Application No: 99.867.5
File No: 2000/029709 clin

Request for ADEC Advice
August, 2000

Application Type: 1 A (New Chemical Entity)

Product: Actos® brand of pioglitazone hydrochloride.

Applicant: Eli Lilly Australia Pty Ltd

Dose Form: Uncoated tablets containing base equivalent 15, 30 and 45mg pioglitazone.

Requested Indication:
ACTOS is indicated for the treatment of type 2 diabetes mellitus inadequately controlled by diet. ACTOS is effective as a single agent and may also be used in combination with sulfonylureas, metformin or insulin when diet plus the single agent does not result in adequate glycaemic control.

Dosing Regimen:
30mg daily, taken as a single dose with or without food. After four weeks the dose may be increased to 45mg daily.

Background:
Pioglitazone is a thiazolidinedione derivative that has structural similarities to troglitazone and rosiglitazone. Eli Lilly claims that pioglitazone, unlike rosiglitazone, raises HDL-cholesterol, lowers plasma triglycerides and free fatty acids.

This application included a full data package. Full individual patient data were not supplied by the applicant and were not requested by the clinical evaluator. The FDA evaluation reports were also made available.

Since the application was made, pioglitazone was registered in the USA (to Takeda Pharmaceuticals and to Eli Lilly) and in the EU (to Takeda Pharmaceuticals).

PART II
The pharmaceutical chemistry evaluator notes that the molecule has one chiral centre and that pioglitazone is supplied as a racemic mixture. Pioglitazone is practically insoluble in water and is present as a single crystal form. Specifications for the active, including particle size, are satisfactory. All chemistry and quality control matters have been resolved.

Five bioavailability studies were reviewed. None involved the 30mg tablet proposed for registration. The 15mg and 45mg tablets were found to be bioequivalent (rate & extent of absorption) in a 2 period, open, crossover study in 24 healthy male volunteers. A justification for not conducting a bioequivalence study on the 30mg tablet was considered acceptable regarding part II matters.

A fed v fasting study, using the 45mg tablet, in 23 healthy male and female volunteers, suggested that food slowed the rate of absorption but did not affect the extent of absorption of pioglitazone. In fact, C_{max} was 18% higher in the fed state.

An absolute, open bioavailability study included 7 male volunteers who completed the study. The 7.5mg tablet is not proposed for registration [and its relationship to the proposed formulations is unclear]. The absolute bioavailability of a 7.5mg oral tablet v 5mg IV infusion was c. 83%. The pharmaceutical subcommittee noted that pioglitazone is metabolised by CYP 3A4 and has some active metabolites. The Subcommittee noted a lack of drug interaction studies. Suggestions were made in respect of the product information document.

Comments: Inspection of the labels suggests that each product does not have a distinct trade name i.e. they are not named Actos®15, Actos®30 & Actos®45 but Actos® without a qualifying term to reflect the strength.

The clinical aspects of a justification for not conducting a bioequivalence study on the 30mg strength are acceptable. The presence of active metabolites is part of this justification. These were shown to have similar elimination half lives to pioglitazone in study PNFP-018.

PART III

The preclinical evaluator notes that almost all of the data comply with GLP requirements.

Pioglitazone increased insulin sensitivity in several animal models of insulin resistance. In rat and murine models, dose-dependent reductions in plasma glucose, triglycerides and non-esterified fatty acids were observed. Pioglitazone was not effective in rats with insulin deficiency. The preclinical data suggested that pioglitazone exerts its effect on pathways distal to the insulin receptor. There is increased sensitivity to insulin in the liver, adipose tissue and skeletal muscle. There were 3 active metabolites: M-II, M-III and M-IV of which M-IV is the predominant human metabolite. It exists as **four** stereoisomers. Their activities are not known.

Pioglitazone was associated with plasma volume expansion and with cardiac hypertrophy in rats and dogs. This effect was also noted in insulin-deficient rats, suggesting it is attributable to pioglitazone. Sodium retention may contribute to the plasma volume expansion.

With regard to toxicokinetic calculations, pioglitazone was orally bioavailable in rats, dogs, mice, cynomolgus monkeys and humans. Metabolic pathways were broadly similar. The exposure to total active compounds may be higher in humans at the therapeutic doses than in all species tested (see table 1.1, page 10 of the report). The toxicities seen in adipose tissue, myocardium, bone marrow and urinary tract (transitional cell epithelium) are therefore possible at therapeutic doses.

Pioglitazone was not carcinogenic. It was not teratogenic but was associated with increased post-implantation losses in rabbits and rats.

Overall, a lack of interaction data with other antidiabetic drugs was of concern.

Amendments to the text of the product information document have been suggested.

Part IV

The clinical evaluator notes that three studies contributed pharmacodynamic data from patients with non-insulin dependent diabetes mellitus. These enrolled a total of 90 male and female patients and were respectively of single blind, open and double blind design. The doses used ranged from 15, 30 or 60 mg/day for 2 weeks in the first study and 30mg per day for 12 weeks only in the second and third studies. The evaluator noted a fall in triglycerides in the first two studies, evidence of improved glycaemic control (lowered fasting plasma glucose, increased insulin sensitivity).

The volume of distribution was small after IV administration (c. 18.75L). Pioglitazone was poorly distributed into erythrocytes. A radiolabel study suggests that the metabolites of pioglitazone appear in the urine and the faeces in similar amounts. Pioglitazone is extensively metabolised: two metabolites (M-III and M-IV) are active. Pioglitazone has an elimination half-life of c. 5h but M-III and M-IV have elimination half lives of >1 day.

A multidose 7 day study in 56 males suggested dose proportionality for $AUC_{144\text{-}168h}$ over a dose range of 2-60mg pioglitazone daily.

Moderate renal impairment did not impair the clearance of pioglitazone but severe renal impairment (creatinine clearance < 30mL/minute) resulted in lower AUC values for pioglitazone and M-III and M-IV. Hepatic impairment may not have had a significant effect upon the total exposure to pioglitazone and its active metabolites.

Elderly (ages 65-73 years) subjects achieved slightly higher AUC values than middle aged (35-49 years) adults.

Female subjects tended to exhibit a higher AUC for pioglitazone and M-III than males, and a less marked increase in AUC for M-IV versus males. The evaluator did not consider these differences to be important.

Drug interaction studies suggested no interactions with warfarin, phenprocoumon, digoxin, metformin and glipizide.

Efficacy

1. Monotherapy

The studies are summarised at pages 46-54 of the report.

Study PNFP-001.6 was a phase II-III, double blind, placebo-controlled, 6 month dose ranging (7.5, 15, 30 or 45mg per day of pioglitazone) study in type 2 diabetic patients. After a placebo 8 week run-in period, 408 patients were randomised, of whom 202 completed 26 weeks of double blind treatment. The results are tabulated at pages 95-103 of the report. 7.5mg pioglitazone daily was ineffective. The higher doses showed an initial latency period to onset of effect. Fasting C-peptide levels and serum triglycerides also showed a treatment effect that was dose-dependent.

Study EC 201 was a randomised, placebo controlled, double blind study in 56 centres that compared placebo to pioglitazone 15 or 30mg/day in patients already on diet therapy. A 10 week diet therapy run-in was followed by a 26 week study drug phase. There were 76, 83 & 76 patients in each respective group. The ITT results regarding HbA_{1c} are shown on page 79 of the report.

Study PNFP-012.2 was a double blind; placebo controlled parallel group study with dose escalation to 30 or 45mg pioglitazone daily. It is of note that glycaemic control was improved in both active treatment groups but blood lipid changes showed a dose dependent effect - see pp.84-85.

Study EC204 included a 4-8 week run-in with diet therapy + placebo followed by placebo or pioglitazone (escalated to 45mg daily) or glibenclamide (escalated to 5mg daily) for 26 weeks.

Of 270 randomised patients, 212 completed. Both active treatments were statistically superior to placebo in terms of glycaemic control. Glibenclamide tendered to be superior regarding HbA_{1c} but this did not reach statistical significance. Pioglitazone was associated with a significant fall in fasting C-peptide levels.

Combination therapy

These studies involved the addition of pioglitazone to existing oral treatments or insulin. The studies were of four months duration, after a screening and run-in period.

The doses of pioglitazone, as add-on therapy, were 15 or 30mg daily. The designs were similar: randomised, double blind, parallel groups.

Study PNFP-010 was in patients poorly controlled on sulfonylureas.

Study PNFP-014 involved patients on insulin alone or with pioglitazone.

Study PNFP-027 included patients poorly controlled with metformin.

All three studies provided significant evidence of benefit, for both 15mg & 30mg pioglitazone daily over 4 months, in terms of glycaemic control.

Overall, the evaluator was of the view that pioglitazone was effective in improving glycaemic control whether as monotherapy or as add on therapy. Lipid changes included a fall in triglyceride levels, a rise in HDL levels and a minor rise in LDC cholesterol levels.

Safety

Upper respiratory tract infection, peripheral oedema, myalgia and weight gain were associated with proglitazone treatment and less so with control treatments. A fall in haematocrit and haemoglobin was attributed to haemodilution.

The evaluator notes that patients with pre-existing ischaemic heart disease and cardiac failure were not included in the studies. [Echocardiographic data from two studies of efficacy and safety were presented. No treatment associated effects were seen.]

A number of changes to the product information document have been suggested.

Overall, the evaluator finds in favour of registration for the proposed indication but suggests a maximal dose of 45mg pioglitazone/day.

Additional data
On 18th July, 2000 the European Agency for the Evaluation of Medicinal products announced that the CPMP recommended the granting of marketing authorisation. This was a restricted approval (to Takeda Europe): The approved indication is: "Pioglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose (sic) of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients.
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated."

It is of note that additional trials will be performed to address potential long-term cardiovascular safety concerns. This reflects the lack of data in patients with cardiovascular disease, in particular cardiac failure.

The applicant has provided copies of the EMEA's questions and Takeda's responses. The narrative components are supplied to the Committee for information.

Eli Lilly also provided copies of US adverse event reports.

COMMENTS

At the present time, the risk:benefit balance supports registration. The beneficial effect on lipids is an advantage over rosiglitazone, however the EMEA has identified a rise in LDL-cholesterol in the most obese.

Long term weight gain is a common effect of other registered oral antidiabetic drugs.

PROPOSED ACTIONS

I propose to register pioglitazone as proposed by the applicant. The maximal daily dose should be 45mg per day. The applicant should amend the text of the product information documents in line with the evaluators' suggestions.

Submitted to the ADEC for advice.

Neil Mitchell

Dr Neil Mitchell
Delegate of the Secretary
21st August 2000