

NEWS



The European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended approval of a new somatostatin analogue, Signifor®, for the treatment of Cushing's disease, making it the first approved medical therapy for the rare hormonal disorder.

Cushing's disease is rare, debilitating and life-threatening, and is estimated to affect approximately 0.4 in 10,000 people in the EU. The new medicine is intended for the treatment of the disease in patients who are not able to have surgery, or for those whom surgery has proved unsuccessful.

The disease develops when a tumor of the pituitary gland produces an excessive

amount of ACTH, stimulating the adrenal glands to grow and release large amounts of cortisol into the blood. The resultant symptoms include weight gain, excessive coarse hair growth on the face, high blood pressure, bruising and weakening of the muscles and bones.

Surgical removal of the pituitary tumor is first-line therapy for sufferers of Cushing's disease. At present, there are no approved medical treatments for those that cannot be cured by surgery. Consequently, the European Medicines Agency recommendation for approval of Signifor (pasireotide) is the initial step in making a drug, which has been studied and for which specific information on its use is provided, available to European patients.

Signifor, a somatostatin analogue, attaches to somatostatin receptors in the tumor cells of the pituitary gland, thereby blocking the release of ACTH. This relieves the symptoms of Cushing's disease by reducing cortisol levels. In clinical trials it was shown to reduce urine cortisol levels by at least 50% in 41% of patients given a 900 µg dose, and in 34% of patients treated with a 600 µg dose.

“...the European Medicines Agency recommendation for approval of Signifor (pasireotide) is the initial step in making a drug ... available to European patients.”

The CHMP noted that the safety profile of Signifor is similar to that of other somatostatin analogues, which have been approved in the EU for a number of years. Doctors are advised in the product information to monitor patients for heart and liver problems and, with these precautions, the CHMP concluded that the benefits of Signifor outweigh its risks as a second-line treatment for patients with Cushing's disease.

The CHMP's recommendation has been forwarded to the EC for the adoption of an opinion.

Written by Lucy Marum, Assistant Commissioning Editor.

Source: European Medicines Agency recommends approval of new medicine for Cushing's disease: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/01/news_detail_001426.jsp&mid=W00b01ac058004d5c1&jsenabled=true

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US FDA approves combination pill for Type 2 diabetes

A combination pill, containing the dipeptidyl peptidase-4 inhibitor, linagliptin and metformin hydrochloride, has been approved by the US FDA for the treatment of Type 2 diabetes in adults. Jentadueto®, from Boehringer Ingelheim Pharmaceuticals, Inc., and Eli Lilly & Co., provides a twice daily single-tablet treatment. The linagliptin/metformin combination can be used alone or with a sulfonylurea.

Linagliptin was granted FDA approval in May 2011 for providing improved blood glucose control in adults with Type 2 diabetes. It can be used in combination with other therapeutics or as a stand-alone treatment.

In a clinical trial, linagliptin with metformin led to reductions in hemoglobin A1c levels of up to 1.7%. The 24-week, randomized, double-blinded, placebo-controlled study involved 791 adults with Type 2 diabetes that was inadequately managed with diet and exercise.

Lance Sloan, Texas Institute for Kidney and Endocrine Disorders, TX, USA, explained the benefits of a single-tablet diabetes medication, “Most people with Type 2 diabetes require more than one medication to help lower their blood sugar, due to the complex nature of Type 2 diabetes.” He added that Jentadueto is “a good option for people who need an

additional medication, and for whom both linagliptin and metformin is appropriate.”

The new treatment is not indicated for patients who have Type 1 diabetes, or for those who have diabetic ketoacidosis. The linagliptin/metformin combination pill has not been studied in combination with insulin. The most common adverse effects of treatment with the pill are diarrhea and nasopharyngitis.

“In a clinical trial, linagliptin with metformin led to reductions in hemoglobin A1c levels of up to 1.7%.”

The company notes that patients treated with the drug combination and sulfonylurea more commonly reported hypoglycemia than those treated with a combination of placebo, sulfonylurea and metformin. Pancreatitis was also more common in patients randomly assigned to receive linagliptin.

Written by Lucy Marum, Assistant Commissioning Editor.

Sources: Drugs@FDA: FDA approved drug products label and approval history: linagliptin; metformin: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#applist; Combination Type 2 diabetes pill gets FDA nod: www.medscape.com/viewarticle/757821?src=rss



Melatonin mutations linked to diabetes risk

An international team of researchers has demonstrated that mutations of the melatonin receptor gene can result in the risk of developing Type 2 diabetes, increasing by almost seven-times. The researchers from France, the UK and Canada hope that their work could contribute to the development of medication for the treatment or prevention of diabetes.

Type 2 diabetes affects 300 million people worldwide and is characterized by excess blood glucose and insulin resistance. Factors that can contribute to the onset of the disease include a high-fat and -sugar diet and lack of exercise, combined with genetic factors. Studies have also shown that disorders causing a reduction in the duration and quality of sleep are high-risk factors, although no previous work has described a possible link between diabetes and the biological clock.

It is known that insulin production reduces at night to prevent hypoglycemia, rising again during the day, when most people eat, to avoid hyperglycemia.

The research team sequenced the *MT2* gene, which encodes the melatonin receptor, in 7600 subjects, including both diabetics and people with normal blood-sugar levels. A total of 40 rare mutations of the melatonin receptor were found, with 14 of these causing the receptor to become non-functional and therefore melatonin insensitive. Results presented by the team suggest that the risk of developing Type 2 diabetes was nearly seven-times greater in people exhibiting these mutations.

The authors of the study suggest that their findings could be used to develop new diabetes treatments that focus on adjusting MT2 receptor activity to control the associated metabolic pathways. They also highlight the importance of personalized treatment options for diabetic patients, due to the range of genetic causes of the disease.

Written by Lucy Marum, Assistant Commissioning Editor.

Source: Bonnefond A, Clément N, Fawcett K *et al.* Rare *MTNR1B* variants impairing melatonin receptor 1B function contribute to Type 2 diabetes. *Nature Genetics* doi:10.1038/ng.1053 (2012) (Epub ahead of print).

US FDA considers safety of Omalizumab use in pediatric patients

The Pediatric Advisory Committee Panel for the US FDA has recommended a return to routine monitoring in patients aged 6–11 years who are receiving the asthma medication omalizumab.

The latest safety information on the drug was presented by Amy Taylor based at the Center for Drug Evaluation and Research, FDA (MD, USA). The drug is indicated for use in patients who have moderate to severe persistent allergic asthma, and who are aged 12 years and over.

Previously, two clinical studies were conducted in 926 patients aged 6–11 years. It was shown that the rate of asthma exacerbation was reduced significantly in patients given omalizumab. Other secondary measures, including β -agonist use, air flow and nocturnal symptoms scores, did not differ significantly

between groups. There were no unusual safety trends noted in the studies, nor were there any cases of anaphylaxis or death. Malignancies were reported in patients in the placebo group, although none were reported in those patients receiving treatment.

As a result of these data, FDA approval was not granted to omalizumab in the USA. The drug was approved for patients aged 6–11 years by the EU in 2009.

A Taylor presented new safety reports, collected between 4 January 2010 and 31 July 2011, that revealed there were 81 serious pediatric cases, five of which resulted in death. Of these five, two were in pediatric patients and three were fatal outcomes *in utero*. There were also 33 hypersensitivity reactions, ten respiratory or asthma exacerbation cases, eight infection cases, and seven neuropsychiatric adverse events.

During her presentation, A Taylor said that no new safety signals in pediatric patients were identified, adding that the “FDA recommends returning to routine monitoring.” The 20-member panel voted in favor of this recommendation.

Sheldon L Kaplan from Baylor College of Medicine (TX, USA) voted yes on the panel. However, he added that the two cases of nephrotic syndrome in 2100 patients was a safety signal and should be highlighted for further evaluation.

The advice of advisory panels is not always followed by the FDA.

Written by Lucy Marum, Assistant Commissioning Editor.

Sources: FDALive meetings: Pediatric Advisory Committee Meeting, Date: 9/22/11-9/23/11: www.fdalive.com/pastmeetings.cfm?committeekey=60; FDA panel says omalizumab safe in pediatric patients: www.medscape.com/viewarticle/757825?src=rss

US FDA has approved vismodegib for the treatment of advanced basal cell carcinoma

Vismodegib (Erivedge™) is the first drug indicated for the treatment of basal cell carcinoma (BCC), the most common type of skin cancer in the EU, USA and Australia, to gain US FDA approval. It has first-in-class specificity to the hedgehog pathway – abnormal hedgehog signalling is implicated in more than 90% of BCC cases and vismodegib is a ligand-specific inhibitor of this pathway. It suppresses hedgehog signaling by binding to and interfering with the smoothed transmembrane receptor, preventing abnormal signaling.

“In patients with locally advanced BCC it was shown to shrink lesions in 27 out of 63 cases...”

The approval came after a new drug application was submitted to the FDA in September 2011 based on Phase II data from the ERIVANCE BCC trial. The drug then underwent a subsequent priority review by the FDA, which led to its

approval. The drug is indicated for patients with BCC that has metastasized to other parts of the body, relapsed after surgery or is unable to be treated with radiation or surgery.

The Phase II study was an international, single-arm, multicentre, two-cohort, open-label trial of 96 patients. The drug was shown to achieve its primary end point of overall response rate assessed by independent review. In patients with locally advanced BCC it was shown to shrink lesions in 27 out of 63 cases and, in patients with metastatic BCC, lesions were reduced in ten out of 33 cases. The mean duration of response was 7.6 months. The drug has been shown to have relatively low toxicity; however, adverse events such as muscle spasms, hair and weight loss, diarrhea, fatigue, reduced appetite, constipation, vomiting and loss of taste in the tongue were observed.

The approval of the drug came with a boxed warning of potential risk of death

or severe birth defects to unborn babies. The drug is being marketed by Genetech, USA, part of the Roche group, as a once-daily capsule and costs US\$7500 per month. Duration of treatment is expected to be approximately 10 months. A marketing authorization application for vismodegib has been submitted by Roche in the EU in order for European patients to gain access to the drug, while a Phase II safety trial is also underway in order to potentially gain marketing authorisation worldwide.

The drug is currently undergoing trials for other indications such as colorectal cancer, small-cell lung cancer, advanced stomach cancer and pancreatic cancer.

Written by Claire Attwood, Assistant Commissioning Editor.

Source: Genetech newsroom: FDA approves Erivedge™ (vismodegib) capsule, the first medicine for adults with advanced basal cell carcinoma: www.gene.com/gene/news/press-releases/display.do?method=detail&id=13827