

News from the EMA

SECTION EDITORS



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Re-analysis of data on use of breast cancer medicine Tyverb following treatment with trastuzumab

April 30, 2019 – European Medicines Agency (EMA) is updating the prescribing information for Tyverb (lapatinib) following detection of errors in results of a study involving post-menopausal women who had 'HR+/HER2+' breast cancer and whose disease had worsened despite previous treatment with trastuzumab. The results had indicated a benefit of Tyverb over trastuzumab when each medicine was used together with an aromatase inhibitor. While there are no new safety concerns with Tyverb, data on its benefit over trastuzumab in this patient population are currently being re-evaluated.

The detected errors were included in the prescribing information for Tyverb on July 30, 2018. However, these will now be removed while data are being re-analysed. In the meantime, the prescribing information will be amended to state, as before, that no data are available on the effectiveness of Tyverb compared with trastuzumab in this combination in patients

previously treated with trastuzumab.

In the light of this new information, doctors currently treating patients with Tyverb in combination with an aromatase inhibitor, whose disease had worsened despite previous treatment with trastuzumab, should decide whether to continue with the same therapy or consider an alternative treatment.

Tyverb is a cancer medicine used to treat patients with HER2+ breast cancer. This means that a specific protein called HER2 (also known as ErbB2) is present on the surface of the cancer cells. Tyverb is used in the following ways:

- in combination with capecitabine (another cancer medicine) when the cancer is advanced or metastatic and got worse following previous treatment including an anthracycline and a taxane (other types of cancer medicines) and following treatment of the patient's metastatic disease with trastuzumab (another cancer medicine). 'Advanced' means

that the cancer has started to spread locally and 'metastatic' means that the cancer has spread to other parts of the body;

- in combination with trastuzumab for metastatic cancer that does not respond to hormones (hormone receptor-negative disease), and which got worse when previously treated with a combination of trastuzumab and other cancer medicines (chemotherapy);
- in combination with an aromatase inhibitor (another type of cancer medicine) in women who have been through the menopause, when the cancer is metastatic and responds to hormones. This combination is used in women who do not currently need to receive chemotherapy to treat their cancer.

Tyverb was originally granted a conditional marketing authorisation valid throughout the EU in June 2008 and was switched to a full marketing authorisation on February 17, 2015.

Withdrawal of marketing authorisations for fenspiride medicines

May 24, 2019 – EMA's safety committee (PRAC) has recommended that the marketing authorisations for fenspiride medicines be revoked, so the medicines can no longer be marketed in the European Union (EU). This follows a review that has confirmed that these cough medicines could cause heart rhythm problems.

The PRAC considered all the available evidence in its review, including case reports and nonclinical studies (including hERG channel binding). This included cases of QT prolongation and torsades de pointes (abnormalities of the heart's electrical activity that may lead to heart rhythm disturbances) in patients using these medicines, results of laboratory studies, data from published literature and stakeholder input.

Heart rhythm problems can be serious and occur suddenly, and it is not feasible to identify in advance the patients who may be at risk of

these problems with fenspiride. In contrast, fenspiride medicines are used to treat non-serious cough. Therefore, the PRAC considered that these medicines should no longer be marketed.

Fenspiride medicines are available as syrup or tablets and used in adults and children from the age of 2 years to relieve coughs resulting from lung diseases. In the EU, fenspiride medicines are available under various brand names (Elofen, Epistat, Eurefin, Eurespal, Fenspogal, Fosidal, Kudorp, Pneumorel, Pulneo, Еуреспал and Сиреспн).

The review of fenspiride was initiated on February 14, 2019, at the request of France, under Article 107i of Directive 2001/83/EC. At that time, the PRAC recommended that supply of fenspiride medicines be suspended as a precautionary measure while the review was ongoing. Because fenspiride medicines are all licensed at national level, the PRAC recommen-

datation will now be sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) to make a decision about its implementation. The CMDh is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU, Iceland, Lichtenstein and Norway.



EMA facilitates early engagement with medicine developers to combat antimicrobial resistance

May 24, 2019 – EMA has opened up an early dialogue through its Innovation Task Force (ITF) to all medicine developers who work on therapeutic approaches for the treatment or prevention of bacterial and fungal infections. ITF is a forum for dialogue between regulators and developers of innovative emerging therapies, methods and technologies, in the early stages of research and development. ITF is usually reserved for innovative medicines. Given the growing threat to public health caused by antimicrobial resistance and the need for new treatments, EMA is inviting all developers working on medicines for the treatment or prevention of life-threatening microbial infections to enter into early dialogue with the Agency to help strengthen the drug development pipeline for new antimicrobials.

The emerging and steady increase of microbes that are resistant to antimicrobial treatments threatens the effective treatment of patients with infectious diseases. According to a World Health Organization (WHO) report, approximately 700,000 people die from drug resistant infections globally each year, a figure that could rise to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken.

Without a sustained effort to contain antimicrobial resistance, common diseases are becoming untreatable and lifesaving medical procedures riskier to perform.

Stimulating the development of new medicines to treat resistant bacterial or fungal infections is one pillar in the fight against this threat, and a high priority for EMA and the European medicines regulatory network.

The ITF will facilitate an early interaction and broad-ranging discussion between innovators and regulatory authorities, which will help developers' orientation and subsequent use of formal regulatory tools such as EMA's scientific advice. The service is free of charge and any new medicinal product for the treatment of a life-threatening or debilitating fungal or bacterial infection would be considered for discussion in the ITF.

This platform for early dialogue will ultimately contribute to prioritising

and speeding up the development of antimicrobial medicines, which is in line with the European Parliament Resolution of 13 September 2018 on "A European One Health Action Plan against Antimicrobial Resistance".

Interested medicine developers are encouraged to complete the ITF briefing meeting request form and send it to itfsecretariat@ema.europa.eu to discuss their development plans for medicinal products addressing bacterial and fungal infections.



Strengthening engagement between EMA and general practitioners

June 6, 2019 – The EMA and the two major organisations representing general practitioners (GPs) and family physicians in Europe – the European Union of General Practitioners (UEMO) and the European section of the World Organization of Family Doctors (WONCA) – and the major organisation representing primary care professionals in Europe, the European

Forum for Primary Care (EFPC), have signed a joint statement committing to strengthening interaction between EMA and this important group of healthcare professionals.

While EMA benefits from an existing framework of interaction with healthcare professionals – including physicians, pharmacists and nurses – interactions with GPs and family physicians and

feedback from primary care to EMA are currently limited. Developing a strong working relationship with this very large group of physicians aims to:

- help EMA gain a better understanding of how medicines are being used in real life and the potential impact of specific regulatory actions on patient care;
- facilitate the incorporation of views and input from GPs and family physicians into the Agency's activities;
- raise awareness amongst GPs and family physicians of the role and activities of the EU medicines regulatory network.

The statement includes a concrete action plan to 2020 to guide EMA, UEMO, EFPC, and WONCA in their joint work. Specific areas of collaboration include involving GPs and family physicians in EMA evaluation activities, developing communication activities relevant to GPs and family physicians, as well as exploring options for further collaboration with existing research networks in primary care, with a focus on generating real-world evidence. The action plan also identifies opportunities for cooperation in regulatory science training.

The development of the joint statement follows a workshop which took place in 2016 with representatives of GPs and family physicians in order to explore new ways to engage with these providers of primary care in EU Member States and further involve them in EMA activities.

Progress will be monitored and discussed within the EMA GP/family physician expert group and reported to the EMA healthcare professionals' working party.



Bacterial lysate medicines for respiratory conditions to be used only for prevention of recurrent infections

June 28, 2019 – EMA is recommending that bacterial lysate medicines authorised for respiratory conditions should only be used for the prevention of recurrent respiratory infections, with the exception of pneumonia. This follows a review that concluded that there are no robust data showing that these medicines are effective at treating existing respiratory infections, or for the prevention of pneumonia, therefore they should not be used for these purposes.

In the review, EMA's human medicines committee (CHMP) considered the results of clinical studies, data on side effects reported with these medicines, and advice from an expert group on infectious diseases.

Although data are limited, the review found some evidence of effectiveness of these medicines in the prevention of recurrent respiratory tract infections and the safety profile is in line with what is expected for this type of product.

The CHMP therefore recommended that use of the medicines for prevention can continue, but the companies must provide further data on safety and effectiveness from new clinical studies by 2026.

Bacterial lysate medicines are made from bacterial cells that are broken down and are intended to stimulate the immune system to recognise and fight infections. These medicines are taken by mouth (as capsules, tablets,

New treatment for children with type 2 diabetes

June 28, 2019 – EMA's human medicines committee (CHMP) has recommended granting an extension of indication to Victoza (liraglutide) to include the treatment of children and adolescents aged 10 years or older with type 2 diabetes. This medicine is already approved for use together with diet and exercise in adults with type 2 diabetes, on its own or as an add-on to other diabetes medicines.

Type 2 diabetes is a chronic disease in which the pancreas does not make enough insulin to control the level of glucose (sugar) in the blood or when the body is unable to use insulin effectively. It can lead to serious complications if a person does not receive treatment. According to the WHO, type 2 diabetes has increasingly been reported in children and adolescents recently, so much so that in some parts of the world type 2 diabetes has become the main type of diabetes in children.

The recommended treatment for paediatric type 2 diabetes is similar to that in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly healthy eating and exercise, followed by the use of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

Currently, the only two approved treatment options for paediatric type 2 diabetes patients in most countries are metformin and insulin. However, more than half of young patients do not achieve glycaemic control on metformin alone, even when combined with lifestyle interventions, and treatment with insulin has considerable side effects such as weight gain, or a high risk of

hypoglycaemia. Therefore, there is a medical need for alternative treatment options for children and adolescents with type 2 diabetes.

Victoza is the first non-insulin, besides metformin, to get a positive opinion for paediatric use for type 2 diabetes. The active substance in Victoza, liraglutide, is an 'incretin mimetic'. This means that it acts in the same way as incretins, a group of metabolic hormones that stimulate an increase of the amount of insulin released by the pancreas in response to food. This helps with the control of blood glucose levels. Liraglutide has been used in adults for approximately ten years, so there is an extensive amount of data available in particular with regards to safety.

The efficacy and safety of Victoza in children and adolescents was investigated in a placebo-controlled trial with 134 patients with type 2 diabetes aged 10–17 years. This study was carried out in accordance with a Paediatric Investigation Plan, which was agreed by the Agency's Paediatric Committee (PDCO).

The study compared patients in the liraglutide group with a placebo group over 26 weeks. Patients treated with Victoza, with or without insulin, experienced a clinically relevant reduction in the levels of glycated haemoglobin (HbA1c) that is measured via a blood test to evaluate average blood sugar levels in a patient over a period of weeks or months. A higher number of patients experienced hypoglycaemic episodes in the liraglutide group than in the placebo group irrespective of prior insulin use.



The results of the trial demonstrated that the safety profile of Victoza in this population is comparable to that in adults. The most common side effects were nausea, vomiting, diarrhoea, headache and abdominal pain.

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

granules/powder for making up an oral mixture or drops), dissolved under the tongue (as tablets), inhaled through the nose (as a liquid) or given by injection into a muscle or under the skin.

Bacterial lysate medicines are sold under several brand names including Broncho Munal, Broncho Vaxom, Buccalin, Immubron, Immucytal, Ismigen, Lantigen B, Luivac, Ommunal, Paspas, Pir-05, Polyvaccinum, Provax, Respivax and Ribomunyl.

