資料５－３

# フランスにおける疫学研究（CNAMTS 試験）の結果について（英語訳）

（フランス保健製品衛生安全庁(AFSSAPS)公表資料の英語訳）

（武田薬品工業株式会社提出資料）

# Risk of bladder cancer in people with diabetes treated with pioglitazone in France: a group study on SNIIRAM and PMSI data.

***Caisse nationale de l'assurance maladie, Paris, France.***

*Final Report 7/06/2011*

*Abstract*

**Background:** Several studies have suggested a link between treatment with Pioglitazone and the occurrence of bladder cancer. This drug in the glitazones family received marketing approval in Europe in 2000 and was marketed in France in 2002. Its indication is the treatment of type 2 diabetes as monotherapy in case of intolerance to metformin, dual or triple therapy combined with other anti-diabetics. The main objective of this study sponsored by Afssaps, was to clarify the existence of a possible link between exposure to pioglitazone and the incidence of bladder cancer in people with diabetes treated in France.

**Method:** This group study was conducted using data from the National health insurance System across regimes (SNIIRAM) linked with data from the Program medicalization of information systems (PMSI). The group included 1,491,060 patients with diabetes (defined by treatment with a specific drug) on national health schemes and aged between 40 and 79 years in 2006. Patients who had bladder cancer prior to entry into the group or within 6 months following entry into the group were excluded. Exposure to pioglitazone (and each anti-diabetic) was SNIIRAM-defined by at least two reissues of the active ingredient in 6 consecutive months. Monitoring focused on the period of four years from 2006 to 2009. Incidents of bladder cancer cases were identified through hospitalizations reported in the PMSI with a principal or related diagnosis of cancer in the bladder and also a surgical tracer and / or bladder instillation agent by pharmacological urethral catheterization and / or chemotherapy and / or radiotherapy.The relationship between exposure to each type of diabetes and the incidence of cancers of the bladder, lung, head and neck, colorectal, female breast and kidney was objectified by the hazard ratio (HR) estimated by Cox models adjusted for age, sex and other anti-diabetic treatments. The dose-effect relationship was studied by classifying patients according to cumulative doses and length of exposure. The group exposed to pioglitazone was compared with a control group for variables linked to tobacco consumption, a first risk factor in bladder cancer.

**Results:** The exposed group comprised 155,535 diabetic patients and the control group 1,335,525 diabetics. There were 175 incidents of bladder cancer cases in the exposed group and 1,841 in the control group. The use of pioglitazone was significantly associated with the incidence of bladder cancer (adjusted HR 1.22 [95% CI 1.05 to 1.43]). There was a dose-response relationship with a significant risk for people with a cumulative dose greater than or equal to 28, 000 mg (adjusted HR 1.75 [95% CI 1.22 to 2.50]) and with exposure times of 12 to 23 months (adjusted HR 1.34 [95% CI 1.02 to 1.75]) and more than 24 months [adjusted HR 1.36 [95% CI 1.04 to 1.79]). Analysis by gender only found a significant association between pioglitazone and bladder cancer in men (adjusted HR 1.28 [95% CI 1.09 to 1.51]). For all other cancers studied (lung, head and neck, colorectal, female breast and kidney) there was no increased risk associated with exposure to pioglitazone.

**Conclusion:** The analysis of this group of diabetic patients followed in France between 2006 and 2009 confirms the hypothesis of the existence of a statistically significant association between exposure to pioglitazone and incidence of bladder cancer. The observed results are similar to those obtained on a group at Kaiser Permanente in Northern California. These results on pioglitazone, an anti-diabetic drug prescribed over the long term, are interpreted in the context of evaluating the risk-benefit ratio of this substance.

**Keywords:** pioglitazone, bladder cancer, adverse effects, group, databases, data SNIIRAM, PMSI

*This work was started on 11.04.2011 and the report was sent to the French Agency Safety of Health Products (AFSSAPS) to be presented to the Committee for marketing authorization of drugs (AMM) of 09.06.2011 (Appendix 3).*

*Declaration of conflict of interest: The authors of this work are employees of the National health insurance scheme (public). None of the authors of this report has had an income from a pharmaceutical company in the last three years.*

## 1. Background

Pioglitazone belongs to the pharmacotherapeutic class glitazones1 category and is used in the treatment of type 2 diabetes. It received approval for marketing (AMM) in the U.S. in 1999 and Europe in 2000 via a European centralized procedure with Ireland as Member State Reporter and Portugal co-Reporter. In France pioglitazone was marketed in 2002.

Pioglitazone is indicated in the treatment of patients with type 2 diabetes:
1) as monotherapy particularly in overweight patients, not controlled by diet or exercise and for whom metformin is contraindicated or not tolerated.

2) as dual oral therapy in combination with metformin particularly in overweight patients where the maximum oral dose tolerated in oral monotherapy with metformin does not provide adequate glycemic control; a sulphonylurea, only in patients intolerant to metformin or for whom metformin is contraindicated, where the maximum tolerated dose in oral monotherapy with sulphonylurea does not provide adequate glycemic control.

3) in triple combination oral therapy with metformin and a sulphonylurea, particularly in overweight patients where the combinations mentioned above do not provide adequate glycemic control.

Pioglitazone is also indicated in combination with insulin in type 2 diabetic patients when inadequately controlled by insulin and in whom metformin is contraindicated or poorly tolerated.
Two specialties are available in France: Actos ® (pioglitazone 15 and 30 mg: the 45 mg dose is not marketed) and Competact ® (combination of pioglitazone 15 mg + metformin 850 mg, AMM in July 2006). This combination is indicated for the treatment of type 2 diabetic patients, especially where overweight, which is inadequately stabilised by the maximum tolerated dose of metformin alone.

*1. The other drug representing the class of glitazones (also known as thiazolidinediones), Rosiglitazone was withdrawn from the market November 3, 2010. The withdrawal followed the recommendations of the European Medicines Agency (EMEA) which concluded that the benefit / risk ratio of rosiglitazone was unfavorable due to the increased cardiovascular risk.*

## Pioglitazone and bladder cancer

A possible association between pioglitazone and bladder cancer has been suggested by several studies.

In preclinical studies, male rats treated with pioglitazone more often developed bladder tumors than those receiving placebo. This has not been observed in female rats at the same dose or with mice [1]. Besides this data, there is a biological plausibility with a potential mechanism related to “promoter" capacities of peroxisome proliferator-activated receptor (PPAR) $\gamma$ and / or PPAR$\alpha$ agonists in bladder tumors [2-3]. In addition, the inducing properties of pioglitazone (and / or its metabolites) cannot be excluded.

Available data in humans come from the PROactive study and also from pharmaco-epidemiological studies based on Kaiser Permanente North California (KPNC). Data from spontaneous reports have also been analyzed.

PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) was a multicenter randomized double blind study (Pioglitazone vs placebo) of type 2 diabetics at high cardiovascular risk recruited between May 2001 and April 2002. In the pioglitazone

group there were 14 cases of bladder cancer (0.5%) against 6 in the placebo group (0.2%) for a median follow-up of 34.5 months. After a blind study of 20 cases of bladder cancer, oncologists eliminated 11 cases. 6 cases remained in the pioglitazone group and 3 cases in the placebo group diagnosed in the second year of exposure [4-5]. Results monitored over a longer period are underway but the results have not been published to date.

In 2003, the Food and Drug Administration (FDA) asked the pharmaceutical firm to conduct a pharmacovigilance study on pioglitazone to determine whether treatment with pioglitazone increased the risk of bladder cancer. The study included patients with diabetes, aged at least 40 years belonging to Kaiser Permanente Northern California between 01/01/1997 and 31/12/2002, with no diagnosis of bladder cancer at baseline in the group. The group included 193,099 patients with diabetes after the various exclusions including 30,173 exposed 162, 926 and unexposed. The median duration of exposure to pioglitazone was 3.3 years (0.2 to 8.5 years). There were 90 cases of bladder cancer in those exposed to pioglitazone and 791 among unexposed. After adjustment for age, sex and other antidiabetic treatments there was no significant association between exposure to pioglitazone and risk of bladder cancer in the group overall (HR 1.2 [95% CI 0.9 to 1.5]). Full adjustment (age, race, sex, smoking, socio-economic status, profession at risk [painter, driver, barber], the circumstances favoring the detection of bladder cancer and the likelihood of receiving pioglitazone [duration of diabetes, HbA1c, heart or kidney failure]) gave the same result.

The investigators felt that there was no significant difference in the risk of bladder cancer between exposed groups and those not exposed. However, there was a significant increased risk of bladder cancer in patients with an exposure to pioglitazone for longer than 24 months (HR 1.4 [95% CI 1.03 to 2.0]) and those who were exposed to a cumulative dose of 28,000 mg of pioglitazone (HR 1.4 [95% CI 0.96 to 2.1]) [6]. According to the same study, no association between exposure to pioglitazone and other forms of cancer was found for any other cancer in the body [7].

The authors of the interim report of the study scheduled to last 10 years have concluded that short-term use of pioglitazone was not associated with increased incidence of bladder cancer, but that use longer than 2 years was slightly associated with increased risk.

The study was completed by a case-control study based on the group, including cases of bladder cancer detected between 1 October 2002 and April 30, 2008 [6]. Exposure to pioglitazone was associated with an increased risk of cancer by a factor of 2.7. This association was similar after adjustment for ethnicity, smoking, high risk activities, urinary tract infection and HbA1c (OR = 2.7 [95% CI 1.3 to 5.3]). Furthermore, analysis of levels of exposure to pioglitazone showed that patients who developed bladder cancer were potentially those treated with higher doses and for longer periods. No other therapeutic class of type 2 diabetes was associated with risk of bladder cancer in the same case-control study. However, in the case-control study the response rate to telephone interview was related to case versus control status and exposure to pioglitazone which overestimated the risks of exposure to pioglitazone [(2).] After taking into account these differences in response rates through application of appropriate methods, the results of the case-control study were similar to those of the group study [8].

In view of these results, in September 2010 the FDA issued a warning and recommendations to health professionals. .... *An Increased risk of bladder cancer was observed among patients with the longest exposure to Actos, as well as "in those exposed to the highest cumulative dose of Actos.*

*Recommendations: Healthcare professionals should continue to follow the recommendations in the drug label when prescribing Actos. Patients should continue taking Actos unless told*

*otherwise by their healthcare professional. Patients who are concerned about the possible risks associated with using Actos should talk to their healthcare professional....[9]*

Piccinni et *al*. investigated through spontaneous reports to the FDA, the association between the use of pioglitazone and bladder cancer. All notifications concerning pairing of antidiabetic drugs and bladder cancer were analyzed. Between 2004 and 2009, 93 cases were reported corresponding to 138 possible pairings (pioglitazone, 31; insulin, 29; metformin, 25; sulphonamide, 13; exenadine, 8; other 22). The odds ratio for pioglitazone was 4.30 (95% CI 2.82 to 6.52) [10]. The authors admit a certain bias due to a possible side effect which might partially explain the association [11].
However, the authors observed a significant relationship in 2004, which preceded the publication of the PROactive study [4] and the revision of the "label", the equivalent to the summary of product characteristics, in the United States.

A preliminary assessment of available data was undertaken by the Cnamts in the last quarter of 2010. It was estimated that in France the number of people who used pioglitazone was about 105,000 in 2006, 150,000 in 2007, 177,000 in 2008, 205,000 in 2009 and 240,000 in 2010 (source sample GP-Cnamts beneficiaries). Furthermore it was observed that cases of bladder cancer treated in hospital could be identified by therapeutic procedures combined with diagnoses in the PMSI. In France the first case reported spontaneously was in of 2007 and 15 cases were reported in April 2011.

As part of a broader study, on 01.17.2011 Afssaps referred to Cnamts to assess the risk from pioglitazone based on the French data, using available databases or already established study groups.

The authors of this work have developed a detailed protocol which was reviewed and accepted by Afssaps on 10/03/2011. This report describes the methodology and results of analysis conducted using the available databases. The CNIL authorization for Cnamts to consult the SNIIRAM databases for years not available through standard procedure was obtained on 04.03.2011 (Appendix 2). The updated databases have been effective since mid-April 2011 (Appendix 3).

The main objective of this study was to clarify the existence of a possible link between exposure to pioglitazone and bladder cancer in people treated for diabetes in France. This possible association was tested depending on length of exposure to pioglitazone and the cumulative dose of exposure.

## 2. Method

### Data source:

In France, the system of social protection of health insurance is made up of several different schemes, covering the entire population, that is to say 65 million inhabitants in 2010. The general system - health insurance for paid employees (CNAMTS), covers approximately 86% of the population residing in France. The National Insurance Scheme for paid workers and farmers (MSA) and that of Independent Workers (RSI) represent 5% each, and 12 additional plans cover the remaining 4% of the population. The information system known as SNIIRAM

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[2] *A selection bias in which a case has a higher probability of being reported if it is exposed to a known factor or perceived as being the cause of the event studied.*

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(National health insurance across regimes) contains extensive individualized and anonymous data on all health expenditure [12-13]. This information can be linked to PMSI data (Program of medicalisation of information systems), which provides medical information on all hospitalised patients, including diagnosis codes with ICD-10 (10th version of International Classification of disease) [14]. The implementation of SNIIRAM was approved by the National Computer and Freedoms Commission (CNIL).

We conducted this group study of exposed v non-exposed cases using anonymous data from people covered by the general scheme except for local schemes - some 49.7 million people. For these people, the match rate between data for claims and the hospitalisation database was 97% as of 2007 and about 90% in 2006. The database records for repayments list comprehensively all health care expenses that are reimbursed, including drugs, outpatient medical care and nursing, required or executed by a health professional (general practitioners, specialists, nurses, biologists, pharmacists, etc.). This medico-administrative database does not directly advise on the medical indication (diagnosis) of each repayment, but provides diagnoses of several chronic diseases that are regarded as serious and costly diseases of long duration or ALD (a condition of long duration). These patients with ALD are reimbursed at 100% at the request of the patient, family or attending physician, after approval by a health insurance doctor. The ALD are coded in ICD-10. Short stay admissions or day hospitalization in public and private hospitals are registered and documented in the PMSI, particularly for diagnostic care coded with ICD-10. In addition, homogeneous groups of patients (GHM) are also available to classify patients into subgroups according to medical procedure and diagnostic care. So called important medical procedures are classified according to the PMSI and codes of Classification of common medical procedures (CCAM).

The general purpose of the study was to consider a retrospective group of patients treated with antidiabetics in 2006 and followed until 2009, compared to patients exposed and not exposed to pioglitazone. The collection of data on exposure to pioglitazone was created from data for reimbursement of SNIIRAM. The occurrence of bladder cancer was determined from PMSI hospitalization data in OLS fields (medicine, surgery and obstetrics).

Data entered for the care of a condition of long duration (ALD), those concerning occupational diseases, and PMSI-SSR (Program of Medicalisation of Information systems care or rehabilitation) and HAD-PMSI data (Program of medicalisation of information systems on a hospital at home) were also taken into account in determining the occurrence of cancer.

**Definition of incident cases of bladder cancer**

The classification of bladder tumors, their inclusion in cancer registers and coding of tumor behavior (benign, uncertain, intraepithelial malignant, infiltrating malignant) are still the subject of much debate [15]. To ensure consistency, the incidence data presented in France for cancer records only invasive tumors ≥ T1. Intraepithelial tumors and superficial tumors classified pTa are not taken into account [16, 17]. All data is available on the website of the Institute for Public Health Surveillance [18]. Incidence rates standardized to the world population are estimated at 14.6 per 100,000 men and 2.0 per 100,000 women giving a sex ratio (M / F) 7.3.

In 2010 the estimated number of new cases was approximately 10,740 (8,940 men and 1,800 women). The number of deaths was estimated at 4,670 (3,510 men and 1,160 women).

Only 11 departments collected exhaustive data on bladder cancer in France between 2006 and 2009. In addition, these data were not linked with PMSI and SNIIRAM data. The incident cases of bladder cancer were therefore defined from PMSI hospitalization data between 2005

and 2010 and from SNIIRAM.

Admissions for short stay and day hospitalization in public and private hospitals are recorded and documented in PMSI , particularly diagnoses that are classified code ICD-10 and important medical procedures classified according to the Common Classification of medical procedures (CCAM) [19]. The definition adopted excluded prior bladder cancers, excluding on the one hand patients who were hospitalised with a diagnosis of bladder cancer from January 2005 until six months plus after entry into the group and secondly those with ALD for bladder cancer whose date of onset was more than six months previously .

Cases of bladder cancer were identified by hospitalisations reported to the PMSI with a principal diagnosis of/ or related link to bladder cancer and where at the same time use of a surgical tracer and / or vesical instillation pharmacological agent by urethral catheterization and / or chemotherapy and / or radiotherapy was reported (Table I).

Surgical procedures selected included all total cystectomies[(3)] by laparotomy and partial cystectomies by laparotomy or laparoscopy (Table II). This surgical act was classified with a principal diagnosis code linked to ICD-10, including the first three characters C67,i.e. for bladder cancer.

Where a pharmacological agent was placed in the bladder by urethral catheterization, and for chemotherapy and radiation therapy the same principle was applied. For the latter two cases, however, diagnosis of bladder cancer was mainly found by diagnostic link, the primary diagnosis being by therapeutic act coding; the principles of diagnostic coding defined by the PMSI and malignant tumors are listed in Appendix 1 [20]. This algorithm was also adapted for radiotherapy in private practice which is not subject to registration in PMSI (Table I)

[(3)] *Cystectomy – Removal of the bladder*

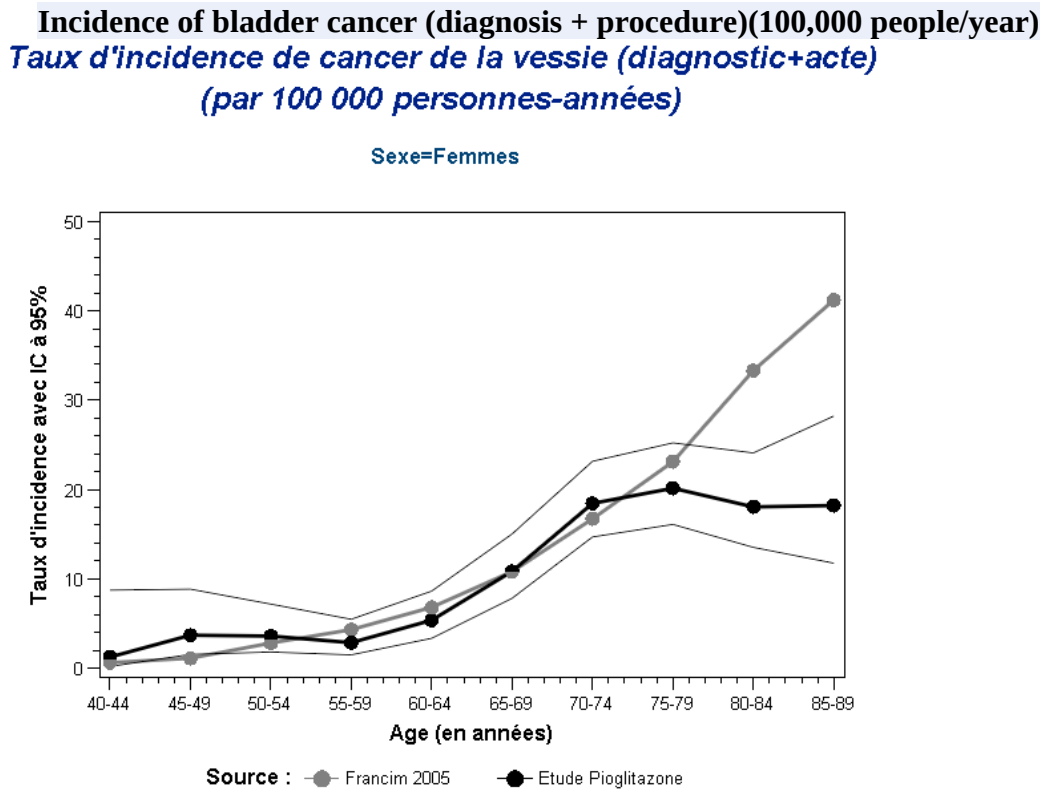
| | |
|---|---|
| Hospitalization for bladder cancer<br>(stay in Medical Surgical Obstetrics or day hospital) | At least 6 months prior to group entry:<br>· No hospitalization OLS HAD or SSR (from January 2005) with ICD10 code (three characters) equivalent to C67 (malignant bladder tumor) in any position<br><br>· No long-term illness (ALD) with ICD10 code (three characters) equivalent to C67 (malignant bladder tumor) with<br>start date prior to entry into the study. |
| | AND<br>From 6 months + of entry into the group:<br>at least one OLS hospitalization<br>· With ICD10 code (three characters) C67 (malignant bladder tumor) as<br>- Primary Diagnosis (PD) (1) or<br>- Diagnosis related (DR) (1) or<br>- Significantly associated Diagnosis (SAD)<br>where the PD or the DR (three character code) is equal to<br>C77 (malignant neoplasm of lymph nodes, secondary and unspecified)<br>C78 (secondary malignant neoplasm of respiratory organs and gut) or<br>C79 (malignant neoplasm in other secondary seats)<br><br>AND<br>• For the same hospital stay :<br>- A specific ACPC procedure (1) and / or code Z511<br>(Radiotherapy) as PD and / or code Z510 (chemotherapy) as PD AND / OR<br>- Between three months before hospitalisation and 3 months after:<br>An ACPC radiotherapy (paragraph 19.01.10 of version 23) in the community (source: SNIIRAM) |

**Table II: Table II: List of bladder surgeries held in the Common Classification of medical procedures (CCAM)**

| CCAM Code | CCAM label |
|---|---|
| JDFA001 | Total cystectomy with cutaneous ureterostomy, by laparotomy |
| JDFA003 | Total cystectomy with transintestinal cutaneous ureterostomy by continent detubulated loop, by laparotomy |
| JDFA004 | Supratrigonal cystectomy with enlargement detubulated enterocystoplasty, by laparotomy |
| JDFA005 | Total cystectomy, by laparotomy |
| JDFA006 | Total cystectomy with ureterocolic anastomosis and construction of a rectosigmoid or ileorectosigmoid detubulated reservoir, by laparotomy |
| JDFA008 | Total cystectomy with transintestinal cutaneous ureterostomy by non-detubulated loop, by laparotomy |
| JDFA009 | Total cystectomy with direct ureterocolic anastomosis, by laparotomy |
| JDFA011 | Partial cystectomy, by laparotomy |
| JDFA014 | Partial cystectomy with implantation of material for interstitial irradiation of the bladder, by laparotomy |
| JDFA015 | Supratrigonal cystectomy with enlargement detubulated enterocystoplasty and ureterovesicular reimplantation, by laparotomy |
| JDFA016 | Total cystectomy with orthotopic replacement enterocystoplasty (neobladder) by detubulated loop, by laparotomy |
| JDFA017 | Partial cystectomy with ureterovesicular reimplantation, by laparotomy |
| JDFA019 | Total vesicle-prostate-bladder resection with direct ureterocolic anastomosis, by laparotomy |
| JDFA020 | Total vesicle-prostate-bladder resection with transintestinal cutaneous ureterostomy by continent detubulated loop, by laparotomy |
| JDFA021 | Total vesicle-prostate-bladder resection with orthotopic replacement enterocystoplasty (neobladder) by detubulated loop, by laparotomy |
| JDFA022 | Total vesicle-prostate-bladder resection with ureterocolic anastomosis and construction of a rectosigmoid or ileorectosigmoid detubulated reservoir, by laparotomy |
| JDFA023 | Total vesicle-prostate-bladder resection with cutaneous ureterostomy, by laparotomy |
| JDFA024 | Total vesicle-prostate-bladder resection, by laparotomy |
| JDFA025 | Total vesicle-prostate-bladder resection with transintestinal cutaneous ureterostomy by non-detubulated loop, by laparotomy |
| JDFC023 | Partial cystectomy, by coelioscopy |

With this algorithm the M / F ratio was 7.4 or very close to that of cancer records published by InVS (7.3) [16].

Comparison of incidence rates by age and sex showed a close proximity between our data and reported incidence in the registers. However from 80 years the curves differed significantly, probably because at that age all cancers are not treated or at least cannot be treated with such strong therapy. We have, therefore, pragmatically chosen to limit our study to the age groups 40-79 years.



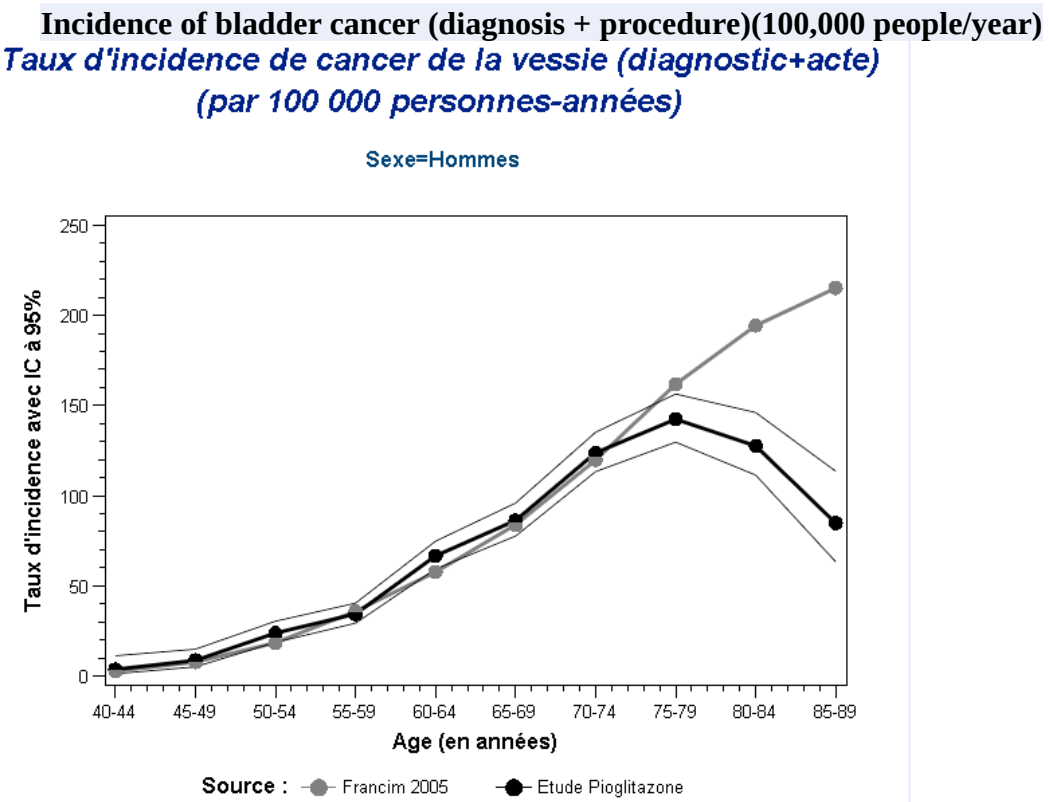
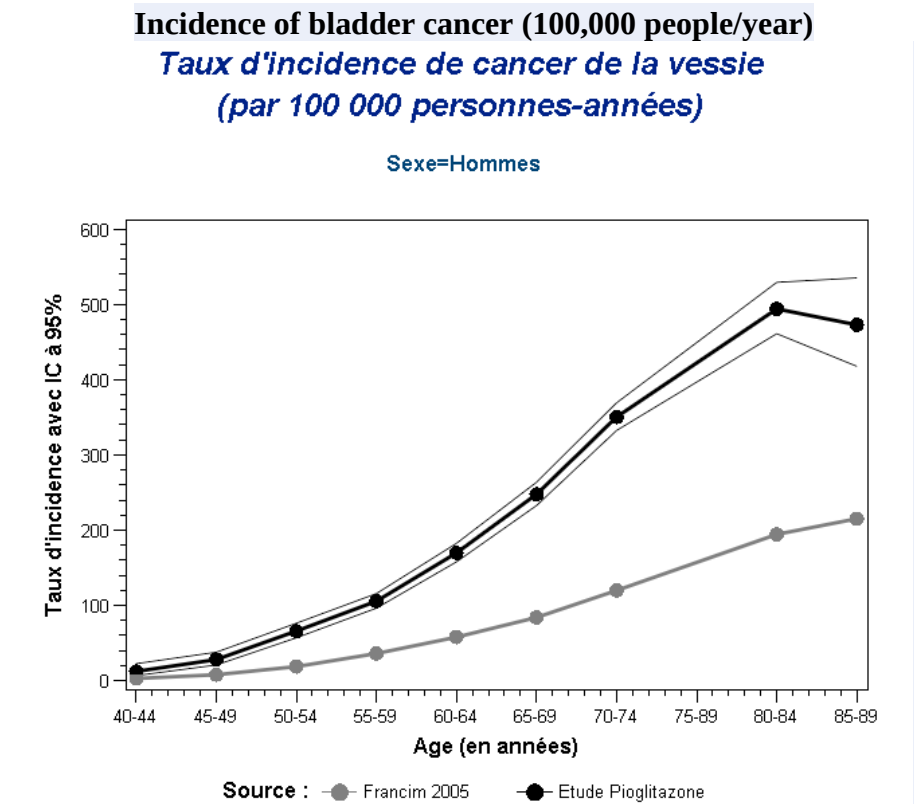




Figure 1: Showing the incidence of bladder cancer by age and by sex: Francim registered data and pioglitazone study criteria

Another broader definition of bladder cancer was explored. This consisted in inclusion of all those hospitalised with a primary diagnosis of /or linked to bladder cancer. This broader criterion had the effect of including endoscopic resection of bladder lesions carried out (as listed below) with diagnosis of bladder cancer.

JDNE001 Destruction of bladder lesion, by endoscopy
JDFE002 Resection of 1 to 3 bladder tumors, by endoscopy
JDFE001 Resection of 4 or more bladder tumors by endoscopy
JDFC001 Excision of bladder diverticulum, by laparascopy
JDFA002 Excision of bladder diverticulum, by laparotomy

The "broad" definition showed an incidence multiplied by 2.9 compared to the definition used.



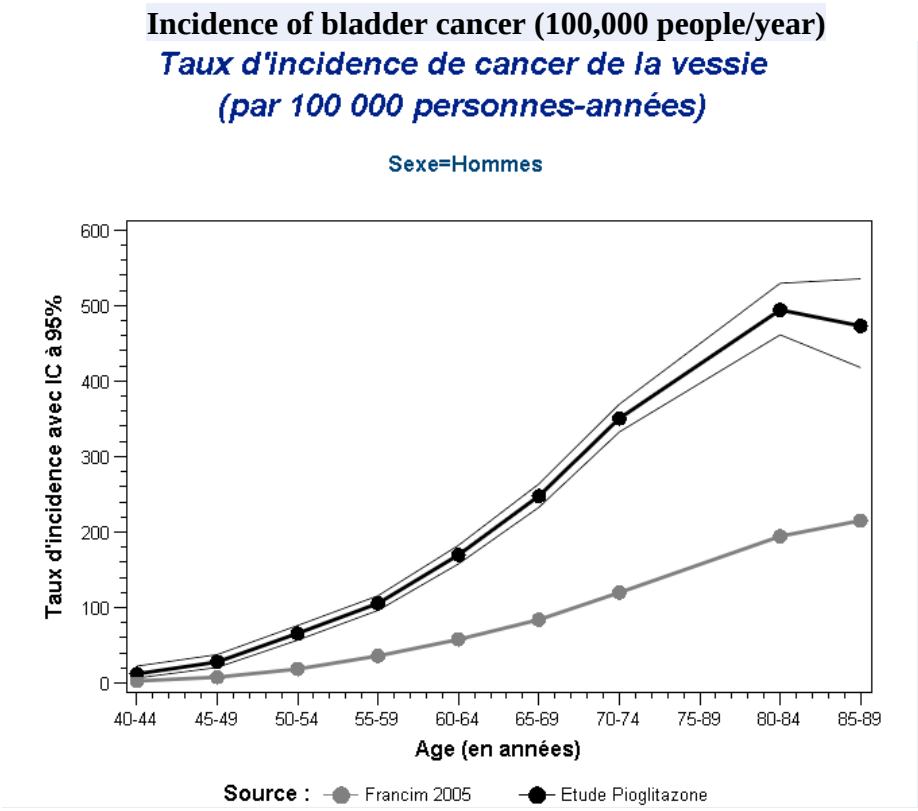




Figure 2: Showing the incidence of bladder cancer by age and by sex: Francim registered data and pioglitazone study criteria

Those eligible for this study group met all the following criteria:

1) Aged 40-79 years at December 31, 2006;
2) Affiliated to the general health insurance (excluding local schemes)
3) Having diabetes, defined by the dispensing of at least one antidiabetic medication in 2006 (pioglitazone, other glitazones, metformin, sulphonamides, other oral medications and / or insulin) i.e. the whole ATC A10 classification (except benfluorex mostly used for patients without diabetes).

The date when an antidiabetic drug was first dispensed in 2006 marks the entry of the patient in the study.

**Exclusion criteria for the study group:** patients for whom bladder cancer was detected before study entry or within 6 months and patients with occupational bladder cancer.

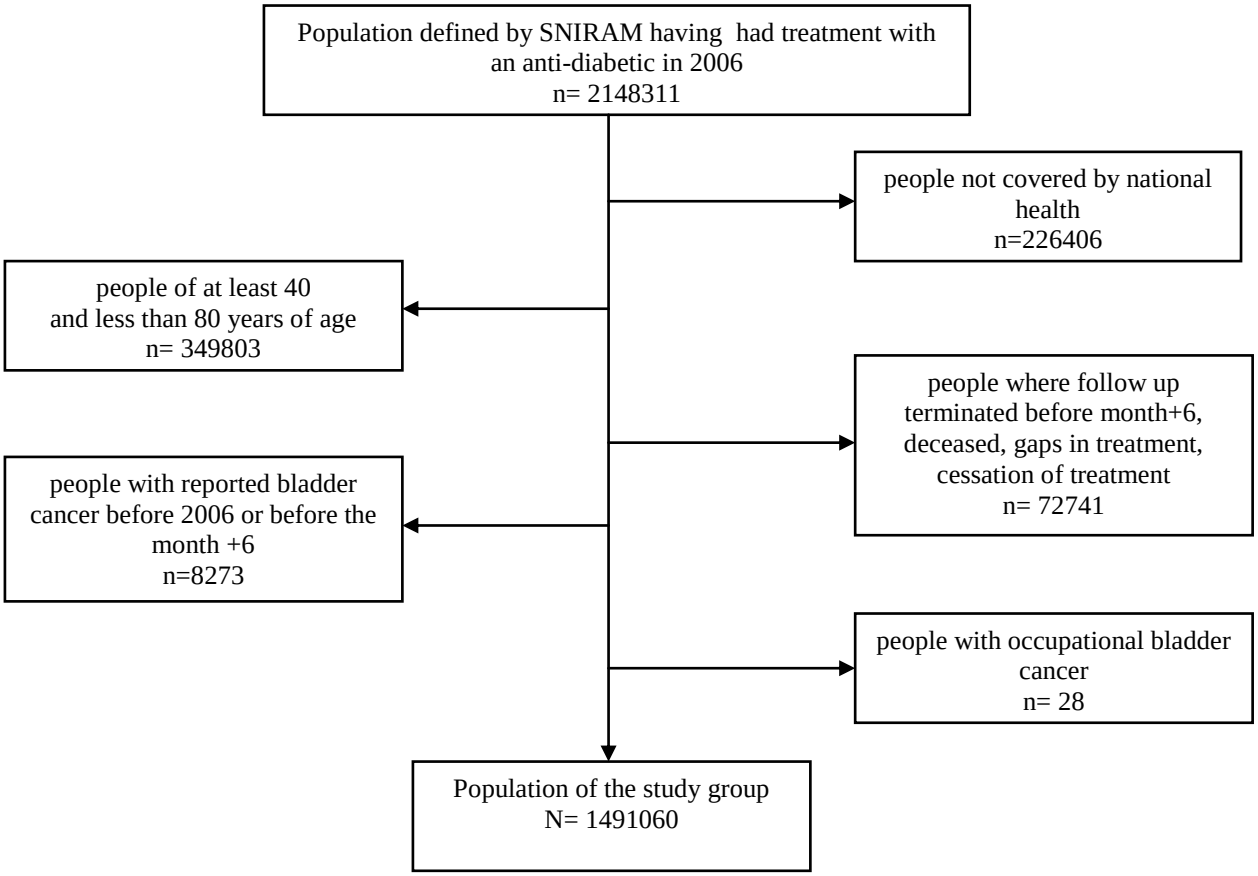



**Figure 2: Diagram showing make-up of the study group**

**Definition of exposure**

Exposure to pioglitazone is described as follows: at least two administrations during a period of six months between 2006 and 2009. Exposure was coded as a unidirectional time-dependent variable: a patient is deemed to be exposed from the fourth calendar month after the first issue until the end of follow-up.

**Table III: Criteria used for inclusion of persons in the diabetes study group and for defining exposure to pioglitazone**

| | |
|---|---|
| **Patients in Group** | - At least one instance of reimbursement in 2006 of anti-diabetic drugs (ATC A10 except benfluorex)<br>- Age greater than or equal to 40 years and less than 80 years on 31/12/2006 |
| **Exposed** | - At least two instances of repayments for pioglitazone in 6 months between 2006 and 2009<br><br>- 3556324 ACTOS 15MG box of 28<br>- 3556353 ACTOS 30MG box of 28<br>- 3716880 ACTOS 15MG box of 84<br>- 3716911 ACTOS 30MG box of 84<br>- 3773837 COMPETACT 15MG/850MG CPR box of 60<br>- 3773889 COMPETACT 15 mg/850 mg CPR box of 180 |
| **Unexposed-** | - No more than one instance of reimbursement for pioglitazone in a period of 6 consecutive months between 2006 and 2009 |

Exposure to all other classes of antidiabetic medication in 2006 (rosiglitazone, metformin, sulphonamides, other oral agents and insulin) is defined similarly.

The period of patient follow-up ends with the first of the following events:
1) registration of bladder cancer, 2) the patient's death, 3) more than 4 consecutive calendar months without any drug reimbursement - all drugs combined [(4)] 4) end of study follow-up on December 31, 2009.

The duration of exposure and cumulative doses were calculated and presented using the same intervals as in the Kaiser Permanente Northern California study [6].

Potential variable factors were ages put into 5 year groupings, sex and prescription of other antidiabetic drugs

[(4)] *End of follow up in this case was the second calendar month after the last reimbursement*

Furthermore, exposure to tobacco is not directly measurable in the databases, so the groups were compared for this factor in the following way:

1. By comparing the incidence rates in both exposed and non-exposed groups in the incidence of lung and head and neck cancers that are markers of smoking consumption in each group
2. By taking into account the consumption of chronic obstructive pulmonary disease drugs in

2006 and / or hospitalization with a coding for smoking. For drug consumption at least three different dates of prescription are noted in 2006 for Spiriva ® or Combivent ®, where the indications are continuous bronchodilator therapy to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD). Hospitalisations for specific ICD10 codes recorded in the PMSI from 2006 were taken into account (Table IV)

**Table IV: Criterion for the definition of smoking**

**Pharmaceutical specialties used for treating chronic obstructive pulmonary disease (COPD)**

| | |
|---|---|
| Pharmaceutical specialties used for treating chronic obstructive pulmonary disease (COPD) | 3382568 COMBIVENT 100 MCG/20 MCG/DOSE SUSPENSION NHALER 200 DOSES<br>3819203 SPIRIVA RESPIMAT 2,5 MCG/DOSE SOLVENT INHALER 60 DOSES<br>3686920 SPIRIVA 18 MCG POWDER CAPSULE INHALER30 |
| CIM10 code linked to smoking | F17 (3 characters) - mental and behavioural problems related to smoking<br>Z71.6 - Advice on smoking<br>Z72.0 Difficulties linked to smoking (without abuse) |

3. Since social factors are a determinant in cancer, the cost coverage rate for supplementary universal health coverage (CMUc) in people under 60 was compared between groups. Treatment for long term diseases linked to smoking is more frequent in people classified CMUc [21].

**Statistical Analysis**

**In terms of statistical analysis the following methods were used:**
To compare characteristics of patients exposed to pioglitazone vs. unexposed:
chi2 test for subtle variables and Wilcoxon test for continuous variables.

**For the link between exposure to pioglitazone and bladder cancer:**
Cox model adjusted for grouped potential factors for confusion: age, sex, other antidiabetic treatments. Exposure to pioglitazone and other treatments have been incorporated into the model as time-dependent variables.

These same tests were performed for five other types of cancer, lung cancer, head and neck cancer, colorectal cancer, female breast and kidney cancer.

The extracted data were available to CNAMTS staff statisticians authorised to "medical authority" level (data access "Medical" with authorisation for cross-reference to "sensitive" material - profile ref 30). The data were processed by CNAMTS in a secure environment (secure local terminals with access card and password).

Data were analyzed using SAS software.

Use of SNIIRAM by authorized officers of the CNAMTS was approved by the CNIL in November 2001 and in a ministerial decree of 11 April 2002 relating to its implementation. In October 2007, a second order allowed the use of variables with the exact date of death issued by INSEE and the National Retirement Fund. CNIL authorisation to allow CNAMT to update

the SNIIRAM databases for the years 2006 to 2010 was obtained on 04.03.2011 (Appendix 2).

For sensitivity analysis two further tests were conducted:

- Group with the use of a broader definition of bladder cancer [(5)]
- Group analysis based on the methods of the Lewis study (KPNC): inclusion of subjects over 80 years of age with KPNC definitions on start date of exposure.

*[(5)] The broader definition used takes into account all hospital stays and day visits concerning bladder cancer diagnosis. Compared to the definition (procedure + diagnosis) more specific but reductive in the number of cases, this second definition de facto includes all procedures including bladder tumor resection by endoscopy and bladder lesion destruction by endoscopy (JDFE001, JDFE001, JDNE001, JDFC001, JDFA002).*

## 3. RESULTS

### 3.1 Description of the study group

The study included 1,491,060 diabetic people insured by the state aged between 40 to 79 years, including 155,535 exposed to pioglitazone.

Pioglitazone users included the same proportion of men as non-users (53.8% vs. 53.4%). The average age of exposure was younger: 61.5 years against 63.4 years for non-exposed. People under 70 years accounted for 75.6% of the exposed group vs. 67.1% of unexposed (Table V).

Pioglitazone users simultaneously and / or successively used metformin (82.7% vs. 68.2%) and sulphonylureas (72.2% vs. 55.5%) more often but less often insulin (19.2% vs. 27.6%).

In patients who had used pioglitazone, the median follow-up between the beginning and end of exposure monitoring in the investigation was 29 months. The median duration of pioglitazone therapy[6)] was 23 months from January 2006. However 25% of users were already users of pioglitazone in January 2006. Exposure data are described in Table VI.

*[(6)] Last date of prescription – first date of prescription (from January 1st 2006) + 30 days*

### 3.2. Association between exposure to pioglitazone and bladder cancer

The group exposed to pioglitazone included 155,535 people with diabetes and the unexposed group 1,335,525 people with diabetes. At the end of follow up there were 175 incident cases of bladder cancer in the group exposed to pioglitazone and 1,841 in the unexposed group.

After adjusting for age, sex and other antidiabetics, pioglitazone use was significantly associated with the incidence of bladder cancer (HR 1.22 [95% CI 1.05 to 1.43]). There was a dose-effect relationship with significant risk for a treatment period of 12 to 23 months (adjusted HR 1.34 [95% CI 1.02 to 1.75]) and greater than or equal to 24 months [adjusted HR 1.36 [95% 1.04 to 1.79]). The risk was increased by 75% for cumulative doses greater than or equal to 28,000 mg (HR 1.75 [95% CI 1.22 to 2.50]) (Table VII).

Analysis by gender found a significant association between pioglitazone and bladder cancer in men (HR 1.28 [95% CI 1.09 to 1.51]) with a dose-effect relationship: duration greater than or equal to 24 months [adjusted HR 1.44 [95% CI 1.09 to 1.91]) and cumulative dose greater than or equal to 28,000 mg (adjusted HR 1.88 [95% CI 1.30 to 2.71]).

This association was not found among women for whom there were only 13 incident cases of

bladder cancer among those exposed and 213 among unexposed.

Further analysis based on a broader definition of bladder cancer which included endoscopic tumor resection found a significant association with an adjusted HR of 1.13 [95% CI 1.03 to 1.25]) and a dose-effect for a treatment duration of greater than or equal to 24 months [adjusted HR 1.23 [95% CI 1.03 to 1.47]) and cumulative doses ≥ 28,000 mg (adjusted HR 1.44 [95% CI 1.13 to 1.84]).

### 3.3. Association between exposure to pioglitazone, smoking, CMUC and other cancers

The "extra risk" factor relative to smoking criteria among patients exposed to pioglitazone compared with non-exposed was 0.79 (95% CI: 0.76 to 0.82). After adjusting for age and sex (using the Mantel-Haenszel method), this relative risk remained unchanged 0.79 (95% CI: 0.76 to 0.82, P value <0.0001).

An additional element was the extent of the risk of lung and head and neck cancer in the pioglitazone group (adjusted HR 0.94 [95% CI 0.87 to 1.02] and
0.85 [95% CI 0.73 to 0.99] (Table VIII).

The proportion of patients under 60 covered by CMUC in the population on glitazone was lower than that of people not on glitazone (12.9 vs. 15.0%).

There was no significant association between exposure to pioglitazone and colorectal, female breast and kidney cancer (Table IX)

## 4. Discussion

We described the results of a group study conducted at the request of Afssaps in response to alerts and an epidemiological study by the *Kaiser Permanente Northern California* [6] which led to consideration of a link between prolonged exposure to pioglitazone and increased risk of bladder cancer. This group of 1.5 million people with diabetes followed between 2006 and 2009 showed that the use of pioglitazone was associated with a
statistically significant increased risk of bladder cancer (HR 1.22 [95% CI 1.05 to 1.43]). This risk was higher for larger cumulative doses of pioglitazone (HR adjusted for doses ≥ 28,000 mg 1.75 [95% CI 1.22 - 2.50]) and longer-term use (adjusted HR for a period greater than or equal to 24 months 1.36 [95% CI 1.04 to 1.79]). The effect was more pronounced in men and was not observed in women. By way of sensitivity analysis, two other types of analysis that showed comparable results were carried out.

One of the strengths of our study is that it used two exhaustive, completely different databases, completely independent in terms of data collection. The search for a possible increased risk of developing bladder cancer among users of pioglitazone in diabetic patients has been performed using both hospital diagnoses and reimbursement data. Information on drug reimbursement is collected regularly and thoroughly by the remote transmission by pharmacists through a national network of health insurance. Data on hospital admissions in the PMSI database is also regularly collected by the Technical hospitalization information agency (ATIH) since each hospital doctor in France is required to complete the standardised discharge summaries including diagnostics care and major medical procedures carried out [19,20]. Linking between these two databases (independent in terms of data collection) makes it impossible, in principle, to make a biased observation on diagnoses for hospital treatment of bladder cancer according to exposure to pioglitazone prescribed and taken as outpatient medicine.

Another point is the systematic availability of data on reimbursed medicines, antidiabetic products are all covered by health insurance and there is no speciality pharmaceutical self-

medication with AMM for diabetes. Sending information by computer systematically avoids recall bias of patients even though there is a very good concordance for anti-diabetics between data from patients and data for reimbursement of health insurance with a kappa measured at 0.93 [22].

By requiring "exposed" patients to fulfill the criteria of two pioglitazone prescriptions within six months we have minimized the possibility of misclassification of exposed and unexposed patients. People who had only one dose of pioglitazone (n = 15,756) were not classified as exposed. It is probable that in these cases patients do not consume the entire package (due to early side effects or other reasons for discontinuation), or there was an error at the point of allocation. People who have had several prescriptions of pioglitazone but at no time in a period of 6 consecutive months (n = 4746) were not classified as exposed according to the definition of exposure. Some of these patients could have actually been exposed to pioglitazone. However, this misclassification is unlikely to be significant given that low consumption is hardly likely to alter the risk of cancer. In addition, because they represented a small proportion (3.1%) of those who met the conditions of exposure and a tiny proportion (0.4%) of the population classified as not exposed, the potential impact on estimation of the association is very limited. Finally the big packs of pioglitazone, which contain about three months of treatment had a marginal impact on the number of prescriptions in 6 months because they were only marketed in December 2009.

This study of 1.5 million patients with nearly 160,000 exposed to pioglitazone with a median follow up of 29 months gave similar results to those performed on the KPNC which covered 193,000 with 30,000 patients exposed to pioglitazone ( median follow up of 3.3 years). A similar increased risk was found (HR 1.22 [95% CI 1.05 to 1.43]) vs. (HR 1.2 [95% CI 0.9 to 1.5]) in the Lewis study. Each study had a similar dose-effect: after 2 years of exposure in our study HR 1.36 [95% CI 1.04 to 1.79] vs. for (HR 1.4 [95% CI 1.03 to 2.0]). This closeness of results between two studies in databases of different populations, with health systems and different countries could be an important argument for consolidating the results already observed.

Two other factors reinforce the plausibility for a specific association between pioglitazone and bladder cancer: firstly, none of the other oral agents was associated with an increased risk of bladder cancer and secondly, pioglitazone was not associated with an increased risk for other cancers. In most analyses insulin seemed associated with an increased risk of cancer (except breast cancer). This is reported in the literature [23-26]. However we must stress that our observational study was specifically designed to measure the risk of pioglitazone compared with bladder cancer and that interpretations of results on other antidiabetic agents (oral or insulin) or other cancers should be made with considerable caution.

However, our study had a number of limitations.

One of the most important is the lack of adjustment for smoking known to be the main risk factor for bladder cancer after age and (male) sex [27.28]. The concept of current or former smoking is not known in health insurance databases. Several points, however, seem to still be able to answer this question. Firstly, results reported by Lewis in the KPNC study are identical with a limited adjustment for age and sex or after full adjustment which takes smoking into account. Secondly, we have observed less exposure to smoking in the population exposed to pioglitazone, which is consistent with the incidence of lung and head and neck cancer that we observed in exposed patients but also with a less socially disadvantaged population. Thus, the influence of smoking could only have led to an underestimation of the relationship between pioglitazone and bladder cancer.

One point concerns the lack of adjustment for the duration of diabetes, a possible risk factor for bladder cancer. Adjusting for insulin exposure and the number of therapeutic classes

(single, dual, triple therapy) for group entry did not alter the results of the HR calculated (data not shown). In addition, subjects exposed to pioglitazone were, on average, almost two years younger on entering the group and they were less likely to have taken insulin. These two facts do not make a favourable argument for the importance of a greater length of diabetes as a factor in those exposed to pioglitazone.

Another limitation of our study is the criterion used to define incidence of bladder cancer which was not, as is usual, the result of pathological analysis. It was based on a combination of two criteria researched from the PMSI, the first being the diagnosis of bladder cancer as coded by the hospital physician and reported in the PMSI. This coding must take place subsequent to pathological tests, if it is not known at discharge from hospital [19,20]. A second criteria was added for the same hospital stay or outpatient visit: a related treatment linked with a diagnosis of bladder cancer. Only "serious" treatments were chosen: total or partial cystectomy, chemotherapy, radiotherapy and introduction of a pharmacological agent into the bladder by urethral catheterization. The probable result is a selection of more advanced more aggressively treated bladder cancer. We found incidence rates very close to those reported in both sexes up to age 80. However, there is a probability of underestimate in our data. Indeed, several studies report a small increased risk of cancer in general [26] in the diabetic population and bladder cancer in particular. The meta-analysis of Larson et al., reported an increased risk of bladder cancer (RR = 1.24 95% CI 1.08 to 1.42) comparing type 2 diabetes to non-diabetics from 16 studies [29]. Recently, a group of authors studied the specific causes of death among diabetics. The risk of death from cancer of the bladder of diabetes patients was estimated at 1.40 (1.01 to 1.96) [30]. These elements would be in favour of an underestimate of the number of cases of bladder cancer found from our study. But because of the way information on cases was collected this underestimate cannot be clarified. We have also noted that the broader criteria analysis, which integrates endoscopic resections, found the same significant association between exposure and risk of bladder cancer, which is an argument for the robustness of our results.

The use of the PMSI in observational studies of pharmaco-epidemiology is a promising approach to measure the relative and absolute risks of disease requiring hospitalisation and possibly constituting a serious adverse event [31,32]. This approach will in the future, as in epidemiology [33,34] require more work in the validation of algorithms using a combination of diagnostic codes of disease, procedure codes and data outside the scope of the PMSI. Note however that for pharmaco-epidemiology studies, using PMSI seems to be a less biased source in so far as exposed and unexposed subjects are classified by the same hospital coding procedures.

**5. Conclusion:**

The analysis of this study group of 1.5 million patients with diabetes in France between 2006 and 2009 confirms the hypothesis of the existence of a statistically significant association between exposure to pioglitazone and the incidence of bladder cancer. The results observed on a wider population are similar to those obtained from the Kaiser Permanente Northern California group study. These data on pioglitazone, a diabetes treatment to be prescribed for long periods, are to be considered by experts from the regulatory health authorities [35.37] in the context of evaluating the benefit-risk ratio of pioglitazone.

### *Table V: Characteristics of patients in the cohort (age, sex and exposure to classes of antidiabetic agents)*

| Characteristics | Total | Not exposed to Pioglitazone | % | Exposed to Pioglitazone | % |
|---|---|---|---|---|---|
| Total population | 1 491 060 | 1 335 525 | | 155 535 | |
| Female | 694 474 | 622 694 | 46,6% | 71 780 | 46,2% |
| Male | 796 586 | 712 831 | 53,4% | 83 755 | 53,8% |
| | | | | | |
| 40 to 44 years | 55 903 | 49 789 | 3,7% | 6 114 | 3,9% |
| 45 to 49 years | 94 472 | 82 593 | 6,2% | 11 879 | 7,6% |
| 50 to 54 years | 158 419 | 137 813 | 10,3% | 20 606 | 13,2% |
| 55 to 59 years | 237 091 | 207 912 | 15,6% | 29 179 | 18,8% |
| 60 to 64 years | 237 327 | 210 837 | 15,8% | 26 490 | 17,0% |
| 65 to 69 years | 230 578 | 207 344 | 15,5% | 23 234 | 14,9% |
| 70 to 74 years | 254 631 | 232 172 | 17,4% | 22 459 | 14,4% |
| 75 to 79 years | 222 639 | 207 065 | 15,5% | 15 574 | 10,0% |
| | | | | | |
| Exposure to Pioglitazone | 155 535 | | | 155 535 | 100,0% |
| Exposure to Rosiglitazone | 153 334 | 126 876 | 9,5% | 26 458 | 17,0% |
| Exposure to Metformin | 1 039 844 | 911 143 | 68,2% | 128 701 | 82,7% |
| Exposure to Sulphoamides | 853 605 | 741 380 | 55,5% | 112 225 | 72,2% |
| Exposure to other oral antidiabetic agents | 440 633 | 371 447 | 27,8% | 69 186 | 44,5% |
| Exposure to Insulin | 398 835 | 368 913 | 27,6% | 29 922 | 19,2% |

### **Table VI:** *Number of patients exposed to pioglitazone by cumulative dose and duration of exposure*

| Characteristics | number | % |
|---|---|---|
| *Cumulative dose at the end of the follow-up (1)* | | |
| < 10 500 mg | 66 332 | 44,4% |
| 10 500 to 28 000 mg | 54 956 | 34,3% |
| ≥ 28 000 mg | 34 247 | 21,2% |
| *Duration of exposure (1)* | | |
| < 360 days | 58 756 | 37,8% |
| 360 to 720 days | 36 482 | 23,5% |
| ≥ 720 days | 60 297 | 38,8% |

(1) after 1st January 2006

**Table VII.** Risk of bladder cancer [*definition with acts and diagnosis*] in diabetic patients aged 40 - 79 years according to exposure to pioglitazone. 2006 cohort follow-up until the end of 2009. CNAMTS data.

| | | Total | | | | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | |
| No. of patients in the study | | 1 491 060 | | | | 796 586 | | | | 694 474 | | | |
| No. of cases arising | | 2 016 | | | | 1 790 | | | | 226 | | | |
| Model 1 | Male | 7,65 | 6,66 | 8,79 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,41 | 0,10 | 2,39 | 0,68 | 8,40 | 0,17 | 2,98 | 0,35 | 25,49 | 0,32 |
| | 50 to 54 years | 5,70 | 2,08 | 15,60 | 0,00 | 6,64 | 2,09 | 21,13 | 0,00 | 2,90 | 0,36 | 23,15 | 0,32 |
| | 55 to 59 years | 7,89 | 2,93 | 21,28 | 0,00 | 9,65 | 3,08 | 30,25 | 0,00 | 2,30 | 0,29 | 18,11 | 0,43 |
| | 60 to 64 years | 15,34 | 5,72 | 41,13 | 0,00 | 18,82 | 6,04 | 58,67 | 0,00 | 4,31 | 0,57 | 32,37 | 0,16 |
| | 65 to 69 years | 20,61 | 7,70 | 55,19 | 0,00 | 24,57 | 7,89 | 76,50 | 0,00 | 8,69 | 1,19 | 63,35 | 0,03 |
| | 70 to 74 years | 30,37 | 11,36 | 81,17 | 0,00 | 35,54 | 11,43 | 110,49 | 0,00 | 14,74 | 2,05 | 105,93 | 0,01 |
| | 75 to 79 years | 35,08 | 13,12 | 93,80 | 0,00 | 41,32 | 13,28 | 128,53 | 0,00 | 16,02 | 2,23 | 115,14 | 0,01 |
| | **Exposure to Pioglitazone** | **1,22** | **1,05** | **1,43** | **0,01** | **1,28** | **1,09** | **1,51** | **0,00** | **0,78** | **0,44** | **1,37** | **0,39** |
| | Exposure to Rosiglitazone | 1,08 | 0,92 | 1,26 | 0,35 | 1,10 | 0,93 | 1,30 | 0,25 | 0,89 | 0,53 | 1,49 | 0,66 |
| | Exposure to Metformin | 1,03 | 0,93 | 1,13 | 0,60 | 1,03 | 0,93 | 1,14 | 0,58 | 0,99 | 0,75 | 1,31 | 0,96 |
| | Exposure to Sulphoamides | 0,92 | 0,84 | 1,01 | 0,08 | 0,91 | 0,83 | 1,01 | 0,06 | 0,99 | 0,76 | 1,30 | 0,95 |
| | Exposure to other oral antidiabetic agents | 1,00 | 0,90 | 1,11 | 0,93 | 0,95 | 0,85 | 1,07 | 0,40 | 1,36 | 1,02 | 1,81 | 0,04 |
| | Exposure to Insulin | 1,08 | 0,97 | 1,21 | 0,15 | 1,08 | 0,96 | 1,21 | 0,20 | 1,10 | 0,81 | 1,50 | 0,53 |
| Model 2 | Male | 7,64 | 6,65 | 8,78 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,41 | 0,10 | 2,39 | 0,68 | 8,39 | 0,17 | 2,98 | 0,35 | 25,50 | 0,32 |
| | 50 to 54 years | 5,70 | 2,08 | 15,59 | 0,00 | 6,64 | 2,09 | 21,12 | 0,00 | 2,90 | 0,36 | 23,16 | 0,32 |
| | 55 to 59 years | 7,88 | 2,92 | 21,26 | 0,00 | 9,64 | 3,08 | 30,22 | 0,00 | 2,30 | 0,29 | 18,11 | 0,43 |
| | 60 to 64 years | 15,33 | 5,72 | 41,09 | 0,00 | 18,80 | 6,03 | 58,60 | 0,00 | 4,31 | 0,57 | 32,38 | 0,16 |
| | 65 to 69 years | 20,60 | 7,70 | 55,17 | 0,00 | 24,56 | 7,89 | 76,46 | 0,00 | 8,69 | 1,19 | 63,36 | 0,03 |
| | 70 to 74 years | 30,36 | 11,36 | 81,16 | 0,00 | 35,53 | 11,43 | 110,47 | 0,00 | 14,74 | 2,05 | 105,94 | 0,01 |
| | 75 to 79 years | 35,08 | 13,12 | 93,81 | 0,00 | 41,33 | 13,29 | 128,55 | 0,00 | 16,02 | 2,23 | 115,14 | 0,01 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone < 10500 mg** | **1,12** | **0,89** | **1,40** | **0,34** | **1,17** | **0,92** | **1,48** | **0,21** | **0,77** | **0,36** | **1,65** | **0,51** |
| | **Exposure to Pioglitazone 10500 to 28000 mg** | **1,20** | **0,93** | **1,53** | **0,16** | **1,24** | **0,96** | **1,60** | **0,10** | **0,84** | **0,35** | **2,06** | **0,71** |
| | **Exposure to Pioglitazone . ≥28000 mg** | **1,75** | **1,22** | **2,50** | **0,00** | **1,88** | **1,30** | **2,71** | **0,00** | **0,57** | **0,08** | **4,11** | **0,58** |
| | Exposure to Rosiglitazone | 1,09 | 0,93 | 1,27 | 0,30 | 1,11 | 0,94 | 1,31 | 0,21 | 0,89 | 0,53 | 1,49 | 0,66 |
| | Exposure to Metformin | 1,03 | 0,93 | 1,13 | 0,56 | 1,03 | 0,93 | 1,14 | 0,54 | 0,99 | 0,75 | 1,31 | 0,96 |
| | Exposure to Sulphoamides | 0,92 | 0,84 | 1,01 | 0,09 | 0,92 | 0,83 | 1,01 | 0,07 | 0,99 | 0,76 | 1,30 | 0,95 |
| | Exposure to other oral antidiabetic agents | 1,00 | 0,90 | 1,11 | 0,95 | 0,95 | 0,85 | 1,07 | 0,41 | 1,36 | 1,02 | 1,81 | 0,04 |
| | Exposure to Insulin | 1,09 | 0,98 | 1,22 | 0,13 | 1,09 | 0,97 | 1,22 | 0,17 | 1,10 | 0,81 | 1,50 | 0,53 |
| Model 3 | Male | 7,64 | 6,65 | 8,78 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,41 | 0,10 | 2,39 | 0,68 | 8,39 | 0,17 | 2,98 | 0,35 | 25,50 | 0,32 |
| | 50 to 54 years | 5,70 | 2,08 | 15,59 | 0,00 | 6,64 | 2,09 | 21,12 | 0,00 | 2,90 | 0,36 | 23,16 | 0,32 |
| | 55 to 59 years | 7,88 | 2,92 | 21,26 | 0,00 | 9,64 | 3,08 | 30,22 | 0,00 | 2,30 | 0,29 | 18,11 | 0,43 |
| | 60 to 64 years | 15,33 | 5,72 | 41,09 | 0,00 | 18,80 | 6,03 | 58,60 | 0,00 | 4,31 | 0,57 | 32,38 | 0,16 |
| | 65 to 69 years | 20,60 | 7,69 | 55,15 | 0,00 | 24,55 | 7,88 | 76,43 | 0,00 | 8,69 | 1,19 | 63,36 | 0,03 |
| | 70 to 74 years | 30,35 | 11,36 | 81,12 | 0,00 | 35,51 | 11,42 | 110,42 | 0,00 | 14,74 | 2,05 | 105,95 | 0,01 |
| | 75 to 79 years | 35,07 | 13,11 | 93,77 | 0,00 | 41,30 | 13,28 | 128,48 | 0,00 | 16,02 | 2,23 | 115,15 | 0,01 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone (duration < 360 days)** | **1,05** | **0,82** | **1,36** | **0,68** | **1,10** | **0,84** | **1,43** | **0,49** | **0,76** | **0,34** | **1,72** | **0,51** |
| | **Exposure to Pioglitazone(duration 360 to 719 days)** | **1,34** | **1,02** | **1,75** | **0,03** | **1,39** | **1,06** | **1,84** | **0,02** | **0,87** | **0,32** | **2,35** | **0,79** |
| | **Exposure to Pioglitazone (duration ≥720 days)** | **1,36** | **1,04** | **1,79** | **0,02** | **1,44** | **1,09** | **1,91** | **0,01** | **0,71** | **0,22** | **2,23** | **0,56** |
| | Exposure to Rosiglitazone | 1,09 | 0,93 | 1,27 | 0,30 | 1,11 | 0,94 | 1,31 | 0,21 | 0,89 | 0,53 | 1,49 | 0,66 |
| | Exposure to Metformin | 1,03 | 0,94 | 1,13 | 0,56 | 1,03 | 0,93 | 1,14 | 0,54 | 0,99 | 0,75 | 1,31 | 0,96 |
| | Exposure to Sulphoamides | 0,92 | 0,84 | 1,01 | 0,09 | 0,92 | 0,83 | 1,01 | 0,07 | 0,99 | 0,76 | 1,30 | 0,95 |
| | Exposure to other oral antidiabetic agents | 1,00 | 0,90 | 1,11 | 0,96 | 0,95 | 0,85 | 1,07 | 0,42 | 1,36 | 1,02 | 1,81 | 0,04 |
| | Exposure to Insulin | 1,09 | 0,98 | 1,22 | 0,13 | 1,09 | 0,97 | 1,22 | 0,17 | 1,10 | 0,81 | 1,50 | 0,53 |

Model 1 : adjustment age, sex and class of antidiabetic agent; Model 2: adjustment age, sex and class of antidiabetic agent and cumulative dose of exposure to pioglitazone; Model 3: adjustment age, sex and class of antidiabetic agent and duration of exposure to pioglitazone.

**Table VIII.** Risk of bladder cancer *(broad definition)*,lung cancer and ENT cancer in diabetic patients aged 40 - 79 years according to exposure to pioglitazone. 2006 cohort and follow-up until the end of 2009.CNAMTS data.

| | | **Bladder Cancer (broad criterion)** | | | | **Lung Cancer** | | | | **ENT Cancer** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | |
| No. of patients in the study | | 1 491 060 | | | | 1 493 472 | | | | 1 495 411 | | | |
| No. of cases arising | | 5 853 | | | | 9 298 | | | | 2 868 | | | |
| Model 1 | Male | 6,51 | 6,03 | 7,03 | 0,00 | 4,78 | 4,52 | 5,05 | 0,00 | 4,12 | 3,74 | 4,54 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 1,38 | 4,58 | 0,00 | 2,53 | 1,84 | 3,47 | 0,00 | 2,51 | 1,70 | 3,71 | 0,00 |
| | 50 to 54 years | 5,01 | 2,86 | 8,77 | 0,00 | 3,75 | 2,79 | 5,06 | 0,00 | 3,21 | 2,22 | 4,66 | 0,00 |
| | 55 to 59 years | 7,81 | 4,50 | 13,55 | 0,00 | 5,64 | 4,21 | 7,54 | 0,00 | 3,49 | 2,43 | 5,03 | 0,00 |
| | 60 to 64 years | 12,52 | 7,24 | 21,66 | 0,00 | 7,30 | 5,46 | 9,75 | 0,00 | 3,81 | 2,65 | 5,47 | 0,00 |
| | 65 to 69 years | 18,62 | 10,78 | 32,17 | 0,00 | 8,27 | 6,19 | 11,04 | 0,00 | 3,72 | 2,59 | 5,35 | 0,00 |
| | 70 to 74 years | 26,41 | 15,30 | 45,59 | 0,00 | 9,59 | 7,18 | 12,80 | 0,00 | 3,69 | 2,57 | 5,31 | 0,00 |
| | 75 to 79 years | 32,59 | 18,88 | 56,26 | 0,00 | 10,25 | 7,68 | 13,69 | 0,00 | 3,28 | 2,28 | 4,74 | 0,00 |
| | **Exposure to Pioglitazone** | **1,13** | **1,03** | **1,25** | **0,01** | **0,94** | **0,87** | **1,02** | **0,15** | **0,85** | **0,73** | **0,99** | **0,04** |
| | Exposure to Rosiglitazone | 1,04 | 0,95 | 1,15 | 0,40 | 0,91 | 0,84 | 0,99 | 0,02 | 0,79 | 0,67 | 0,92 | 0,00 |
| | Exposure to Metformin | 0,99 | 0,93 | 1,04 | 0,66 | 0,88 | 0,84 | 0,92 | 0,00 | 0,75 | 0,69 | 0,81 | 0,00 |
| | Exposure to Sulphoamides | 1,01 | 0,95 | 1,06 | 0,85 | 0,93 | 0,90 | 0,97 | 0,00 | 0,89 | 0,82 | 0,96 | 0,00 |
| | Exposure to other oral antidiabetic agents | 0,98 | 0,92 | 1,04 | 0,47 | 1,01 | 0,96 | 1,06 | 0,62 | 0,88 | 0,80 | 0,97 | 0,01 |
| | Exposure to Insulin | 1,15 | 1,08 | 1,23 | 0,00 | 1,23 | 1,17 | 1,29 | 0,00 | 1,24 | 1,14 | 1,36 | 0,00 |
| Model 2 | Male | 6,51 | 6,03 | 7,02 | 0,00 | 4,78 | 4,52 | 5,05 | 0,00 | 4,12 | 3,74 | 4,53 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 1,37 | 4,58 | 0,00 | 2,53 | 1,84 | 3,47 | 0,00 | 2,51 | 1,70 | 3,71 | 0,00 |
| | 50 to 54 years | 5,00 | 2,86 | 8,77 | 0,00 | 3,75 | 2,79 | 5,06 | 0,00 | 3,21 | 2,22 | 4,66 | 0,00 |
| | 55 to 59 years | 7,81 | 4,50 | 13,54 | 0,00 | 5,64 | 4,21 | 7,54 | 0,00 | 3,49 | 2,43 | 5,02 | 0,00 |
| | 60 to 64 years | 12,51 | 7,23 | 21,65 | 0,00 | 7,30 | 5,46 | 9,75 | 0,00 | 3,81 | 2,65 | 5,47 | 0,00 |
| | 65 to 69 years | 18,61 | 10,77 | 32,16 | 0,00 | 8,27 | 6,19 | 11,04 | 0,00 | 3,72 | 2,59 | 5,35 | 0,00 |
| | 70 to 74 years | 26,41 | 15,30 | 45,58 | 0,00 | 9,59 | 7,18 | 12,80 | 0,00 | 3,69 | 2,57 | 5,31 | 0,00 |
| | 75 to 79 years | 32,59 | 18,88 | 56,26 | 0,00 | 10,25 | 7,68 | 13,69 | 0,00 | 3,28 | 2,28 | 4,74 | 0,00 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone < 10500 mg** | **1,06** | **0,93** | **1,22** | **0,38** | **0,95** | **0,84** | **1,06** | **0,33** | **0,81** | **0,65** | **1,00** | **0,06** |
| | **Exposure to Pioglitazone 10500 to 28000 mg** | **1,13** | **0,97** | **1,32** | **0,11** | **0,93** | **0,82** | **1,06** | **0,29** | **0,82** | **0,64** | **1,05** | **0,12** |
| | **Exposure to Pioglitazone . ≥28000 mg** | **1,44** | **1,13** | **1,84** | **0,00** | **0,96** | **0,76** | **1,20** | **0,70** | **1,15** | **0,79** | **1,69** | **0,46** |
| | Exposure to Rosiglitazone | 1,05 | 0,95 | 1,15 | 0,35 | 0,91 | 0,84 | 0,99 | 0,02 | 0,79 | 0,68 | 0,92 | 0,00 |
| | Exposure to Metformin | 0,99 | 0,94 | 1,05 | 0,69 | 0,88 | 0,84 | 0,92 | 0,00 | 0,75 | 0,69 | 0,81 | 0,00 |
| | Exposure to Sulphoamides | 1,01 | 0,95 | 1,06 | 0,82 | 0,93 | 0,90 | 0,97 | 0,00 | 0,89 | 0,82 | 0,96 | 0,00 |
| | Exposure to other oral antidiabetic agents | 0,98 | 0,92 | 1,04 | 0,49 | 1,01 | 0,96 | 1,06 | 0,62 | 0,88 | 0,80 | 0,97 | 0,01 |
| | Exposure to Insulin | 1,15 | 1,08 | 1,23 | 0,00 | 1,23 | 1,17 | 1,29 | 0,00 | 1,25 | 1,14 | 1,36 | 0,00 |
| Model 3 | Male | 6,51 | 6,03 | 7,03 | 0,00 | 4,78 | 4,52 | 5,05 | 0,00 | 4,12 | 3,74 | 4,53 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 1,37 | 4,58 | 0,00 | 2,53 | 1,84 | 3,47 | 0,00 | 2,51 | 1,70 | 3,71 | 0,00 |
| | 50 to 54 years | 5,01 | 2,86 | 8,77 | 0,00 | 3,75 | 2,79 | 5,06 | 0,00 | 3,21 | 2,22 | 4,65 | 0,00 |
| | 55 to 59 years | 7,81 | 4,50 | 13,55 | 0,00 | 5,64 | 4,21 | 7,54 | 0,00 | 3,49 | 2,43 | 5,02 | 0,00 |
| | 60 to 64 years | 12,52 | 7,24 | 21,65 | 0,00 | 7,30 | 5,46 | 9,75 | 0,00 | 3,80 | 2,65 | 5,47 | 0,00 |
| | 65 to 69 years | 18,61 | 10,77 | 32,16 | 0,00 | 8,26 | 6,19 | 11,04 | 0,00 | 3,72 | 2,59 | 5,35 | 0,00 |
| | 70 to 74 years | 26,41 | 15,30 | 45,58 | 0,00 | 9,59 | 7,18 | 12,80 | 0,00 | 3,69 | 2,57 | 5,31 | 0,00 |
| | 75 to 79 years | 32,59 | 18,88 | 56,25 | 0,00 | 10,25 | 7,68 | 13,69 | 0,00 | 3,28 | 2,28 | 4,74 | 0,00 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone (duration < 360 days)** | **1,08** | **0,94** | **1,25** | **0,27** | **0,88** | **0,77** | **0,99** | **0,04** | **0,75** | **0,59** | **0,96** | **0,02** |
| | **Exposure to Pioglitazone(duration 360 to 719 days)** | **1,12** | **0,94** | **1,33** | **0,22** | **1,09** | **0,95** | **1,25** | **0,21** | **0,80** | **0,60** | **1,06** | **0,12** |
| | **Exposure to Pioglitazone (duration ≥720 days)** | **1,23** | **1,03** | **1,47** | **0,02** | **0,89** | **0,76** | **1,04** | **0,13** | **1,08** | **0,83** | **1,40** | **0,58** |
| | Exposure to Rosiglitazone | 1,05 | 0,95 | 1,15 | 0,36 | 0,91 | 0,84 | 0,99 | 0,03 | 0,79 | 0,68 | 0,92 | 0,00 |
| | Exposure to Metformin | 0,99 | 0,94 | 1,04 | 0,68 | 0,88 | 0,84 | 0,92 | 0,00 | 0,75 | 0,69 | 0,81 | 0,00 |
| | Exposure to Sulphoamides | 1,01 | 0,95 | 1,06 | 0,83 | 0,93 | 0,90 | 0,98 | 0,00 | 0,89 | 0,82 | 0,96 | 0,00 |
| | Exposure to other oral antidiabetic agents | 0,98 | 0,92 | 1,04 | 0,48 | 1,01 | 0,96 | 1,06 | 0,61 | 0,88 | 0,80 | 0,97 | 0,01 |
| | Exposure to Insulin | 1,15 | 1,08 | 1,23 | 0,00 | 1,23 | 1,17 | 1,29 | 0,00 | 1,25 | 1,14 | 1,36 | 0,00 |

Model 1 : adjustment age, sex and class of antidiabetic agent; Model 2: adjustment age, sex and class of antidiabetic agent and cumulative dose of exposure to pioglitazone; Model 3: adjustment age, sex and class of antidiabetic agent and duration of exposure to pioglitazone.

**Table IX.** Risk of colorectal cancer, breast cancer (female) and cancer of kidney in diabetic patients aged 40 - 79 years according to exposure to pioglitazone. 2006 cohort and follow-up until the end of 2009.CNAMTS data.

| | | Colorectal Cancer | | | | Breast Cancer | | | | Kidney Cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | |
| No. of patients in the study | | 1 485 146 | | | | 671 510 | | | | 1 495 787 | | | |
| No. of cases arising | | 10 618 | | | | 6 820 | | | | 2 861 | | | |
| Model 1 | Male | 1,71 | 1,65 | 1,78 | 0,00 | | | | | 1,89 | 1,74 | 2,04 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,04 | 1,40 | 2,97 | 0,00 | 1,50 | 1,20 | 1,87 | 0,00 | 0,99 | 0,66 | 1,47 | 0,95 |
| | 50 to 54 years | 3,93 | 2,79 | 5,55 | 0,00 | 1,61 | 1,31 | 1,99 | 0,00 | 1,60 | 1,13 | 2,27 | 0,01 |
| | 55 to 59 years | 6,07 | 4,33 | 8,51 | 0,00 | 2,09 | 1,72 | 2,55 | 0,00 | 1,88 | 1,34 | 2,63 | 0,00 |
| | 60 to 64 years | 9,56 | 6,84 | 13,36 | 0,00 | 2,67 | 2,20 | 3,25 | 0,00 | 2,71 | 1,95 | 3,78 | 0,00 |
| | 65 to 69 years | 12,52 | 8,96 | 17,49 | 0,00 | 2,87 | 2,36 | 3,49 | 0,00 | 3,00 | 2,16 | 4,17 | 0,00 |
| | 70 to 74 years | 16,30 | 11,68 | 22,75 | 0,00 | 2,82 | 2,32 | 3,42 | 0,00 | 3,53 | 2,55 | 4,90 | 0,00 |
| | 75 to 79 years | 19,32 | 13,84 | 26,97 | 0,00 | 2,46 | 2,02 | 2,99 | 0,00 | 3,63 | 2,61 | 5,05 | 0,00 |
| | **Exposure to Pioglitazone** | **0,97** | **0,90** | **1,05** | **0,45** | **0,91** | **0,83** | **1,00** | **0,05** | **0,91** | **0,79** | **1,06** | **0,22** |
| | Exposure to Rosiglitazone | 0,88 | 0,82 | 0,95 | 0,00 | 0,80 | 0,73 | 0,88 | 0,00 | 0,98 | 0,86 | 1,13 | 0,80 |
| | Exposure to Metformin | 1,02 | 0,98 | 1,07 | 0,25 | 0,92 | 0,88 | 0,97 | 0,00 | 0,97 | 0,89 | 1,05 | 0,39 |
| | Exposure to Sulphoamides | 1,04 | 1,00 | 1,08 | 0,05 | 0,97 | 0,92 | 1,02 | 0,18 | 1,07 | 0,99 | 1,15 | 0,09 |
| | Exposure to other oral antidiabetic agents | 1,03 | 0,98 | 1,08 | 0,25 | 0,94 | 0,89 | 1,00 | 0,05 | 1,05 | 0,96 | 1,15 | 0,28 |
| | Exposure to Insulin | 1,05 | 1,01 | 1,11 | 0,03 | 0,86 | 0,81 | 0,91 | 0,00 | 1,09 | 1,00 | 1,20 | 0,05 |
| Model 2 | Male | 1,71 | 1,65 | 1,78 | 0,00 | | | | | 1,89 | 1,74 | 2,04 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,04 | 1,40 | 2,97 | 0,00 | 1,50 | 1,20 | 1,87 | 0,00 | 0,99 | 0,66 | 1,47 | 0,95 |
| | 50 to 54 years | 3,94 | 2,79 | 5,56 | 0,00 | 1,61 | 1,31 | 1,99 | 0,00 | 1,60 | 1,13 | 2,27 | 0,01 |
| | 55 to 59 years | 6,07 | 4,34 | 8,51 | 0,00 | 2,09 | 1,72 | 2,55 | 0,00 | 1,88 | 1,34 | 2,63 | 0,00 |
| | 60 to 64 years | 9,56 | 6,84 | 13,37 | 0,00 | 2,67 | 2,20 | 3,25 | 0,00 | 2,71 | 1,95 | 3,78 | 0,00 |
| | 65 to 69 years | 12,52 | 8,96 | 17,49 | 0,00 | 2,87 | 2,36 | 3,49 | 0,00 | 3,00 | 2,16 | 4,17 | 0,00 |
| | 70 to 74 years | 16,30 | 11,68 | 22,75 | 0,00 | 2,82 | 2,32 | 3,42 | 0,00 | 3,53 | 2,55 | 4,90 | 0,00 |
| | 75 to 79 years | 19,32 | 13,84 | 26,96 | 0,00 | 2,46 | 2,02 | 2,99 | 0,00 | 3,63 | 2,61 | 5,05 | 0,00 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone < 10500 mg** | **1,03** | **0,93** | **1,14** | **0,52** | **0,92** | **0,81** | **1,04** | **0,19** | **0,94** | **0,77** | **1,15** | **0,54** |
| | **Exposure to Pioglitazone 10500 to 28000 mg** | **0,92** | **0,82** | **1,05** | **0,21** | **0,91** | **0,78** | **1,06** | **0,22** | **0,87** | **0,68** | **1,11** | **0,25** |
| | **Exposure to Pioglitazone . ≥28000 mg** | **0,85** | **0,67** | **1,06** | **0,15** | **0,86** | **0,64** | **1,16** | **0,34** | **0,93** | **0,61** | **1,41** | **0,72** |
| | Exposure to Rosiglitazone | 0,88 | 0,82 | 0,95 | 0,00 | 0,80 | 0,73 | 0,88 | 0,00 | 0,98 | 0,86 | 1,12 | 0,79 |
| | Exposure to Metformin | 1,02 | 0,98 | 1,07 | 0,27 | 0,92 | 0,88 | 0,97 | 0,00 | 0,97 | 0,89 | 1,05 | 0,38 |
| | Exposure to Sulphoamides | 1,04 | 1,00 | 1,08 | 0,06 | 0,97 | 0,92 | 1,02 | 0,17 | 1,07 | 0,99 | 1,15 | 0,09 |
| | Exposure to other oral antidiabetic agents | 1,03 | 0,98 | 1,07 | 0,26 | 0,94 | 0,89 | 1,00 | 0,05 | 1,05 | 0,96 | 1,15 | 0,28 |
| | Exposure to Insulin | 1,05 | 1,00 | 1,10 | 0,04 | 0,86 | 0,81 | 0,91 | 0,00 | 1,09 | 1,00 | 1,20 | 0,06 |
| Model 3 | Male | 1,71 | 1,65 | 1,78 | 0,00 | | | | | 1,89 | 1,74 | 2,04 | 0,00 |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,04 | 1,40 | 2,97 | 0,00 | 1,50 | 1,20 | 1,87 | 0,00 | 0,99 | 0,66 | 1,47 | 0,95 |
| | 50 to 54 years | 3,93 | 2,79 | 5,55 | 0,00 | 1,61 | 1,31 | 1,99 | 0,00 | 1,60 | 1,13 | 2,27 | 0,01 |
| | 55 to 59 years | 6,07 | 4,33 | 8,51 | 0,00 | 2,09 | 1,72 | 2,55 | 0,00 | 1,88 | 1,34 | 2,63 | 0,00 |
| | 60 to 64 years | 9,56 | 6,84 | 13,36 | 0,00 | 2,67 | 2,20 | 3,25 | 0,00 | 2,71 | 1,95 | 3,78 | 0,00 |
| | 65 to 69 years | 12,52 | 8,96 | 17,49 | 0,00 | 2,87 | 2,36 | 3,49 | 0,00 | 3,00 | 2,16 | 4,17 | 0,00 |
| | 70 to 74 years | 16,30 | 11,68 | 22,75 | 0,00 | 2,82 | 2,32 | 3,42 | 0,00 | 3,53 | 2,55 | 4,90 | 0,00 |
| | 75 to 79 years | 19,32 | 13,84 | 26,97 | 0,00 | 2,46 | 2,02 | 2,99 | 0,00 | 3,63 | 2,61 | 5,05 | 0,00 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone (duration < 360 days)** | **1,06** | **0,96** | **1,18** | **0,24** | **0,91** | **0,79** | **1,04** | **0,16** | **0,95** | **0,77** | **1,18** | **0,67** |
| | **Exposure to Pioglitazone(duration 360 to 719 days)** | **0,80** | **0,69** | **0,93** | **0,00** | **0,92** | **0,78** | **1,10** | **0,36** | **0,84** | **0,64** | **1,11** | **0,23** |
| | **Exposure to Pioglitazone (duration ≥720 days)** | **1,00** | **0,87** | **1,15** | **0,97** | **0,90** | **0,74** | **1,08** | **0,27** | **0,91** | **0,69** | **1,21** | **0,52** |
| | Exposure to Rosiglitazone | 0,88 | 0,82 | 0,95 | 0,00 | 0,80 | 0,73 | 0,88 | 0,00 | 0,98 | 0,86 | 1,12 | 0,78 |
| | Exposure to Metformin | 1,02 | 0,98 | 1,07 | 0,26 | 0,92 | 0,88 | 0,97 | 0,00 | 0,97 | 0,89 | 1,04 | 0,38 |
| | Exposure to Sulphoamides | 1,04 | 1,00 | 1,08 | 0,06 | 0,97 | 0,92 | 1,02 | 0,18 | 1,07 | 0,99 | 1,15 | 0,09 |
| | Exposure to other oral antidiabetic agents | 1,03 | 0,98 | 1,07 | 0,26 | 0,94 | 0,89 | 1,00 | 0,05 | 1,05 | 0,96 | 1,15 | 0,28 |
| | Exposure to Insulin | 1,05 | 1,00 | 1,10 | 0,03 | 0,86 | 0,81 | 0,91 | 0,00 | 1,09 | 1,00 | 1,20 | 0,06 |

Model 1 : adjustment age, sex and class of antidiabetic agent; Model 2: adjustment age, sex and class of antidiabetic agent and cumulative dose of exposure to pioglitazone; Model 3: adjustment age, sex and class of antidiabetic agent and duration of exposure to pioglitazone.

**Table X.** Risk of bladder cancer [*definition with acts and diagnostics*] in diabetic patients over 40 years of age according to exposure to pioglitazone. 2006 cohort and follow-up until the end of 2009. CNAMTS data.

| | | Total | | | | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | | HR with 95% CI and P value | | | |
| No. of patients in the study | | 1 716 589 | | | | 879 702 | | | | 836 887 | | | |
| No. of cases arising | | 2 346 | | | | 2 051 | | | | 295 | | | |
| Model 1 | Male | 7,39 | 6,54 | 8,36 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,42 | 0,10 | 2,40 | 0,68 | 8,41 | 0,17 | 2,96 | 0,35 | 25,29 | 0,32 |
| | 50 to 54 years | 5,71 | 2,09 | 15,63 | 0,00 | 6,66 | 2,09 | 21,16 | 0,00 | 2,88 | 0,36 | 22,98 | 0,32 |
| | 55 to 59 years | 7,91 | 2,93 | 21,32 | 0,00 | 9,67 | 3,09 | 30,28 | 0,00 | 2,29 | 0,29 | 18,02 | 0,43 |
| | 60 to 64 years | 15,37 | 5,73 | 41,19 | 0,00 | 18,83 | 6,05 | 58,67 | 0,00 | 4,31 | 0,58 | 32,30 | 0,15 |
| | 65 to 69 years | 20,59 | 7,69 | 55,13 | 0,00 | 24,51 | 7,88 | 76,28 | 0,00 | 8,70 | 1,20 | 63,24 | 0,03 |
| | 70 to 74 years | 30,25 | 11,32 | 80,83 | 0,00 | 35,35 | 11,37 | 109,84 | 0,00 | 14,79 | 2,06 | 106,02 | 0,01 |
| | 75 to 79 years | 34,78 | 13,01 | 92,98 | 0,00 | 40,92 | 13,16 | 127,22 | 0,00 | 16,12 | 2,25 | 115,59 | 0,01 |
| | 80 to 84 years | 31,46 | 11,72 | 84,44 | 0,00 | 37,02 | 11,86 | 115,62 | 0,00 | 14,43 | 1,99 | 104,37 | 0,01 |
| | 85 to 89 years | 23,64 | 8,61 | 64,88 | 0,00 | 24,89 | 7,74 | 80,04 | 0,00 | 14,62 | 1,96 | 108,78 | 0,01 |
| | 90 years and over | 16,26 | 5,10 | 51,88 | 0,00 | 19,84 | 5,13 | 76,69 | 0,00 | 6,77 | 0,70 | 65,09 | 0,10 |
| | **Exposure to Pioglitazone** | **1,15** | **0,99** | **1,33** | **0,07** | **1,18** | **1,01** | **1,39** | **0,04** | **0,89** | **0,55** | **1,44** | **0,62** |
| | Exposure to Rosiglitazone | 1,14 | 0,99 | 1,32 | 0,07 | 1,14 | 0,98 | 1,33 | 0,10 | 1,16 | 0,76 | 1,78 | 0,49 |
| | Exposure to Metformin | 0,99 | 0,91 | 1,08 | 0,79 | 0,99 | 0,90 | 1,09 | 0,82 | 0,98 | 0,77 | 1,25 | 0,87 |
| | Exposure to Sulphoamides | 0,97 | 0,89 | 1,06 | 0,49 | 0,95 | 0,87 | 1,05 | 0,32 | 1,08 | 0,85 | 1,38 | 0,51 |
| | Exposure to other oral antidiabetic agents | 0,97 | 0,88 | 1,06 | 0,48 | 0,94 | 0,84 | 1,04 | 0,22 | 1,17 | 0,91 | 1,52 | 0,23 |
| | Exposure to Insulin | 1,10 | 1,00 | 1,22 | 0,05 | 1,10 | 0,98 | ---1,22 | 0,09 | 1,14 | 0,88 | 1,49 | 0,32 |
| Model 2 | Male | 7,38 | 6,53 | 8,34 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,42 | 0,10 | 2,40 | 0,68 | 8,40 | 0,17 | 2,96 | 0,35 | 25,29 | 0,32 |
| | 50 to 54 years | 5,71 | 2,09 | 15,61 | 0,00 | 6,65 | 2,09 | 21,14 | 0,00 | 2,88 | 0,36 | 22,96 | 0,32 |
| | 55 to 59 years | 7,90 | 2,93 | 21,29 | 0,00 | 9,65 | 3,08 | 30,24 | 0,00 | 2,29 | 0,29 | 18,01 | 0,43 |
| | 60 to 64 years | 15,35 | 5,73 | 41,13 | 0,00 | 18,80 | 6,04 | 58,58 | 0,00 | 4,31 | 0,58 | 32,29 | 0,15 |
| | 65 to 69 years | 20,58 | 7,69 | 55,09 | 0,00 | 24,49 | 7,87 | 76,23 | 0,00 | 8,70 | 1,20 | 63,21 | 0,03 |
| | 70 to 74 years | 30,24 | 11,32 | 80,81 | 0,00 | 35,34 | 11,37 | 109,82 | 0,00 | 14,78 | 2,06 | 106,00 | 0,01 |
| | 75 to 79 years | 34,79 | 13,01 | 93,00 | 0,00 | 40,92 | 13,16 | 127,24 | 0,00 | 16,12 | 2,25 | 115,59 | 0,01 |
| | 80 to 84 years | 31,48 | 11,73 | 84,50 | 0,00 | 37,06 | 11,87 | 115,72 | 0,00 | 14,43 | 1,99 | 104,38 | 0,01 |
| | 85 to 89 years | 23,67 | 8,62 | 64,96 | 0,00 | 24,93 | 7,75 | 80,17 | 0,00 | 14,62 | 1,97 | 108,82 | 0,01 |
| | 90 years and over | 16,28 | 5,10 | 51,93 | 0,00 | 19,87 | 5,14 | 76,80 | 0,00 | 6,77 | 0,70 | 65,10 | 0,10 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone < 10500 mg** | **0,98** | **0,79** | **1,22** | **0,88** | **1,01** | **0,80** | **1,27** | **0,96** | **0,85** | **0,45** | **1,60** | **0,61** |
| | **Exposure to Pioglitazone 10500 to 28000 mg** | **1,19** | **0,94** | **1,51** | **0,14** | **1,23** | **0,96** | **1,58** | **0,10** | **0,90** | **0,40** | **2,03** | **0,80** |
| | **Exposure to Pioglitazone . ≥28000 mg** | **1,78** | **1,26** | **2,52** | **0,00** | **1,85** | **1,29** | **2,65** | **0,00** | **1,10** | **0,27** | **4,47** | **0,89** |
| | Exposure to Rosiglitazone | 1,16 | 1,00 | 1,34 | 0,05 | 1,16 | 0,99 | 1,35 | 0,07 | 1,17 | 0,76 | 1,79 | 0,48 |
| | Exposure to Metformin | 0,99 | 0,91 | 1,08 | 0,85 | 0,99 | 0,90 | 1,09 | 0,88 | 0,98 | 0,77 | 1,25 | 0,88 |
| | Exposure to Sulphoamides | 0,97 | 0,89 | 1,06 | 0,54 | 0,96 | 0,87 | 1,05 | 0,36 | 1,09 | 0,85 | 1,38 | 0,51 |
| | Exposure to other oral antidiabetic agents | 0,97 | 0,88 | 1,07 | 0,50 | 0,94 | 0,85 | 1,04 | 0,24 | 1,17 | 0,91 | 1,52 | 0,23 |
| | Exposure to Insulin | 1,11 | 1,00 | 1,23 | 0,04 | 1,10 | 0,99 | 1,23 | 0,07 | 1,14 | 0,88 | 1,49 | 0,32 |
| Model 3 | Male | 7,38 | 6,53 | 8,35 | 0,00 | | | | | | | | |
| | 40 to 44 years (reference) | | | | | | | | | | | | |
| | 45 to 49 years | 2,51 | 0,85 | 7,42 | 0,10 | 2,40 | 0,68 | 8,40 | 0,17 | 2,96 | 0,35 | 25,28 | 0,32 |
| | 50 to 54 years | 5,71 | 2,09 | 15,61 | 0,00 | 6,65 | 2,09 | 21,14 | 0,00 | 2,88 | 0,36 | 22,96 | 0,32 |
| | 55 to 59 years | 7,90 | 2,93 | 21,29 | 0,00 | 9,65 | 3,08 | 30,24 | 0,00 | 2,29 | 0,29 | 17,99 | 0,43 |
| | 60 to 64 years | 15,34 | 5,73 | 41,13 | 0,00 | 18,80 | 6,04 | 58,57 | 0,00 | 4,31 | 0,58 | 32,26 | 0,16 |
| | 65 to 69 years | 20,57 | 7,68 | 55,06 | 0,00 | 24,48 | 7,87 | 76,19 | 0,00 | 8,69 | 1,20 | 63,16 | 0,03 |
| | 70 to 74 years | 30,22 | 11,31 | 80,75 | 0,00 | 35,31 | 11,36 | 109,73 | 0,00 | 14,77 | 2,06 | 105,92 | 0,01 |
| | 75 to 79 years | 34,76 | 13,00 | 92,92 | 0,00 | 40,89 | 13,15 | 127,13 | 0,00 | 16,11 | 2,25 | 115,52 | 0,01 |
| | 80 to 84 years | 31,46 | 11,72 | 84,43 | 0,00 | 37,02 | 11,86 | 115,61 | 0,00 | 14,42 | 1,99 | 104,33 | 0,01 |
| | 85 to 89 years | 23,65 | 8,62 | 64,90 | 0,00 | 24,91 | 7,75 | 80,08 | 0,00 | 14,62 | 1,96 | 108,78 | 0,01 |
| | 90 years and over | 16,27 | 5,10 | 51,91 | 0,00 | 19,86 | 5,14 | 76,78 | 0,00 | 6,77 | 0,70 | 65,08 | 0,10 |
| | **No exposure to Pioglitazone** | | | | | | | | | | | | |
| | **Exposure to Pioglitazone (duration < 360 days)** | **0,91** | **0,71** | **1,15** | **0,42** | **0,93** | **0,72** | **1,20** | **0,57** | **0,77** | **0,38** | **1,55** | **0,46** |
| | **Exposure to Pioglitazone(duration 360 to 719 days)** | **1,34** | **1,04** | **1,73** | **0,02** | **1,39** | **1,07** | **1,82** | **0,01** | **0,94** | **0,39** | **2,29** | **0,90** |
| | **Exposure to Pioglitazone (duration ≥720 days)** | **1,38** | **1,06** | **1,79** | **0,02** | **1,41** | **1,07** | **1,86** | **0,01** | **1,10** | **0,45** | **2,68** | **0,84** |
| | Exposure to Rosiglitazone | 1,16 | 1,00 | 1,34 | 0,05 | 1,16 | 0,99 | 1,35 | 0,07 | 1,17 | 0,77 | 1,79 | 0,47 |
| | Exposure to Metformin | 0,99 | 0,91 | 1,08 | 0,87 | 0,99 | 0,90 | 1,09 | 0,89 | 0,98 | 0,77 | 1,25 | 0,89 |
| | Exposure to Sulphoamides | 0,97 | 0,89 | 1,06 | 0,55 | 0,96 | 0,88 | 1,05 | 0,36 | 1,09 | 0,85 | 1,38 | 0,50 |
| | Exposure to other oral antidiabetic agents | 0,97 | 0,88 | 1,07 | 0,51 | 0,94 | 0,85 | 1,04 | 0,24 | 1,17 | 0,91 | 1,52 | 0,22 |
| | Exposure to Insulin | 1,11 | 1,01 | 1,23 | 0,04 | 1,10 | 0,99 | 1,23 | 0,07 | 1,15 | 0,88 | 1,49 | 0,31 |

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Annex 1

**Coding principle for the main or related diagnosis**

The main diagnosis is the health problem that prompted admission of the patient to the medical unit (MU), determined on leaving the MU. The MD must be determined in conformity with the guide to clinical situations (and in light of the coding possibilities offered by the 10th revision of the international classification of diseases (ICD-10).

The MD may be:

- a disease, a syndrome, a symptom, a traumatic lesion or an intoxication classified in chapters I to XIX or chapter XXII1 of ICD-10
- or one of the entities classified in chapter XXI Factors influencing health status and contact with health services ("Z" codes)

On the other hand, use of chapter XX External causes of morbidity and mortality (codes starting with the letters V, W, X and Y) is not authorised for coding of the MD.

The MD is determined at the end of the patient's stay in the medical unit. It is stated in light of all the medical information concerning the patient, including the results of examinations carried out during the stay that become available after the patient has left (anatomopathology, virology...).

The role of the related diagnosis (RD), in association with the MD and when the latter is not sufficient, is to account for management of the patient in medical-economic terms. It is determined on the basis of three principles.

- there is no need to mention a related diagnosis unless the MD is coded with chapter XXI of the ICD-10;
- the RD is a chronic or long-term disease or a permanent condition, present at the time of the stay that is the object of the summary;
- the RD answers the question: "for what disease or condition was management of the situation registered as MD undertaken?"

1) There is no need to mention a related diagnosis unless the MD is coded with chapter XXI of the ICD-10 ("Z" codes). In effect, the medical imprecision of certain "Z" codes sometimes has as corollary an imprecision from the point of view of the classification of homogeneous patient groups (HPG). Obviously it is with this failing that the PMSI is concerned.

However, the fact that an RD should be mentioned only if the MD is a "Z" code does not mean that an RD is obligatory every time the MD is a "Z" code. In particular, the RD must also obey the other two principles set out below.

2) The RD is a chronic or long-term disease or a permanent condition, present at the time of the stay that is the object of the summary.

The RD cannot be an acute problem. If such a problem was present at the time of admission or if it was the reason for admission then it is the MD, or else another problem ranks as MD and it is therefore an associated diagnosis2. If it is part of the patient's history, the problem no longer exists and cannot appear in the RUM (Medical Unit Summary) coded other than as an element of the patient's history, with chapter XXI of ICD-10.

Coding principle for malignant tumours in the PMSI (Programme for Medicalisation of Information Systems).

**summary of sheet III [Coding guidelines: volume 3, Tumours]**

A tumour is defined in the coding guidelines as a mass formed in the body by the proliferation of cells constituting a pathological tissue (neoplasia), the abnormalities and aggressiveness of development of which beyond certain limits determine whether it is benign or malignant in nature; taking of a sample followed by microscopic examination is necessary to assert this diagnosis.

Malignant tumour, the primary or secondary nature of which is not specified.
The summary of chapter II of volume 1 of ICD-10 indicates that codes C00 to C75 are those for "malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue". That is to say, any malignant tumour not specifically identified as secondary (or metastatic) must be treated as a primary tumour and coded as such.

Use of codes for "neoplasms of uncertain or unknown behaviour" (D37-D48)
Codes D37-D48 should not under any circumstances be used while awaiting full results of analysis of a lesion of neoplastic appearance: the correct label should be chosen taking into account all the relevant information for the most accurate diagnosis possible, and in particular the conclusions of the anatomopathological examination.
particular case: bladder polyp is usually a papilloma, which the coding proposal in volume 3 suggests may be regarded as a neoplasm of uncertain behaviour (D41.4).

Annex 2 CNIL Authorisation

The Vice-Chairman delegate

Mr. Frederic VAN ROEKEGHEM
DIRECTOR GENERAL OF THE NATIONAL HEALTH INSURANCE FUND FOR EMPLOYEES - CNAMTS
26-50 AVENUE DU PROFESSEUR ANDRE LEMIERRE
75986 - PARIS CEDEX 20

*For the attention of Mrs. Debeaux*

Paris, 04 March 2011

Our ref.: EGY/DP/AE111011
Re.: NOTIFICATION OF AUTHORISATION

**Decision DE-2011-011 authorising the NATIONAL HEALTH INSURANCE FUND FOR EMPLOYEES (CNAMTS) to undertake a processing of personal health data for the purpose of verifying the possible association between patients treated with Pioglitazone (antidiabetic agent) and the occurrence of bladder cancer (Authorisation request 1485424)**

Dear Director-General

You submitted to this committee a request for authorisation in respect of a processing of personal data for the purpose of:

VERIFYING THE POSSIBLE ASSOCIATION BETWEEN PATIENTS TREATED WITH PIOGLITAZONE (ANTIDIABETIC AGENT) AND THE OCCURRENCE OF BLADDER CANCER

This processing pertains to the procedure of article 36, article 62 and subsequent articles of the amended law of 6 January 1978.

This Committee notes that in order to conduct this study, which has also been requested by AFSSAPS, the CNAMTS wishes to make use of the computer backups of the National Inter-Regime Health Insurance System (SNIIRAM) for the years 2006 to 2009.

You state that physical and logical security measures will be put in place to ensure the confidentiality of the data and that the computer processing of the data will be undertaken under your responsibility and that of your colleagues.



I draw to your attention the obligations henceforth incumbent upon these persons, who must:
- use the files only for purposes of comparative analysis of care activities,

- respect the secrecy of the information made available and ensure that secrecy is respected by all persons liable to work on these data, such persons being bound in writing to professional secrecy,
- take all useful precautions to preserve the security of the information thus transmitted and particularly to prevent them being deformed, damaged or communicated to unauthorised third parties,
- not to retrocede or disclose to third parties the information supplied in any form whatsoever,
- not to undertake any processes of reconciliation, interconnection, linking or matching with any directly or indirectly nominative data file or any information liable to reveal a person's identity and/or health status,
- not to misuse the information provided, in particular for purposes of research or identification of persons.

In addition, the person responsible for the project must undertake that information extracted from data files and liable to be disseminated will be presented solely in the form of aggregated statistics, in such a way that the persons concerned cannot be identified.

The retention period as regards data categories is fixed at 10 years.

In application of articles 15 and 69 of the aforementioned law and decision no. 2009-674 of 26 November 2009 delegating the powers of the National Committee on Computing and Freedoms (NCIL) to its chairman and vice-chairman, I authorise the implementation of this processing.

Yours sincerely

*Signature*

Emmanuel de GIVRY

National Committee on Computing and Freedoms
8 rue Vivienne CS 30223 75083 PARIS Cedex 02 Tel.: 01 53 73 22 22 Fax: 01 53 73 22 00
www.cnil.fr
FRENCH REPUBLIC

Annex 3 **Study timetable and work load**

**Study timetable**

Letter from the director-general of AFSSAPS to the director-general of CNAMTS on **17/01/2011** asking to carry out *a risk assessment on the basis of a processing of French data, using the data bases available or cohorts already constituted*.

Between mid-January and mid-February, exploratory analyses subject to regulatory constraints (SNIIRAM reimbursement data, years available 2009 and 2010; PMSI data, year available 2009).

Draft protocol drawn up and a request to reload reimbursement data for 2006 to 2008 sent to the CNIL on **16/02/2011**.

Favourable response from the CNIL on **4/03/2011.**

Full reload of SNIIRAM data bases for 2006-2008 (restitution of data stored on tape); data on-line as of **11/04/2011.**

Data validated and study conducted from **11/04/2011.**

This report passed on to AFSSAPS on **30/05/2011.**

**Work load (as at 30/05/2011)**

- as statistician: 3 months (full-time equivalent)
- as doctor: 2 months (full-time equivalent)