IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

54TH EDITION

Strontium ranelate (Protelos): restricted indications, new contraindications, and warnings due to risk of serious cardiac disorders

An EU review co-ordinated by the European Medicines Agency (EMA) of available safety data for strontium ranelate (Protelos) has raised concern about its cardiovascular safety beyond the already recognised risk of venous thromboembolism, with no observed risk in mortality[1]. An analysis of randomised controlled trial data from studies in approximately 7,500 post-menopausal women with osteoporosis has identified an increased risk of serious cardiac disorders, including myocardial infarction (1.7% versus 1.1 % with placebo), with a relative risk of 1.6 (95% CI = [1.07 ; 2.38]). Furthermore, there was also an imbalance of serious cardiac events, both in a study in osteoporotic men, and in a study in osteoarthritis.

A full evaluation of the benefits and risks of strontium ranelate will be undertaken at EU level over the coming months and pending any further recommendations to help minimise the risk of serious cardiac events, the following advice should be followed:

Advice for healthcare professionals:

- Use of strontium ranelate is now restricted to treatment of severe osteoporosis:
  - in post menopausal women at high risk of fracture.
  - in men at increased risk of fracture.
- in post menopausal women at high risk of fracture.
- in men at increased risk of fracture.
- Treatment with strontium ranelate should only be initiated by a physician with experience in the treatment of osteoporosis, and the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks.
- Strontium ranelate is contraindicated in patients with ischaemic heart disease, peripheral arterial disease or cerebrovascular disease; a history of these conditions or in patients with uncontrolled hypertension.
- Prescribers are advised to assess the patient's risk of developing cardiovascular disease before starting treatment and thereafter at regular intervals. Patients with significant risk factors for cardiovascular events (e.g hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration of the benefit-risk balance of such treatment.
- Treatment with strontium ranelate should be discontinued if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.
- Healthcare professionals should review patients at a routine appointment and consider whether or not to continue treatment.

This information has been highlighted on the IMB and EMA websites [2] and through distribution of a letter from the Marketing Authorisation Holder to healthcare professionals. Further updates will be provided when the current evaluation has been completed.

Key Message

- **The EMA has recommended restrictions in the use of strontium ranelate (Protelos) with restricted indications, new contraindications and warnings due to the risk of serious cardiac disorders**
- **A full evaluation of the benefits and risks of strontium ranelate (Protelos) in the approved indications will now be conducted and any further conclusions resulting from this evaluation will be communicated as appropriate.**
- **Healthcare professionals should review patients at a routine appointment and consider whether or not to continue treatment.**

1 48th edition of the IMB DSN http://www.imb.ie/images/uploaded/documents/Drug%20Safty%20Newsletter%20(Website)%2048%20final%20version.pdf

2 http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/04/WC500142507.pdf

In this edition

Lenalidomide (Revlimid) – risk of serious hepatic adverse reactions – routine monitoring of liver function now recommended

Lenalidomide (Revlimid) is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Lenalidomide is an immunomodulatory agent similar to thalidomide and has antineoplastic, antiangiogenic and proerythropoietic properties.

Suspected adverse hepatic reactions have been reported in <1% of patients treated. Of these reactions, abnormal liver investigation results, and clinical signs and symptoms of hepatic disorders are the most common (58.7%). The spectrum of hepatic reactions reported includes hepatic failure, fibrosis, and cirrhosis (17.2%); cholestasis and jaundice of hepatic origin (13.8%). The remaining reports (10%) describe non-infectious hepatitis, liver-related coagulation and bleeding disorders, and neoplasms. A fatal outcome was reported in 5% of cases.

In many of the cases, including most with a fatal outcome, there were confounding risk factors for liver disease such as history of hepatic and renal disorders including viral hepatitis; progression of myeloma; myeloma involvement of the liver; prior chemotherapy; infection or sepsis; and concomitant medications known to cause liver injury, particularly antibiotics.

Among nine liver biopsies performed in patients with hepatic reactions, six showed histological evidence of drug-induced liver injury. In addition, there have also been a substantial number of cases where liver function has improved on discontinuation of lenalidomide, some cases of positive rechallenge, and some cases of negative rechallenge at a lower dose.

Review of the available evidence suggests that lenalidomide may be associated with drug-induced liver injury. The results of liver biopsies and cases in which there has been a positive dechallenge or a positive rechallenge provide the most convincing evidence of a causal association. The most common hepatic reactions observed in patients treated with lenalidomide are abnormalities of liver enzymes presenting as hepatocellular injury, and/or with a cholestatic pattern. Elevations of liver enzymes frequently occur soon after initiation of treatment with lenalidomide; the median time to onset appears to be 41 days, but reactions have been reported from one day to more than three years after the start of treatment. Early elevations in liver enzymes are usually moderate and may normalise without progression to major liver toxicity. Serious liver injury due to lenalidomide has been reported in relatively small numbers of patients and appears to be idiosyncratic. Predisposing factors that may increase the risk of serious liver injury with lenalidomide include elevated baseline liver enzymes, increased age, concomitant treatment with known hepatotoxic medicines and pre-existing viral liver disease.

Advice to Healthcare Professionals:

- Routine monitoring of liver function with the same frequency as haematological monitoring* (see details below) is recommended for patients receiving lenalidomide. This is particularly important in patients with a history of, or concurrent, viral liver infection, or when lenalidomide is given at the same time as other medications known to be associated with liver injury.
- Healthcare professionals should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.
- Impairment of liver function generally resolves when lenalidomide treatment is stopped. Once abnormal liver function parameters return to baseline, resumption of treatment with lenalidomide at a lower dose may be considered.
- Lenalidomide is excreted mainly by the kidneys and therefore it is important to adjust the dose in patients with renal impairment to avoid high plasma levels which may increase the risk of hepatotoxicity as well as haematological side effects.

* Haematological monitoring recommendations for lenalidomide are as follows: a complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.

Key Message

- **Elevations in liver enzymes may occur soon after initiation of treatment with lenalidomide. Serious liver injuries (potentially fatal) such as toxic hepatitis, hepatic failure and cholestatic hepatitis have also been reported with the overall rate of hepatic reactions estimated as occurring in <1% of patients treated.**
- **Routine monitoring of hepatic function is recommended for all patients receiving lenalidomide, particularly in patients with a history of, or concurrent, viral liver infection or in patients receiving other medications known to be associated with liver injury.**
- **Healthcare professionals should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.**
- **The dose should be adjusted in patients with renal impairment to avoid high plasma levels which may increase the risk of severe hepatotoxicity as well as haematological side-effects.**

Methylphenidate-Containing Medicines – availability of web-based educational tools

Methylphenidate* is a CNS stimulant currently authorised in Ireland as part of a comprehensive programme for the treatment of attention-deficit hyperactivity disorder (ADHD) in children 6 years of age and over when remedial measures alone prove insufficient. The IMB previously highlighted issues associated with its use, most recently following an EU review in 2009 to highlight guidance to support safe and effective use (**http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000218.jsp&mid=WC0b01ac058004d5c1**). Web-based prescribing tools have recently been made available at **www.methylphenidate-guide.eu** This website contains materials to aid the prescriber in the decision to prescribe and also to aid with the monitoring of patients treated with methylphenidate-containing products.

The materials on the website should be read in conjunction with current versions of the product information (Summaries of Product Characteristics are available at **www.imb.ie**). Healthcare Professionals are additionally reminded of the following recommendations:

- Treatment with methylphenidate should be supervised by a specialist in childhood or adolescent behavioural disorders
- Diagnosis should be made according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria or ICD-10 (International Classification of Diseases 10th revision) guidelines, and should be based on a complete history and evaluation and not solely on the presence of one or more symptom(s)
- Children and adolescents should have rigorous pre-treatment screening, including a complete history and relevant examination (including psychiatric disorders or symptoms, cardiovascular status, height, and weight)
- Patients should be monitored regularly during methylphenidate treatment, including: blood pressure and pulse; height, weight, and appetite; onset or worsening of psychiatric symptoms (such as depression, suicidal thoughts, hostility, anxiety, agitation, psychosis, or mania); and symptoms suggestive of heart disease (which should prompt specialist cardiac evaluation)
- Treatment should be interrupted at least yearly to determine whether continuation is needed

Advice for Healthcare Professionals

- Be aware of the prescribing and monitoring recommendations for the appropriate use of methylphenidate-containing medicines as outlined in the Summaries of Product Characteristics.
- Web-based prescribing tools for methylphenidate-containing medicines are available at **www.methylphenidate-guide.eu**
- The prescribing tools are intended to act as a resource to aid prescribing decisions and ongoing monitoring of patients.
- The prescribing tools should be used in conjunction with the product information for each individual product.
- Please report suspected adverse reactions associated with use of methylphenidate to the IMB, via the online reporting/downloadable form options (**www.imb.ie**) or by telephone (01 – 6764971).

Key Message

- **Prescribing and monitoring advice for appropriate use of methylphenidate-containing medicines should be followed.**

* Products available include Concerta XL Prolonged Release Tablets, Medikinet Tablets, Medikinet MR Modified Release Capsules, Ritalin Tablets, Ritalin LA Prolonged Release Capsules, Equasym XL Modified Release Capsules

Registration/Notification Reminder

Have you submitted your email details or registered with the IMB website to allow you to continue to receive the Drug Safety Newsletter (DSN) electronically? As highlighted in the IMB's 53rd Edition published in May, the IMB intends to phase out postal distribution of the DSN over the coming months and to make electronic distribution the main method of circulation, to ensure important safety updates are issued promptly. To ensure you can continue to receive all issues of the DSN, please register on the IMB website (**www.imb.ie**) to receive an alert when a new issue is published, or submit your email address to **imbpharmacovigilance@imb.ie**, to allow an electronic version to be emailed directly to you. Registration on the IMB website also allows you to receive other information/alerts issued by the IMB.

Cinacalcet (Mimpara) – Risk of QT prolongation/ventricular arrhythmias

Cinacalcet (Mimpara) is a calcimimetic agent that increases the sensitivity of the calcium sensing receptor to extracellular calcium. It is indicated in the treatment of secondary hyperparathyroidism (HPT) in adult patients with end stage renal disease on maintenance dialysis therapy. It is also indicated for reduction of hypercalcaemia in patients with parathyroid carcinoma, and in patients with primary hyperparathyroidism for who parathyroidectomy would be indicated on the basis of serum calcium levels, but in who parathyroidectomy is not clinically appropriate or is contraindicated. It was licensed for use through a common EU assessment procedure in 2004.

A number of cases of QT prolongation/ventricular arrhythmias were identified in association with cinacalcet use and the contribution of cinacalcet to this effect cannot be excluded, particularly considering its effect on calcium levels. This signal was reviewed at EU level in late 2012. It was noted that whereas a direct effect on cardiac repolarisation may not have been observed, a potential role of cinacalcet in development of QT prolongation/ventricular arrhythmias due to hypocalcaemia cannot be excluded, considering in particular the pharmacodynamic effect of cinacalcet and that a number of cases were reported with concurrent hypocalcaemia.

As a consequence of the new information and that decreases in serum calcium may prolong the QT interval, potentially resulting in ventricular arrhythmia, information on the potential for QT-prolongation and ventricular arrhythmia secondary to hypocalcaemia was added to the product information. Prescribers are reminded that since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia. During dose titration, serum calcium levels should be monitored frequently, and within one week of initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate steps should be taken, including adjustment of concomitant therapy.

A Direct Healthcare Professional Communication (DHPC) was issued by the Marketing Authorisation Holder (MAH) for Mimpara at the end of March 2013 (**http://www.imb.ie/images/uploaded/documents/Mimpara-DHCP-IRELAND.PDF**). The purpose of this communication was to inform prescribers that a fatal case with severe hypocalcaemia had been reported in a paediatric patient during a paediatric investigational study. Mimpara is approved only for use in adults and the Summary of Product Characteristics gives detailed information on the management of hypocalcaemia in patients treated.

Advice to Healthcare Professionals

- Prescribers are reminded that since cinacalcet lowers serum calcium, patients should be monitored carefully for the occurrence of hypocalcaemia.
- During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate steps should be taken, including adjustment of concomitant therapy
- Caution is advised in patients with other risk factors for QT-prolongation such as patients with known congenital long QT syndrome or patients receiving drugs known to cause QT prolongation.

Key Message

- **Cases of QT-prolongation and ventricular arrhythmia have been reported in patients treated with cinacalcet.**
- **Serum calcium levels should be monitored frequently, within one week of initiation of treatment or dose adjustment and approximately monthly in patients on maintenance doses**
- **Caution is advised in patients with other risk factors for QT-prolongation.**