1 July 2010
EMA/425259/2010
Patient Health Protection

European Medicines Agency 2011 Priorities for Drug Safety Research

Anti diabetic drugs: Cardio/cerebrovascular adverse effect and pancreatitis/ pancreatic cancer

Type 2 diabetes mellitus (T2DM) is a progressive disorder caused by a combination of insulin resistance and beta cell dysfunction. It is associated with an increased and premature risk of cardiovascular disease as well as specific microvascular complications such as retinopathy, nephropathy and neuropathy. Patients with insulin resistance often have several known risk factors for cardiovascular events, such as obesity, dyslipidemia, and hypertension. Other emerging risk factors include hyperinsulinemia, elevated C-reactive protein, elevated plasminogen activator inhibitor levels, and small, dense, low-density lipoproteins.

Oral therapy for type 2 diabetes mellitus can safely assist patients in achieving glycaemic control in the short to medium term. However, the progressive nature of type 2 diabetes usually requires a combination of two or more oral agents in the longer term, often progressing into insulin therapy. The impact of different drugs, even within a single class, on the risk of long-term vascular complications has come under scrutiny (*e.g.* potential detrimental effects of rosiglitazone on myocardial events).

Several new drugs with glucose-lowering efficacy have recently become available. These include (i) injectable glucagon-like peptide-1 (GLP-1) receptor agonists (exenatide, liraglutide) and oral dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin); and (ii) the amylin analogue pramlintide.

Adverse effect reports of cardio/ cerebrovascular disorders and pancreatitis/ pancreatic malignancies have caused concerns regarding the long term use of these therapies*,e..g.* recent publication of evidence suggesting potential detrimental effects of rosiglitazone on myocardial events. Pancreatitis has been reported in sitagliptin and exenatide-treated patients.

The possible relationship between anti-diabetic drugs and the risk of cardio/ cerebrovascular disorders and pancreatitis/ pancreatic malignancies are currently under review of the EMEA. On the basis of the currently available data, a relationship between anti-diabetic drugs and cardio/cerebrovascular disorders and pancreatitis/ pancreatic malignancies cannot be confirmed nor excluded. However, the concerns raised by these data require further in-depth evaluation.

Areas of particular interest for research include:

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8660
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

- The effect of time and/or intensity of anti-diabetic treatment on the likelihood of developing cardio/cerebrovascular AEs and pancreatitis/ pancreatic malignancy
- Determination of the background incidence of cardio/cerebrovascular disorders and pancreatitis/ pancreatic malignancies in the T2DM patient population
- Elucidation of potential mechanisms *e.g.* cancer initiation/promotion
- Dose-response effects
- Identification of risk factors for developing cardio/cerebrovascular AEs and pancreatitis/ pancreatic malignancy in patients treated with anti-diabetics *e.g.* indication for treatment (i.e. disease stage at which each treatment is started), age, sex, disease (including severity), body mass index (BMI), menopausal status, parity, socioeconomic status, prior and during treatment.
- Methodologies for early clinical detection of cardio/cerebrovascular AEs and pancreatitis/ pancreatic malignancy
- Methodologies for screening/predicting patients at high risk of developing cardio/cerebrovascular AEs and pancreatitis/ pancreatic malignancy.

Suitable research methodologies could include long-term epidemiological follow-up studies of T2DM populations, subgroup analyses to study risk factors and important effect modifiers, intensive monitoring studies as methods to capture early stages of diseases, and non-clinical mechanistic studies.