

Pioglitazone Prescriber's Guide: Appropriate Patient Selection And Patient Risk Management

Following a review by the European Medicines Agency (EMA) of the association between pioglitazone containing medicines and an increased risk of bladder cancer, the agency indicated that although there is a small increased risk of bladder cancer with pioglitazone, it should remain available as a treatment option for certain patients with Type 2 diabetes, but only when certain other treatments (metformin) have not been suitable or have failed to work adequately.

Several recommendations were made regarding the management of the risk of bladder cancer through careful patient selection and ongoing monitoring for efficacy in individual patients.

The EMA has requested that an Educational Pack is provided to all physicians and healthcare professionals who may potentially prescribe/use pioglitazone in Europe. This Prescriber's Guide provides information on appropriate patient selection, based on the EMA review, the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet.

Healthcare professionals should ensure that they are familiar with the updated SmPC accompanying this prescribing guide to ensure they are fully aware of the potential risks involved, and to ensure that the optimal benefit-risk balance is maintained for each patient.

Background

Pioglitazone is indicated for use as monotherapy, dual oral therapy or triple oral therapy in patients who are unable to use metformin and in those for whom inadequate glycaemic control is achieved despite maximum tolerated dose of therapy with metformin, or a sulphonylurea, or both. Pioglitazone is also indicated for combination with insulin in Type 2 diabetes mellitus patients with insufficient glycaemic control on insulin, for whom metformin is inappropriate because of contraindications or intolerance.

Full product information is available on the EMA website www.ema.europa.eu or the Medicines Information Online website www.medicines.ie.

Pioglitazone should not be used as first line therapy for the treatment of Type 2 diabetes mellitus.

- After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess the adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

Risk Management Guidance For Bladder Cancer; Heart Failure And Use In The Elderly

1. Bladder Cancer

In humans, bladder cancer is a rare event [Tyczynski 2003] and Type 2 diabetic patients have a 40% higher incidence than the general non-diabetic population [Larsson 2006, MacKenzie 2011]. The data accumulated in the context of pioglitazone studies suggest a small increased risk for patients on pioglitazone; with data from clinical trials and epidemiological studies suggesting an early (risk with short term use) and late effect (risk with prolonged use) respectively.

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

Clinical Management Principles

Since a small increased risk of bladder cancer has recently been recognised as being associated with pioglitazone use, the prescriber should incorporate the following into their routine medical practice when initiating pioglitazone therapy.

- Pioglitazone is contraindicated in patients with current bladder cancer or a history of bladder cancer.
- Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region).
- Pioglitazone is contraindicated in patients with uninvestigated macroscopic haematuria

- Any unexplained haematuria should be investigated before starting pioglitazone therapy. During treatment, patients should be advised to report haematuria, or other symptoms such as dysuria, or urinary urgency to their physician promptly.
 - Testing for haematuria should be performed regularly as part of routine diabetic urinalysis. If haematuria is symptomatic, persistent or visible and if other causes cannot be identified, patients should be referred to a specialist for follow-up.

2. Fluid Retention and Congestive Heart Failure (CHF):

- Pioglitazone is contraindicated in patients with heart failure or a history of heart failure.
- Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction, symptomatic coronary artery disease, or the elderly), physicians should start with the lowest available dose and increase the dose gradually.
- Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve.
- Since insulin and pioglitazone are both associated with fluid retention, concomitant administration of pioglitazone and insulin may increase the risk of oedema.
- Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

3. Elderly Patients

- Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.
- In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly.
- Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin.

PREScribing ALGORITHM

PIOGLITAZONE

Pioglitazone should not be used as first-line therapy

In Europe, pioglitazone is indicated as second or third line treatment of Type 2 diabetes mellitus as described below:

as **monotherapy**

- in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as **dual oral therapy** in combination with

- metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in Type 2 diabetes mellitus patients with insufficient glycaemic control on insulin, for whom metformin is inappropriate because of contraindications or intolerance.

