Takeda UK Limited

Takeda House, Mercury Park,
Wycombe Lane, Wooburn Green,
High Wycombe, Buckinghamshire,
HP10 0HH, United Kingdom.

www.takeda.co.uk

T: 01628 537900
F: 01628 526615

27th March 2007

Dear HealthCare Professional Letter

IMPORTANT SAFETY INFORMATION REGARDING FRACTURES WITH PIOGLITAZONE

Re: Increased Incidence of Fractures in Female Patients Receiving Long-Term Treatment with pioglitazone – containing medicines (ACTOS®, GLUSTIN®, COMPETACT® and TANDEMACT®) in clinical trials

Dear HealthCare Professional,

Further to discussions with European regulatory agencies including the Irish Medicines Board, Takeda UK Limited is writing to inform you of important, new safety data concerning pioglitazone-containing products, i.e., ACTOS®/GLUSTIN® (pioglitazone) Tablets, COMPETACT® (pioglitazone and metformin hydrochloride) Tablets, and TANDEMACT® (pioglitazone and glimepiride) Tablets. These products are used to treat Type II diabetes mellitus. The information may be summarised as follows:

- **Recent analysis of clinical trial data identified an increased risk of fracture in female patients treated with pioglitazone, compared with those treated with a comparator (either placebo or active).**
- **The explanation for this finding is currently unknown and further evaluation is ongoing.**
- **The risk of fracture should be considered in the care of female patients with Type II diabetes mellitus who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered.**
- **There was no increased risk of fracture identified in men.**

Clinical trial data:
Pooling data across the clinical trials, there were more than 8,100 patients in the pioglitazone-treated groups and over 7,400 patients in the comparator-treated groups, corresponding to just under 12,000 patient years exposure per group.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is therefore 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%) of pioglitazone treated female patients experienced fractures compared to 23/905 (2.5%) of patients treated with comparator.

The risk of fractures should be considered in the long term care of women treated with pioglitazone.

The explanation for this finding is currently unknown. It should also be noted that none of the pioglitazone studies in the database addressed, or were designed to, study the effect on bone, but reports of fractures were collected as part of the adverse event data collection. Due to the limitations of the existing dataset, multiple known risk factors for fractures cannot be excluded as confounding variables. Further evaluation of these findings is ongoing.

The risk of fracture and need for appropriate management should be considered in the care of patients, in particular female patients, when treating or considering treatment with Pioglitazone.

Any suspected adverse drug reactions should be notified to the Irish Medicines Board or the company in the usual way.

Should you have any questions or require additional information, please contact the Head of Medical Affairs on +44 1628 537921 or the Takeda Medical Information Department on +44 1628 537900.

Yours faithfully

Michelle Swift
Head of Medical Affairs