

News from the EMA

SECTION EDITORS



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New safety features for medicines sold in the European Union

February 8, 2019 – As of February 9, 2019, most prescription medicines and some over-the-counter medicines for human use supplied in the European Union (EU) are required to have a unique identifier (a two-dimension barcode) and an anti-tampering device on their outer packaging. The anti-tampering device is a safety feature that shows whether the packaging has been opened or altered since it left the manufacturer, thereby ensuring that the content of the packaging is authentic. These mandatory safety features are a key measure of the Falsified Medicines Directive which is part of the EU's strategy to strengthen the security of the supply chain of medicines.

Falsified medicines are fake medicines that are passed off as real, authorised medicines. In June 2011, the EU strengthened the protection of patients and consumers by adopting a new Directive on falsified medicines for human use. The Directive introduced new harmonised, pan-European measures, structured around four pillars:

1. Tougher rules on import of active substances;
2. Strengthened supply chain and requirements for wholesale distributors;
3. A common, EU-wide logo to identify legal online pharmacies;

4. Obligatory safety features (i.e. the unique identifier and an anti-tampering device on the outer packaging of medicines).

The fourth pillar on safety features was the final aspect of the Falsified Medicines Directive to be addressed, and this safety feature has now become mandatory.

The safety features are implemented through a delegated regulation that comes into application on 9 February 2019. It will apply in all EU/European Economic Area (EEA) Member States, except for Greece and Italy, who have until 2025 to update their already existing tracking systems.

The safety features will help protect European citizens against the threat of falsified medicines, which may contain ingredients, including active ingredients, which are of low quality or in the wrong dosage and could potentially put patients' health at risk. The unique identifier and the anti-tampering device on the packaging of the medicines will guarantee medicine authenticity for the benefit of patients and will strengthen the security of the medicine supply chain, from manufacturers to distributors to pharmacies and hospitals.

Manufacturers will upload the information contained in the unique identifier for each individual medicine to a central EU repository. The repository is part of an end-to-end medicines verification system introduced by the regulation. Depending on the source of the medicine, wholesalers will also need to scan medicines at different points in the supply chain to verify their authenticity. Pharmacies and hospitals will then scan each medicine at the end of the supply chain to verify their authenticity and check them out from the repository before dispensing them to patients. Although the safety features are now a legal requirement, medicines that were released for sale or distribution without the safety features before 9 February can still be dispensed.

Also, a new reporting form is available on European Medicines Agency (EMA)'s website to be used by pharmaceutical companies when notifying EMA of any suspected falsification of their centrally authorised medicines. The new form is specifically for notifications related to suspected and confirmed falsified medicines and suspicious offers and is an important step in streamlining processes for reporting and investigating falsifications of centrally authorised medicines.

European Union and Switzerland to improve information-sharing on good manufacturing practice through use of EudraGMDP database

February 21, 2019 — The Swiss Agency for Therapeutic Products (Swissmedic) has started in 2019 to enter information on Good manufacturing practice (GMP) compliance as well as on manufacturing authorisations related to Swiss manufacturers into the EU's EudraGMDP database. This applies for all new or renewed manufacturing authorisations and the related GMP certificates issued using new templates (similar to those of EMA). This will allow replacing the current practice of issuing paper documents, i.e. GMP certificates for certain regulatory procedures and therefore should lead to easier information-sharing and efficiency gains for all stakeholders.

The EudraGMDP database is the EU's database on manufacturing, import and wholesale-distribution authorisations, and GMP and Good distribution practice (GDP) certificates. A public version of the database has been available since 2011 and gives public access to the information in the database that is not commercially confidential or contains personal data. This

means that the GMP compliance status of manufacturing facilities can be readily verified online by all stakeholders, including importers, manufacturers and regulatory authorities.

This latest development is part of the mutual recognition agreement (MRA) between the EU and Switzerland, operational since June 2002 and most recently updated in August 2017. The latest amendment introduced the provisions on data entry to EudraGMDP by the Swiss authorities. Swissmedic has 'read and write' access to the data base and will be entering GMP compliance information on Swiss manufacturers, including those exporting to the EU. As a consequence, the regulatory requirement to provide original paper GMP certificates issued by EU or Swiss authorities will be replaced by either the provision of a reference to an entry in EudraGMDP or by means of a downloadable file or printout from the data base.

The details of the specific applicability of this measure depend on the respective regulatory procedures, e.g., as regards importation or



marketing authorisation, and are clarified in relevant notices of each party. In cases where a certificate of GMP compliance cannot be accessed via the EudraGMDP database, the document will have to be requested following the "traditional" procedures directly from the competent authority which inspected the manufacturer in question.

EMA offers 'read and write' access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA. Since 2013, the Japanese authorities also enter data into EudraGMDP which allows waiving the need for paper GMP certificates for certain procedures.

New add-on treatment for patients with severe asthma

March 1, 2019 – EMA's human medicines committee (CHMP) has recommended granting an extension of indication to Dupixent (dupilumab) as an add-on maintenance treatment for adult and adolescent (12 years and older) patients with certain forms of severe asthma.

Asthma is a chronic lung disease caused by the interaction of genetic and environmental factors. It causes airways to narrow and swell and

to produce mucus. The main symptoms are coughing, wheezing, shortness of breath but severe asthma attacks can even lead to hospitalisation. Currently, there is no cure for asthma and treatments available are used to control the symptoms (reliever) or to reduce the frequency and severity of the attacks (controller). Therapeutic options are limited for patients with severe asthma whose symptoms cannot be controlled with the available treatments such as high dose inhaled corticosteroids.

Dupixent is a human monoclonal antibody that reduces inflammation observed in the airways through inhibition of the signalling of two key proteins (interleukin-4 and interleukin-13). This represents a novel mechanism of action to the available therapeutic options in severe asthma patients. Dupixent is already approved in the EU for adult patients with atopic dermatitis who are candidates for systemic therapy. The CHMP's opinion recommends to extend the indication to add-on maintenance treatment for adult and adolescent (12 years and older) severe asthma patients with type II inflammation characterised

by increased blood eosinophils and/or raised exhaled nitric oxide measured by FeNO test and inadequately controlled by inhaled high dose corticosteroids plus another asthma medicinal product.

The benefits and safety of Dupixent have been studied in three pivotal trials including a total of 2,888 patients. In the clinical trials conducted, Dupixent demonstrated benefit to patients by reducing severe asthma exacerbations and improving lung function. The most common side effects of Dupixent are infections, eye disorders (conjunctivitis and related conditions) and injection site reactions.

The opinion adopted by the CHMP at its February 2019 meeting is an intermediary step on Dupixent's path to patient access in this new indication. 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.



First treatment for rare disease characterised by high levels of triglycerides in blood



March 1, 2019 – EMA has recommended granting a conditional marketing authorisation (CMA) for Waylivra (volanesorsen), the first medicine for the treatment of the familial chylomicronaemia syndrome (FCS). FCS is a rare genetic disease that prevents the body from breaking down fats (lipids). Patients with this condition have extremely high levels of triglycerides in their blood. This causes a range of symptoms including for instance severe abdominal pain, potentially fatal attacks of acute pancreatitis, hepatosplenomegaly, diabetes, lack of concentration, memory loss and fat-filled spots on the skin (called xanthomas).

There is currently no authorised medicine available to treat this rare disease. Patients need

to strictly limit their fat intake through diet, but this is not always feasible and sufficiently effective to reduce the level of triglycerides and prevent pancreatitis. Existing lipid-lowering medications are only minimally effective to reduce triglyceride levels in patients with FCS and there is an urgent unmet medical need for new treatments to help patients to manage this disease.

The benefits and safety of Waylivra were investigated in a phase III clinical study involving 66 patients with FCS. Data from this study showed that levels of triglycerides in the blood of patients treated with Waylivra decreased on average by 77% after 3 months' treatment, compared to an increase of 18% in the placebo-receiving control group. The observed substantial

reduction in levels of triglycerides is expected to lead to a reduction in the incidence of potentially life-threatening pancreatitis. The most common side effects are reduced platelet counts and injection site reactions. A number of cases of severe platelet reduction were observed in the Waylivra trials, which may result in an increased risk of bleeding. To manage this risk, a number of additional risk minimisation measures will be implemented including strict dosing guidance based on regular platelet monitoring and specific information to patients and their carers on this potential risk. As part of the CMA, the applicant is also required to conduct a study that further investigates the safety and efficacy of the medicine and the feasibility of implemented risk minimisation measures.

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

FCS was granted an orphan designation in the EU in February 2014. At the time of orphan designation, it was considered that the condition affected less than 1 in 100,000 persons. As always at the 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 Waylivra's orphan status and granting this medicine ten years of market exclusivity.

EMA confirms omega-3 fatty acid medicines are not effective in preventing further heart problems after a heart attack

March 29, 2019 – EMA has confirmed that omega-3 fatty acid medicines containing a combination of an ethyl ester of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a dose of 1 g per day are not effective in preventing further problems with the heart and blood vessels in patients who have had a heart attack. This is the outcome of a re-examination requested by some of the companies that market the medicines

concerned, following EMA's original recommendation in December 2018. This means that these medicines should no longer be used in this way. However, they can still be used to reduce levels of certain types of blood fat called triglycerides.

The review concerned omega-3 fatty acid medicines containing a combination of EPA and DHA and focused on the medicines' use in patients who have had a heart attack. EPA and

DHA are commonly found in fish oils. Omega-3 fatty acid medicines are taken by mouth and have been authorised for use after a heart attack in combination with other medicines, in several EU countries since 2000, at a dose of 1 g per day. At the time of their authorisation, available data showed some benefits in reducing serious problems with the heart and blood vessels.

EMA's committee for human medicines, CHMP, has re-assessed the evidence

New add-on treatment to insulin for treatment of certain patients with type 1 diabetes

March 1, 2019 – EMA's human medicines committee (CHMP) has adopted a positive opinion for Zynquista (sotagliflozin) intended as an adjunct to insulin for certain patients with type 1 diabetes mellitus. Zynquista is a small molecule with dual inhibitor activity on SGLT1 and SGLT2. It works in the kidneys to prevent reabsorption of glucose from the urine and in the proximal intestine to delay and reduce glucose absorption into the blood stream, which helps lower the blood sugar level. This medicine is the second SGLT inhibitor for the treatment of type 1 diabetes to be recommended for authorisation.

Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus who have failed to achieve adequate glycaemic control despite optimal insulin therapy. Patients considered for this treatment should fulfill certain requirements and should have a body mass index (BMI) higher than 27 kg/m².

Type 1 diabetes is an autoimmune disease in which the immune system mistakenly attacks the insulin-producing beta cells in the pancreas. Without insulin, the body cannot maintain proper blood glucose levels. Patients with type 1 diabetes require lifelong insulin therapy.

In spite of improvements in insulin, its methods of administration and monitoring of blood glucose, a proportion of patients with the disease are unable to achieve or maintain recommended blood sugar levels with insulin alone. Hyper- and hypoglycaemia and weight gain are common and patients' life expectancy is still significantly reduced compared to the general population, mainly due to the increased risk of heart disease. Thus, there is a need for new

therapies as an adjunct to insulin therapy, to better manage blood sugar levels and other cardiovascular risk factors.

The CHMP's positive opinion is based on data from three phase 3 studies including 1,853 patients with type 1 diabetes mellitus. The main benefit of treatment with sotagliflozin in patients with type 1 diabetes is its ability to improve glycaemic control. Other effects include weight and blood pressure reductions and reduced variability of glucose levels.

Despite precautionary measures during treatment with sotagliflozin, there is a considerable increase in the risk of diabetic ketoacidosis (DKA), a potentially life-threatening complication. Because the increased risk is of concern,

the CHMP recommends limiting the use in type 1 diabetes mellitus patients as follows: treatment should only be considered in overweight or obese patients with a BMI higher than 27 kg/m². Use of Zynquista is not recommended in type 1 diabetes mellitus patients with low insulin requirements. During treatment with Zynquista, insulin therapy should be continuously optimised to prevent ketosis and DKA and the insulin dose should only be reduced to avoid hypoglycaemia. This treatment should only be initiated and supervised by specialist doctors. Patients should be able and committed to control ketone levels in their body. They should be educated about risk factors for DKA and how to recognise its signs and symptoms.



accumulated over the years on these medicines for this specific use and consulted additional experts in the field. It concluded that, although there are no new safety concerns, the effectiveness of these medicines in preventing recurrence of problems with the heart and blood vessels has not been confirmed. EMA concluded that the marketing authorisations of these medicines should be updated to remove this use.

