SCIENTIFIC DISCUSSION

1. Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.
Therefore, consent from the MAH of the Competact application, which had been submitted as a full application under Art 8(3) of Directive 2001/83/EC as amended, has been given allowing access to Module 2 to Module 5 of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved.

Competact is indicated in the treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone. This formulation combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: pioglitazone, a member of the thiazolidinedione class and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones act primarily by reducing insulin resistance and biguanides act primarily by decreasing endogenous hepatic glucose production.

Quality, safety and efficacy of Pioglitazone/Metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets are identical to the up to date quality, safety and efficacy profile of Competact.

The application for Pioglitazone/Metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets consists only of Module 1 information.

The approved indication is: treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.

2. Quality aspects

Since this application is an informed consent of the Competact application, the quality data in support of the Pioglitazone/Metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets application are identical to the up-to-date quality data of the Competact dossier which have been assessed and approved (including all post-marketing procedures).

3. Non-clinical aspects

Since this application is an informed consent of the Competact application, the non-clinical data in support of the Pioglitazone / metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets application are identical to the up-to-date non-clinical data of the Competact dossier, which have been assessed and approved (including all post-marketing procedures).

4. Clinical aspects

Since this application is an informed consent of the Competact application, the clinical data in support of the Pioglitazone / metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets application are identical to the up-to-date clinical data of the Competact dossier, which have been assessed and approved (including all post-marketing procedures).

- User Consultation

Consultation with target patient groups has not been undertaken for Pioglitazone / metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets. However as part of a follow up measure for the reference product Competact, readability testing was performed and reviewed by the CHMP. The updates to the Competact Package Leaflet in view of the assessment of this follow up measure have also been taken into account in the Pioglitazone/Metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets package leaflet.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table: Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Hepatic dysfunction	1. Routine pharmacovigilance including review in PSURs 2. Annual review and report on Hepato-biliary events. 3. Results from completed hepatic safety study in pioglitazone 4. Trend analysis on frequency of reporting.	Contraindication for use in hepatic impairment in section 4.3 of the SPC. Precautions and recommendations for assessing ALT levels in section 4.4 of the SPC. Elevated hepatic function tests and hepatocellular dysfunction in section 4.8
Heart failure	1. Routine pharmacovigilance including review in PSURs 2. Analysis from ongoing clinical trials 3. Final analysis of PROactive long-term trial.	Contraindication in section 4.3 of the SPC Precautions and recommendations in section 4.4 of the SPC.
Weight gain / peripheral oedema	1. Routine pharmacovigilance including review in PSURs 2. Results from PROactive study 3. Analysis from ongoing clinical trials 4. Pioglitazone clinical trial to investigate mechanisms 5. Review of ADR reports to assess compliance with SPC recommendations	Precautions and recommendations in section 4.4 of the SPC.
Neoplasia	1. Routine pharmacovigilance including review in PSURs 2. Analysis from ongoing clinical trials 3. Final study report from PROactive study and long term follow up. 4. Analyses from KPNC cohort study	Statement of finding of bladder hyperplasia / neoplasia in rats in section 5.3 of the SPC.

	5. Non-clinical study in male rats	
Macular oedema	1. Routine pharmacovigilance including review in PSURs. 2. Pioglitazone clinical trial to investigate mechanisms	RMP, risk minimisation for macular oedema: Warning in Section 4.4 of the SPC for macular oedema and decreased visual acuity; mentioning of macular oedema as ADR in Section 4.8 SPC.
Bone fracture	1. Routine pharmacovigilance including review in PSURs. 2. Expert consultation to evaluate feasibility of further investigations.	Section 4.4 and 4.8 of the SmPC and the Package Leaflet updated to reflect finding.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Since this application is an informed consent of the Competact application, the CHMP considered that the risk-benefit balance of Pioglitazone / metformin hydrochloride Takeda 15 mg/850 mg film-coated tablets was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

Treatment of type 2 diabetes mellitus patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone.