IRISH MEDICINES BOARD

# Drug Safety NEWSLETTER

43rd EDITION

## Pioglitazone – New contraindications and warnings following European review of bladder cancer risk

**(Actos, Glustin, Competact, Glubrava, Tandemact)**

Pioglitazone belongs to the class of medicines known as 'thiazolidinediones' and is used in the treatment of type 2 diabetes as second-line therapy (see Summary of Product Characteristics for full details of licensed indications). Pioglitazone (Actos and Glustin) was first authorised through a centralised European assessment procedure in 2000 with subsequent authorisation of combination products with metformin (Competact and Glubrava) and glimepiride (Tandemact) in 2006 and 2007.

The risk of bladder cancer in association with pioglitazone has been kept under close review since the marketing authorisation was first granted in 2000. As part of the ongoing evaluation of this issue, the marketing authorisation holder, Takeda, is conducting a number of post-authorisation studies, including a ten-year epidemiological study (Kaiser Permanente Northern California study (KPNC)) aimed at identifying incident malignancies associated with pioglitazone treatment in a cohort of diabetic patients. While initial study reports had not confirmed a clear association between the use of pioglitazone and the occurrence of bladder cancer, the third interim report did provide a signal of a potential increased risk in those with the longest exposure and highest cumulative dose.

Subsequently and following increased reporting of cases of bladder cancer in France and the US, a European-wide review of pioglitazone-containing medicines was initiated in March 2011 at the request of the European Commission. The European Medicines Agency's Committee for Human Medicinal Products (CHMP) reviewed all available data on the occurrence of bladder cancer, including results of preclinical studies, clinical studies, epidemiological studies and spontaneous reports. The Committee also considered the advice from its Scientific Advisory Group (SAG) on Diabetes/Endocrinology.

The CHMP concluded that the evidence from the different sources shows that there is a small increased risk of bladder cancer with pioglitazone. Recently available data from epidemiological studies (third interim analysis of the KPNC cohort and nested case control studies, French CNAMTS cohort study and studies conducted in the GPRD database) point to a small increased risk (relative risk ranging from 1.15 to 1.33 across studies) of bladder cancer in diabetic patients treated with pioglitazone, in particular in patients treated for the longest durations and with the highest cumulative doses.

Additionally, in a meta-analysis of randomised controlled clinical trials, 19 out of 12,506 patients taking pioglitazone had bladder cancer (0.15%) compared with 7 out of 10,212 patients not taking pioglitazone (0.07%) (HR=2.64 (95% CI 1.11-6.31, P=0.029). 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. A possible risk after short term treatment cannot be excluded.

The CHMP concluded that there are some patients who cannot be adequately treated by other therapies and who could benefit from pioglitazone subject to additional monitoring requirements and further risk minimisation measures as outlined overleaf.

In this edition

## Advice to Healthcare Professional

- Use of pioglitazone is now contraindicated in patients with:
  - current active bladder cancer or
  - a history of bladder cancer or
  - uninvestigated macroscopic haematuria.
- Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. Any unexplained 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.
- In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully before initiating treatment in the elderly.
- Prescribers should review the treatment of patients currently on pioglitazone and new patients after 3 to 6 months treatment (and regularly thereafter) to ensure that only patients who are deriving sufficient benefit continue to take it. Pioglitazone should be discontinued in patients who do not respond adequately to treatment (e.g. reduction in HbA1c).
- Prescribers should consider patients risk factors for bladder cancer (such as age, smoking and exposure to certain chemicals or treatments) before starting pioglitazone and in those already taking it.
- Patients currently on pioglitazone should be advised to have their treatments evaluated by their doctor at their next scheduled appointment.
- Any suspected adverse reactions with use of pioglitazone should be reported to the Irish Medicines Board.

**Key Message:**

- **There is a small increased risk of bladder cancer with use of pioglitazone; epidemiological data suggest a relative risk of around 1.2 (ranging from 1.15 to 1.33 for ever use across studies). The benefit-risk balance remains positive in a limited population of type 2 diabetics. Prescribers are advised to carefully select patients based on individual patient's risk factors and to periodically review the efficacy of the patient's treatment in order to optimise the benefit-risk margin at the individual patient level by ensuring that only patients who are deriving sufficient benefit continue to take it.**

## Dexrazoxane (Cardioxane) – Restrictions for use

Dexrazoxane (Cardioxane) is currently indicated for use in patients with cancer to prevent chronic cumulative cardiotoxicity caused by treatment with doxorubicin and epirubicin.

A European-wide review of the risks and benefits of dexrazoxane was recently completed by the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency. This review was conducted following concerns that it could be linked to an increased risk of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) following data from studies in the United States reporting cases of AML and MSD in children, as well as on a small number of cases of AML reported in adult breast cancer patients receiving dexrazoxane.

Following review of the available data, the CHMP concluded that there was evidence of serious harm in children and adolescents receiving dexrazoxane and that the benefits of the medicine do not outweigh the risks in this age group. The CHMP therefore recommended contraindicating dexrazoxane in patients under the age of 18.

With respect to the use of dexrazoxane in adults, the Committee concluded that the benefits of dexrazoxane only outweigh the risks in adult patients with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300 mg/m$^2$ of doxorubicin or 540 mg/m$^2$ of epirubicin. It also recommended that the use of dexrazoxane when used with doxorubicin should be reduced from a dose ratio of 20:1 (20 parts dexrazoxane to 1 part doxorubicin) to a ratio of 10:1. The dose ratio of dexrazoxane to epirubicin remains unchanged at 10:1.
Further information is available on **www.ema.europa.eu**

**Key Message:**

- **Dexrazoxane is now contraindicated for use in children and adolescents under the age of 18 years.**
- **Use in adults is restricted to patients with advanced or metastatic breast cancer who have previously received a minimum cumulative dose of 300 mg/m $^2$ doxorubicin or 540 mg/m$^2$ epirubicin.**
- **The dose ratio for dexrazoxane to be used in combination with doxorubicin has been reduced and is now 10:1 for dexrazoxane: doxorubicin.**
- **When deciding to use dexrazoxane, prescribers should carefully assess the possible benefits in relation to the protection of the heart against the short- and long-term risks, particularly the risk of AML and MDS.**

## Dronedarone (Multaq) – Update on benefit-risk review

Dronedarone was authorised via a centralised European assessment procedure in 2009. It is authorised for use in clinically stable adult patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

Following reports of severe liver injury associated with use of dronedarone, a European-wide review of its benefits and risks was initiated in January 2011(see IMB Drug Safety Newsletter February 2011). The scope of this review has been extended to evaluate preliminary data from the PALLAS (Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy) study. These data show an increased risk of cardiovascular side effects such as cardiovascular death, stroke and cardiovascular hospitalisation in patients with permanent atrial fibrillation. These new data could have an impact on the use of the medicine in its currently approved indication.

As the information from PALLAS has only recently become available, the CHMP will continue to assess these new data in depth, together with all other available data on the benefits and risks of Multaq and issue further advice when the review is finalised in September 2011.

Pending finalisation of the current review, prescribers are reminded to follow the recommendations in the product information with respect to the indication, contraindications and warnings. Specifically, prescribers are advised to monitor patients regularly in order to ensure that their condition remains within the authorised indication and do not progress to permanent atrial fibrillation.

### Advice to Healthcare Professionals

- Prescribers are reminded to strictly adhere to the authorised indication for Multaq as detailed in the Summary of Product Characteristics (SPC) available on **www.ema.europa.eu**
- Patients should be monitored regularly to ensure that their condition remains within the authorised indication and does not progress to permanent atrial fibrillation.
- Prescribers are also reminded to consider current contraindications and warnings for Multaq use, including the requirement to monitor liver function prior to initiation of treatment and then monthly for six months, at months 9 and 12, and periodically thereafter. Treatment should be discontinued if there are signs of potential liver damage.
- The following contraindications and warnings in the summary of product characteristics in relation to cardiovascular risk are particularly relevant:
  - Multaq is contraindicated in patients with bradycardia <50 beats per minute and in patients in unstable haemodynamic conditions, including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients).
  - Multaq is not recommended in stable patients with NYHA III or LVEF <35%.
  - If heart failure develops or worsens, consider the suspension or discontinuation of Multaq.
  - INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonist as per their label. (This recommendation is in the process of being added to the summary of product characteristics.)

**Key Message:**

- **The European Medicines Agency is currently reviewing the benefits and risks of the anti-arrhythmic medicine dronedarone. Preliminary data from a clinical study (PALLAS) have shown an increased risk of cardiovascular side effects such as cardiovascular death, stroke and cardiovascular hospitalisation in patients with permanent atrial fibrillation. These new data could have an impact on the use of the medicine in its approved indication, "adult clinically stable patients with a history of, or current, non-permanent atrial fibrillation, to prevent recurrence or to lower ventricular rate". Awaiting finalisation of the review, prescribers are reminded to follow current recommendations pending further advice in September.**

### View the Drug Safety Newsletter online or via email

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## Gardasil – Overview of National Monitoring Experience

The HSE human papillomavirus (HPV) Schools Immunisation Programme commenced in May 2010 and recently completed its first year of the programme. It is estimated that over 159,000 doses of Gardasil have been distributed, with at least 145,000 doses administered up to June 2011 as part of the programme. No new risks have been identified for Gardasil during monitoring of national use. The balance of benefits and risks for the vaccine is positive.

Prior to the introduction of the programme, the Irish Medicines Board (IMB) actively encouraged reporting of national experience with Gardasil through a variety of sources, including direct communications with healthcare professionals involved in the programme and publication of a special insert in the Drug Safety Newsletter (Issue 37 – May 2010). A total of 416 reports of adverse events associated with use of Gardasil were notified to the IMB up to the end of June 2011.

The majority of the reports received were non-serious and consistent with the expected pattern of adverse effects for the vaccine, as described in the product information. Vaccination related events were the most commonly reported effects with dizziness and/or headache described in a significant majority of the reports received. Other commonly reported symptoms included malaise, gastrointestinal symptoms, syncope and skin and injection site reactions. There were five reports of seizure, two occurring in patients with epilepsy, one of whom was recently diagnosed prior to vaccination.

Reports of allergic-type reactions including skin rashes, urticaria and flushing were also received, with six reports of anaphylactic/anaphylactoid-type reactions, all patients recovered following treatment. Anaphylaxis is a very rare side effect of most vaccines. Appropriate medical treatment and supervision should always be readily available in case of a serious allergic reaction and possibly a rare anaphylactic event following the administration of the vaccine.

The first year of the Schools Immunisation Programme is now complete and as national reporting experience has been consistent with the known safety profile of the vaccine, the IMB will discontinue publication of regular updates on national monitoring experience on its website. At this time too, reporters are advised that routine notification of expected, non-serious effects is no longer necessary, but are requested to continue to notify any suspected, serious adverse reactions that are considered of concern using the usual reporting options (available on www.imb.ie). The IMB will continue to monitor national experience with use of Gardasil, in the context of global safety data and will collaborate, as appropriate with EU and International counterparts in the evaluation of these data, communicating nationally, as necessary.

## Direct Healthcare Professional Communications published on the IMB website since the last Drug Safety Newsletter

| Product | Safety Issue |
|---|---|
| Actos (pioglitazone) and Competact (pioglitazone & metformin) | Increased risk of bladder cancer with pioglitazone containing medicines |
| Cardioxane (dexrazoxane) | Association with an increased risk of secondary malignancies in children |
| Multaq (dronedarone) | Information on preliminary study results showing increased cardiovascular risk |
| Thyrogen (thyrotropin alfa) | Update on supply and recommendations on treatment for patients. |
| Quinine Sulphate 300mg tablets | Product information changes regarding restrictions for use for nocturnal leg cramps |
| Ketoprofen | Reminder about the risk minimization measures for ketoprofen-containing topical formulations |
| Regranex Gel (becaplermin) | Cessation of supply in Europe |

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Drug Safety – August 2011 – Issue Number 43

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