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Pioglitazone is an anti-diabetic drug marketed since 2000 under the brand name Actos® by the firm Takeda with initial co-promotion by Eli Lilly. In June 2011, more than a decade later bladder cancers were identified in male rats treated with pioglitazone, the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) concluded that there was a slight increase of risk of bladder cancer associated with the use of pioglitazone, and recommended the application of safety measures such as restriction of use and patients monitoring. After these warnings, numerous pioglitazone users claimed that the drug caused them to develop bladder cancer and the firms involved were sued in several lawsuits in the U.S.

The firms' behavior in the pioglitazone bladder cancer affair has already been criticized for several aspects: i) the wrong pharmacological presentation of pioglitazone as a selective Peroxisome Proliferator-Activated Receptor γ (PPAR γ) agonist whereas it belongs to the dual PPAR γ/α agonists, a class which has been associated with bladder tumors[1]; ii) the mistaken number of bladder cancer cases in the placebo group of the

PROactive trial hiding a statistically significant risk of bladder cancer[2]; or iii) the alleged lack of reporting of post-marketing bladder cancers to the FDA.[3] In the context of one of the first pioglitazone lawsuits, the U.S. District Court for the Western District of Louisiana made accessible through its website the 68-page legal memorandum of sworn testimonies supporting the arguments against the firm.[4] These documents reveal unknown examples of the firms' poor conduct regarding drug safety assessment and management of pioglitazone. We discuss here the most relevant pieces of information.

The hidden and untruthful animal data

Since the marketing of the drug, the firm's explanation for the bladder cancers found in the male rats exposed to pioglitazone was the "crystalluria hypothesis" *i.e.* that bladder cancers were due to the formation of irritant microcrystals in the bladder, secondary to a pH change that only occurs in rats. The lawsuit document shows that the firm pushed this explanation knowing its lack of sustainability. As explained by the expert Dr Jennifer Southgate, animal data did not provide clear evidence of the alleged change in urine pH, nor show a clear correlation between the presence of microcrystals and cancer. Furthermore, the observed type of cancer (transitional cell cancers) did not correspond to the type expected with this kind of irritation (squamous cell cancers).[4] . As it has also been discussed elsewhere,[5] this rather supports that occurrence of bladder cancer is not specific to rats and can also affects humans. Moreover, the lawsuit document indicates that, for the authorization of pioglitazone in 1999, the firm omitted to report to the FDA one kidney tumor and occurrences of simple hyperplasia in exposed rodents.

The hidden KPNC analysis

When pioglitazone was authorized in 1999, regulators asked the firm to conduct a post-marketing study to address the concerns raised about bladder cancer in pre-marketing animal studies. Thus, a prospective cohort study based on a Californian health care plan, the Kaiser Permanente Northern California (KPNC), was started in 2003 (4 years later) for a duration of ten years. In 2009, its third interim analysis (from 2003 to 2008) showed an increased risk of bladder cancer for patients using

pioglitazone for more than two years (HR=1.4, 95% CI: 1.03-2.0). These results were transmitted (one year later) to the FDA which issued an alert on its website in September 2010, and they were finally published in 2011.[6] In order to address confounding by race/ethnicity, smoking or duration of diabetes, the firm performed an additional nested case-control analysis of the cohort using data retrieved by telephone interviews.[6] The lawsuit document shows that its results, by nature less subject to residual confounding, indicated in fact "even higher risks and across more populations" but they were not disclosed to the FDA nor published by the firm, which alleged in court that data collection was biased.[4]

The hidden disproportionality signal

Published in 2011, an analysis of the FDA adverse event reporting system database found that, between 2004 and 2009, bladder cancers were 4.3-fold more frequently reported with pioglitazone than with other anti-diabetic drugs (this is called a "disproportionality" analysis).[7] These type of results are usually considered as pharmacovigilance signals which urge further investigations. The lawsuit documents indicated that, as of 2005, the firm had conducted a similar disproportionality study whose primary analysis showed a statistically significant 190% increase of bladder cancer reports with pioglitazone. At this time, the firm transmitted non-significant secondary disproportionality analyses to the FDA but not the primary significant one.[4]

The "ghost" meta-analysis study

During the revaluation of pioglitazone by the EMA in 2011, the firm was asked to conduct a meta-analysis from its clinical trial database. Involving about 22,000 patients, there were 19 cases in the pioglitazone group versus 7 in the comparator group, resulting in a HR of 2.64 (95% CI: 1.11 - 6.31, p=0.029).[8] Lawsuit documents proves that the data to conduct this meta-analysis was available to the firm from as early as 2004, and demonstrated that the firm intentionally never analyzed it. For instance, an expert hired by the firm to conduct a meta-analysis of pioglitazone clinical trials on cardiovascular outcome, was expressively told not to use the data to assess the bladder cancer risk.[4] Meta-analysis of clinical trials is commonly considered as

the type of study with the highest level of evidence. As Dr David Kessler, former commissioner of the FDA, confirmed, this data should have been provided to the FDA as of 2004 and would have resulted in a warning about bladder cancer risk for humans being added to the drug label, 7 years earlier than it actually was. It is interesting to note that the re-analysis of the PROactive trial data, removing the mistaken bladder cancer case in the placebo group, resulted in a similar HR of 2.83 (95% CI: 1.02 – 7.85, p=0.040).[2]

Ghostwriting

Internal documents show that many of the firm's employees were involved in ghostwriting and that this was considered as a recognized method to ensure "timely progress" of the firm's publications. The firm's director of the U.S. Medical and Scientific Affairs acknowledged that ghostwritten documents were sent to the FDA and to the U.S. medical community and that some of these documents concerned the question of bladder cancer associated with pioglitazone. Furthermore, it has been shown that, in 2003, the firm's causation trial expert sent a "white paper" regarding bladder cancer to the FDA which was partly written by firm's employees before the expert even began consulting with the firm.[4]

Conclusion

In September 2014, the U.S. District Court for the Western District of Louisiana condemned Takeda and Eli Lilly for "wanton and reckless" conduct failing to adequately warn about the potential risk of bladder cancer with pioglitazone which they knew about.[9] The firm were ordered to pay more than $9 billion in punitive damage to the plaintiffs, but this amount was later reduced to a total of $36.8 million. In April 2015, Takeda agreed to pay $2.37 billion to settle thousands of bladder cancer lawsuits involving its drug. That makes, with Merck paying $4.85 billion for heart attacks cases related to Vioxx® in 2007, one of the largest pharmaceutical company payouts in history.

The examples presented here prompt us to be aware that every level of data production by the firms (basic pharmacology, animal study, clinical and epidemiologic research) could be subject to misconduct such as hiding and manipulating data which

eventually results in delay or lack of crucial safety information for the regulators, the health care professionals and their patients.

Competing interests: the authors have no relevant interests to declare.

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