

PIOGLITAZONE EDUCATIONAL MATERIALS

Accord Healthcare Limited, UK
Actavis UK Ltd
Arrow Generics Ltd/Specifar SA
Brown & Burk UK Ltd
Dr Reddy's Laboratories (UK) Ltd
Morningside Healthcare Ltd
Mylan Inc
Ranbaxy UK
Teva UK Ltd
Tillomed/Specifar SA
Torrent Pharma (UK) Ltd
ZeNTIVA

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Dear Healthcare Professional

Educational materials on risk of bladder cancer and heart failure with pioglitazone

In July 2011 a review of pioglitazone by the European Medicines' Agency concluded that there is a small increased risk of bladder cancer following pioglitazone treatment, although its benefits continue to outweigh its risks in a limited population of type 2 diabetic patients¹.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has requested that all Marketing Authorisation Holders for pioglitazone-containing products should provide an Educational Pack to physicians and healthcare professionals expected to prescribe or use pioglitazone in the UK. You have been identified as a healthcare professional in this group.

The companies listed above have collaborated in the preparation of these educational materials. Approved product information is available by following individual company weblinks listed in Annex 2. The educational materials consist of the following:

- Annex 1: a **Prescriber Guide** summarizing the recent changes to the product information for pioglitazone with respect to the risks of bladder cancer and heart failure and regarding use in the elderly.

The key points are:

1. *Pioglitazone should be discontinued in patients who fail to show an adequate response to treatment (eg reduction in HbA1c).*
2. *Pioglitazone is contraindicated in patients with a history of, or current, bladder cancer and uninvestigated macroscopic haematuria. Patients should be carefully evaluated before initiation of, and during, treatment for the presence of risk factors for bladder cancer and for symptoms suggestive of possible bladder cancer.*
3. *Pioglitazone is contraindicated in patients with cardiac failure (NYHA stages I to IV). Those at risk for developing cardiac failure should be prescribed the lowest available dose with gradual up-titration, and should be carefully monitored for signs of heart failure.*
4. *Given the age-related risks (especially bladder cancer, fractures and heart failure), the risk to benefit ratio of using pioglitazone should be carefully considered in the elderly. The elderly are at particular risk of serious heart failure when pioglitazone is given in combination with insulin.*

The prescriber guide can also be accessed electronically at the MHRA website (<http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/glitazonesfordiabetes/index.htm>) and is available from the Marketing Authorisation Holders (details given in Annex 2).

- Annex 2: **internet links to the product information** (Summary of Product Characteristics and Patient Information Leaflet) for each pioglitazone-containing medicine marketed by the companies listed above. The relevant Summary of Product Characteristics should be consulted before pioglitazone is prescribed. Contact details for each Marketing Authorisation Holder are also provided in Annex 2.

¹ CHMP review of pioglitazone-containing medicines (EMA/CHMP/562496/2011); July 2011

Please review the enclosed materials to ensure that you are aware of the latest information regarding the risks of pioglitazone and of the need to carefully consider the balance of benefits and risks in individual patients before pioglitazone is prescribed.

Yours faithfully

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<p>Dr Reddy's Laboratories (UK) Ltd</p> <p>John Barber Head of Pharmacovigilance QS/QA</p>	<p>Morningside Healthcare Ltd</p> <p>Danesh Gadhia Director</p>	<p>Mylan Inc (t/a as Generics UK Ltd)</p> <p>Balwant Heer VP Global Head - Product Safety and Risk Management</p>
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<p>Teva UK Ltd</p> <p>Dr Ewan Walters Medical Director</p>	<p>Torrent Pharma (UK) Ltd.</p> <p>Brian Lalor Regulatory Affairs Officer</p>	<p>ZeNTIVA</p> <p>Dr Tony Whitehead UK Medical Director</p>

**PRESCRIBERS GUIDE
USE WITH PIOGLITAZONE
15 MG, 30 MG AND
45 MG TABLETS**

ADVICE FOR PRESCRIBERS

A recent review of a pioglitazone by the European Medicines' Agency (EMA) concluded that there is a small risk of bladder cancer following pioglitazone treatment, although its benefits continue to outweigh its risks in a limited number of type 2 diabetic patients¹. The Medicines and Healthcare Products Regulatory Agency (MHRA) has requested that an Educational Pack is provided to all physicians and healthcare professionals expected to prescribe or use pioglitazone in the UK. The pack 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 familiarize themselves with the SmPC provided in this pack to ensure they are fully aware of all risks involved when considering use of pioglitazone in individual patients.

Adverse events should be reported. Reporting forms and Information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to the products licence holder.

Sep 2011 Ref: 1282-1284.001v1

Initiation of Treatment (Section 4.1 of SmPC)

Pioglitazone should not be used as first line therapy for the treatment of type 2 diabetes. The use of other diabetes therapy should be ruled out before initiating treatment with pioglitazone. Pioglitazone is indicated in the treatment of type 2 diabetes:

as **monotherapy**

- in adult 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 adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.
- a sulphonylurea, only in adult 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 adult 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 adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess 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.

Bladder cancer (Sections 4.3, 4.4 and 4.8 of SmPC)

Pioglitazone is contraindicated in patients with current bladder cancer, a history of bladder cancer and uninvestigated macroscopic haematuria

- 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 area).
- Any macroscopic haematuria should be investigated before starting pioglitazone therapy.
- Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone than 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.

Heart failure (Sections 4.3, 4.4 and 4.8 of SmPC)

Pioglitazone is contraindicated in patients with cardiac failure or history of cardiac failure (NYHA stages I to IV).

- 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, or 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 and when used in combination with insulin.
- Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

Treatment of the elderly (Sections 4.1, 4.2 and 4.4 of SmPC)

In the light of age-related risks (especially bladder cancer, fractures and heart failure), the risk to benefit ratio should be considered carefully before and during treatment in the elderly.

The elderly population is more prone to medication-related adverse events due to the clinical complexity of their care. Congestive heart failure is more common in advanced age, as is the incidence of cancer and the increased risk of falls and bone fractures. Therefore, there are some special recommendations for the treatment of elderly patients with pioglitazone.

- Prescribers should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin.
- Combination use with insulin should be considered with caution in the elderly because of increased risk of serious heart failure.

Please refer to the Summary of Product Characteristics before prescribing.

¹CHMP review of pioglitazone-containing medicines (EMA/CHMP/562496/2011) July 2011

**ANNEX 2 – LINKS TO PRODUCT INFORMATION
(BY MARKETING AUTHORISATION HOLDER, IN ALPHABETICAL ORDER)**

Accord Healthcare Limited, UK

Marketing Authorisation pending. Once approved, product information will be available at <http://www.medicines.org.uk/emc/>
For further information: Medical Information – 01271 311257

Actavis UK Ltd

Marketing Authorisation pending. Once approved, product information will be available at <http://www.medicines.org.uk/emc/>
For further information: Medical Information – 01271 311257

Arrow Generics Ltd

www.arrowgenerics.co.uk
<http://www.arrowgenerics.co.uk/page/20/education.htm>
For further information: Medical Information – medinfo@arrowgenerics.com or 01438 737630

Brown & Burk UK Ltd

<http://bbukltd.com/Pioglitazone2.pdf>
For further information contact: Medical Information - anisa@bbukltd.com or 07939233375

Dr Reddy's Laboratories (UK) Ltd

<http://www.drreddys.com/unitedkingdom/pioglitazone.html>
For further information contact: Medical Information - 01753 512500

Morningside Healthcare Ltd

<http://www.morningsidehealthcare.com/endocrine-system>
For further information contact: Medical information- medicalenquiry@morningsidehealthcare.com or 0116204595001509 217705

Mylan

<http://www.mylan.co.uk/pioglitazone.html>
For further information contact: Medical Information – info@mylan.co.uk or 01707 853000

Ranbaxy (UK) Ltd

Marketing Authorisation pending. Once approved, product information will be available at <http://www.medicines.org.uk/emc/>
For further information: Medical Information – 01271 311257

Specifar SA see Arrow Generics Ltd

www.arrowgenerics.co.uk
<http://www.arrowgenerics.co.uk/page/20/education.htm>
For further information: Medical Information: medinfo@arrowgenerics.com or 01438 737630

Teva UK Ltd

Marketing Authorisation pending.
www.tevauk.com
For further information contact: Medical Information - medinfo@tevauk.com or 0207 5407117

Tillomed Laboratories Ltd

<http://www.specifar.gr/?p=1987>
For further information contact: Medical Information - info@tillomed.co.uk or 01480 402400

Torrent Pharmaceuticals Ltd

<http://www.torrentpharma.com/pi-uk.html>
http://www.torrentpharma.com/download/prescribers_guide_fo_%20pioglitazone.pdf
For further information contact: 01293 574180

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<http://www.medicines.org.uk/emc/medicine/25674/Spc/Pioglitazone+15mg+Tablets/>
<http://www.medicines.org.uk/emc/medicine/25673/Spc/Pioglitazone+30mg+Tablets/>
<http://www.medicines.org.uk/emc/medicine/25672/Spc/Pioglitazone+45mg+Tablets/>
<http://www.medicines.org.uk/EMC/medicine/25671/PIL/Pioglitazone+15mg%2c+30mg+%26+45mg+Tablets/>
For further information contact: Medical Information – UK-medicalinformation@sanofi.com or 01483 554831