News from the EMA

SECTION EDITOR

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EMA recommendations on testing for the enzyme dihydropyrimidine dehydrogenase prior to treatment with fluorouracil, capecitabine, tegafur, and flucytosine

April 30, 2020 – EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur. Patients who completely lack DPD must not be given any fluorouracil medicines. For patients with partial deficiency, the doctor may consider starting cancer treatment at lower doses than normal or stopping flucytosine treatment, if severe side effects occur. These recommendations do not apply to fluorouracil medicines used on the skin for conditions such as actinic keratosis and warts, as only very low levels of the medicine are absorbed through the skin.

A significant proportion of the general population has a deficiency of DPD, which is needed to break down fluorouracil and the related medicines capecitabine, tegafur and flucytosine. As a result, following treatment with these medicines, fluorouracil can build up in their blood, leading to severe and life-threatening side effects such as neutropenia (low levels of neutrophils, a type of white blood cells needed to fight infection), neurotoxicity (damage to the nervous system), severe diarrhoea and stomatitis (inflammation of the lining of the mouth).

Patients can be tested for DPD deficiency by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations in the gene for DPD. Relevant clinical guidelines should be taken into consideration. Therapeutic drug monitoring of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions.

Fluorouracil given by injection or infusion and its prodrug medicines (capecitabine and tegafur) are used to treat various cancers. They work by interfering with enzymes involved in making new DNA, thereby blocking the growth of cancer cells. Fluorouracil applied to the skin is used for various skin conditions such as actinic keratosis and dermal warts.

Flucytosine is related to fluorouracil and is used to treat severe yeast and fungal infections, including some forms of meningitis (inflammation of the membranes that surround the brain and spinal cord). As treatment for severe fungal infections should not be delayed, the pre-treatment testing for DPD deficiency (which may take up to one week) is not required in these cases. Nevertheless, treatment with flucytosine is contraindicated in patients with known complete DPD deficiency due to the risk of life-threatening toxicity. In case of drug toxicity, consideration should be given to stopping treatment with flucytosine. Determination of DPD activity may be considered where drug toxicity is confirmed or suspected.

The review concerned fluorouracil medicines given by injection or applied to the skin as well as medicines containing capecitabine and tegafur taken by mouth (so-called fluorouracil prodrugs), which are converted to fluorouracil in the body. It also includes the antifungal medicine flucytosine which is given by injection or by mouth and some of which is converted into fluorouracil in the body. The review was initiated March 2019 at the request of the French Medicines Agency (ANSM). The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

EMA commissions independent research to prepare for real world monitoring of COVID-19 vaccines

May 27, 2020 – EMA is engaging early with researchers to ensure that a European infrastructure will be in place to effectively monitor COVID-19 vaccines in the real world, once these are authorised in the European Union. The Agency has signed a contract with Utrecht University as coordinator of the EU Pharmacoepidemiology and Pharmacovigilance Research Network, a public-academic partnership of 22 European research centres, to conduct preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice. The ACCESS (vACcine Covid-19 monitoring readinESS) project will be led by the University Medical Center Utrecht (UMCU) and Utrecht University.

To authorise any COVID-19 vaccine, EMA will need to have strong evidence from clinical trials on the safety, efficacy and the quality of this vaccine. Once on the market, approved vaccines will be monitored closely, by the Agency and its PRAC, through planned and routine pharmacovigilance activities, including the spontaneous reporting of suspected side effects reported by patients and healthcare professionals through Eudravigilance, the European database of suspected adverse reactions to medicines. The infrastructure put in place by Utrecht University will provide additional information from clinical practice to complement data collected pre-authorisation through clinical trials and post-authorisation through spontaneous reporting.

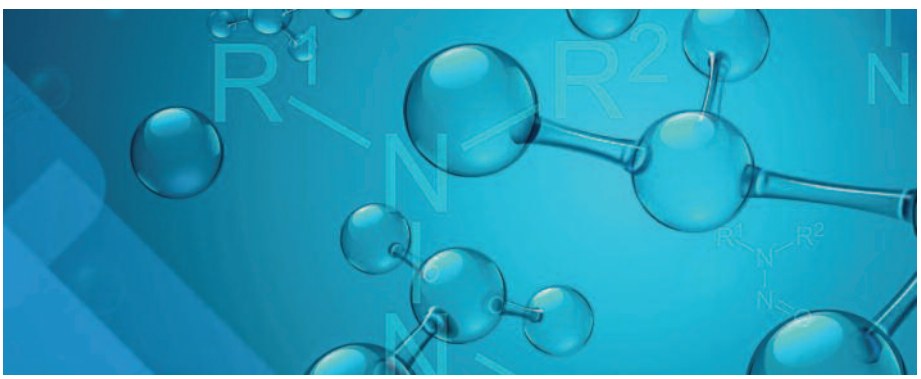
The researchers will identify a Europe-wide network of data sources (including health insurance records, GP and hospital health records) and examine their utility in monitoring the coverage, safety and effectiveness of COVID-19 vaccines. The commissioned research will also identify possible adverse events of special interest that might need extra consideration in the monitoring of COVID-19 vaccines.

The research commissioned by EMA will be complemented by international collaboration on COVID-19 vaccine monitoring as agreed by the International Coalition of Medicines Regulatory Authorities (ICMRA) at its meeting on 19 May 2020. First deliverables of the commissioned research are planned for August 2020 with a final delivery by the end of the year.

European regulators make recommendations drawing on lessons learnt from presence of nitrosamines in sartan medicines

June 23, 2020 – The European medicines regulatory network has issued recommendations on impurities in medicines following the conclusion of an exercise to draw on lessons learnt from the presence of nitrosamines in a class of blood pressure medicines known as sartans. Although the exercise focused on nitrosamines in sartans, the recommendations will help reduce the risk of impurities being present in other medicines and ensure that regulators are better prepared to manage cases of unexpected impurities in the future.

The recommendations aim to clarify the roles and responsibilities of companies involved in the manufacture of medicines and to amend guidance on controlling impurities and good manufacturing practice. The recommendations also cover the management of impurities once detected, communication with patients and healthcare professionals, and international cooperation. The full recommendations are on EMA's website.



Nitrosamines are classified as probable human carcinogens (substances that could cause cancer) based on animal studies. The network noted that nitrosamines were not previously recognised as potential impurities in sartan medicines, and these recommendations will help both regulators and companies better prevent and mitigate the risks of these and other impurities in the future.

Regulators in the EU first became aware that nitrosamines were present in some sartan medicines in mid-2018. The discovery led to swift regulatory action, including the recall of medicines and measures to stop the use of active substances from certain manufacturers. A subsequent EU review, which concluded in April 2019, established the sources of nitrosamines and set out new manufacturing requirements for sartans. In September 2019, EMA launched an Article 5(3) procedure to provide additional guidance to companies that make and market medicines in the EU.

First COVID-19 treatment recommended for EU authorisation

June 25, 2020 – EMA's human medicines committee (CHMP) has recommended granting a conditional marketing authorisation to Veklury (remdesivir) for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.

Remdesivir is the first medicine against COVID-19 to be recommended for authorisation in the EU. Data on remdesivir were assessed in an exceptionally short timeframe through a rolling review procedure, an approach used by EMA during public health emergencies to assess data as they become available. From 30 April 2020, the CHMP began assessing data on quality and manufacturing, non-clinical data, preliminary clinical data and supporting safety data from compassionate use programmes, well in advance of the submission of the marketing authorisation application on 5 June.

The assessment of the dossier has now concluded with today's recommendation, which is mainly based on data from study NIAID-ACTT-1, sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), plus supporting data from other studies on remdesivir.

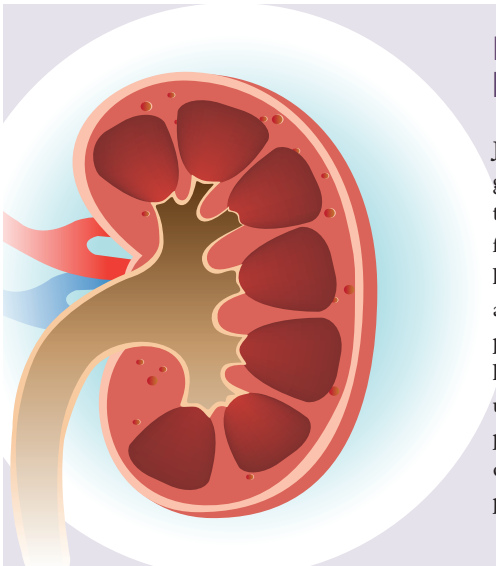
Study NIAID-ACTT-1 evaluated the effectiveness of a planned 10-day course of remdesivir in over 1,000 hospitalised patients with COVID-19. Remdesivir was compared with placebo (a dummy treatment) and the main measure of effectiveness was patients' time to recovery (defined as no longer being hospitalised and/or requiring home oxygen or being hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care).

Overall, the study showed that patients treated with remdesivir recovered after about 11 days, compared with 15 days for patients given placebo. This effect was not observed in patients with mild to moderate disease: time to recovery was 5 days for both the remdesivir group and the placebo group. For patients with severe disease, who constituted approximately 90% of the study population, time to recovery was 12 days in the remdesivir group and 18 days in the placebo group. However, no difference was seen in time to recovery in patients who started remdesivir when they were already on mechanical ventilation or ECMO (extracorporeal membrane oxygenation). Data on the proportion of patients who died up to 28 days after starting treatment are currently being collected for final analysis.

Taking into consideration the available data, the Agency considered that the balance of benefits and risks had been shown to be positive in patients with pneumonia requiring supplemental oxygen; i.e., the patients with severe disease. Remdesivir is given by infusion (drip) into a vein and its use is limited to healthcare facilities in which patients can be monitored closely; liver and kidney function should be monitored before and during treatment, as appropriate.

In order to better characterise the effectiveness and safety of remdesivir, the company will have to submit the final reports of the remdesivir studies to the Agency by December 2020, and further data on the quality of the medicine, as well as the final data on mortality, by August 2020.

During the assessment of remdesivir, the CHMP had the support of experts from the COVID-19 EMA pandemic task force (COVID-ETF), which was established to bring together the most relevant expertise from the European medicines regulatory network to assist Member States and the European Commission in dealing with the development, authorisation and safety monitoring of medicines and vaccines against COVID-19.



New treatment to enable kidney transplant in highly sensitised patients

June 26, 2020 – EMA has recommended granting a conditional marketing authorisation in the European Union for Idefirix (imlifidase), the first treatment for adult patients waiting for a kidney transplant, who are highly sensitised against tissue from the donor and who have a positive crossmatch test against an available kidney from a deceased donor. Idefirix should be used complementary to existing allocation programmes for patients with a very low chance of finding a matching kidney despite such programmes.

When a kidney from a deceased donor is offered for transplant, crossmatch tests are performed against all patients on the waiting list. The test checks whether a patient has specific antibodies against the potential donor.

Highly sensitised patients have exceptionally high antibody levels that react to the donor's tissue which shows up as a positive crossmatch test, making it more likely that the body will reject the donor organ. Patients with this result are therefore not eligible for transplant, and the available kidney is typically offered to other patients on the waiting list. There is an unmet medical need to desensitise these patients and

COVID-19: EMA sets up infrastructure for real world monitoring of treatments and vaccines

July 24, 2020 – EMA has now set up an infrastructure to support the monitoring of the efficacy and safety of COVID-19 treatments and vaccines when used in day-to-day clinical practice. This is underpinned by three contracts for observational research that EMA has signed with academic and private partners over recent months, to be ready to effectively monitor vaccines in the real world as soon as they are authorised and support the safe and effective use of COVID-19 vaccines and medicines.

The latest contract was finalised in mid-July with Utrecht University and the UMCU as coordinators of the CONSIGN project ('COVID-19 infectiOn aNd medicineS In preGNancy'). This project will collect data on the impact of COVID-19 in pregnancy in order to guide decision-making about vaccine indications, vaccination policies and treatment options for COVID-19 in pregnant women. CONSIGN will analyse existing data sources (e.g. electronic health records, hospital data) and cohorts of pregnant women to provide information on the effect of infection and its treatments in different trimesters of pregnancy and on neonates. The project will be carried out in collaboration with the ConcePTION consortium, which was established under the EU's Innovative Medicines Initiative, the COVI-PREG project and the International Network of Obstetric Survey Systems network.

In June, EMA contracted the company IQVIA with a project to build a framework for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients. This project will include the identification of large national cohorts of COVID-19 patients and appropriate comparator groups, the development of a study protocol template for multinational studies as well as the establishment of a collaborative framework for researchers. The project will be carried out in collaboration with the European Health Data & Evidence Network consortium, which was established under the Innovative Medicines Initiative and includes the Erasmus Medical Centre in Rotterdam and the University of Oxford as project lead and research coordinator, respectively.

In May, EMA commissioned the ACCESS project ('vACcine Covid-19 monitoring readinESS') for preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice, once authorised.

Observational research is an important pillar in the post-marketing surveillance of COVID-19 treatments and vaccines and EMA has called for transparency for protocols and results, as well as collaboration between researchers, to ensure high-quality, powerful studies. To facilitate this, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is coordinated by EMA, has set up a dedicated COVID-19 response group. EMA and ENCePP are encouraging researchers to register their pharmacoepidemiological studies (and make study protocols and reports public) in the European Union electronic register of post-authorisation studies (EU PAS Register), to ensure transparency on the various research efforts.

EMA is also fostering international collaboration on observational research through the ICMRA, with the agreement to step up co-operation in three areas: pregnancy research, building international clinical cohorts of COVID-19 patients and preparing a strong infrastructure for monitoring the safety and effectiveness of vaccines.

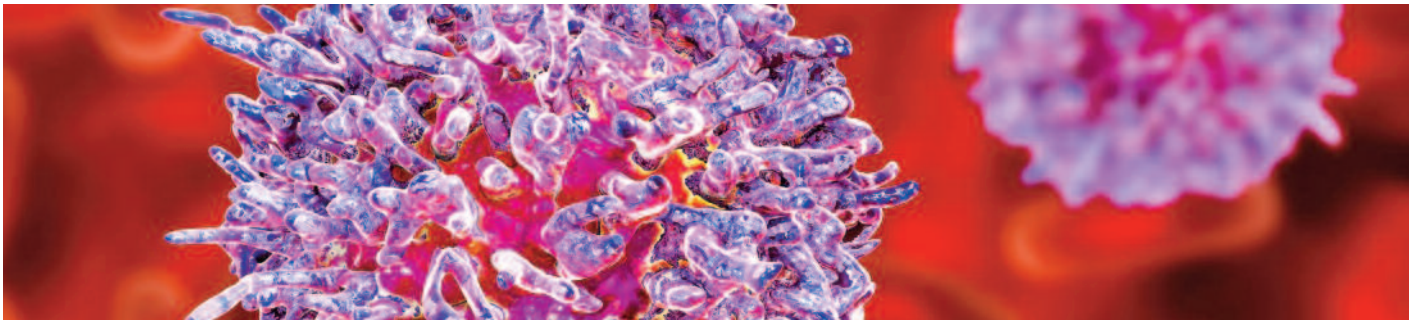
The outcome of the various projects conducted on observational research will be fed into the work of EMA's COVID-19 EMA pandemic Task Force (COVID-ETF) and EMA's scientific committees, to ensure that this evidence is translated into scientific opinions on the optimal use of the medicines and vaccines concerned.

convert a positive crossmatch into negative for them to become eligible for kidney transplantation.

Idefirix is made of an enzyme derived from the bacterium Streptococcus pyogenes, which breaks down antibodies called Immunoglobulins G (IgG). IgG is produced by the patient against the transplanted organ. By breaking down IgG, the medicine is expected to prevent the patient's immune system from attacking the newly transplanted organ, thereby reducing the risk that the organ will be rejected.

The efficacy and safety of Idefirix as a pre-transplant treatment to reduce donor specific IgG and enable highly sensitised transplant candidates to be eligible for kidney transplantation, was studied in three open label, single arm, six-month clinical trials. In these studies, 46 sensitised patients were transplanted. All patients who were crossmatch positive when included in the study were converted to negative within 24 hours after treatment with imlifidase. The studies showed excellent results on kidney function and graft survival after six months. The most common adverse reactions reported with this treatment were infections, such as pneumonia, urinary tract infection and sepsis and infusion-related reactions. The effect of Idefirix is temporary, and therefore does not preclude the need for standard immune suppression in kidney transplant patients.

Idefirix (Hansa Biopharma AB, Sweden) was designated as an orphan medicinal product and was supported through EMA's PRIority MEdicines (PRIME) scheme, which provides early and enhanced scientific and regulatory support to medicines that have the potential to address patients' unmet medical needs. Idefirix is recommended for a conditional approval. This type of approval allows the Agency to recommend a medicine for marketing authorisation with less complete data than normally expected, in cases where the benefit of a medicine's immediate availability to patients outweighs the risk inherent in the fact that not all the data are yet available. The company must now submit additional efficacy and safety data based on one observational follow-up study and one post-approval efficacy study.



First antibody-drug conjugate for multiple myeloma patients with limited treatment options

1July 24, 2020 – EMA's CHMP has recommended granting a conditional marketing authorisation in the European Union for Blenrep (belantamab mafodotin) to treat adult patients with relapsed and refractory multiple myeloma who no longer respond to treatment with an immunomodulatory agent, a proteasome inhibitor and a CD-38 monoclonal antibody.

Multiple myeloma is a cancer of a type of white blood cell called plasma cells that is responsible for about 2% of all cancer deaths. Normal plasma cells are found in the bone marrow and are an important part of the immune system. Plasma cells make the antibodies that enable the body to recognise and attack germs such as viruses or bacteria. They originate from B-cell lymphocytes and form when B-cells respond to an infection. When plasma cells become cancerous, they no longer protect the body from infections and produce abnormal proteins that can cause problems affecting the kidneys, bones or blood.

A range of new medicines for the treatment of multiple myeloma have been developed and approved in recent years, leading to a steady overall improvement in survival of patients. However, for patients who have already been treated with three major classes of drugs (immunomodulatory agents, proteasome inhibitors and monoclonal antibodies) and no longer respond to these drugs, the outlook is still bleak. There is an unmet medical need for new treatments that improve survival of these patients beyond the currently observed three months or less.

Blenrep has a new mechanism of action that targets B-cell maturation antigen (BCMA), a protein that is present on the surface of virtually all multiple myeloma cells. BCMA is absent from normal B-cells, making it an ideal drug target. Structurally, Blenrep is an antibody-drug conjugate that combines a monoclonal antibody with maleimidocaproyl monomethyl auristatin F (mcMMAF), which is a cytotoxic agent. The medicine binds to BCMA on myeloma cell surfaces and once inside the myeloma cell, the cytotoxic agent is released leading to apoptosis, the 'programmed' death of the cancerous plasma cells.

The main study on which the CHMP's recommendation for a conditional marketing authorisation is based was a phase 2, open label, randomised, two-arm study. The study investigated the efficacy and safety of two doses of belantamab mafodotin in multiple myeloma patients whose disease was still active after three or more lines of therapy and who no longer responded to treatment with immunomodulatory drugs and proteasome inhibitors and who did not respond to treatment with an anti-CD38 monoclonal antibody. The most common side effects found in participants in clinical trials with Blenrep were keratopathy (a disease affecting the cornea, the transparent layer in front of the eye that covers the pupil and iris) and thrombocytopenia (a condition that causes low blood platelet counts, which can lead to bleeding and bruising).

In order to better characterise the effectiveness and safety of the medicine, the company will have to submit the results of a randomised confirmatory (phase 3) trial comparing Blenrep with pomalidomide plus low-dose dexamethasone, which is a standard treatment option for relapsed and refractory multiple myeloma. The company is also required to submit the final results of the pivotal phase 2 study.

Blenrep (from GlaxoSmithKline Limited) was accepted in EMA's PRIME scheme and has benefited from the extra support offered by the Agency. Blenrep was designated as an orphan medicinal product on 16 October 2017. Following this positive CHMP opinion, the Committee for Orphan Medicinal Products will assess whether the orphan designation should be maintained.