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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Market authorization granted for Bydureon™ – the first once-weekly medication for Type 2 diabetes

It has been announced that the European Commission has granted marketing authorization for Bydureon™ (exenatide extended-release for injectable suspension), making it the first once-weekly treatment for Type 2 diabetes.

Exenatide extended-release is a glucagon-like peptide-1 (GLP-1) receptor agonist, which delivers glycemic control in a single-weekly dose. It has been indicated for the treatment of Type 2 diabetes in adult patients, in combination with metformin, a sulfonylurea, a thiazolidinedione, metformin plus a sulfonylurea, or metformin plus a thiazolidinedione. It is to be given as one injection under the skin, once a week on the same day, in the abdomen, thigh or back of the upper arm.

The active substance in exenatide is an 'incretin mimetic', therefore it acts in the same way as incretins, by increasing the amount of insulin released by the pancreas in response to food in order to control blood glucose levels. Exenatide extended-release builds upon 6 years of market experience with Byetta® (exenatide) injection, which is a twice-daily form of exenatide available to over 70 countries worldwide.

> "Bydureon™ is the first and only once-weekly treatment for Type 2 diabetes and has demonstrated powerful efficacy in multiple clinical trials."

The European Marketing Authorization of exenatide extended-release has followed a review of the submission package, which included data from studies in the DURATION clinical program. According to the European Medicines Agency, in all four studies, exenatide extended-release was more effective than the comparator treatments for reducing levels of HbA1c in the blood:

- Study 1: exenatide extended-release reduced HbA1c levels on average by 1.9% after 30 weeks of treatment, compared with 1.5% reduction with exenatide given twice daily;
- Study 2: exenatide extended-release reduced HbA1c levels on average by 1.6% after 24 weeks of treatment, compared with 0.9% reduction with exenatide given twice daily;
- Study 3: exenatide extended-release reduced HbA1c levels on average by of 1.4% after 26 weeks of treatment, compared with 0.8 and 1.1% reduction with sitagliptin and pioglitazone, respectively;
- Study 4: exenatide extended-release average reduced HbA1c levels on average by 1.5% after 26 weeks, compared with an average reduction of 1.3% with insulin glargine;

Therefore, results of the DURATION clinical program demonstrated that exenatide extended-release caused improvements in glycemic control with a single dose per week, based on blood sugar levels reducing between 1.5 and 1.9% after 6 months, as measured by the A1C test.

In clinical trials the most common side-effect with exenatide extended-release was mild-to-moderate nausea. This affected approximately 20% of patients, but in most patients did decrease over time. Other side-effects commonly noted were vomiting, diarrhea and constipation. Although exenatide extended-release was not studied as a weight-loss product, most patients taking the drug did lose weight.

Celebrating the results in the press release, Enrique Conterno, president of Lilly Diabetes, stated that, "as the global impact of diabetes continues to expand, so does the need for innovative medicines to help people living with diabetes successfully fit treatment into their lives". He continued, "Bydureon is the first and only once-weekly treatment for Type 2 diabetes and has demonstrated powerful efficacy in multiple clinical trials".

Sources: Bydureon™ receives marketing authorization in Europe: www.newsroom.lilly.com/releasedetail.cfm?ReleaseID=586295; European medicines agency: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002020/human_med_001457.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp&jsenabled=true

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New option to protect patients from developing venous blood clots following knee or hip replacement surgery

Bayer HealthCare have announced the US FDA approval of rivaroxaban (Xarelto®), the first once-daily, oral anticoagulant for the prophylaxis of deep-vein thrombosis (DVT).

The American Academy of Orthopedic Surgeons claims that over 800,000 Americans undergo knee or hip replacement surgery each year. An increased risk of DVT can be associated with such procedures, whereby if all or part of a DVT breaks off it can cause a pulmonary embolism. As such, it is known that DVT and pulmonary embolisms are the leading causes of re-hospitalization following joint replacement surgery.

The use of blood thinners (i.e., anticoagulants) has been recommended by the American College of Chest Physicians to immediately follow knee or hip replacement surgery through to an extended use postdischarge, to help reduce such risks. Recommendations have previously stated that anticoagulants should be used for at least 10 days after knee replacement and up to 35 days after hip replacement; however, full compliance with these guidelines with previously available options has not been widely observed.

Rivaroxaban is a new oral anticoagulant with FDA approval in venous thromboembolism prophylaxis, to be used on patients undergoing knee or hip replacement surgery. It has been is approved for use at a 10-mg dose, as one tablet to be taken once daily following surgery, for 35 and 12 days following hip and knee replacement, respectively.

> "Xarelto® has a proven clinical benefit over one of today's most widely used options in preventing these potentially life-threatening blood clots..."

From the clinical development program, Phase III data for rivaroxaban demonstrated superior efficacy, both in head-to-head comparison with enoxaparin and in comparing 5-weeks rivaroxaban (extended duration) with 2-weeks enoxaparin (short duration) followed by placebo. Rivaroxaban and enoxaparin from these trials demonstrated similar safety profiles, which included low rates of major bleeding.

Commenting on the press release, Louis Kwong, Professor of Orthopedic Surgery at Harbor-UCLA Medical Center (LA, USA), who was involved with the rivaroxaban clinical trial program in this indication, stated that, "the approval of once-daily Xarelto tablets will provide a new option to help protect patients in the USA from developing venous blood clots following knee or hip replacement surgery". Kwong continued, "Xarelto has a proven clinical benefit over one of today's most widely used options in preventing these potentially life-threatening blood clots, and the use of a once-daily pill may play an essential role in helping to simplify clinical practice".

Source: US FDA approves Xarelto® (rivaroxaban tablets) for the prophylaxis of deep-vein thrombosis: www.press.bayerhealthcare.com/en/press/news-details-page.php/14247/2011-0333

New research highlights that trial population does not represent US lung cancer patients

Research presented at the 14th World Conference on Lung Cancer in Amsterdam (The Netherlands), has highlighted that the elderly, women and ethnic minorities are not enrolled frequently enough in lung cancer trials, stating that current numbers do not reflect the prevalence of US lung cancer patients.

The researchers obtained their results of clinical trial enrolment by reviewing the US FDA's drug approval trial data over the last decade for the treatment of non-small-cell lung cancer. With this, they compared the number of US patients diagnosed with lung cancer from 1975 to 2008, according to data released on 15 April 2011 from the National Cancer Institute's SEER.

Data from SEER demonstrates that from the total number of US lung cancer patients, 58% were male and 42% female. However, between January 2000 and December 2010, the ten national and international trials for agents approved to treat non-small-cell lung cancer, contained enrollees that were 68% male and 32% female.

Research also focused on African–Americans, as they are known to develop lung cancer at higher rates (73 per 100,000) than Caucasians (68 per 100,000). It was found that only 2% of trial participants were African–American. The researchers noted overall that Caucasians made up 78% of the trial population, whereas minority populations such as Asians and Hispanics made up 15% and 2% of the trial population, respectively.

Researchers also assessed the representation of age. Data from SEER showed that 73% of US lung cancer patients were older than 65; however, the drug trial population contained only 36% of patients over 65 years of age.

Commenting on the results, Shakun Malik, Medical Officer at the FDA (Maryland, USA) said that the "results suggest that the trial population used for approval of drugs do not represent well the US population who may receive the marketed agent". He continued, noting that the results were "concerning particularly for older patients who may experience greater toxicity when given the same dose and combination of drugs based on testing in a younger population".

Source: Women, elderly and minorities poorly represented in lung cancer drug trial data submitted to US FDA: www.iaslc.org/assets/WCLC-328-6-July-1000.pdf

GLOW2 Phase III study shows glycopyrronium bromide to improve lung function in COPD

Novartis' once-daily long-acting muscarinic antagonist (LAMA), glycopyrronium bromide (NVA237), has demonstrated superior 24-h bronchodilation ($p < 0.001$) and comparable efficacy with open-label tiotropium (Spirivic® HandiHaler®) in a Phase III study in patients with chronic obstructive pulmonary disease (COPD).

GLOW2, a 52-week, double-blind, placebo-controlled parallel-group study involving 1066 patients was designed to assess the efficacy, safety and tolerability of glycopyrronium bromide in patients with COPD. Results of an explanatory arm of the study where glycopyrronium bromide was compared with open-label tiotropium bromide 18 µg, also a LAMA, demonstrated that glycopyrronium bromide produced similar improvements in lung function in COPD patients as tiotropium.

Both primary and secondary end points of the GLOW2 study were met. Glycopyrronium bromide showed superior 24-h bronchodilation to placebo at 12 weeks measured by trough forced expiratory volume in 1 s (FEV1), the primary end point of the study. Key secondary end points met in GLOW2 included improvement in breathlessness assessed using the Transition Dyspnea Index at 26 weeks and improved quality of life as measured by the St George's Respiratory Questionnaire at 52 weeks.

GLOW2 also revealed that glycopyrronium bromide was safe and well tolerated, exhibiting a similar incidence of adverse events compared with patients with placebo and open-label tiotropium.

It is believed that the data obtained from the GLOW2 study will be used to support an application for regulatory approval, which is expected to be filed before the end of 2011.

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The results of the GLOW2 follow those announced in April 2011 from the first Phase III clinical trial with glycopyrronium bromide. The GLOW1 study, a double-blind 26-week study met its primary end point by demonstrating superior bronchodilation to placebo at 12 weeks measured by trough FEV1 ($p < 0.001$). Further efficacy and safety results from GLOW2 will be presented at a scientific congress in 2012 and further data from GLOW1 will be presented at the European Respiratory Society Congress in Amsterdam (The Netherlands) in September 2011.

Source: Novartis newsroom: media releases: www.novartis.com/newsroom/media-releases/en/2011/1527049.shtml

CRASH collaborators highlight the potential of a cheap, off-patent drug for brain trauma

Millions of people each year are treated for head injury; however, there is currently no proven effective treatment for this condition, which can frequently involve bleeding into the head, producing further brain damage.

Previous results from the CRASH group have documented a placebo-controlled trial of 20,211 adult patients with trauma, showing that an early administration of a short-course of tranexamic acid (TXA) can reduce blood loss in surgical patients and the risk of death with traumatic bleeding.

"...although the results are not definitive they provide hope about the potential effectiveness of this simple drug for head injury patients."

Since TXA was shown to reduce clot breakdown, the CRASH collaborators hypothesized that it could reduce bleeding into the brain and improve patients' outcomes. To assess this, the CRASH-2 collaborators conducted a nested randomized placebo-controlled trial of 270 patients with traumatic brain injury, named the CRASH-2 trial, to evaluate the effect of TXA on intracranial hemorrhage.

The new results, published recently in the *British Medical Journal*, measured the main outcomes of intracranial hemorrhage growth, between hospital admission and 24–48 h later, including adjustments for Glasgow coma score, age, time from injury to the scan and initial hemorrhage volume.

The analysis was conducted by intention to treat and the main results demonstrated:

- Mean total hemorrhage growth in the TXA and placebo groups were 5.9 and 8.1 ml, respectively (adjusted difference -3.8 ml);
- Six (5%) patients in the TXA group versus 12 (9%) in the placebo group had new focal cerebral ischemic lesions (adjusted odds ratio: 0.51; 95% CI: 0.18–1.44);
- 14 (11%) patients in the TXA group versus 24 (18%) in the placebo group died.

From their results the authors concluded that, "neither moderate benefits nor moderate harmful effects of TXA in patients with traumatic brain injury can be excluded". The researchers noted that, "the nonsignificant trends to beneficial effects justify a randomized controlled trial to evaluate the effectiveness of the early administration of TXA in patients with traumatic brain injury".

According to the collaborators, led by the London School of Hygiene and Tropical Medicine (LSHTM; UK), the results highlight the potential of a simple injection for patients with head injury. Commenting on the LSHTM blog, Pablo Perel, based in the Clinical Trials Unit at LSHTM stated that, "although the results are not definitive they provide hope about the potential effectiveness of this simple drug for head injury patients". He continued, "if such an inexpensive and widely practicable treatment were found to improve patient outcomes after head injury this would have major implications for clinical care". It has been announced that the forthcoming CRASH-3 trial will determine reliably the effectiveness of TXA in patients with head injury.

Sources: CRASH-2 collaborators. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011(343), d3795 (2011); Potential of simple injection on patients with head injury: http://blogs.lshtm.ac.uk/news/2011/07/01/potential-of-simple-injection-on-patients-with-head-injury-2/

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