IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

38th EDITION

Rosiglitazone (Avandia/Avandamet) and Cardiovascular Risk

Rosiglitazone (Avandia/Avandamet) is a medicinal product authorised for use across the European Union through the European licensing process, as a second line treatment in the management of type II diabetes, which should only be used when other treatments have either failed, or are unsuitable for a patient.

Use of Avandia (rosiglitazone) has been contraindicated in patients with heart failure or a history of heart failure since its first authorisation in July 2000. A combination of rosiglitazone with metformin was subsequently approved as Avandamet and this is also contraindicated in patients with heart failure or a history of heart failure. Since authorisation, use of these medicines has been further restricted several times by the introduction of new warnings and contraindications on their use in patients with heart problems.

The European Committee on Medicinal Products for Human Use (CHMP) is currently reviewing rosiglitazone to determine the impact of new published data on the risk of cardiovascular problems on the benefit-risk profile of these medicines. The new data include two published studies examining rosiglitazone[1,2] and newly available information from the US Food and Drug Administration which raise concerns regarding the cardiovascular risk with rosiglitazone compared with both placebo and pioglitazone.

The new studies involved a large number of diabetic patients and add to the accumulating evidence from different global data sources and different types of studies on rosiglitazone and cardiovascular risk.

Pending the outcome of the CHMP review, prescribers should review patients in line with the recommended monitoring to ensure that all contraindications and warnings are strictly observed. Prior to initiation of new treatment and in the ongoing monitoring of patients, doctors should pay particular attention to the information outlined below.

Cardiovascular Warnings and Contraindications:

- Rosiglitazone must not be used in patients with current or previous heart failure and in patients with acute coronary syndrome.
- The use of rosiglitazone is not recommended in patients with ischaemic heart disease or peripheral arterial disease.
- Rosiglitazone and insulin should only be used together in exceptional cases and under close supervision.

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Monitoring requirements:

- Prescribers are required to monitor patients for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure.
- Increased monitoring of the patient is recommended if rosiglitazone is used in combination with metformin and insulin.
- Rosiglitazone should be discontinued if any deterioration in cardiac status occurs.

Further information, including the full prescribing information for Avandia/Avandamet is available on the EMA website at **www.ema.europa.eu**

It is anticipated that the Europe-wide review of available data on the risk and benefits of rosiglitazone will be completed by September 2010. The IMB is actively involved in this review, through its membership of the relevant EU Committees and will communicate the outcome, when available.

Key Message:

- **Rosiglitazone is a second line treatment in type II diabetes, which should only be used when other treatments have either failed or are unsuitable for a patient.**
- **Prescribers should review patients in line with the recommended monitoring requirements to ensure that all contraindications and warnings are strictly observed.**
- **New data concerning rosiglitazone and cardiovascular risk are under evaluation at EU level and an update on the outcome of this evaluation and any regulatory recommendations will be communicated, when available.**

References:

1. Graham DJ et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA doi:10.1001/jama.2010.920.
2. Nissen SE et al. Rosiglitazone revisited. An updated meta analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med doi: 10.1001/archinternmed. 2010.207

Isotretinoin (Roaccutane) – Risk of serious skin conditions

Isotretinoin is authorised for oral use for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. Isotretinoin should only be prescribed by or under the supervision of a physician with expertise in the use of systemic retinoids for the treatment of severe acne.

The current product information for isotretinoin refers to the occurrence of skin reactions including erythema and localised exfoliation. Acute hypersensitivity reactions including allergic skin reactions are also listed.

A European review recently considered the available data relating to the risk of serious skin conditions including erythema multiforme (EM), Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) with isotretinoin containing medicines for oral use. A thorough assessment of worldwide spontaneous case reports and the available scientific literature was undertaken. In May 2010, the PhVWP agreed that the risk of erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis could not be excluded based on the available data and that information regarding the risk of these serious skin reactions should be added to the product information to increase awareness of their potential association with isotretinoin which may be difficult to diagnose within a patient population with existing severe acne.

Key Message:

- **There have been rare post-marketing reports of severe skin reactions (e.g. erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) associated with isotretinoin use.**
- **As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8 of the SmPC), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions.**
- **If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.**

Warfarin – close monitoring of INR required if switching brands

Background

Warfarin is indicated for the prophylaxis of venous thrombosis and pulmonary embolism, and for use in the treatment of these conditions to prevent their extension. It is also licensed for the prevention of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.

There are two brands of warfarin currently licensed and marketed in Ireland - Warfant and Warfarin Teva. Warfarin Teva was first marketed in Ireland in 2008 and the SmPC highlights the importance of close monitoring of patients following a change in their warfarin treatment:
'*If this preparation replaces or is replaced by another warfarin product, the patient should be monitored closely in the period immediately following the change.*'

Summary of the Safety Concern

The IMB has received reports of clinically significant changes in INR potentially associated with switches in warfarin brands. Healthcare professionals are reminded that, switching brands requires appropriate INR monitoring as recommended following the initiation of any new warfarin product.

A communication to healthcare professionals highlighting the need for close monitoring of INR if switching brands of warfarin tablets was recently issued by the marketing authorization holder for Warfarin Teva in agreement with the IMB. A copy of this communication is available on the IMB website (**www.imb.ie**).

Advice to Healthcare Professionals:

- Warfarin products should be prescribed and dispensed by brand name. It is important that patient records (including dispensing records) reflect the product dispensed with details of the brand name. The brand name should also be recorded in the patient's Warfarin Book.
- It is essential to verify which product the patient is currently using prior to new prescribing/dispensing or dosage adjustment. If a patient presents with a prescription for a new brand of warfarin, it is important to ensure that those involved in INR monitoring or in interpreting INR results are aware of the brand change particularly when considering dosage adjustment.
- If switching to a different warfarin brand, it is important to ensure the patient's INR is closely monitored in line with the recommendations in the SmPC and local guidance (where applicable) for INR monitoring following initiation of warfarin therapy.
- All patients taking warfarin should be advised of any changes in the brand prescribed or dispensed and the requirement for additional INR monitoring in the event of switching.
- Any suspected adverse reactions associated with warfarin should be reported to IMB in the usual way particularly any associated with changes in INR following brand switches.

Key Message:

- **Careful monitoring of INR is important if switching warfarin brands.**

Carbapenems – Update on interaction with Valproic Acid/Sodium Valproate

Carbapenems are a class of beta-lactam antibiotics with broad-spectrum antibacterial activity. The licensed indications include the treatment of the following infections when caused by susceptible bacteria: nosocomial pneumonia; complicated intraabdominal infections; and complicated urinary tract infections. At present, four carbapenems are authorised for use in Ireland; Meropenem, Ertapenem, Doripenem and Imipenem*.

Valproic acid/sodium valproate** is an anticonvulsant used primarily for the treatment of generalised, partial, or other epilepsy.

An interaction between carbapenems and valproic acid has been described in a number of case reports and one study published in the literature.[1] The mechanism for this interaction has not been fully elucidated; however, several potential mechanisms have been proposed in the literature.[2] The IMB previously highlighted this potential interaction, specifically in relation to doripenem in the July 2009 edition of the Drug Safety Newsletter.[3]

A more recent, unpublished pharmacokinetic study of 24 healthy human volunteers found that concomitant administration of valproic acid and doripenem resulted in a rapid and substantial fall in plasma valproate levels. Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustments are unlikely to manage this interaction, which could lead to inadequate seizure control.

A European review of data for the remaining carbapenems found that decreased valproic acid/sodium valproate levels have also been reported when co-administered with other carbapenems, with 60–100% decreases in valproic acid levels being observed within about 2 days. This interaction is therefore likely to be a class effect. Concomitant use of carbapenems and valproic acid/sodium valproate is not recommended, and prescribers should consider alternative antibacterial therapy. This advice will be reflected in the product information.[4]

Key Message:

- **A clinically significant interaction between carbapenems and valproic acid/sodium valproate results in reduced valproate plasma concentrations with potential for inadequate seizure control.**
- **Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustments are unlikely to manage this interaction.**
- **Concomitant use of carbapenems in patients taking valproic acid/sodium valproate is not recommended, and prescribers should consider alternative antibacterial therapy.**

* Brands Include:
Meropenem (Meronem)
Ertapenem (Invanz)
Doripenem (Doribax)
Imipenem (Primaxin & Imipenem/Cilastatin MedReg)

** Epilim Range

References:
1. Spriet I, et al. *Ann Pharmacother* 2007; 41: 1130–36.
2. Mori H, et al. *Drug Metab Rev* 2007;39: 647–57.
3. IMB Drug Safety Newsletter; Issue no 32: July 2009
4. EU PharmacovigilanceWorking Party Report http://www.ema.europa.eu/pdfs/human/phvwp/3313810en.pdf

BCG Vaccine SSI and Severe Local Reactions

BCG Vaccine SSI [Danish 1331 strain] was first authorised in Ireland in 2001 for immunisation against tuberculosis and has been used in the immunisation programme since the withdrawal of the Evans BCG vaccine from the Irish market in July 2002. The IMB has closely monitored and highlighted experience with use of BCG Vaccine SSI since its introduction.

As indicated in the product information, the expected response to vaccination includes a slight swelling at the injection site followed by a small ulcer. Patients may also experience some swelling of glands in the armpit, less than one centimetre across. The product information advises that if the swelling at the injection site persists or if the ulcer/swelling is larger than one centimetre across follow-up with the relevant Healthcare Professional is recommended.

Uncommon adverse reactions (i.e. occurring with a frequency of more than one in a thousand but less than one in a hundred) include headache, fever, swelling of glands in the armpit to more than 1cm across and a discharging ulcer at the injection site.

Local reactions which occur rarely (i.e. with a frequency of less than one in a thousand but more than one in ten thousand), include lymphadenopathy, abscess formation and/or secondary infection.

The reporting pattern of adverse reactions remains consistent with the expected incidence of reactions. The majority of reported cases continue to involve severe local reactions, some of which concerned abscess formation, lymphadenopathy and/or secondary infection. Some of these more extensive reactions required treatment with antibiotics and/or surgical intervention (drainage).

The overall reporting pattern of suspected adverse reactions continues to be consistent with the expected incidence of reactions. However, because of the severity of some cases and the issues associated with follow up, referral and further intervention where necessary, the IMB wishes to again highlight the potential for serious adverse reactions associated with BCG Vaccine SSI particularly if the vaccine is inadvertently administered subcutaneously or intramuscularly rather than intradermally. Detailed information and advice on dosing, administration and the safety profile of the product can be accessed in the SmPC available on the IMB website **www.imb.ie**

Key Message:

- **The overall pattern of adverse reactions associated with BCG Vaccine SSI remains consistent with the frequency and severity of expected reactions.**
- **It is important to administer the vaccine intradermally in order to minimise the occurrence of severe local reactions.**

Bevacizumab (Avastin): Hypersensitivity and infusion reactions

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody and is licensed for the treatment of certain cancer types in combination with other chemotherapeutic agents (see product information for full list of licensed indications).

A recent review of cumulative cases of hypersensitivity and infusion-related reactions from clinical trials and post marketing reports has provided sufficient evidence to confirm a causal role of bevacizumab in the occurrence of these reactions. The risk of patients experiencing hypersensitivity reactions/infusion reactions has been identified in up to 5% of patients treated with bevacizumab. The majority of reactions reported to date have been mild to moderate, with more severe reactions noted in 0.2% of patients.

The product information has been updated to reflect this information and these updates have been communicated via a Direct Healthcare Professional Communication which is available on the IMB website (**www.imb.ie**).

Key Message:

- **Patients should be closely monitored during and after bevacizumab infusion. If a hypersensivity/infusion reaction occurs, the infusion should be stopped and appropriate therapies administered.**
- **The decision to re-challenge patients should be based upon individual goals of therapy and accurate assessment of the severity of the hypersensitivity/infusion reaction.**

occurred 6 days after initial exposure. Recently, two case reports of fatal hypersensitivity reactions during and immediately following panitumumab infusion have been received; these patients had previously experienced hypersensitivity reactions to cetuximab and oxaliplatin, respectively.

The product information has been updated to reflect this information and these updates have been communicated via a Direct Healthcare Professional Communication, which is available on the IMB website (**www.imb.ie**).

Panitumumab (Vectibix): serious hypersensitivity and infusion reactions

Panitumumab (Vectibix) is indicated as monotherapy for the treatment of patients with EGFR (epidermal growth factor receptor)-expressing metastatic colorectal carcinoma with non-mutated (wild type) *KRAS* after failure of chemotherapy regimens.

The Marketing Authorisation Holder conducted a cumulative review of hypersensitivity and infusion-related reactions associated with panitumumab following new reports of serious hypersensitivity reactions (including anaphylaxis) in patients receiving panitumumab, some of which were fatal.

Across all clinical studies, infusion-related reactions (occurring within 24 hours of any infusion), were reported in 3% of panitumumab treated patients, most were mild to moderate. Of these, less than 1% were considered severe and potentially life-threatening.

One clinical trial report described a fatal case of angioedema occurring 2 days after exposure, following a prior episode of angioedema which

Key Message:

- **Patients should be closely monitored for hypersensitivity or infusion related reactions both during and after administration of panitumumab.**
- **Panitumumab is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to this medicine.**
- **Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab should be permanently discontinued if a severe or life-threatening reaction occurs during or post infusion.**
- **In patients with a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of the infusion; it is recommended to maintain this lower infusion rate in all subsequent infusions.**
- **Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late-onset reaction, made aware of the symptoms and instructed to contact their physician if symptoms of hypersensitivity occur.**

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