

〔 Proposed〕 Revision of the package insert of Pioglitazone Hydrochloride

Current	Proposed revision (underlined parts are added)
<p>Important Precautions</p> <p>None</p> <p>Other Precautions</p> <p>(1) In the 24-month studies of rats and mice, bladder cancers were observed in male rats treated orally with pioglitazone hydrochloride (3.6mg/kg/day and above).</p>	<p>Important Precautions</p> <p><u>Overseas epidemiological studies that included patients with diabetes suggested an increased risk of bladder cancer in patients taking pioglitazone. Some epidemiological study results also showed a tendency for longer dosing period of pioglitazone to increase the risk of bladder cancer. Therefore, the following precautions are recommended (See the section of Other Precautions):</u></p> <ul style="list-style-type: none"> • <u>Pioglitazone is not to be used in patients with active bladder cancer. The benefits and risks should be considered in patients with a prior history of bladder cancer to determine whether the drug should be administered.</u> • <u>Patients or their families are to be given a full explanation of the risk of bladder cancer before initiating the therapy. Patients should be instructed to see their doctor immediately if they have any signs or symptoms of blood in the urine, pollakiuria or pain on urination during the treatment with this drug.</u> • <u>Physicians should perform a urine test periodically during the treatment with this drug. If any abnormalities are observed,</u>

appropriate measures should be taken. Patients should continue to be carefully monitored also after the treatment with this drug.

Other Precautions

(1) In the 24-month studies of rats and mice, bladder cancers were observed in male rats treated orally with pioglitazone hydrochloride (3.6mg/kg/day and above).

(2) In an epidemiological study including patients with diabetes, the interim analysis showed no overall significant increase in the risk of bladder cancer with pioglitazone use (Hazard Ratio [HR] 1.2, 95% Confidence Interval [CI] 0.9 to 1.5). A stratified analysis, however, showed a significant increase of the bladder cancer risk in the duration of administration \geq 2-year subgroup(HR 1.4 [95% CI 1.03-2.0]).

In another epidemiological study, there was a statistically significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents (HR 1.22; 95% CI 1.03 to 1.43). The results also showed a statistically significant increase of the bladder cancer risk for the duration of administration \geq 1-year subgroup (HR 1.34; 95% CI 1.02 to 1.75).