Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

Translated by Pharmaceuticals and Medical Devices Agency

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan
E-mail: safety.info@pmda.go.jp

Safety measures for the diabetes medication "pioglitazon-containing products"

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Subcommittee on Drug Safety

1. The products

<Non-proprietary name> : pioglitazone hydrochloride

<Brand name> : ACTOS Tablets, SONIAS Combination Tablets
METACT Combination Tablets (Takeda Pharmaceuticals Company Limited)

<Generic drugs for pioglitazone tablets> : Scheduled listing date of the standard drug price: 24 June 2011

<Pharmacological Characteristics> : improve insulin resistance and lower blood glucose

<Annual estimated number of patients taking these medicines> : approximately 1.32 million (estimation by the company : FY2009)

2. Risk of bladder cancer with pioglitazone-containing products

(1) The result of a epidemiological study in France (CNAMTS : retrospective research)

・Overall, the result showed that there was approximately 1.2- fold increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients never exposed to pioglitazone. (HR= 1.22　95% CI 1.05-1.43)

・The results showed a tendency that more cumulative dose and longer duration of administration increased the risk of bladder cancer.
(a duration of pioglitazone therapy from 12 to 23 months was associated with approximately 1.3-fold increase in the risk (HR= 1.34 95%CI 1.02−1.75)、a duration of pioglitazone therapy≧24 months was associated with approximately 1.4-fold increase in the risk (HR=1.36 95%CI1.04-1.79)

(2) The result of an interim analysis (in 2010)of a epidemiological study in the U.S (Kaiser Permanente Northern California (KPNC) Study : prospective study)

・The result showed that there was approximately 1.2- fold increase in the risk of bladder cancer in patients exposed to pioglitazone compared to patients never exposed to pioglitazone. (HR=1.2 95%CI 0.9−1.5)
・There was no overall statistically significant increased risk of bladder cancer with pioglitazone use; however, it showed a tendency that longer dosing period of pioglitazone increased the risk of bladder cancer.
(a duration of pioglitazone therapy ≧24 months was associated with increased risk of bladder cancer. (HR=1.4 95% CI 1.03−2.0)。
・The ten-year observational study is ongoing.

(3) On the other hand, some epidemiological studies suggested no increased risk of bladder cancer with patients exposed to pioglitazone.

(4) The result of animal studies

Mutagenicity testing pioglitazone was negative. In a carcinogenicity study conducted in rats, an increased risk of bladder cancer was observed in male rats. It is estimated that calcified lesion including bladder calculus might lead to bladder cancer.

3. Measures taken in foreign countries

(1) France and Germany announced their decision as “a measure to suspend the use of pioglitazone in new patients” (France: on 9 June 2011/ Germany: on 10 June 2011) the French regulatory authority (afssaps) will force a recall on 11 July 2011.

(2) European Medicines Agency (EMA) will assess relevant data including the results of the French study and discuss the action on these medicines across the whole EU.

(3)On 15 June 2011, the U.S. Food and Drug Administration (FDA) has issued recommendations, which include that patients with active bladder cancer should not use pioglitazone on 15 June 2011.

The label for pioglitazone-containing medicines will be revised. FDA will continue to evaluate data including the ongoing prospective epidemiological study.

4. Proposed interim measure

(1) Epidemiological studies in France and the U.S. showed a possible small increased risk of bladder cancer with longer duration of pioglitazone use. As an interim measure, subcommittee recommends that the following revisions of PRECAUSTIONS of Labeling be required to the Marketing Authorization Holders (MAHs) of pioglitazone (Details are attached as an Annex) Subcommittee also recommends that the risk should be carefully interpreted in the light of limitations of these epidemiological studies.

- Pioglitazone is not to be used in patients with active bladder cancer.
- Patients are to be informed of the risk of bladder cancer.
- Physicians should perform urine tests periodically for signs of haematuria and other symptoms. etc.

(2) The MAHs will provide educational materials of the risk in accordance with revision of PRECAUTIONS.

(3) MHLW/PMDA continues to collect information including ongoing prospective epidemiological study in the U.S. and assess the results, in collaboration with outcomes of FDA and EMA. MHLW/PMDA will consider further measures as needed.

(reference 1) Epidemiology of bladder cancer

Age-adjusted incidence rate of bladder cancer in Japanese: 12/100,000 (Male)
Incidence rate of bladder cancer in Caucasian: approximately 20/100,000
Quoted from JACR Monograph No.12

(reference 2) Actions taken in France and Germany

In 9 June 2011, French regulatory authority (Afssaps) informed the public that pioglitazone containing products should not be newly prescribed following the result of epidemiological study which suggested increased risk of bladder cancer. Afssaps also recommended that patients currently taking these products should not stop the medications with their own judgment and consult with their doctor. German BfArM took a similar action.

(reference 3) Actions taken in the U.S.

The following alerts will be added to the labeling of pioglitazone, which include that pioglitazone should not be used in patients with active bladder cancer. The patient Medication Guide for these medicines will also be revised.

FDA will continue to evaluate data from the KPNC epidemiological study, and will also conduct a review of the results from the French study. FDA will update healthcare professionals and patients when more information becomes available.

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.
- Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.
- Encourage patients to read the Medication Guide they get with their pioglitazone medicine.
- Report adverse events involving pioglitazone medicines to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Related information :

PMDA Risk Communication:

"Updated information about pioglitazone and increased risk of bladder cancer":dated16 June 2011

http://www.pmda.go.jp/english/service/pdf/risk/20110622-1_risk.pdf