EMERGENT THERAPIES

ONCE-DAILY INHALER PROVIDES NEW OPTION FOR ASTHMA AND COPD

A new, once-daily treatment for asthma and COPD, combining the inhaled corticosteroid fluticasone furoate and the long-acting beta2-agonist vilanterol, has been licensed in the UK and across most of Europe.

Relvar® is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older, as well as for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) and a history of exacerbation in spite of regular bronchodilator therapy.

Administered once-daily using Ellipta®, a new dry powder inhaler, Relvar is available in two strengths for asthma (92/22mcg and 184/22mcg) and one for COPD (92/22mcg) and has demonstrated 24-hour efficacy in both indications.

The cost of Relvar Ellipta is £27.80 for the low-mid dose and £38.87 for the higher dose.

Summary of product characteristics for Relvar Ellipta is available at www.medicines.org.uk/emc/28495.

NOVEL TREATMENT FOR INCURABLE BACK PAIN CONDITION

A new monoclonal antibody, recently made available in the UK and Ireland, has shown encouraging results in tackling a challenging cause of chronic back pain. The launch of certolizumab pegol (Cimzia®) will provide clinicians with a new option for the treatment of adult patients with severe active axial spondyloarthritis (axSpA).

The condition – which comprises severe active ankylosing spondylitis (AS) and severe active axSpA without radiographic evidence of AS – is currently incurable, but supporting data for certolizumab suggest that patients can experience symptomatic improvements as early as one week.

Patients treated with certolizumab also reported improved workplace and household productivity and increased participation in social and daily activities, compared with those vs. placebo.

According to Dr Stefan Siebert, a consultant rheumatologist at NHS Greater Glasgow and Clyde, these findings are particularly encouraging, since axSpA affects a lot of people under the age of 40 who are still active and working full time.

"For years, early diagnosis of axial spondyloarthritis has proved challenging, with no effective treatments. However, with advances in imaging technology, better diagnostic criteria and new treatments we now have the opportunity to improve patients' symptoms and avert long-term disability," he said.

Since 2009 certolizumab pegol has been approved in the EU in combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis in adult patients, inadequately responsive to disease-modifying anti-rheumatic drugs.

The safety profile for axSpA patients treated with certolizumab was consistent with that seen in patients with rheumatoid arthritis.

ANTI-OBESITY TREATMENT NEARS LAUNCH

European marketing authorisation is being sought for a 3mg dose of liraglutide, a once-daily human GLP-1 analogue, as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity, or who are overweight with comorbidities.

The submission is based primarily on data from the Phase 3 SCALET clinical trial programme, which involved more than 5,000 people with obesity or who are overweight with comorbidities.

the SCALET data have consistently demonstrated that liraglutide 3 mg, in combination with diet and exercise, induces and maintains weight loss, while also significantly improving obesity-related comorbidities such as hypertension, dyslipidaemia and sleep apnoea.

Furthermore, in people with obesity and type 2 diabetes or pre-diabetes, liraglutide 3 mg has been shown to significantly improve glycaemic control, in addition to lowering weight.

EC APPROVES ADDITIONAL PNEUMONIA INDICATION FOR SYNFLORIX

The European Commission (EC) has authorised an additional indication for the vaccine Synflorix for immunization against pneumonia caused by *Streptococcus pneumonia* in children from six weeks up to five years of age.

This approval is based on results from a Phase 3 double-blind, randomized, controlled trial named COMPAS.

The efficacy study for this latest-generation pneumococcal conjugate vaccine (PCV) was conducted in 63 centres in South America, involving 24,000 children.

Synflorix was previously licensed for Active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumonia.*

The summary of product characteristics for Synflorix is available at www.medicines.org.uk/emc/22743

TECHNOLOGY APPRAISALS

AFLIBERCEPT GAINS ACCEPTANCE FOR MACULAR OEDEMA

The VEGF innibitor aflibercept (EYLEA®) has received a green light from NICE for treatment of visual impairment caused by macular oedema, in final draft guidance published in December.

NICE recommends aflibercept solution for injection specifically to treat macular oedema secondary to central retinal vein occlusion (CRVO). The approval is conditional on the manufacturer, Bayer, making the treatment available to the NHS under terms agreed with the Department of Health as part of a patient access scheme.

Macular oedema is characterised by a reduction in the number of connective tissues around the capillaries and an

increased amount of the protein vascular endothelial growth factor (VEGF), which causes the blood retinal barrier to become porous. As a result, plasma can leak into the retina, causing oedema.

Final published guidance is expected in February 2014.
www.http://guidance.nice.org.uk/TA294

CLINICAL DATA

LIXISENATIDE EFFICACY UNAFFECTED BY TIME OF ADMINISTRATION

Results of a 24-week Phase IIIb clinical study have shown that the once-daily prandial glucagon-like peptide-1 receptor agonist (GLP-1 RA) lixisenatide (Lyxumia®) met its primary endpoint of non-inferiority in blood sugar lowering (HbA1c) when administered either before breakfast or the main meal of the day.

These results indicate that lixisenatide can effectively lower blood sugar at either time of administration.

Findings from the trial, involving 451 patients with type 2 diabetes, also showed that a comparable reduction in body weight, regardless of the meal before which lixisenatide was administered, was achieved. In addition, gastrointestinal tolerability was comparable regardless of time of administration, with no cases of severe hypoglycemia in either arm.

Reference: Ahren B, et al. Oral presentation December 5, 2013, 10:45–12:45 [ABS OP-0454]).

TRIAL HIGHLIGHTS POSSIBLE RISKS IN EARLY WARFARIN THERAPY

Patients with atrial fibrillation (AF) have nearly double the risk of suffering a stroke in the first 30 days after starting warfarin compared to non-users, according to a study of over 70,000 patients.

The study, published in the European Heart Journal, found that the risk was particularly high in the first week after patients started to take the drug. However, once the first 30 days had elapsed, the risk of a stroke halved in patients taking warfarin compared to non-users.

Carried out using the UK Clinical Practice Research Datalink – the world's largest primary care database, the study, followed the patients for up to 16 years until an ischaemic stroke, death or end of registration with their primary care practice.

During that time, a total of 5519 patients experienced a stroke (2% per year). During the first 30 days after starting warfarin, there was a 71% increased risk of ischaemic stroke when compared with patients taking no anti-coagulant drugs. The highest risk was in the first week of use, peaking on the third day after starting warfarin.

One explanation for the findings, the researchers believe, may be that while the warfarin blocks the activation of clotting factors II, VII, IX and X, it also deactivates two other proteins, C and S, which are themselves anticoagulants. Previous research has already suggested that warfarin may lead temporarily to a hypercoagulable state.

"There is no question that warfarin is highly effective in preventing strokes in patients with atrial fibrillation; thus, our finding that the initiation of warfarin may be associated with an increased risk of stroke should not deter physicians and patients from using this drug," said lead researcher Dr Laurent Azoulay from McGill University, Montreal. "However, the results of our study suggest that physicians should be vigilant when initiating warfarin, particularly in the first week of use."

The authors suggest that, pending investigations as to whether the newer anticoagulants also carry this early risk, a "bridging strategy" using heparin at the initiation of warfarin treatment could be considered as a way to reduce the increased risk in the first 30 days of use.

STUDY GETS UNDERWAY TO ASSESS EFFICACY OF CCB IN ALZHEIMER'S DISEASE

Recruitment for an extensive European study to investigate whether the calcium channel blocker nivaldipine may also help patients with Alzheimer's disease (AD) is currently under way.

Nivadipine is licensed in a number of countries and has demonstrated proven efficacy and safety as an antihypertensive. The planned study in patients with AD was prompted by pre-clinical research which has shown that nilvadipine also counters the formation of amyloid plaques in animal brains.

Labelled the NILVAD study, it will recruit 500 people, including 60 in the UK, with mild to moderate AD to examine the effects of nilvadipine compared to placebo on the rate of deterioration in memory and cognition over an 18 month period.

The major European research collaboration, which has attracted EU funding of almost 6 million euros is being coordinated from Trinity College in Dublin, Ireland. Research teams in 11 European and Scandinavian countries, including the UK, France, Netherlands, Greece, Hungary, Italy and Germany, are also taking part.

The NILVAD trial is due to finish recruitment of participants in December 2014.

REGULATORY NEWS

REGULATORS REMOVE QUESTION MARKS OVER HAEMOPHILIA TREATMENTS

Following a review of the second generation factor VIII products Kogenate and Helixate, The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that there is no increased risk of developing antibodies (factor VIII inhibitors) against these medicines when compared with other factor VIII products in previously untreated patients with haemophilia A.

The benefits from taking Kogenate or Helixate therefore continue to outweigh the risks, the regulator states.

The PRAC review followed results from studies showing development of factor VIII inhibitors in about a third of all the children.

Although this reduces the benefit of treatment and makes bleeding more likely, is a known risk of all factor VIII products, and some studies have suggested that children given so-called second generation full-length recombinant factor VIII products were more likely to develop antibodies than those given a third generation recombinant product.

POLYPHARMACY: IT'S COMPLICATED

New data has put in question the commonly held belief that polypharmacy is always hazardous and may even represents poor care.

A recent study published in the *British Journal of Clinical Pharmacology* has found that patients with a single illness who take many drugs have an increased risk of being admitted to hospital, but for patients with multiple conditions, polypharmacy is now associated with a near-normal risk of admission.

The research team, based in Scotland, analysed Scottish NHS primary care data for 180,815 adults with long-term clinical conditions. They identified the numbers of regular medications each person was taking and linked this to whether or not the person was admitted to hospital in the following year.

Findings showed that for patients with only a single medical condition, taking 10 or more medications was associated with a more than three-fold increase in the chance of having an unplanned hospitalisation, compared to patients who took only one to three medicines.

In contrast, patients with six or more medical conditions who used 10 or more medications only increased their relative chance of admission by a factor of 1.5.

Lead author Dr Rupert Payne, who works at the Cambridge Centre for Health Services Research, commented: "This work is highly relevant to the development and assessment of prescribing skills in general practice where the majority of long-term clinical care is undertaken and where doctors often prescribe drugs for long periods of time."

CHILDHOOD OBESITY – NO SUBSTITUTE FOR PARENTAL ROLE MODEL

Obese or overweight parents confer a risk of obesity to their offspring – and they only compound the problem by restricting their pre-school children's access to the food in which they themselves overindulge.

This is one implication of findings from a study carried out at the University of Illinois, which also identified inadequate sleep as one of the three leading risk factors of obesity in young children.

The researchers reached their conclusions after compiling the results from an extensive survey of 329 parents and children recruited from a major child-care programme. The survey was coupled with home visits to check height and weight and key aspects of the participants' history.

From 22 variables that had previously been identified as predictors of child obesity, the three that emerged as the strongest risk factors were inadequate sleep, high parental BMI and, surprisingly, parental restriction of a child's eating in order to control his weight.

"The three that emerged as strong predictors did so even as we took into account the influence of the other 19. Their strong showing gives us confidence that these are the most important risk factors to address," said lead researcher Professor Brent McBride.

"Parents should recognize that their food preferences are being passed along to their children and that restricting their children's access to certain foods will only make them want those foods more," he added.

REVIEW SUGGESTS WELCOME DOWNTURN FOR DEMENTIA INCIDENCE

The medical community has become all but resigned to the seemingly relentless trend of rising dementia incidence as the population ages. But findings from a review by researchers in Seattle, USA now encouragingly suggest that the age-specific incidence of the condition is actually declining.

The review, published online in the *New England Journal of Medicine*, was based on an analysis of five recent studies, all of which show decreasing rates of age-standardised dementia during the last 30 years. The authors say the consistency of the findings is compelling and encouraging.

The downward trend in dementia incidence seems to correlate to earlier and more prolonged education, improvements in healthcare and lifestyle and increased awareness regarding the prevention of heart disease.

Specific factors that were associated with a reduced risk for dementia included physical activity, reducing vascular risk factors, retiring later, educated parents (especially an educated mother), maintaining social activities, and getting treatment for depression.

"We believe these reports are intriguing and inform our understanding of potentially modifiable factors that contribute to the epidemic of this common and often tragic condition," they write. "Knowing about contributing factors is especially important for the study and development of prevention strategies."

STUDY SHEDS LIGHT ON THE PROTECTIVE EFFECT OF HIGH-FIBRE DIET

It has been known for many years that a fibre-rich diet protects us against obesity and diabetes, but the mechanisms involved have until now remained elusive.

Now, a French-Swedish research team has succeeded in unravelling this mechanism, which involves the intestinal flora and the ability of the intestine to produce glucose between meals.

Fibres present in many vegetables are fermented by intestinal bacteria into short-chain fatty acids such as propionate and butyrate, which can in fact be assimilated in the human body. The team set out to explore whether this mechanism could be linked to the capacity of the intestine to produce glucose, a process which would trigger a range of protective effects against diabetes and obesity, including a reduced sensation of hunger, enhanced energy expenditure at rest and suppressed production of glucose in the liver.

The researchers subjected rats and mice to diets enriched with fermentable fibres, or with propionate or butyrate. By observing gene expression they showed that the intestine of these animals used propionate and butyrate as precursor to increase the production of glucose.

Predictably, mice fed a fat- and sugar-rich diet, but supplemented with fibres, became less fat than control mice and were also protected against the development of diabetes.

The researchers concluded that it is the production of glucose by the intestine from propionate and butyrate that is behind the positive effects of fermentable fibres on the organism.

Writing in the journal *Cell*, the authors say their findings should make it possible to propose nutritional guidelines and to highlight new therapeutic targets for preventing or treating diabetes and obesity.