *Trypanosoma brucei gambiense*.

HAT is a life-threatening, neglected tropical disease that is endemic in sub-Saharan Africa. There are two forms of sleeping sickness, depending on the parasite involved: *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense*. The vast majority (98%) of reported cases are caused by *T. b. gambiense*. Most cases occur in the Democratic Republic of the Congo, with the remainder located in bordering central African countries.

HAT caused by *T. b. gambiense* is characterised by a more chronic disease evolution. Within a few weeks of infection, patients can experience bouts of fever, headaches, joint and muscle pains and itching. Over time the disease invades the central nervous system. Patients display neurological signs including mental confusion, slurred speech, seizures, difficulty in walking and talking and worsening sleep disturbances. If left untreated, the disease is usually fatal within a time span of two to three years.

Currently therapy is selected based on how much the central nervous system is affected. Treatments include intra-

muscular injections of pentamidine, which are painful and only adequate for the earlier stage of the disease. Other treatments are available, e.g., a combination of oral nifurtimox and intravenous infusion of eflornithine (NECT) as reference therapy when the disease has advanced and affects the central nervous system. However, all these treatments require a minimum health infrastructure and personnel, not readily available in some remote areas.

Fexinidazole Winthrop, as an exclusively oral treatment regimen for the disease, could potentially allow quicker and wider access to treatment because distribution and administration of tablets is easier. It was developed by the applicant in partnership with the Drugs for Neglected Diseases initiative, a non-profit drug research and development organisation based in Switzerland.

The benefits and safety of Fexinidazole Winthrop were evaluated in three clinical studies involving 749 patients across the different stages of the disease. The studies showed high cure rates in patients after ten days of treatment, especially in the earlier stage of the disease. However, for patients whose central nervous system is already severely affected, Fexinidazole should only be

given under strict supervision in hospital when no other adequate treatment is available or tolerated. The most common side effects observed were vomiting, nausea, headache, insomnia, weakness, dizziness and tremor.

Because there were a small number of cases of late relapse in the studies, the CHMP recommends a follow-up monitoring of up to 24 months to ensure the surveillance of potential relapses. All eligible patients should receive Fexinidazole under supervision of trained healthcare staff to ensure full compliance.

Fexinidazole Winthrop was submitted to EMA under a regulatory procedure (Article 58) which allows the Agency to assess the quality, safety and efficacy of a medicine and give an opinion on its benefit-risk balance when used in low- and middle-income countries outside the EU. Medicines submitted under this programme are assessed by EMA in collaboration with the World Health Organization. They must meet the same standards as medicines intended for EU citizens. This is the tenth medicine recommended by EMA under Article 58.

The scientific opinion from the CHMP helps to support regulators in countries where regulatory capacity may be limited, by providing an expert evaluation of the medicine when used in local practice. National regulators can use the CHMP's scientific assessment to decide on the use of the medicine in their countries.



EMA gives guidance on safety monitoring of medicines used in children



November 30, 2018 – EMA has published the new good pharmacovigilance practice (GVP) chapter IV on specific considerations for the paediatric population. It offers a holistic view of paediatric pharmacovigilance and provides guidance on how to make best use of existing tools and processes to address the specific needs and challenges of safety monitoring of medicines used in children. In addition, it advises on how to adapt regulatory requirements to the paediatric population in the European Union.

The new GVP chapter covers approved medicines with a paediatric indication or with an ongoing paediatric development, but also medicines only approved for adults when they are used off-label to treat children, i.e., for a medical purpose not in accordance with the terms of the marketing authorisation.

A dedicated approach to pharmacovigilance in children is especially important given that paediatric clinical trials are often limited in size and duration, and adverse reactions in children



Revised guideline to assess risk of human medicines for the environment

November 30, 2018 – EMA has published a revision of its guideline on the environmental risk assessment (ERA) of human medicines for a 6-month public consultation. Stakeholders are invited to send their comments by June 30, 2019, to era_dg@ema.europa.eu using the template provided.

The presence of biologically-active pharmaceuticals in the environment is a growing concern, because some of these substances have shown direct effects on wildlife at or below the concentrations found in water and soil. For example, male fish exposed to the main ingredient in the contraceptive pill may become feminised and this can affect the capacity of the population to reproduce. Pharmaceuticals may also have indirect effects, e.g., a recent study shows that pharmaceutical compounds detected in surface waters can transfer from invertebrate larvae to the predators that feed on them.

Human medicines may enter the environment during their manufacture, use and disposal. The ERA is based on the use of the product and the physico-chemical, ecotoxicological and fate

properties (degradation, persistence) of its active substance.

Environmental risk assessment of medicines ensures that the potential effects of pharmaceuticals on the environment are studied and that adequate precautions are taken in case specific risks are identified. Performing an ERA is mandatory for any pharmaceutical company submitting a marketing authorisation application for a medicine, regardless of the type of medicine. Appropriate details are included in the European Public Assessment Report of approved medicines, so that this information is available to the public.

The revision of EMA's guideline on ERA introduces a decision tree clarifying when ERA studies are required and provides more detailed technical guidance to applicants to increase the consistency of the assessments. One of the most notable changes introduced in the proposed revision is the introduction of the term 'endocrine active substances', to include all compounds that affect development or reproduction. Additionally, guidance is provided

for the estimation of the exposure of predators to pharmaceuticals through the food chain ('secondary poisoning'), as well as directly through the environment. The revision also proposes to limit the use of a laboratory test method – the Organisation for Economic Co-operation and Development (OECD) 308 environmental fate test to certain categories of substances and this will reduce the burden of testing on applicants.

The revision of the ERA guideline is based on a concept paper issued in 2014 and the work of a group of experts led by the Safety Working Party of EMA's CHMP. It builds on the twelve years of experience gained since the original guideline was published and aims to facilitate the work for both applicants and regulators in the interest of environmental protection.

In the interest of animal welfare, the guideline encourages applicants to share data generated for the ERA, implementing the principles of 3Rs (Replacement, Reduction and Refinement) – in accordance with Directive 2010/63/EU to avoid unnecessary repetition of studies.

may substantially differ – in terms of frequency, nature, severity and presentation – from those occurring in adults.

The guidance focuses on aspects of pharmacovigilance of particular relevance to the use of medicines in children, such as off-label use and medication errors, and contains paediatric-specific guidance on all major pharmacovigilance tools and processes, including risk management plans, periodic safety update reports, post-authorisation safety studies, signal management

and safety communication.

It also highlights the need to include comprehensive information in adverse drug reaction reports, such as the child's age, weight and height, as well as, the indication or intention of use of the medicine, including its strength, dose and pharmaceutical form. This is important for all actors involved in safety reporting of medicines in children, including pharmaceutical companies, sponsors of clinical studies and regulatory authorities, but also

parents/carers, healthcare professionals, patient and healthcare professional organisations, and organisations of national healthcare systems.

The new GVP chapter was finalised after careful consideration of the extensive feedback received during a public consultation, and replaces EMA's human medicines committee's (CHMP) 2007 guideline on conduct of pharmacovigilance for medicines used by the paediatric population.