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## **Frequently Asked Questions on the Link between Pioglitazone and Bladder Cancer**

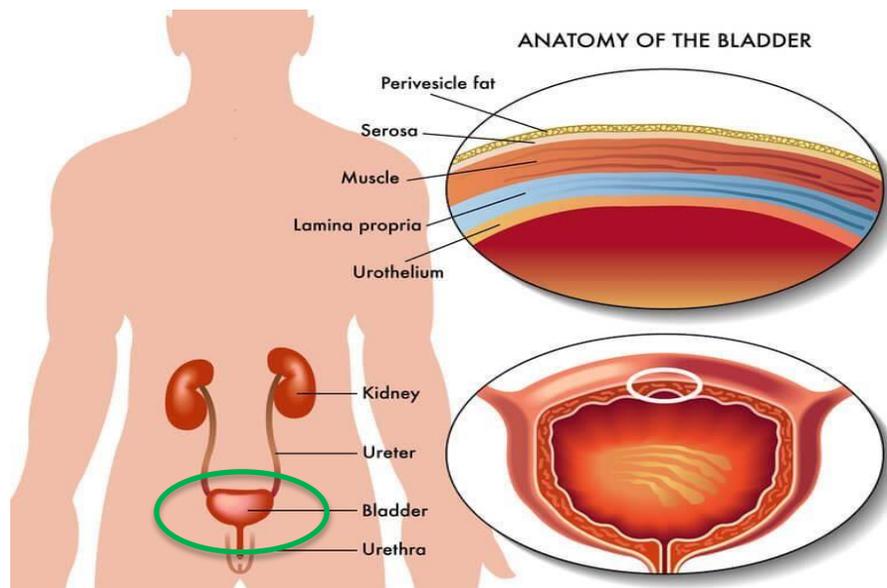
### **What is Pioglitazone?**

Pioglitazone belongs to a group of medicines known as thiazolidinediones (or Glitazones) used for the management of Type 2 diabetes in addition to diet and exercise.<sup>1</sup> Pioglitazone works by increasing the body's sensitivity to insulin, a natural substance produced by the pancreas that helps control blood glucose levels. Pioglitazone's action that increases the body's sensitivity to insulin is linked to its ability to bind to peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) receptors found in tissues such as adipose tissue, skeletal muscle, and liver. Activation of PPAR $\gamma$  receptors is important for insulin's glucose-lowering action in the body.

Pioglitazone is not used to treat Type 1 diabetes (a condition in which the body does not produce insulin) or diabetic ketoacidosis (a serious condition that may develop in Type 1 and sometimes Type 2 diabetes if high blood glucose is not treated). In addition to the use of Pioglitazone to control blood glucose in Type 2 diabetes, there is evidence that it could reduce the number of heart attacks in people living with diabetes.<sup>2</sup> On the other hand, there have also been concerns that the use of Pioglitazone may be associated with the risk of developing cancer of the urinary bladder. However, while some studies suggest that this may be the case, others suggest no added risk.

### **What is Bladder cancer?**

Bladder cancer is cancer that starts in the urinary bladder. The urinary bladder is a hollow, muscular organ in the lower abdomen (Refer to Fig. 1, below).



**Fig. 1:** The Bladder

Adopted from: <http://www.treatlyme.net/treat-lyme-book/category/bladder/> Accessed Oct 11, 2017

The bladder's role is to hold urine until it leaves the body through the urethra.

Bladder cancer begins when cells in the urinary bladder start to grow uncontrollably. As more cancer cells develop, they can spread to other areas of the body.<sup>3</sup>

### **What is the Evidence that Pioglitazone causes Bladder Cancer?**

The findings of a five year interim analysis of a large observational study using the Kaiser Permanente Northern California database showed that the use of pioglitazone for 24 months or more was associated with an increased risk of bladder cancer.<sup>4</sup> However, in the final analysis of the Kaiser Permanente Northern California study, which used the same cohort with follow-up extended to ten years, the use of pioglitazone was no longer significantly associated with an increased risk of bladder cancer in a duration-response fashion.<sup>5</sup> The most recent meta-analysis which reviewed twenty-six studies found no difference in the incidence of bladder cancer among patients using pioglitazone compared with non-users.<sup>6</sup>

### **How could Pioglitazone increase the risk of Bladder Cancer?**

Although studies suggest PPAR $\gamma$  agonists are involved in known tumour-suppression pathways, mechanisms linking thiazolidinediones with the development or progression of



bladder neoplasms have not been fully elucidated.<sup>7</sup> How pioglitazone could increase the risk of bladder cancer is therefore still being studied by the scientific community.

### **What are the risk factors for Bladder Cancer?**

Risk factors of bladder cancer include smoking, exposure to certain chemicals, previous cancer treatment, chronic bladder inflammation and a personal or family history of cancer. Increasing age, male gender and being of white race are also known risk factors.<sup>7</sup>

### **What are the symptoms for Bladder Cancer?**

Bladder cancer signs and symptoms may include blood in urine (haematuria), painful urination and pelvic pain. Haematuria may appear as bright red or cola-coloured urine, but sometimes may not show any change in the urine colour and may only be detected during a microscopic examination of the urine in the laboratory.

### **When should you see a doctor?**

Patients should contact their Doctor or healthcare professionals if they experience any of the following signs or symptoms after starting pioglitazone, as these may be due to bladder cancer:

- Blood or a red color in the urine,
- New or worsening urge to urinate
- Pain when urinating

### **Are there Pioglitazone-Containing Medicines on the Ghanaian Market?**

Yes there are pioglitazone-containing medicines registered by the FDA on the Ghanaian market. Pioglitazone-containing medicines registered by the FDA have the following brand names; Diavista, LG-Glizone, Nilgar, Pilgat and Piotex.

### **What is the FDA Doing to regulate Pioglitazone-containing Medicines? The FDA has taken a number of steps listed below:**

- Communication to healthcare professionals not to use pioglitazone as the first choice for the treatment of Type 2 diabetes mellitus but used only in patients in whom glycaemic targets cannot be reached with other oral therapies (sulphonylureas and metformin), or in whom other therapies are contraindicated, and to inform them about the potential risk factors.



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- Companies marketing pioglitazone containing products are also requested to indicate the potential adverse effect in the product package and also indicate those in whom pioglitazone should not be used. Other countries such as the United States of America and Canada have similar labelling requirements for pioglitazone containing products.
- As part of the FDA's Safety Monitoring Programme, companies marketing pioglitazone are required to monitor and report adverse drug events to the FDA.

The FDA will continue to monitor and evaluate the scientific evidence and update healthcare professionals and the public with any new information.

### **What Should Patients do?**

Patients should never take any medicine containing pioglitazone by themselves or upon recommendation from friends or family. Patients who are concerned about the risk of bladder cancer with the use of pioglitazone should talk to their Doctor or healthcare professional.

### **How to Report Adverse Reactions to Pioglitazone and other products**

#### ***Healthcare Professionals***

- Complete Adverse Reaction Reporting Form and submit
  - Online : <http://adr.fdaghana.gov.gh/>
  - Mobile Number : 024 431 0297
  - Email : [drug.safety@fdaghana.gov.gh](mailto:drug.safety@fdaghana.gov.gh).

#### ***Patients and Consumers***

- Talk to your Doctor, Pharmacist, Nurse
  - SMS Short code : 4015
  - Mobile Number : 024 431 0297
  - Online : <http://adr.fdaghana.gov.gh/patient.php>
  - Email : [drug.safety@fdaghana.gov.gh](mailto:drug.safety@fdaghana.gov.gh)

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