Overview of cardiac adverse drug reactions reported in association with rosiglitazone

Introduction
Recently, the possible effect of rosiglitazone on cardiovascular morbidity and mortality by inducing acute myocardial infarction and acute heart death has drawn a lot of attention [1,2]. Therefore, an overview is provided of all cardiac adverse drug reactions (ADRs) on rosiglitazone, reported to the Netherlands Pharmacovigilance Centre Lareb.

Rosiglitazone (Avandia®) is a thiazolidinedione indicated in the treatment of type 2 diabetes mellitus:

as monotherapy
- in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as dual oral therapy in combination with
- metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulphonylurea

as triple oral therapy in combination with
- metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy

Contraindications include cardiac failure or history of cardiac failure (NYHA class I to IV). Section 4.4 of the EPAR mentions elevated risk of fluid retention and cardiac failure. Increased monitoring of susceptible patients is recommended and because of an increased incidence of cardiac failure observed in clinical trials with concomitant insulin use, rosiglitazone is contraindicated in combination with insulin [4].

Reports
On August the 14th 2007, the Lareb database contained a total number of 109 reports on rosiglitazone. In 21 of these reports, one or more of the reported adverse drug reactions referred to the MedDRA System Organ Class ‘cardiac disorders’.

Lareb received twelve reports directly from pharmacists (5), general practitioners (5), specialist doctor (1) or consumer (1). The other nine reports were sent via Marketing Authorisation Holders (MAH). Five of the patients were male, 16 were female.

Cardiac failure or closely related symptoms were reported in 14 cases. Medical history of these patients included previous heart failure or fluid retention (5
patients), use of cardiac medication like ACE inhibitors, β-Blockers or Calcium-Blockers (5) and in four reports no information was present. One patient suffered from a non fatal cardiac arrest two years of after start of rosiglitazone. The other cases concerned fluid retention without further cardiac complaints or diagnosis (3 patients), palpitations (2), and one patient with unspecified cardiac complaints. In only one of these reports insulin was reported as concomitant medication.

In 4 cases (A, K, P, R) a fatal outcome was reported. These cases will be described in more detail.
Case A was reported by a MAH and concerns a 71 years old female who died according to the primary source reporter from acute liver necrosis and cardiac failure occurred during one of the stages.

Case K reported by a general practitioner concerns a 72 years old male who perceived acute cor pulmonale, one year after start of rosiglitazone. Autopsy showed dilated right ventricle in absence of recent infarction and was interpreted as acute right heart failure.

Case P from a MAH describes a male patient of unknown age with a history including cardiac failure and infarction who perceived deterioration of existing decompensation, unknown time after start of rosiglitazone.

Case R from a MAH concerns a female 84 years old known with end stage heart failure resulting in respiratory failure while on rosiglitazone therapy for unknown time. Autopsy revealed myocardial ischemia, oedema, pleural fluid and pneumonia.

Literature
Rosiglitazone use is associated with mild-to-moderate edema in placebo-controlled clinical trials. A more than two-fold increase in risk for heart failure was noted in the interim analysis of the RECORD trial [3]. The Food and Drug Administration is investigating conflicting data from clinical trials regarding the possible association of rosiglitazone with myocardial infarction and other serious cardiovascular events, including heart-related mortality. Two Food and Drug Administration advisory committees recently recommended that the FDA should keep rosiglitazone on the market, despite concerns about the raised risk of heart attack in some patients [5].

Conclusion
This overview on cardiac ADRs and rosiglitazone reported to Lareb gives some background information. Cases received by Lareb mainly involve cardiac failure or fluid retention. In the majority of these reports pre-existing cardiac history or treatment is present.
References
2. Hoekstra JBL, Bossuyt PMM, de Vries JH. Twijfels aan de cardiovasculaire veiligheid van rosiglitazon.