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Assessment report for Actos, Glustin, Competact, Glubrava, Tandemact

INN: Pioglitazone, pioglitazone+glimepiride, pioglitazone+metformin

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Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Executive summary

Pioglitazone was first approved in 1999 in the United States and in 2000 in the European Union as Actos. Pioglitazone is also authorised in the EU as the fixed-dose combination products Competact and Glubrava (pioglitazone + metformin) and Tandemact (pioglitazone + glimepiride). Pioglitazone is a member of the thiazolidinedione (TZD) class of antidiabetic agents.

The issue of bladder cancer was discussed at the level of the Pharmacovigilance Working Party (PhVWP) meeting in February 2011, following an increase of reports of bladder cancer in the United States as well as seven new cases reported in France. A review of the available evidence on bladder cancer risk with pioglitazone was initiated, including studies conducted by the MAH, preclinical data and the Eudravigilance database. This review included interim data from the KPNC study, a ten year cohort study with a nested case control study conducted among patients with diabetes, designed to investigate all types of cancer and specifically bladder cancer incidence in association with pioglitazone use. The CHMP considered that the accumulated evidence in totality represented a clinically relevant signal that required further evaluation.

On the basis of this new information, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004, requesting the CHMP to assess the impact of this new information on the benefit-risk balance for the centrally authorised pioglitazone-containing medicinal product and to give its opinion on measures necessary to ensure the safe and effective use of pioglitazone-containing medicinal products and on whether the marketing authorisation for these products should be maintained, varied, suspended or revoked.

2. Background information on the procedure

Pioglitazone is a member of the thiazolidinedione (TZD) class of antidiabetic agents. TZDs improve glycaemic control by improving insulin sensitivity at key sites of insulin resistance by binding to nuclear peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake. By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, the drug improves the patients' sensitivity to insulin. This mechanism is unique to the TZD class.

Pioglitazone was first approved in 1999 in the United States. First approval in Europe was in 2000, via the Centralised procedure, for the treatment of non-insulin dependent diabetes mellitus. At the time of approval, the CHMP considered that the benefit/risk profile of pioglitazone was favourable for a restricted indication in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea in combination with metformin or with a sulphonylurea. In 2006, the indication was extended to the use of pioglitazone as triple oral therapy in combination with metformin and a sulphonylurea, in patients with insufficient glycaemic control despite dual oral therapy (II/0024) and in 2007, a new therapeutic indication for use of pioglitazone in combination with insulin was approved (II/0025). Pioglitazone is therefore currently authorised under the names Actos and Glustin in the following indications:

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

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

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

Pioglitazone is also authorised as the following combination products:

- Competact and Glubrava (pioglitazone + metformin) are authorised for 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.
- Tandemact (pioglitazone + glimepiride) is authorised for the treatment of patients with type 2 diabetes mellitus who show intolerance to metformin or for whom metformin is contraindicated and who are already treated with a combination of pioglitazone and glimepiride.

The latest PSUR (23rd) estimates the worldwide exposure to pioglitazone to over 20 million patient-years.

At the time of initial marketing authorisation, the pre-clinical data on pioglitazone raised concerns of urothelial hyperplasia with progression to bladder carcinoma in rat lifetime studies, which identified tumours in the urinary bladder of male rats. It was agreed that information relating to this issue should be monitored closely post-marketing and in the context of the granting of the marketing authorisation, the MAH agreed to put in place follow-up measures to monitor diabetic patients in a post-marketing surveillance study. Subsequent to the authorisation, the MAH conducted a mechanistic study into the cause of tumours in the male rat, concluding that pioglitazone caused a hyperplastic response in the urinary bladder of the rat that was not necessarily associated with microcrystal formation. As a consequence, section 5.3 of the SPC was updated with information on this mechanistic study with a sentence stating that the relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

The clinical signal for the potential association between pioglitazone use and bladder cancer arose from the PROactive (PROspective pioglitAzone Clinical Trial In MacroVascular Events) study where there was a noted imbalance between cases of bladder cancer in patients exposed to pioglitazone compared to patients on placebo. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, due to the biological implausibility of bladder cancer developing in such a short time period, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Based on the limited data in humans to address the issue of bladder cancer risk with pioglitazone treatment, the MAH committed to perform a ten year cohort study with a nested case control study conducted among patients with diabetes with the objective being the measurement of incident malignancies associated with pioglitazone treatment. The data source chosen was members of Kaiser Permanente Northern California (KPNC) healthcare system identified from the diabetes registry, which gathers data from a variety of KPNC electronic medical records to build and follow the registry cohort over time. The KPNC pharmacy database includes information on each outpatient prescription dispensed at a KPNC pharmacy. The KPNC epidemiological study was designed to investigate all types of cancer and specifically bladder cancer incidence in association with pioglitazone use. The study is currently ongoing and interim analyses have been submitted to the CHMP in August 2005, August 2007 and December 2009.

The issue of bladder cancer was discussed at the level of the Pharmacovigilance Working Party (PhVWP) meeting in February 2011, following an increase of reports of bladder cancer in the United States as well as seven new cases reported in France. A review of the available evidence on bladder cancer risk with pioglitazone was initiated, including studies conducted by the MAH, preclinical data and the Eudravigilance database. A report was submitted to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency in March 2011. The CHMP considered that the accumulated evidence in totality represented a clinically relevant signal that required further evaluation. Therefore the European Commission initiated an article 20 procedure of Regulation (EC) No 726/2004 to assess the safety concern of bladder cancer and its impact on the benefit-risk balance of the centrally authorised products containing pioglitazone. The European Commission requested the Committee to give its opinion as to whether measures were necessary to ensure the safe use of these medicinal products and specifically on whether the marketing authorisation should be maintained, varied, suspended or withdrawn.

3. Scientific discussion

3.1. Non-clinical data

The MAH stated that pioglitazone has important efficacious effects in various rodent models of type 2 diabetes mellitus (T2DM), which have led to useful biomarkers in humans. Pioglitazone has favourable effects on the lipid profiles in these animals that are also seen in humans with T2DM, and can also reduce blood pressure in these animal models. However, pioglitazone is also associated with weight gain, the presence of urinary calculi and solids in the bladder. Cardiac hypertrophy occurs in rodents and non-rodents alike. In particular, at the time of initial marketing authorisation, the pre-clinical data on pioglitazone raised concerns of urothelial hyperplasia with progression to bladder carcinoma in rat lifetime studies, which identified tumours in the urinary bladder of male rats. The MAH provided a rationale for why this effect was considered species specific and not transferable to humans, proposing the "crystal hypothesis" according to which the acidic urinary environment of rats predisposes them to microcrystal formation. Tumours were considered secondary to mucosal irritation caused by urinary solids. This mechanism, the alteration of the urinary milieu, has not been generally found in T2DM subjects in the form of renal or urinary stones or solids. However, it was agreed that information relating to this issue should be monitored closely post-marketing and in the context of the marketing authorisation, follow-up measures were put in place to monitor diabetic patients in a post-marketing surveillance study. The MAH conducted a mechanistic study investigating the cause of tumours in the male rat, concluding that pioglitazone caused a hyperplastic response in the urinary bladder of the rat that was not necessarily associated with microcrystal formation. As a consequence, section 5.3 of the SPC was updated with information on this mechanistic study with a sentence stating that the relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

In the case of bladder cancer in the male rat, the CHMP concluded, as have others, that the mechanism is indirect via alterations in the urinary milieu. These alterations result in the formation of urinary solids and crystalluria with calculi formation that settle among the rugae of the ventral surface of the bladder in the quadrapedal rat. They result in chronic minor irritation and inflammation, which is followed by hyperplasia, metaplasia, and ultimately in some animals, cancer over the 2-year duration of the mechanistic study. This mechanism is considered by most to be rodent specific and not to be reflective of human risk (Suzuki 2010) despite the confounding findings of slight hyperplasia in the two-year mechanistic study (Sato 2011). While the MAH acknowledged that the data does not rule out the possibility of an association between pioglitazone and bladder cancer in humans, the CHMP was of the opinion that the preclinical evidence amplify the concerns raised by the signal of bladder cancer identified from the clinical database.

3.2. Clinical safety

3.2.1. Usage patterns

GPRD utilisation study

The MAH presented the overall exposure to pioglitazone in Europe from launch to 31 Jan 2011, showing a total exposure in the EU of 3,340,000 patient years for the mono-product, 1,017,750 for the pioglitazone + metformin combination and 11,200 for the pioglitazone + glimepiride combination. The MAH conducted a GPRD (UK General Practice Research Database**)** drug utilisation study (AD-4833-408) which included all diabetic patients in the GPRD who received at least 1 prescription for pioglitazone, alone or in combination therapy with other oral antidiabetic drugs, or insulin, between 1 Jan 2000 and 31 Dec 2010. Patients must have had at least 12 months between the latest patient registration at the practice and the first pioglitazone prescription in order to ensure sufficient time for recording prior antidiabetic therapies. Continuous exposure was assumed in the absence of gaps greater than one month between the end of one pioglitazone prescription and the start of the next. The level of increased prescribing of pioglitazone was also investigated. 26,044 patients satisfied study criteria. The MAH concluded that the rate of prescribing increased per year until 2008 after which it seems to have stabilised.

Prior to pioglitazone treatment, over 90% of patients had prior oral antidiabetic treatment, the majority of patients were prescribed metformin (60-80%) or gliclazide (20-40%). Some patients were on more than one other oral antidiabetic agent. Between 80-90% of patients on pioglitazone were on concomitant treatment, mainly with metformin. In patients that stopped pioglitazone treatment, 20% were switched to insulin, with or without metformin. In later years, based on other therapies available,

10% of patients began treatment with DPP-IV inhibitors or GLP-1 agonists. For patients on continuous treatment (> 2 months), there was a similar distribution between patients on pioglitazone treatment less than one year (approx 40%) and those on treatment for longer than 2 years (approx 45%), based on data from 2005, 2006 and 2007. The MAH noted a possible underestimation in patients initiated on therapy in the hospital setting, as GPRD will record a later prescription initiation and patients will therefore be on treatment longer than described by GPRD. Around 50% of male patients had a treatment duration of above 2 years in all age groups except those aged above 80 years. Around 28% of patients were less than 50 years at treatment start, 31% were between 50 and 60 years, 27% were between 60 and 70 years and 14% were aged 70 and older. The study data identified that those that stay on treatment for 12 months tend to stay on treatment for between 2 to 5 years, and some are on treatment for longer. Those between aged 50 – 70 years have the longest duration of therapy.

The CHMP noted the MAH calculations and conclusions. The CHMP also noted that the data shows that from 2007 onwards, prior to initiation of pioglitazone therapy, rosiglitazone was used in 10-20% of patients. This suggests that PPAR activation of receptors occurred prior to initiation of pioglitazone treatment. It is considered significant that patients were exposed to thiazolidinedione therapy for longer than apparent in the GPRD database, as a study Ramos-Nino, 2007, identified an association between rosiglitazone and cancer in 1003 patients in the Vermont Diabetes Information System. In this study, there was an overall significant association between cancer and thiazolidinedione treatment (OR 1.59, p=0.04), mainly due to rosiglitazone. There was no significant association between pioglitazone and cancer. The CHMP considered that the utilisation data demonstrates that there is a similar pattern of pioglitazone prescribing across age groups. Female median durations of therapy are slightly lower, but from evaluation of the graphical statistics, the pattern of use between the genders does not appear to be significantly different.

3.2.2. Epidemiological data

The MAH noted that the currently available epidemiological literature shows clear evidence of an increased risk of cancer in patients with type 2 diabetes, and an increased risk of bladder cancer in particular with Larsson et al (Larsson 2006) calculating significant relative risks of 1.37 in case control studies (95% CI: 1.04-1.80) and of 1.43 in cohort studies (95% CI: 1.18-1.74) in a meta-analysis of epidemiological data. The MAH presented the expected incidence rate of bladder cancer in patients with type 2 diabetes mellitus and concluded that the reporting rate of bladder cancer seen in patients treated with pioglitazone is not in excess of the incidence seen in the general diabetic population. The epidemiology of bladder cancer also shows that the risk increases with age in the general population, and there is no evidence that these trends do not apply to the type 2 diabetes population. The progressive nature of type 2 diabetes, requiring changes in pharmacotherapy over time, adds complexity to studies of a long-term outcome such as bladder cancer incidence, as patients are simultaneously aging and developing more progressive disease. Mackenzie et al (MacKenzie 2011) estimate an increased relative risk in patients with the longest diabetes duration (odds ratio for 16 or more years of 3.6, 95% CI: 1.1-11.2) suggesting that disease severity/duration may confer additional increased risk. Pioglitazone is not approved in the EU as first-line therapy in type 2 diabetics and the MAH therefore considered it to be extremely difficult to assess the independent association between pioglitazone use and bladder cancer risk relative to other medications and that there are no solid data to substantiate such a risk. The MAH considered that whilst it is clear from the literature that there is an increased risk of bladder cancer in patients with type 2 diabetes, it is difficult to be certain whether there is any additional increased risk in patients with type 2 diabetes treated with pioglitazone.

Kaiser Permanente Northern California (KPNC) study (3rd interim analysis)

Cohort data from the third interim analysis, submitted in December 2009, identified no significant association between having ever used pioglitazone and bladder cancer (HR 1.2, 95% CI 0.9-1.5). However, long term treatment (>2 years) of pioglitazone was significantly associated with bladder cancer (HR 1.5 95% CI (1.1-2.0). This was associated with a significant test for trend (p=0.01) such that by four years of treatment, the hazard ratio (HR) would increase to 1.7. Patients that were exposed to high cumulative doses greater than 28,000 mg had a statistically significant increased risk of bladder cancer (HR 1.5 95% CI 1.1-2.2). A nested case control study was conducted in order to match the cases and controls on every potential exposure of interest. This analysis produced an odds ratio (OR) of 2.7 (95% CI 1.5-4.9) for the risk of bladder cancer in cases compared to controls that had ever been exposed to pioglitazone. Likewise in this nested case control study, duration of use and high cumulative dose of pioglitazone were significantly associated with bladder cancer. The KPNC authors considered that the results of this nested case control study were biased because controls that

participated were less likely to be current users of pioglitazone compared to controls that did not participate (controls participant 8% vs. controls non participant 13%, p=0.051). Use in participant cases was not significantly different to non-participant cases (cases participant 17% vs. cases non participant 13%, p=0.33). Pioglitazone exposure was similar in participants and non-participants. Sensitivity analyses and weighted analysis produced results similar to the cohort study.

Detailed information on the histopathology of the cases of bladder cancer observed in the pioglitazone exposed group (90 cases) compared to the unexposed group (791 cases) was provided by the MAH. A distribution of cancer stage by exposure status was provided. Regarding the histology, ICD-O histology codes recorded in the KPNC Cancer Registry were used to categorise each cancer as either invasive or in situ and to describe the histology of the cancer. All histology categories for which there were fewer than 5 patients in each of the strata based on medication exposure and invasiveness were combined. ICD-0 data was missing for 15 patients (1 pioglitazone exposed and 14 non-exposed). The majority of cancers in both groups were *in situ* carcinoma, with 9% of the bladder cancers in non-pioglitazone patients classified as regional or advanced at the time of diagnosis vs. 3% in the pioglitazone group. The reasons for this lower incidence of regional or advanced bladder tumours in the pioglitazone exposed group are unknown. For in situ cancer, the distributions of papillary and non-papillary transitional cell carcinoma were similar between exposed and unexposed patients (48.2% and 41.3% respectively). For invasive cancer, pioglitazone exposed patients were more likely to have papillary transitional cell carcinoma 62.5%) and less likely to have transitional cell carcinoma (30%) although this difference was not statistically significant. The KPNC investigators did not assess for bladder cancer related mortality due to the difficulty in assigning cause of death. The CHMP considered that there were no significant differences in cancer histology between patients exposed and unexposed to pioglitazone treatment in the KPNC study.

The MAH also clarified that the use of wide categories in the age adjustment did not lead to an underestimate of risk in the cohort study, by providing results of analyses adjusted for sex and age in 5 and 10 year intervals. As both models produced almost identical, it was considered extremely unlikely that categorisation of age led to an underestimate of risk in the cohort study. The CHMP was reassured that adjusting to a 5 year interval makes no difference to the results of the analysis.

Regarding smoking and the potential for further analysis of the impact of confounding due to smoking history and how it was adjusted for, the MAH provided responses stating that adding smoking to the age- and sex-adjusted HRs resulted in only a very small change in the measured association between pioglitazone and bladder cancer. A possible interaction between smoking and pioglitazone exposure was also tested for by conducting stratified analyses and including an interaction term to the age-, sex-, and other diabetes medications adjusted model. The HR in pioglitazone-exposed smokers was 0.94 (95% CI 0.56-1.59) and among pioglitazone-exposed non-smokers the HR was 1.35 (95% CI 1.03-1.77). The test for interaction was not close to significance (P=0.47). Thus, while the association is statistically significant among non-smokers, there is no statistically significant interaction between pioglitazone and smoking. The CHMP noted that the inclusion of smoking in the adjustment of the hazard ratio appeared overall to not affect it, most likely due to the equal numbers of current smokers in both groups (pioglitazone exposed vs. unexposed). Stratification of the data by smokers showed that the hazard ratio for bladder cancer risk in current smokers was less than the hazard ratio in non-smokers. The bladder cancer risk in non-smokers using pioglitazone was significantly greater (1.35x) compared to those not exposed to pioglitazone. However, it was noted that smokers were categorised as current, not current or missing (with 'missing' grouped with 'not current'). The CHMP concluded that smoking does not have a significant effect on the HR calculated for pioglitazone.

Based on the results from the third interim analysis of the KPNC study, the MAH provided an estimate on the absolute risk posed by long-term pioglitazone therapy and the population impact (based on EU exposure) according to duration of therapy: Less than 1 year HR=0.8 (0.6-1.3); 1 to 2 years HR=1.4 (0.9-2.1); more than 2 years HR=1.4 (1.03-2.0). In order to estimate the absolute excess risk of bladder cancer in patients using pioglitazone, age specific rates were used from the Surveillance Epidemiology and End Results database in the United States (SEER) using data from 2000 to 2008, SEER17, and applied to the distribution of duration and age at initiation from the General Practice Research Database (GPRD) utilisation study conducted by the MAH. The SEER database was used to provide background rates because it provides age-specific incidence rates. The epidemiology of bladder cancer shows that rates are around 4 times higher in males than females, but as there is no reason to expect that gender affects the decision to prescribe pioglitazone, combined gender rates have been used for all age groups and analyses. The GPRD utilisation study was used to identify the distribution of duration of pioglitazone exposure for the years 2005, 2006, and 2007. The percentages used for the calculation were 40% for discontinuation within 1 year, 15% discontinuation between 1 and 2 years

and 45% remaining on therapy for more than 2 years. Incidence rates were calculated for type 2 diabetes patients unexposed to pioglitazone by applying the increased risk of 1.4 estimated by Larsson et al (Larsson 2006) to the age group specific rates from SEER. Incidence rates were calculated for type 2 diabetes patients exposed to pioglitazone by additionally applying the HRs from the KPNC study to the age specific incidence rates for type 2 diabetes, with the age distribution of pioglitazone initiation estimated from the GPRD utilisation study. The MAH also provided explanations on the methodology used for calculating the absolute risk of bladder cancer.

The most recent cumulative pioglitazone exposure data estimate 4,368,950 patient years of pioglitazone exposure in the EU since launch. Based on the background incidence rates of bladder cancer rates in type 2 diabetes patients, 2845 bladder cancers would be expected during 4,368,950 patient years in patients unexposed to pioglitazone.

The CHMP agreed with the MAH use of the KPNC hazard ratios to estimate the incidence of bladder cancer in patients exposed to pioglitazone. According to the KPNC data there is no statistically significantly increased risk of bladder cancer for patients exposed to pioglitazone for less than 2 years, and therefore the estimates for these patients should be similar to the baseline incidence for type 2 diabetes. The only observed increased risk was in patients exposed for more than two years. The CHMP noted that the French CNAMTS study (below) did find a statistically significant association with 1 to 2 years use as well as with use greater than two years, which differs from the KPNC study findings. However, taking into account the hazard ratios for ever use from the KPNC and the French CNAMTS studies and the various methodological aspects, the estimated relative risk for ever use are broadly consistent. The CHMP noted the MAH calculation of an absolute risk for bladder cancer in the EU equating to an excess of 10 in 100,000 person years. As the hazard ratios identified in both the KPNC and the French cohort studies were similar, the CHMP considered the absolute risk estimated by the MAH using the KPNC hazard ratios to be largely unchanged by the availability of the French data if the same methodology was applied to calculating the absolute risk. The CHMP noted that the absolute risk estimate provided by the MAH is a crude estimate which will vary significantly with age.

French Cohort Study by CNAMTS (Caisse nationale de l'assurance maladie des travailleurs salariés) on the potential association between pioglitazone exposure and bladder cancer risk

This cohort study was conducted at the request of the French national agency (Afssaps) to investigate the existence of a possible link between exposure to pioglitazone and the incidence of bladder cancer in French diabetic patients.

The study was conducted using data from the SNIIRAM (National inter-scheme health insurance system) linked to PMSI (information systems medicalisation program) data. This ensured two totally independent databases in terms of data collection, using both diagnoses and hospital reimbursement data. The study included 1,491,060 diabetes patients (diabetes being defined as being treated with an anti-diabetic) who were beneficiaries of the general French health insurance system and aged between 40 and 79 years in 2006. Any patients who had bladder cancer before entry into the cohort or within 6 months of joining the cohort were excluded. Exposure to pioglitazone (and to each antidiabetic treatment) was defined in SNIIRAM by being prescribed the active ingredient at least twice over 6 consecutive months. The study covered a four year period, from 2006 to 2009. Cases of bladder cancer were identified through hospitalisations recorded in PMSI for patients with a principal diagnosis or associated diagnostic of bladder cancer and who received, during the same hospitalisation, a powerful surgical tracer and/or bladder instillation of a pharmacological active substance by urethral catheterisation and/or chemotherapy and/or radiotherapy. The relationship between exposure to each type of diabetes treatment and the incidence of cancers of the bladder, lung, otorhinolaryngologic, colorectal, female breast cancer and kidney were assessed by hazard ratio (HR), estimated by Cox models adjusted to age, gender and other diabetes treatments. The dose-effect relation was studied by classifying patients according to cumulative doses and duration of exposure. The group exposed to pioglitazone was compared to the unexposed group for variables related to smoking, the main risk factor for bladder cancer.

The group exposed to pioglitazone included 155,535 diabetic patients and the non-exposed group included 1,335,525 diabetic patients. There were 175 cases of bladder cancer in the pioglitazone exposed group and 1,841 in the non-exposed group. The use of pioglitazone was significantly associated with bladder cancer (adjusted HR 1.22, 95% CI 1.05 to 1.43) and a dose-response relationship was observed with a significant risk for patients with a dose accumulated greater than or equal to 28 000 mg (adjusted HR 1.75, 95% CI 1.22 to 2.50) and for a duration of exposure of 12 to

23 months (adjusted HR 1.34, 95% CI 1.02 to 1.75) and greater than 24 months (adjusted HR 1.36, 95% CI 1.04 to 1.79). Analysis by gender found a significant association between pioglitazone and bladder cancer only in men (adjusted HR 1.28, 95% CI 1.09 to 1.51). For all other cancers studied (lung, otorhinolaryngologic, colorectal, female breast and kidney) there was no increased risk associated with exposure to pioglitazone.

The authors concluded that the study data supports the hypothesis of the existence of a statistically significant association between exposure to pioglitazone and the incidence of bladder cancer. The results were similar to those obtained in the cohort of Kaiser Permanente Northern California (KPNC). The authors considered that two other factors reinforced the plausibility of a specific association between pioglitazone and bladder cancer: firstly none of the other oral antidiabetics was associated with an increased risk of bladder cancer and secondly pioglitazone was not associated with an increased risk for other cancer. However, the authors acknowledged a number of limitations of the study, especially with regards to the lack of adjustment for smoking, known to be one of the main risk factor for bladder cancer after age and male.

The CHMP assessed the study results and noted that the strength of the study lies in the size of the cohort. The large sample size may have narrowed the confidence intervals around the statistics identified within the KPNC cohort study 3rd interim analysis. However, the CHMP also noted the statistical uncertainties due to the small number of bladder cancer cases despite the large sample size. The hazard ratios, while statistically significant, were modest. The robustness with which patients with a diagnosis of bladder cancer were collected was also considered. Not only were patients with bladder cancer or related diagnoses identified through hospitalisations recorded in PMSI, the information collected was correlated with whether the patient was treated for the diagnosis within the same hospitalisation stay. In this way, it provides a robust account of the number of bladder cases identified and diagnosed correctly. However, the CHMP noted the limitation associated with the absence of detailed information on histology and staging. Other limitations related to the lack of availability of information on potential confounders which required the use of proxy measures for example for smoking and duration of disease and the potential for misclassification of exposure (based on missing on missing information on pre study treatment), potentially limiting the robustness of the characterisation of a dose/duration effect.

Exposure to antidiabetic treatments was defined as SNIIRAM reimbursing for the active ingredient at least twice in 6 consecutive months. As the cohort includes prevalent users of any antidiabetic drug during the study period, a limitation of the study is that at the time they start observation, there is no knowledge of the duration of therapy up until that point, and therefore does not account for possible previous treatments. This is important particularly when considering a duration response effect. The results of the GPRD study indicate a longer time from diagnosis to first hypoglycaemic treatment for pioglitazone users versus non-pioglitazone users (1610 days versus 440 days).

There were 175/155,535 bladder cancer cases in the pioglitazone exposed group compared to 1,841/1,335,525 cases in the unexposed group, which leads to a statistically significant 22 % greater relative risk of an outcome of bladder cancer for a diabetic patient exposed to pioglitazone compared to an non-exposed patient. A dose and time related effect similar to that seen in the KPNC database was observed. Exposure to pioglitazone of over one year increased this relative risk to 34%, which was further increased to 36% at over two years of treatment. In the KPNC study, the association between pioglitazone exposure and bladder cancer risk was only significant after two years of drug exposure, even though the value of the hazard ratio statistic was the same at one year of exposure. The fact that this study showed a statistically significant result at one year may be linked to the increased sample size (approximately seven times larger cohort compared to the KPNC cohort). The median duration of treatment in the cohort was 23 months. The risk of bladder cancer with a pioglitazone exposure of less than one year in duration was not statistically significant (HR 1.05 95% CI 0.82-1.36, p=0.68), which is biologically plausible from the perspective of an epigenetic carcinogen that requires a latency period prior to its carcinogenic effect. However, the possibility of misclassification of exposure due to the absence of information on pre-study treatment is a relevant limitation in interpreting these results.

In the age stratified analysis, men over 50 and women over 65 showed a statistically significant increased risk of bladder cancer. The combined age stratified analysis showed that the risk is significant over the age of 50. In women exposed to pioglitazone, there were only 13 cases of bladder cancer compared to 213 in the unexposed group. Men are at higher risk of bladder cancer and so the evidence reflects the epidemiology of the disease itself as women are more protected from certain cancers until older age. The demographics of the cohort population show that men and women were represented equally in exposed versus unexposed groups. Given the large size of the sample, the

CHMP considered that the cohort is a true reflection of the population of diabetic patients in general. These findings in relation to gender and age highlight the need to consider the clinical significance of the drug-attributable risk to the overall bladder cancer risk in diabetic patients as well as other risk factors.

The CHMP considered the study to be well conducted despite its limitations and its findings were considered generally robust. Overall, the CHMP agreed that this study does support a small increased risk of bladder cancer associated with pioglitazone, which was statistically significant for ever use of the drug and significant at one year duration of therapy The overall HR in the KPNC study was 1.2 (95% CI 0.9-1.5) and the similarity between the hazard ratios in this study and those of the KPNC study were noted The CHMP noted that advanced age is associated with an increased bladder cancer risk. In the age groups over 65 years old, the proportion of patients unexposed to pioglitazone were greater than the proportion exposed, but a significant association between bladder cancer and pioglitazone exposure was observed. The CHMP agreed that the lack of data on smoking exposure in the cohort may confound the association as it is itself a risk factor for bladder cancer. Although the influence it had on the statistical findings in this cohort study is not known, it may have biased the results. The CHMP also considered that the lack of adjustment for advanced stage of diabetes limits the study findings but if it is considered that advanced age is linked with advanced diabetes, which is probable if patients are on long term antidiabetic treatment, then the stratified analyses provided by age are considered to reflect some crude proxy measure of disease severity.

It is therefore acknowledged that some of the uncertainties could impact on the risk estimates in either direction and that while smoking and age are risk factors, they may not be confounders but the possibility of confounding cannot be excluded.

L Wei, TM MacDonald and IS Mackenzie, Medicines Monitoring Unit and Hypertension Research Centre of the University of Dundee (MEMO), Pioglitazone and bladder cancer: A propensity score matched cohort study, (Draft report, May 2011).

A draft report on a cohort study of diabetic patients using the UK GPRD database as a data source was made available to the CHMP. Following the recent concern about pioglitazone use and the risk of bladder cancer in diabetic patients, the authors conducted a study to examine if exposure to pioglitazone use is associated with increased incidence of bladder cancer in type 2 diabetic patients. The study also looked at duration of use. A cohort study was conducted in the GPRD database between 2001 and 2010. A total of 207,714 type 2 diabetic patients aged ≥40 with oral antidiabetic drug treatment were included (23,548 in the pioglitazone group and 184,166 in the other antidiabetic drug treatment group). Patients had at least 90 days follow up. The association between pioglitazone and risk of bladder cancer was assessed by a Cox regression model. A propensity score matched analysis was done in a group of patients without missing baseline characteristics data. The study results showed that 66 bladder cancer occurred in 82,316 person years of follow up for a rate of 80.2 (95% CI 60.8-99.5) per 100,000 person-years in the pioglitazone group and 803 events occurred in 981,575 person-years for a rate of 81.8 (95% CI 76.2-87.5) per 100,000 person-years in the other antidiabetic drug treatment group. Pioglitazone was not found to increase the risk of bladder cancer significantly (adjusted HR of 1.15, 95% CI 0.83-1.61) compared with other antidiabetic drug treatment. The HRs for patients who had minimum follow up of 1 year or two years were 1.12 95% CI 0.76-1.63 and 1.19 95% CI 0.74-1.91. In a matched propensity score analysis in which both groups had similar baseline characteristics (16,095 patients in each group), the adjusted HRs were 1.16 (95% CI 0.76-1.78), 1.18 (95% CI 0.73-1.93) and 1.06 (95% CI 0.58-1.95) for patients with follow up time >3 months, 12 months or 24 months, respectively. The authors concluded that the results suggested that pioglitazone is not to be associated with an increased risk of bladder cancer in type 2 diabetic patients.

The CHMP noted that this report was submitted as a draft. The study was considered similar in design and in patient number to the KPNC study (n for KPNC = 193,099, n for GPRD = 207,714). In both data sets, patients were type 2 diabetics aged > 40 years with oral anti-diabetic treatment. In the GPRD study, the percentage of patients with bladder cancer in the pioglitazone group was 0.28% compared to the KPNC study of 0.3%. In the unexposed groups, bladder cancer cases were 0.43% in the GPRD and 0.48% in the KPNC. However, one significant difference between the studies was the lower proportion of patients in pioglitazone in the GPRD study (11.33%) compared to the proportion on pioglitazone in the KPNC study (15.62%).

The CHMP considered that this study did not identify any significant difference in the risk of bladder cancer in diabetic patients treated with pioglitazone versus untreated patients. The event rates were similar between the groups. The authors have calculated unadjusted and adjusted hazard ratios but

have not stated what variables were adjusted for. There is no indication of which variables were confounders or not in the relationship between bladder cancer and pioglitazone. As the two hazard ratios that were calculated showed differences, it is likely there was some confounding, accounting for multivariate analysis did increase the HR above 1 but not significantly so.

Baseline characteristics between the pioglitazone exposed and unexposed groups were all significantly different; the pioglitazone group included more males and the mean age was lower, there were fewer current smokers, and a higher number of patients with a BMI > 30. The longer average time from the first diagnosis date to the first hypoglycaemic drug treatment date was noted as well as on the fact that in the pioglitazone group, significantly more patients were on 3 or more hypoglycaemic treatments (46% versus 11.8%).

In order to minimise confounding by indication, where patients with more severe illness were more likely to be treated with pioglitazone, the authors calculated a propensity score (i.e. the likelihood that a patient would be treated with pioglitazone based on known baseline characteristics such as age, gender, smoking status, BMI and duration of the disease) for each subject. A propensity score matched cohort analysis (1:1 match) was carried out in patients who did not have any missing data for the baseline characteristics. This analysis showed no difference in duration of disease, yet the data still showed that severity of disease in the pioglitazone group was significantly different. 42.5% of the pioglitazone group were on 3 different hypoglycaemic drug classes compared to 10.3% in the unexposed group. The hazard ratio calculated from this analysis did not alter the study findings overall. No analysis was performed to test the association between cumulative exposure and increased bladder cancer risk (only partially addressed by sensitivity analysis in subgroups of patients who had 1 or 2 years of follow-up time).

MAH GPRD case control study, (AD4833-407), 2011

The MAH performed a nested case control study using the GPRD database (AD4833-407). The population included were type 2 diabetics with oral antidiabetic treatment between 01 Jan 1997 and 31 Dec 2010. Insulin was permitted as an add-on therapy to oral antidiabetics. Out of a cohort of 98,734 patients, 478 eligible cases of bladder cancer were identified and matched to up to 5 controls from the same cohort. Matching was carried out on age (+/ 2 years), gender and GP practice. Conditional logistic regression was used for this matched case-control design. Given the uncertainty over the predictive covariates, univariate analyses were conducted on all covariates: smoking (ever/never), smoking status (recorded as current, past, never) closest to the bladder cancer index date duration of oral antidiabetic therapy (years), use of insulin (yes/no), number of oral antidiabetic classes of drug used (1 to 6) and duration of pioglitazone use (<1 year, 1-2 years >2 years). The univariate models were followed by fitting the full model including all covariates, followed by backwards stepwise procedures (manual and automatic). Finally all models including smoking plus 1 other covariate were fitted.

The study results identified 456 cases and 1884 controls. Cases were more likely to be current or past smokers, use of pioglitazone in the cohort was low (6.63% in controls and 7.83% in cases). The mean age of the cohort was similar (controls 68.37 years, cases 69.21 years). The only statistically significant association was between smoking and bladder cancer (OR=1.62, 95% CI 1.24-2.12) when calculated as a binary variable (never vs. ever use). Further statistics were carried out showing that current use raised the odds ratio compared to both past and never smoking. No significant association was noted for bladder cancer by duration of pioglitazone exposure – the univariate odds ratio associated with pioglitazone exposure was 1.15 (95% CI 0.9-1.37) and the odds ratio for pioglitazone exposure (ever versus never use) after adjustment for smoking was 1.33 (0.88-2.00).

The CHMP considered that the overall results of this nested case control were similar to the results of the KPNC study with respect to never compared to ever exposure to pioglitazone in terms of an unequivocal finding but pointing towards a small but not statistically significant increased relative risk. The odds ratio for pioglitazone exposure (ever versus never use) after adjustment for smoking was 1.33 (0.88-2.00).

While the KPNC study identified a significant association between pioglitazone exposure for long duration of use, this was not evident in the MAH GPRD nested case control study. In addition, this study did not analyse the effect of cumulative dose as done in the KPNC study. It is evident from the data that the majority of patients (51% in cases and controls) were only on one diabetic treatment. The KPNC study included a much larger cohort of patients of 200,000 patients, compared to 2,330 (1,884 controls and 456 cases). The lack of a statistically significant association may therefore be due

to the small sample size and the low use of pioglitazone (only 7.9% of cases were on the drug) and the CHMP therefore considered that this study lacks power due to sample size although it was otherwise well designed.

CHMP conclusions on epidemiological data

Regarding the epidemiological data, the CHMP noted that the three epidemiological studies consistently pointed towards a small increased risk of bladder cancer with pioglitazone ever use. The results from the third interim analysis of the KPNC study cohorts data identified no significant association between having ever used pioglitazone and bladder cancer (HR 1.2, 95% CI 0.9-1.5), however, the hazard ratio with long-term pioglitazone therapy for therapy duration above 2 years was significant (HR 1.4, 95% 1.03-2.0) and patients exposed to high cumulative doses greater than 28,000 mg had a statistically significant increased risk of bladder cancer (HR 1.5 95% CI 1.1-2.2). Increased age and duration of disease were both potential confounding factors.

Similarly, the recently published French CNAMTS study showed a statistically significant association between pioglitazone and bladder cancer (adjusted HR 1.22, 95% CI 1.05 to 1.43) with a significant risk for patients with a dose accumulated greater than or equal to 28 000 mg (adjusted HR 1.75, 95% CI 1.22 to 2.50) and for patients with treatment duration greater than 24 months (adjusted HR 1.36, 95% CI 1.04 to 1.79). The dose and time related effects were similar to those seen in the KPNC and some of the methodological limitations were common to both studies e.g. potential confounding by duration of disease.

Although the hazard ratio estimates were relatively consistent across the studies, they differed in where they reached statistical significance. The French study's finding of statistical significance for an association with ever use may be linked to the increased sample size (the French cohort is about 7 times as big as KPNC cohort of approximately 200,000 patients). Analysis by gender also identified a significant association between pioglitazone and bladder cancer only in men (adjusted HR 1.28, 95% CI 1.09 to 1.51). The French study did not find an association between pioglitazone use for less than one year (HR 1.05, 95% CI 0.82-1.36, p=0.68). The epidemiological data did not provide evidence for an early effect but were not designed to do so because biological plausibility considerations focussed on a later effect. Finally, the MEMO GPRD cohort study found a similar, although non-significant, risk of bladder cancer for pioglitazone (adjusted HR of 1.15, 95% CI 0.83-1.61) compared with other antidiabetic drug treatment. The CHMP was of the opinion that the consistency of the study findings between the two independent cohorts (KPNC and CNAMTS French study) and, to a lesser extent, the independent GPRD study confirms the epidemiological evidence of an association between pioglitazone and a bladder cancer risk, albeit relatively small.

3.2.3. Randomised clinical trials

The MAH stated that the totality of the clinical program of pioglitazone includes over 30,000 patients worldwide and that it includes a number of long-term trials, greater than 1 year in duration, including the PROactive (EC444) study.

Meta-analysis of clinical trials conducted by the MAH, 2011

The MAH conducted a meta-analysis of the clinical trial database (Study AD-4833-406), including 22,000 patients. The PROactive study was analysed separately as the large size (n=5,238) of the study was considered to potentially influence the overall clinical database and subjects were older and had a longer duration of diabetes prior to randomisation compared to the other randomised clinical trials (RCTs). Study duration ranged from less than one year (24 studies) to more than 2 years (6 studies), with 6 studies between 1 and 2 years in duration. The study population was screened to select subjects who did not have conditions that would present undue safety risks, interfere with absorption or metabolism of the study drug, confound the efficacy and safety analyses or interpretation of data or interfere with study objectives. With respect to the demographics of the group, nearly 60% were not current smokers while 97% had no prior cancer history.

Bladder cancer cases detected in the first year of therapy were excluded based on the lack of biological plausibility that a tumour would develop this fast. Primary analysis showed a non-significant HR of 3.481 (95% CI 0.723, 16,755, p=0.120). The number of cases of bladder cancer were small (7 cases in the pioglitazone group 0.06% vs. 2 cases in the comparator group (0.02%). Taking all subjects into

account, not only those where a diagnosis was excluded based on its occurrence within one year of treatment, there were 19 cases in the pioglitazone group (0.15%) vs. 7 cases in the comparator group (0.07%), resulting in a HR of 2.642 (95% CI: 1,106, 6.31, p=0.029), which was statistically significant.

PROactive (PROspective pioglitAzone Clinical Trial In MacroVascular Events) study and the PROactive extension study, 2005.

At the time of marketing authorisation, the MAH was requested to conduct a cardiovascular safety outcome study. The PROactive study (EC444) enrolled 5,238 patients with type 2 diabetes mellitus, randomised to pioglitazone or placebo for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. The mean duration of treatment for PROactive subjects was 2.5 years. For all studies included, the mean duration of treatment was 60 weeks, i.e. just over one year. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. In this study, a higher number of bladder cancers were observed in subjects receiving pioglitazone compared with placebo: 14 subjects (0.5%) pioglitazone vs. 5 subjects (0.2%) placebo. Independent reviews of the bladder cancer cases were performed, and the data safety monitoring committee concluded that this imbalance did not represent an emerging safety signal for bladder cancer and that the PROactive study should be continued as previously planned. Exclusion of early bladder cancer diagnosis resulted in a HR of 2.963 (95% CI: 0.598, 14.682). This reflects 6 reports of bladder cancer in pioglitazone treated patients (0.2%) vs. 2 on placebo (0.1%). When all subjects were included, the HR was of borderline statistical significance (HR 2.739, 95% CI: 0.986, 7.605, p=0.053).

Upon completion of the intial PROactive study, it was agreed to conduct an extension of the study. This extended study (EC445) was designed to observe subjects who had participated in PROactive for up to 10 years beyond completion, with interim reports submitted every 2 years. The aim of the study was to identify the effects of PPAR agonist therapy on mortality, macrovascular morbidity, and incidence of malignancy in high-risk patients with T2DM. Data from the first 6 years are available (2- and 4-year results have already been submitted and reviewed by the CHMP, while the 6-year results are expected on 31 July 2011. During the first 2 years of the extended PROactive study, there was no difference in the incidence of newly diagnosed bladder cancer between the PROactive treatment groups, as reported in the 2-year interim report to this observational study. This was confirmed by the results from the 4-year observation period, during which newly diagnosed bladder malignancies were reported for a total of 20 subjects: 8 (0.4%) in the pioglitazone group and 12 (0.7%) in the placebo group. An interim analysis was recently completed for the 6-year period, and the total number of subjects with reports of bladder cancer increased to 10 in the pioglitazone group (0.5%) and 17 in the placebo group (1.0%). A combined analysis of the data from the double-blind period (EC444) and the 6-year observational period (EC445) was also carried out, comparing subjects who received pioglitazone during either period to subjects who never received pioglitazone or were initially on placebo and had bladder cancer diagnosed prior to pioglitazone treatment. Overall, bladder cancer was reported in 25 subjects (0.9%) who received pioglitazone and 20 subjects (0.8%) who never received pioglitazone (hazard ratio 0.98, 95% CI: 0.6-1.8). The MAH stated that there were limitations of this dataset, in particular that none of the studies were designed to examine bladder cancer (prior history of bladder cancer not excluded and no screening for bladder cancer).

CHMP conclusions on clinical trial data

The CHMP noted the results of the MAH meta-analysis and that the overall number of bladder cancer events in the RCTs was relatively low. A total of 26 bladder cancer events were recorded (19 cases from 12,506 patients in the pioglitazone group (0.15%) and 7 out of 10,212 patients (0.07%) in the comparator group, resulting in a statistically significant HR of 2.642 (95% CI: 1,106, 6.31, p=0.029) when all cases were considered including those with a time to onset of less than one year (sensitivity analysis). The CHMP considered that the meta-analysis had a number of limitations, in particular with regards to duration as the majority of the studies (14) were less than six months in duration. Ten studies were of duration between 6 months and one year. Only 6 studies were longer than 1 year and a further 6 longer than 2 years. In addition, the meta-analysis was based on RCTs that were not designed specifically to capture bladder cancer as a safety outcome. Bladder cancer events were captured purely by a review of MedDRA coding. Given that bladder cancer was not a safety endpoint in the clinical trials, the patients were not screened for bladder cancer prior to enrolment. The CHMP also noted that when patients treated for less than one year are excluded from the analysis (based on biological plausibility) no significant difference exists. However, the CHMP considered that overall, the results show a significantly increased risk of bladder cancer in patients exposed to pioglitazone compared to patients not exposed and given the context for the finding and the presence of

randomisation, the results of the meta-analysis were considered to provide strength of evidence particularly for an early effect. Similarly, in the PROactive study, a higher number of bladder cancers in subjects receiving pioglitazone compared with patients receiving placebo was noted: 14 subjects (0.5%) compared to 5 subjects (0.2%) respectively, when including patients with onset of cancer within the first year (HR 2.739, 95% CI: 0.986, 7.605, p=0.053). The CHMP concluded that the data from the clinical data show a significantly increased risk of bladder cancer in patients exposed to pioglitazone compared to patients not exposed. The CHMP also noted that when patients treated for less than one year are excluded from the analysis (based on biological plausibility) no significant difference exists and therefore considered that potential risk after short term treatment could not be excluded.

3.2.4. Spontaneous reports

The MAH provided a review of cases based on spontaneous reports within the MAH global database for the period 31 July 1999 to 15 March 2011. The criteria for searches in the database were all pioglitazone products (mono-product and fixed combination) and both medically confirmed and non-medically confirmed cases. MedDRA version 13.1 preferred terms that are contained in the high-level term of Bladder neoplasms malignant and the additional preferred term of bladder neoplasm were used.

A total of 68 cases met the criteria, 66 of which were for the mono-product and 2 for the combination pioglitazone + metformin. 85% of cases were reported by health care professionals. The reporting rate equates to 0.03 per 10,000 patient years (68 cases in 20,172,000 patient years based on exposure as of 23rd PSUR dated 31 Jan 2011). Assuming a spontaneous reporting rate of 10%, the incidence rate of bladder cancer in patients exposed to pioglitazone is estimated at 0.3 per 10,000 patient years or 3 per 100,000. The crude incidence of bladder cancer worldwide (not only in patients with diabetes) is 5.7 cases per 100,000 patient-years and based on epidemiological studies, higher in T2DM (Larsson, 2006). Therefore the MAH concluded that the reporting rate is no higher than expected incidence rates.

The MAH noted that 42 of these 68 reports were received after the public FDA announcement on 17 Sep 2010 of their review of the KPNC study, with 64% of these cases originating from the USA and Canada. The MAH considered this frequency of reports to be a stimulated reporting phenomenon based on media attention rather than a change in the actual incidence of bladder cancer in association with pioglitazone. The MAH noted that 12 out of the 42 cases provided no date of onset for the event. Of the remaining 30 cases, 13 had an event onset at least one year prior to the date of reporting, 6 of which had a lag time of 3 to 6 years from onset of event to reporting. Likewise, after the French media announcement and publication of a list of products under close scrutiny, which included pioglitazone, a peak in the number of reports from Europe was noted in February 2011.

The MAH classified the cases of bladder cancer such that only ones where there were no obvious confounders and the time of onset of bladder cancer was possibly associated with pioglitazone based on biological plausibility were identified. Of note is that 71% of cases were in men (reflective of epidemiology of bladder cancer) and that 96% involved patients who were at least 60 years of age (reflective of epidemiology of bladder cancer. 55% were on treatment duration longer than 3 years (only specified in 44 cases). The MAH stated that time to onset was provided for only 45 of the 68 cases and that in 3 of these cases, the bladder cancer occurred prior to initiation of treatment with pioglitazone, while in 12 of the 45 cases (27%), bladder cancer occurred within one year of treatment administration and was not considered to suggest a possible causal association given the long latency period required for development of bladder cancer. No patient was noted to be exposed to chemotherapy with agents known as risk factors for bladder cancer (cyclophosphamide, ifosfamide, cisplatin). In 20 cases, the information was too poorly documented to provide an informed causality.

Discounting poorly documented cases due to lack of information on risk factors (20 cases), those with onset prior to treatment (3 cases) and those considered not related to pioglitazone by the reporter and MAH (4 cases), the MAH noted 41 remaining cases where relevant medical history or risk factors were available. 80% of these cases involved male patients and 51% involved patients at least 70 years old. 41% of involved patients had a history of smoking and 20% had other malignant disease. Only 5% had no additional risk factors other than T2DM. Of these 41 cases, 10 had an onset of event less than one year post initiation of pioglitazone treatment. All these patients had risk factors for development of bladder cancer. 18 of these 31 cases were medically confounded. Therefore out of 68 cases, only 13 remain where no obvious confounding factors exist. Of these, 8 have very limited information provided but time to onset is greater than one year.

The MAH suggested that the recent increase in reports of bladder cancer could be attributable to heightened awareness following media announcements in the United States and France. There continues to be an active pharmacovigilance plan to address the particular issue of bladder cancer, as described in the current Risk Management Plans (RMP) for these products. The pioglitazone PSURs look at malignancy as a noteworthy adverse drug reaction, which is kept under review.

The CHMP was of the opinion that inherent limitations of spontaneous reports preclude their meaningful use in signal evaluation and comparisons of reporting rates with background incidence rates particularly for this type of risk do not allow any conclusions to be made. The CHMP acknowledged that many factors influence spontaneous reporting rates and as a clinical signal exists from the pharmacoepidemiological data, spontaneous reports are only likely to contribute to this signal and will remain hypothesis generating.

The demographics of the cases appear to follow what is already known regarding the epidemiology of bladder cancer as most cases occurred in males that were elderly. Smoking history also featured as a risk factor in 41% of cases where information was available. From the data, 55% of the cases were observed in patients taking pioglitazone for more than 3 years. Very few of the cases could be identified where no confounders were present and treatment with pioglitazone was greater than one year in duration (only 5 cases). A further search of the Eudravigilance database was conducted in order to make the information as current as possible for the purposes of this assessment and included the period 16 March 2011 to 24 May 2011. Events received by the MAH prior to 15 March 2011 were discarded as these would have been captured in the MAH review. This left 14 additional cases of bladder cancer in patients taking pioglitazone or fixed dose combinations thereof. Of these, 2 cases had treatment duration less than one year, and in one case no information was available on duration of treatment. Five cases were in patients that were ex- smokers (2) or current smokers (3). Three of the 14 cases included a personal history of cancer and in one case the patient had been exposed to toxic chemicals as part of occupation. It should be noted that there is now one case where the patient died as a result of metastasis to the brain. In this case, the death occurred one year after abdominal thoracic and pelvis scan were normal post treatment for bladder cancer. From this analysis, the CHMP concluded that there appears to be only one case where a male patient was on treatment for two years prior to bladder cancer diagnosis and had no known/identified risk factors apart from T2DM.

3.2.5. Scientific Advisory Group (SAG) Diabetes/Endocrinology

At the request of the CHMP, a Scientific Advisory Group (SAG) in Diabetes/Endocrinology meeting was held on 05 July 2011.

Regarding the cases of bladder cancer seen in diabetic patients treated with pioglitazone compared to those not treated, the SAG noted that the majority of bladder cancer cases (70-75 %) (grade Ta and T1), which are treated endoscopically and for which the survival rate at 5 years is high (nearly 95 % for the T1 form). It was noted that approximately 50% of the bladder cancer cases observed in the KPNC study were *in situ* tumours, which is unexpectedly high (normally 5-8 %), but this did not appear to be linked to the use of pioglitazone. Taking into account evidence of a relative risk of bladder cancer of 2.77 for smokers vs. non-smokers, the SAG speculated that smoking may have been a confounding factor in the French CNAM study, which would explain the increase in bladder cancers and the simultaneous decrease in breast cancers (due to the anti-oestrogenic effect of smoking). In summary, the possible increase in risk of bladder cancer was considered as relatively small and leading to relatively benign tumours in the majority of cases.

Regarding the position of pioglitazone in the therapeutic strategy for treatment of patients with type 2 diabetes, the experts agreed that the need for pioglitazone is limited. However, taking into account the totality of the risks and the benefits associated with its use, the SAG agreed (with one expert dissenting) that pioglitazone remains useful in the treatment of type 2 diabetes for a small group of patients, as second-line monotherapy. It was also stated that the efficacy and safety profile of pioglitazone is relatively well established while less is known about the long-term safety profile of the alternative treatment products (DPP4 inhibitors, GLP-1 agonists). Based on the new data on bladder cancer, the SAG could not identify any of the currently approved indications, where the benefits would specifically no longer outweigh the risks.

The SAG identified a number of risk factors for bladder cancer, including age, smoking, occupational hazard (current but also historical), drugs and radiation treatment. A family history of bladder cancer was generally not considered to be a significant risk factor.

With regards to risk minimisation measures, the SAG agreed that the major risk factors should be included in the pioglitazone product information. Warnings on the risk of bladder cancer should be issued to patients treated with pioglitazone.

Regarding monitoring and screening, the SAG stated that for detection of bladder cancer the current gold standard is cystoscopy (plus biopsy), which can currently not be replaced by other methods. Available markers and screening via microhaematuria or cytology were seen as having severe limitations and to be insufficient for screening higher risk patients. The SAG also agreed that non invasive screening for bladder cancer is of limited value. Microhaematuria and albuminuria testing for monitoring purposes could be an option but is associated with limitations with regards to value and feasibility. Overall, a systematic bladder cancer screening for monitoring purposes was considered as unrealistic.

The SAG also proposed to define efficacy targets to be achieved or maintained after a defined period of time, to determine whether treatment with pioglitazone should be maintained or discontinued. Another proposal which was considered by the SAG was to restrict the use, or warn about the use, above a certain age as the risk of bladder cancer, as well as other risks, increases disproportionally with age. Gender specific restrictions were not considered useful.

3.2.6. Conclusions on clinical safety

The CHMP took into account the totality of the available data in its assessment of the clinical safety of pioglitazone, in particular in relation to the risk of bladder cancer. The CHMP considered that the evidence provided by the clinical trials data, in particular the meta-analysis of clinical trials provided the most robust evidence.

Regarding the clinical trial data, the CHMP noted the results of the meta-analysis of clinical trials conducted by the MAH. Taking all subjects into account, there were 19 cases of bladder cancer in the pioglitazone group (0.15%) and 7 in the comparator group (0.07%), resulting in a HR of 2.642 (95% CI: 1,106, 6.31, p=0.029), which was statistically significant. Similarly, in the PROactive study, a higher number of bladder cancers in subjects receiving pioglitazone compared with patients receiving placebo: 14 subjects (0.5%) compared to 5 subjects (0.2%) respectively, when including patients with onset of cancer within the first year. The CHMP concluded that the data from the clinical data show a significantly increased risk of bladder cancer in patients exposed to pioglitazone compared to patients not exposed. The CHMP also noted that when patients treated for less than one year are excluded from the analysis (based on biological plausibility) no significant difference exists and therefore considered that potential risk after short term treatment could not be excluded.

Regarding the epidemiological data, the CHMP considered that an increased risk was consistently identified. The results from the third interim analysis of the KPNC study cohorts data identified no significant association between having ever used pioglitazone and bladder cancer (HR 1.2, 95% CI 0.9-1.5). However, the hazard ratio for long-term pioglitazone therapy for therapy duration above 2 years was significant (HR 1.4, 95% 1.03-2.0) and patients exposed to high cumulative doses greater than 28,000 mg had a statistically significant increased risk of bladder cancer (HR 1.5 95% CI 1.1-2.2) although age and duration of disease may be potential confounding factors. Similarly, the recently published French CNAMTS study showed a statistically significant association between pioglitazone and bladder cancer (adjusted HR 1.22, 95% CI 1.05 to 1.43) with a significant risk for patients with a dose accumulated greater than or equal to 28 000 mg (adjusted HR 1.75, 95% CI 1.22 to 2.50) and for patients with treatment duration greater than 24 months (adjusted HR 1.36, 95% CI 1.04 to 1.79). Overall these epidemiological data suggest an increased risk with long term use while the RCT data suggest an early effect. The epidemiological studies excluded cases with an incident diagnosis within 6 months of starting pioglitazone which may have impacted on the detection of an early effect. The impact of potential confounding factors particularly duration of disease and increased age need to be carefully considered in further studies intended to characterise a dose/duration relationship.

The CHMP also considered the results of a nested case control study conducted in GPRD by the MAH and concluded that the overall results of this nested case control were similar to the results of the KPNC study with respect to never use compared to ever exposure to pioglitazone in terms of an unequivocal finding but pointing towards a small but not statistically significant increased relative risk. The odds ratio for pioglitazone exposure (ever versus never use) after adjustment for smoking was 1.33 (0.88-2.00). The lack of a statistically significant association may be due to the small sample size and the low use of pioglitazone (only 7.9% of cases were on the drug) and the CHMP therefore considered that this study lacks power due to sample size although it was otherwise well designed.

Finally, the MEMO GPRD cohort study found a small increased but non-significant risk of bladder cancer for pioglitazone (adjusted HR of 1.15, 95% CI 0.83-1.61) compared with other antidiabetic drug treatment.

Overall, the CHMP concluded that the totality of the available data consistently suggests a small increased risk of bladder cancer associated with the use of pioglitazone. The CHMP also noted that the clinical and the epidemiological datasets suggest divergent evidence with regard to the onset of bladder cancer: while the data from the clinical trials suggest a potential risk after short term treatment, the epidemiological studies show an increased risk in particular with high dose and long treatment duration.

3.3. Risk Management

During the procedure, the MAH updated the RMP to introduce bladder cancer as an identified risk. In addition, the CHMP adopted a number of risk minimisation measures (including an educational pack, including a prescriber guide, targeting all physicians who are expected to prescribe/use pioglitazone), in order to reduce the risk of bladder cancer and others risks associated with pioglitazone, as described in Annex II of the CHMP opinion. The MAH was requested to update the risk management plan (RMP) within one month of the European Commission decision, to include these agreed risk minimisation measures.

In addition changes were introduced to the Summary of Product Characteristics and the Package Leaflet, as discussed in section 2.4. The CHMP also agreed on a Dear Healthcare Professional Communication letter (DHPC), summarising the changes to the SPC, to be circulated to all prescribers, as discussed in Section 4.

As part of the agreed pharmacovigilance activities included in the risk management plan, the MAH will conduct a European multiple database bladder cancer risk characterisation study. The MAH also agreed to conduct a drug utilisation study including assessment of heart failure and insulin, risk minimisation Measures for bladder cancer and implementation of periodic review of response. Details of the agreed studies are provided below.

Drug utilisation study including assessment of heart failure and insulin, Risk Minimisation Measures for bladder cancer and implementation of periodic review of response Protocol submission to CHMP	 28/10/2011
Final Report to CHMP on assessment of heart failure rates and Interim Report to CHMP on assessment of Risk Minimisation Measures for bladder cancer and implementation of periodic review of response Final report to CHMP of implementation of Risk Minimisation Measures for bladder cancer and implementation of periodic review of response	 31/08/2012 31/12/2013
Pan-European multiple database bladder cancer risk characterisation study Feasibility study report Protocol submission to CHMP (if feasibility confirmed) Final report to CHMP	 28/10/2011 31/01/2012 18 months after CHMP protocol approval

Finally, in view of the identified safety concerns, the MAH should submit 6-monthly PSURs until otherwise decided by the CHMP.

3.4. Product information

The CHMP recommended amendments to be introduced in the summary of product characteristics (SPC) and in the package leaflet.

Section 4.1

A statement was inserted that adequacy of response to treatment (e.g. reduction in HbA1c) should be reviewed 3-6 months after initiation of therapy and that pioglitazone should be discontinued failing adequate response. Prescribers are also informed to confirm at subsequent routine reviews that the benefit of pioglitazone is maintained, with a cross-reference to Section 4.4.

Section 4.2
A statement advising physicians to start treatment with the lowest available dose, to be increased gradually, in particular when pioglitazone is used in combination with insulin, was added.

Section 4.3
The use of pioglitazone in patients with current bladder cancer or a history of bladder cancer was contraindicated. Use of pioglitazone in patients with uninvestigated macroscopic haematuria was also contra-indicated.

Section 4.4
A paragraph on bladder cancer was added, to report that cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone, resulting in a hazard ratio of 2.64. Reference was also made to available epidemiological data suggesting a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. The possibility of a tumour promoting effect was mentioned.

The identified risk factors for bladder cancer were mentioned, together with a recommendation that any macroscopic haematuria should be investigated before starting pioglitazone therapy.

A statement advising patients to promptly report macroscopic haematuria or other symptoms such as dysuria or urinary urgency to their physician was added.

Regarding the elderly, statements were inserted, advising that the combination use with insulin should be considered with caution and that the balance of benefits and risks should be considered carefully both before and during treatment.

Section 4.8
The risk of bladder cancer was added to the table of adverse reactions, under the header "Neoplasms benign, malignant and unspecified (including cysts and polyps)" with the frequency "uncommon" for all indications.

4. Overall discussion and benefit/risk assessment

In its assessment of the benefit-risk of pioglitazone, the CHMP considered a range of factors, including the nature and the magnitude of the risks, the beneficial effects of the drug, the conditions of safe use and the ability to identify patients who may be at increased risk.

4.1. Discussion on efficacy

The CHMP noted the efficacy associated with the use of pioglitazone, as identified in clinical trials of over 27000 patients, including 12 long term controlled trials of more than one year in duration. Patients with type 2 diabetes are at increased risk of macro- and microvascular complications including cardiovascular morbidity and mortality, and the major purpose of using antidiabetic drugs is to reduce these risks. Due to the complexity and long duration of studies with such endpoints, reduction of HbA1c has been accepted as a surrogate marker for assessing efficacy and is recommended as primary endpoint in phase III studies. Furthermore, in addition to a clinically relevant reduction of glucose parameters, an oral anti-diabetic (OAD) should preferably show at least neutral or beneficial effects on associated cardiovascular risk factors (e.g. obesity, blood pressure, lipid levels). Other aspects of importance include the incidence of hypoglycaemia and impact on liver and renal function. Efficacy studies of pioglitazone demonstrate decreasing HbA1C levels during the first 8 weeks of treatment and reaching maximum effect at approximately week 16 of treatment. Thereafter, HbA1C control is maintained up to 2 years of treatment. Despite the lag in the antidiabetic effect of pioglitazone compared with sulfonylurea early in treatment, the MAH argues that the efficacy of pioglitazone is better preserved over the long term, whereas other treatments (e.g. sulphonylureas) lose their effectiveness over time. Even though the clinical relevance of increasing insulin sensitivity may not have been firmly shown in clinical studies, insulin resistance is one of the key pathophysiological

mechanisms behind T2DM, particularly for the very obese. More recent drugs (e.g. GLP-1 analogues and DPP-4 inhibitors, as well as SU) all stimulate the pancreatic beta-cells to produce more insulin with the (at least hypothetical) risk of accelerating beta-cell failure and loss of effect. In monotherapy studies, pioglitazone has shown clinically and statistically significant decreases from baseline in HbA1c and FPG at study endpoints compared to placebo (AD-4833/EC404 and AD-4833/EC405). Results from several combination therapy studies indicate that pioglitazone is also effective in combination with a sulfonylurea or with metformin in the treatment of type 2 diabetes (clinically and statistically significant decreases from Baseline in HbA1c and FPG at study endpoint). Results from studies have also shown that pioglitazone in combination with metformin or SU improves glycaemic control for durations of at least 2 years. The effects of adding pioglitazone to existing insulin therapy were evaluated in 4 studies (OPI-502, AD-4833/PNFP-014.2, AD-4833/PNFP-343, H6E-MC-GLAT (12-month), H6E-MC-GLAT (Interim)), showing that the addition of pioglitazone to existing insulin therapy resulted in improvement in glycaemic control that was additive to the effects of insulin alone and that the addition of pioglitazone to existing insulin therapy reduced the mean total daily insulin dosages from baseline levels. Overall, the CHMP considered that there is strong evidence for the glucose reducing effect of pioglitazone. However, neutral effects in terms of macrovascular events need to be factored in as well as the need for treatment options for diabetic patients with renal impairment as discussed below.

Cardiovascular Effects
Morbidity and mortality in T2DM is dominated by CV complications and the CHMP noted the studies conducted on surrogate markers of CV disease and outcomes, discussing in particular the following studies.

The PROactive Study (AD-4833/EC444), 2005
The PROactive study was the first prospective study evaluating the effects of an individual oral hypoglycaemic agent on cardiovascular outcomes in high-risk subjects with type 2 diabetes. Over 5200 adult subjects were randomized to receive pioglitazone or placebo, in addition to their antidiabetic and cardiovascular medications, and were followed for a mean duration of 34.5 months The primary endpoint, a composite of disease and procedural endpoints, was the time to first occurrence of all-cause mortality, nonfatal myocardial infarction (MI) (including silent MI), stroke, acute coronary syndrome (ACS), major leg amputation, coronary artery bypass graft/percutaneous coronary intervention (CABG/PCI), or leg revascularization. The PROactive study failed regarding it's pre-specified primary endpoint, and any benefit suggested by the secondary endpoint suggests an effect in a type 2 diabetic population with extensive disease and being treated concurrently with multiple anti-diabetic and cardiovascular medicines, and treated with 45mg of pioglitazone. As expected, there were increases in weight in the pioglitazone group, and an increase in hypoglycaemia corresponding with better control of diabetes. There was also an increase in cardiac failure in the pioglitazone group. Although these were no new safety issues, the previous safety concerns relating to weigh gain, oedema and heart failure were confirmed. Although the PROactive study suggested that administration of pioglitazone was not associated with an increased cardiovascular risk, the study failed to document a clear benefit, and the safety concerns mentioned above remained, particularly in the context of the new indication which had been approved of pioglitazone in combination with insulin.

Results of the primary endpoint analysis showed that pioglitazone treatment resulted in a 10% decrease in the incidence of first events within the composite compared with placebo; however, this decrease did not reach statistical significance (HR=0.90; 95% CI: 0.80, 1.02; P=0.0954). The main secondary endpoint of PROactive was time to first event in the composite of all-cause mortality, MI (excluding silent MI), or stroke. Death, MI, or stroke was reported for 301/2605 (11.6%) pioglitazone-treated subjects and 358/2633 (13.6%) placebo-treated subjects, with a relative risk reduction of 16% (HR=0.84; 95% CI: 0.72-0.98; P=0.0277).

CHICAGO (OPI-518), 2006
The CHICAGO study evaluated the effect of pioglitazone on Carotid Intima-Media Thickness (CIMT), in over 450 adult subjects randomized to receive pioglitazone or glimepiride for 18 months. At 72 weeks, the absolute change from baseline in CIMT (the primary study endpoint) for pioglitazone treated subjects was -0.001 mm, whereas change in CIMT in the glimepiride group was +0.012 mm (P=0.017).

PERISCOPE (OPI-516), 2008
The PERISCOPE study was designed to compare the effects of pioglitazone vs. glimepiride on progression of atherosclerotic disease as measured by changes in percent atheroma volume (PAV) in the coronary artery using intravascular ultrasound (IVUS), in 360 subjects with type 2 diabetes mellitus and coronary artery disease (CAD) after up to 18 months of treatment. At 72 weeks, the

absolute change from baseline in PAV for pioglitazone treated subjects was -0.161 compared with 0.725 in the glimepiride treatment group (P=0.002).

OPI-526, a meta-analysis of the pioglitazone clinical trial database, 2006
In 2006, the MAH compiled a database of patient-level, time-to-event meta-analysis of deaths and major CV events reported as AEs in randomized, double-blind, comparator-controlled (active or placebo) clinical studies of pioglitazone. At the request of an independent panel of investigators from the Cleveland Clinic, this database was transferred to their care in unabridged format. The results of the subsequent study were published by Lincoff et al in the Journal of the American Medical Association (JAMA) 2007. The primary variable of the Lincoff meta-analysis was the composite endpoint of CV death, MI, or stroke, and the primary analysis included data from all randomized, comparator-controlled clinical trials with patient-level data present in the database (N=16,390). Results of the primary analysis showed a relative risk reduction of 18% (HR=0.82; 95% CI: 0.72-0.94; P=0.005) for the MACE endpoint.

CV Conclusions
The CHMP noted that pioglitazone has not been shown to increase serum lipids and that no indications of a detrimental effect on CV outcome measures were observed in the PROactive study (even though several limitations were noted). A FDA meta-analysis of 29 pioglitazone studies resulted in a HR below 1. Despite the CHF concern, the totality of the data suggests that pioglitazone is at least neutral in terms of macrovascular events, which is clearly important in this patient population. The CHMP considered it important that the CHF risk continues to be appropriately managed in order to optimise the benefit-risk profile.

Hepatic Effects
The CHMP noted the results of clinical study OPI-506, showing that pioglitazone reduced hepatic transaminases and total liver fat content, as well as a publication by Sanyal (2010) suggesting a potential benefit in patients with NASH including transaminases and histology, showing reduction in inflammation and fibrosis. The CHMP was cautious on the significance of the findings of the Sanyal paper, as it studied a non-diabetic patient group with non-alcoholic steatohepatitis (NASH). The primary outcome of the study was not reached with respect to pioglitazone, as no statistically significant difference to placebo was demonstrated in terms of rate of improvement of NASH on the basis of histology findings. Neither vitamin E nor pioglitazone (the two active treatments in the study) showed improvement in fibrosis. Pioglitazone did reduce hepatic steatosis, transaminases and inflammation, however it was specifically acknowledged by the authors that the results may not be generalised to diabetic patients as it is not known whether the response to treatment would be similar.

Lipid Metabolism
Dyslipidemia is a serious co-morbidity commonly associated with type 2 diabetes. Pioglitazone treatment was shown to improve specific lipid markers commonly associated with atherogenic risk by significantly increasing high-density lipoprotein (HDL) cholesterol levels and decreasing triglyceride levels. Although pioglitazone slightly increases low-density lipoprotein (LDL) cholesterol levels, it decreases LDL particle concentration and increases LDL particle size, which is consistent with a less atherogenic profile.

Conclusions on the efficacy and benefits of pioglitazone
The CHMP noted that pioglitazone works through a unique mechanism of action of insulin sensitization and β-cell preservation. Efficacy studies of pioglitazone demonstrate decreasing HbA1C levels during the first 8 weeks of treatment and reaching maximum effect at approximately week 16 of treatment. Thereafter, HbA1C control is maintained for up to 2 years of treatment. In addition to its glycaemic effects, the CHMP considered that pioglitazone also appears to be neutral in terms of macrovascular events based on the current evidence. Pioglitazone has not been shown to increase serum lipids. On the basis of currently available data, the CHMP was of the opinion that pioglitazone continues to fulfil a therapeutic role as an antidiabetic agent, in particular due to its role in combination therapy, with a durable effect on glycaemic control complementing other approved antidiabetic agents.

4.2. Discussion on safety

The CHMP also noted the risks associated with pioglitazone, based on over 22 million patients years of postmarketing experience worldwide and considered the following identified or potential risks:

Weight gain and peripheral oedema

It has been known since the time of approval that treatment with pioglitazone can cause fluid retention. Peripheral oedema is a common adverse event. Weight gain is also a well known adverse event and the mechanism is most likely attributable to both fluid retention and increased fat mass. The long term consequences of weight gain and peripheral oedema are poorly understood.

Cardiac Failure
In the high risk diabetic population of PROactive, more cardiac failure events were reported with pioglitazone than with placebo but without an increase in mortality. On the basis of the data currently available, congestive heart failure (CHF) linked to treatment with pioglitazone appears to be related to volume expansion and not due to ischemic damage or other myocardial toxicity. The SPC contains warnings and precautions as well as contraindications for use of pioglitazone in patients with heart failure. The MAH noted an increased reporting of cardiac failure with insulin based on cumulative post-marketing reports, suggesting a possible association between pioglitazone use with insulin and cardiac failure. The CHMP considered that this reinforces the need for better quantification of the risk of heart failure risk with the use of pioglitazone in combination with insulin. One of the safety concerns driving the benefit-risk margin for this drug is the risk of cardiac failure. It is critically important that this risk is appropriately managed in order to optimise the overall benefit-risk margin for pioglitazone particularly in the context of the new safety concern of bladder cancer.

Anaemia
Anaemia is reported as a common adverse event, most likely as a result of haemodilution.

Macular Oedema
Cases of new onset and worsening diabetic macular oedema in patients receiving pioglitazone have been observed in post-marketing reports. A clear mechanism for TZD involvement is unknown and only a hypothesis of relationship with the TZD-related fluid retention exists.

Bone fractures in women
In the PROactive study, an increased incidence of bone fractures was noted in female type 2 diabetes patients taking pioglitazone (mean duration of diabetes 9.5 years). During a mean follow-up 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone 1.7% (30/1735) versus placebo 2.1% (37/1728) (Dormandy, 2009). A meta-analysis conducted of randomised, controlled, double-blind studies in the pioglitazone clinical trial database identified similar findings and bone fracture was therefore described in the SPC.

Hepatic effects
As a result of the observation of severe idiosyncratic hepatobiliary injury, including hepatic failure, in patients exposed to troglitazone (which was subsequently withdrawn form the market as a result), the MAH has kept pioglitazone under close scrutiny with respect to the induction of adverse hepatic effects. A 3-year hepatic safety study (01-00-TL-OPI-506) did not generate concern. Other long-term trials, including the Quartet trials and PROactive, have consistently shown a normalization of alanine aminotransferase (ALT) in pioglitazone-treated patients and there were no differences in severe hepatic events between pioglitazone and comparator-treated patients. The clinical trial data confirms an absence of severe liver events or laboratory abnormalities without clear alternative aetiology. The CHMP lifted the requirement for an individual annual hepatic safety report in 2008.

Malignancy, specifically Bladder Cancer
A meta-analysis of clinical trials conducted by the MAH identified an HR of 2.642 (95% CI: 1,106, 6.31, p=0.029) when all cases were considered including those with a time to onset of less than one year, which was statistically significant. Similarly, the PROactive study showed a higher number of bladder cancers in subjects receiving pioglitazone compared with patients receiving placebo: 14 subjects (0.5%) compared to 5 subjects (0.2%) respectively, when including patients with onset of cancer within the first year (HR 2.739 (95% CI 0.986, 7.605, p=0.053). Regarding epidemiological data, the CHMP considered that an increased risk was consistently identified. The results from the third interim analysis of the KPNC study cohorts data identified no significant association between having ever used pioglitazone and bladder cancer (HR 1.2, 95% CI 0.9-1.5), however, the hazard ratio with long-term pioglitazone therapy for therapy duration above 2 years was significant (HR 1.4, 95% 1.03-2.0) and patients exposed to high cumulative doses greater than 28,000 mg had a statistically significant increased risk of bladder cancer (HR 1.5 95% CI 1.1-2.2). Similarly, the CNAMTS study showed a statistically significant association between pioglitazone and bladder cancer (adjusted HR 1.22, 95% CI

1.05 to 1.43) with a significant risk for patients with a dose accumulated greater than or equal to 28 000 mg (adjusted HR 1.75, 95% CI 1.22 to 2.50) and for patients with treatment duration greater than 24 months (adjusted HR 1.36, 95% CI 1.04 to 1.79). Finally, the MEMO GPRD cohort study found a similar, although non-significant, risk of bladder cancer for pioglitazone (adjusted HR of 1.15, 95% CI 0.83-1.61) compared with other antidiabetic drug treatment. This was in line with the findings of the GPRD study conducted by the MAH (HR 1.33, CI 95% 0.88-2.00). The CHMP was of the opinion that the consistency of the findings of the KPNC and CNAMTS studies and, to a lesser extent, the GPRD studies, confirms the epidemiological evidence of an association between pioglitazone and a bladder cancer risk, albeit relatively small. The CHMP also noted that while the data from the clinical trials suggest an early effect, the epidemiological studies show an increased risk in particular with high dose and long treatment duration.

4.3. Conclusions on the benefit-risk balance of pioglitazone

In relation to reduction of HbA1c, pioglitazone has a similar effect compared to other OADs, such as sulphonylureas. Pioglitazone is associated with a glucose reducing effect similar to other OADs and a unique mechanism (i.e. for the TZD class) which increases insulin sensitivity, but also with adverse events such as weight gain, fluid retention and risk of heart failure as well as an increased risk of bone fractures which limits its place in the treatment of patients with type 2 diabetes. Even though the clinical relevance of increasing insulin sensitivity may not have been firmly shown in clinical studies, insulin resistance is one of the key pathophysiological mechanisms behind T2DM, particularly for the very obese. Due to the well known adverse events related to fluid retention as well as the increased risk of bone fractures in females, the TZDs of which only pioglitazone now remains in the EU, have been generally considered as second or third line alternatives in the treatment of patients with type 2 diabetes. Concerning the potential increased risk of IHD, antidiabetic drugs should preferably reduce the risk of such events or at least be neutral in this respect. Even though pioglitazone increases the risk for CHF, results from available studies have so far not been associated with a detrimental effect on CV outcome measures.

Regarding the risk of bladder cancer, the available evidence now indicates that pioglitazone is associated with a small increased risk of bladder cancer in diabetic patients, which was identified in both clinical data and in epidemiological data. Although the data have different limitations, the CHMP considered that the totality of the available evidence (non-clinical, PROactive/CT meta-analysis, KPNC, French cohort study) indicate a small increased risk of bladder cancer associated with pioglitazone.

The impact of this increased risk on the overall benefit-risk profile of pioglitazone in the treatment of T2DM was assessed by the CHMP. As the absolute risk is small, a key consideration is whether there is a subpopulation of diabetic patients for which pioglitazone remains a useful therapeutic option. Following the consultation of the SAG Diabetes/Endocrinology, the CHMP noted that the majority of the observed bladder cancers were superficial tumours with a low invasive potential, which are treated endoscopically and for which the survival rate at 5 years is high. The CHMP was also of the opinion that pioglitazone continues to fulfil a therapeutic role as an antidiabetic agent, in particular due to its role in combination therapy, with a durable effect on glycaemic control complementing other approved antidiabetic agent, as second-line therapy in patients for whom metformin is inappropriate because of contraindications or intolerance or where insufficient glycaemic control is achieved despite use of the maximal tolerated dose of monotherapy. However, in order to reduce the risks to an acceptable level and in order to ensure that the benefit-risk of pioglitazone remains positive, the CHMP considered further restrictions of use to be necessary. In particular, use in patients with current bladder cancer or a history with bladder cancer and in patients with uninvestigated macroscopic haematuria should be contra-indicated. The Committee also recommended that the adequacy of response to treatment with pioglitazone should be reviewed after initiation of therapy and that the maintenance of benefit should be regularly confirmed. In addition, risk factors for bladder cancer should be assessed and any macroscopic haematuria should be investigated before initiation of pioglitazone therapy.

5. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing, the CHMP concluded that the available data identifies a small increased risk of bladder cancer associated with the use of pioglitazone. As the RCT data suggest an early effect, while the epidemiological data support an increased risk in patients treated for the longest duration and with the highest cumulative dose, the risk management strategy must take account of the totality of evidence.

The Committee therefore agreed on further restrictions of use, including contra-indications in patients with current bladder cancer or a history with bladder cancer and in patients with uninvestigated macroscopic haematuria together with recommendations to review the response to treatment and the maintenance of benefit. In addition, risk factors for bladder cancer should be assessed and any macroscopic haematuria should be investigated before initiation of pioglitazone therapy. Finally, the CHMP also agreed on further risk minimisation measures, such as educational materials, a Dear Healthcare Professional Communication letter and an update of the risk management plan.

In conclusion the CHMP was of the opinion that the changes introduced to the product information and the agreed risk minimisation measures are sufficient to reduce the small increased risk of bladder cancer associated with pioglitazone to an acceptable level

6. Communication plan

As part of this procedure, the MAH and the CHMP agreed the wording of a 'Dear Healthcare Professional Communication' designed to inform prescribers of pioglitazone of the risk of bladder cancer (see attachment 12). Following the CHMP recommendations, the MAH provided a communication plan which is detailed below. The MAH will distribute the DHPC letter to all medically registered prescribers in the EU member states as per the below timetable.

Date	Action
21st July 2011	Takeda / CHMP agree content of DHCP letter
25th July 2011	Takeda translation of agreed letter
27th July 2011	Member States agree translations
30th July 2011	Takeda initiates distribution of letter

7. Conclusion and grounds for the recommendation

The Committee reviewed the totality of the available data on pioglitazone, including preclinical studies, clinical studies, post-marketing data and epidemiological studies and noted the conclusions of the SAG Diabetes/Endocrinology,

The Committee considered that the available data consistently identified a small increased risk of bladder cancer associated with the use of pioglitazone, in particular in patients treated for the longest duration and with the highest cumulative dose. The Committee also noted that the majority of the observed bladder cancers were superficial tumours with a low invasive potential, which are treated endoscopically and for which the survival rate at 5 years is high.

The Committee noted the current SPC restrictions for pioglitazone, limiting treatment to second-line therapy in patients for whom metformin is inappropriate because of contraindications or intolerance or where insufficient glycaemic control is achieved despite use of the maximal tolerated dose of monotherapy.

The Committee is of the opinion that in view of the small risk of bladder cancer, the marketing authorisation should be varied, to include further restrictions of use are necessary, including contra-indications in patients with current bladder cancer or a history with bladder cancer and in patients with uninvestigated macroscopic haematuria. The Committee also recommended that the adequacy of response to treatment with pioglitazone should be reviewed after initiation of therapy and that the maintenance of benefit should be regularly confirmed. In addition, risk factors for bladder cancer should be assessed and any macroscopic haematuria should be investigated before initiation of pioglitazone therapy.

The Committee also agreed on further risk minimisation measures, such as educational materials, a Dear Healthcare Professional Communication letter and an update of the risk management plan.

The Committee considered that the changes introduced to the product information and the agreed risk minimisation measures could reduce the small increased risk to an acceptable level. The Committee therefore concluded that the benefit-risk of pioglitazone remains positive in the approved indications.

Following a request from the European Commission, the CHMP revised the wording of the product information to draw attention in a clear and transparent manner to the fact that pioglitazone should not be used as a first line treatment.

Divergent positions are presented in the appendix.

Appendix

DIVERGENT POSITIONS

Procedure under to Article 20 of Regulation (EC) No 726/2004

Procedure numbers: EMEA/H/C/0285/A-20/0046
EMEA/H/C/0286/A-20/0044
EMEA/H/C/0655/A-20/0030
EMEA/H/C/0893/A-20/0015
EMEA/H/C/0680/A-20/0022

Centrally authorised pioglitazone-containing medicinal products

Divergent statement

We have a divergent opinion on the above mentioned Marketing Authorisations from that which has been adopted by the CHMP during its October 2011 session:

We consider that the benefit-risk balance of pioglitazone has become negative given the increased risk of bladder cancer in addition to the other well known adverse effects (especially heart failure and bone fracture in post menopausal women) of this medicine, its questionable long term benefit in terms of cardiovascular protection and the available alternative treatments in type 2 diabetic patients.

1. Pre-clinical data indicate an increased frequency of bladder cancer associated with pioglitazone in male rats. Results of the PROactive trial show a significantly higher number of bladder cancer in patients treated with pioglitazone. Data provided by three epidemiologic studies (US, France and UK) provide very similar evidence of an increased risk of bladder cancer, even though the magnitude of such risk is low with a hazard ratio around 1.2, however, likely increasing with cumulative dose and duration of pioglitazone exposure.
2. This increased risk of bladder cancer includes invasive types of bladder cancer with major adverse impact on morbidity and mortality. No biomarker of bladder cancer is available which could provide effective screening and early treatment. Symptoms such as haematuria can occur late after the onset of tumour development and are not specific. Cystoscopy appears to be the only investigational procedure able to adequately establish the diagnosis of bladder cancer but its invasive nature precludes is use for systematic cancer screening.

It appears impossible to define a subpopulation of diabetic patients where the benefits of pioglitazone would outweigh its risks. In addition, according to PROactive long term follow up and utilisation studies, a large proportion of patients stop pioglitazone treatment within the first years of treatment precluding potential long term benefit on prevention of cardiovascular events. The identified increased bladder cancer risk is likely to reduce adherence to pioglitazone long term treatment.

CHMP members expressing a divergent opinion:

Pierre Demolis (FR)	20 October 2011	Signature: ……
Harald Enzmann (DE)	20 October 2011	Signature: ……
Nela Vilceanu (RO)	20 October 2011	Signature: ……