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HPRA DRUG SAFETY NEWSLETTER

88TH EDITION

Granulocyte Colony Stimulating Factors (G-CSFs) – Risk of aortitis

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed reports of aortitis which occurred in healthy subjects and in cancer patients following treatment with granuloctye colony stimulating factors (G-CSFs), such as filgrastim, lenograstim, lipegfilgrastim and pegfilgrastim. Taking account of the available evidence, including adverse reaction reports, the PRAC considered that there is at least a reasonable possibility of a causal association between aortitis and G-CSF treatment. The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for all G-CSFs will be updated accordingly.

G-CSFs, such as filgrastim, lipegfilgrastim, pegfilgrastim and lenograstim, are authorised in Ireland and across the EU as follows:

- Filgrastim and lenograstim – to reduce the duration of neutropenia and occurrence of febrile neutropenia in cancer patients and for the mobilisation of peripheral blood progenitor cells (PBPCs), for patients as well as healthy donors.
- Pegfilgrastim and lipegfilgrastim – reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Advice to Healthcare Professionals

- When considering if aortitis has been caused by a medicine, consider G-CSFs as one of the possible causative medicines.
- Advise patients of the signs and symptoms of aortitis (e.g. fever, abdominal pain, malaise, back pain and increased inflammatory markers) and instruct them to seek medical attention if these symptoms develop.
- In most cases aortitis was diagnosed by a CT scan and symptoms resolved following withdrawal of the G-CSF.

Key Message

Available evidence, including reports of aortitis and biological plausibility, support a reasonable possibility of a causal association between G-CSF treatment and aortitis.

Patients should be advised of the symptoms of aortitis and told to seek medical attention immediately if these symptoms are experienced.

A Direct Healthcare Professional Communication (DHPC) has been circulated to relevant healthcare professionals.

Any suspected adverse reactions should be reported to the HPRA via the available options (www.hpra.ie).

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Ocaliva (obeticholic acid) – Risk of serious liver injury in patients with pre-existing moderate or severe hepatic impairment – reminder of differential dosing recommendations

In the post-marketing setting, in patients with moderate to severe decreases in liver function, being treated for primary biliary cholangitis (PBC), serious liver injury and death have been reported when more frequent dosing of obeticholic acid than recommended was prescribed.

Liver related adverse reactions have occurred both early in treatment and after months of treatment. Due to this serious risk, prescribers are reminded of the following:

Advice to Healthcare Professionals

- The hepatic status of the patient must be assessed prior to treatment with obeticholic acid.
- The dose of obeticholic acid should be adjusted in patients with moderate to severe hepatic impairment (See Table 1 below), in line with the recommendations in section 4.2 of the Summary of Product Characteristics (SmPC).
- During treatment, all patients should be monitored for PBC progression through laboratory and clinical assessment to determine whether dosage adjustment is necessary.
- Patients at an increased risk of hepatic decompensation should be monitored closely, including those with laboratory evidence of worsening liver function or progression to cirrhosis.
- Dosing frequency should be reduced in patients who progress to advanced disease (i.e. from Child-Pugh Class A to Child-Pugh Class B or C).
- A Direct Healthcare Professional Communication (DHPC) was distributed to relevant healthcare professionals in February 2018.
- The approved product information (Summary of Product Characterisitics (SmPC) has been updated to include this information.

Table 1: Dosing regimen by PBC patient population

Staging/Classification	**Non-cirrhotic or Child-Pugh Class A**	**Child-Pugh Class B or C or Decompensated Cirrhotic**
Starting dosage	5mg once daily	5mg once weekly
Dosage titration	For patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin after 6 months of treatment and the patient is tolerating obeticholic acid, titrate up to 10mg once daily.	For patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin after 3 months of treatment and the patient is tolerating obeticholic acid, titrate up to 5mg twice weekly (at least 3 days apart) and subsequently to 10mg twice weekly (at least 3 days apart) based on response and tolerability
Maximum dosage	10mg once daily	10mg twice weekly (at least 3 days apart)

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Key Message

Patients with pre-existing moderate or severe liver impairment who are taking obeticholic acid are at risk of serious liver injury; adequate dose reduction in these patients is therefore essential.

Hepatic status should be evaluated prior to and during treatment with obeticholic acid. Patients with moderate to severe hepatic impairment should have their doses of obeticholic acid adjusted– see Summary of Product Characteristics (SmPC).

All patients should be monitored for Primary Biliary Cholangitis (PBC) progression with laboratory and clinical assessment and the need for dose adjustment should be evaluated at regular intervals.

This medicine is subject to additional monitoring requirements and healthcare professionals are requested to report any suspected adverse reactions associated with its use to the HPRA via the available options (www.hpra.ie).

Clarithromycin - Reminder on cardiovascular safety and risk minimisation advice

Clarithromycin is a well-established antibiotic of the macrolide class. It has long been known and reflected in product information that macrolide antibiotics, including clarithromycin, have been associated with effects on QT prolongation and cardiac arrhythmias. Accordingly, the product information for clarithromycin provides guidance on use in patients at risk of ventricular arrhythmia including those with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia, electrolyte disturbances, patients concomitantly taking other medicinal products associated with QT prolongation and patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see sections 4.3 and 4.4 of the Summary of Product Characteristics).

As part of a recent routine periodic assessment of clarithromycin containing medicines, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) considered the available cumulative evidence to date on the cardiovascular safety of clarithromycin. The PRAC noted that some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. It is recommended, therefore, that consideration of these findings should be balanced with known treatment benefits when prescribing clarithromycin particularly in patients with a high baseline cardiovascular risk.

The product information for clarithromycin-containing medicinal products will be updated to reflect these findings.

Key Message

Clarithromycin should be used with caution in patients at increased risk of ventricular arrhythmias.

In addition, some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin in patients with a high baseline cardiovascular risk.

Any suspected adverse reactions should be reported to the HPRA via the available options (www.hpra.ie)

References:

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Wong, A.Y.S., Chan, E.W., Anand, S., Worsley, A.J., Wong, I.C.K. Managing cardiovascular risk of macrolides : Systemic review and meta analysis. Drug Safety 2017 August ;40(8): 663-677

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Adverse Reaction Reporting - Reminder

Reports of suspected adverse reactions are received by the HPRA from patients/carers, healthcare professionals and Marketing Authorisation Holders (i.e. license holders for a medicine). Information collected through this system is an important method of monitoring drug safety in normal clinical practice, by increasing knowledge about known adverse reactions and also by acting as an early warning system for the identification of previously unrecognised adverse reactions. Such information is one of the tools used by the HPRA in its ongoing safety evaluation of marketed drugs and is vital in identifying drugs where a change in their authorisation status is required such as the addition of warnings and precautions for use, restriction in usage or rarely withdrawal from the marketplace.

There are several options in place for reporting suspected adverse reactions to the HPRA, as follows:

- By following the links ('Report an Issue' tab) to the online reporting options accessible from the HPRA website homepage (www.hpra.ie);
- Using the downloadable report form also accessible for the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost';
- Using the traditional 'yellow card' report, which also utilises a freepost system. 'Yellow cards' are available from the HPRA Pharmacovigilance department on request.

Additional Monitoring

Revisions to medicines legislation introduced the concept of additional monitoring, to support prompt identification of any new safety hazards associated with particular medicines. Healthcare professionals and patients are particularly encouraged and reminded to report all adverse reactions associated with the use of these medicines, identifiable by an inverted black triangle on the product information. An explanatory statement is included both in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) for these medicines, together with the symbol:

▼ This medicinal product is subject to additional monitoring.

Biological Traceability

The EU and national legislation requires clear identification of any biological medicinal product which is the subject of a suspected adverse reaction report, indicating that the brand name and batch number of the product should be specified on relevant reports submitted.

Key Message

Several options are available to reports suspected adverse reactions to medicines to the HPRA.

Medicines subject to additional monitoring are identifiable by a black inverted triangle accompanied by an explanatory statement in the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)). All suspected adverse reactions associated with these medicines should be reported.

When reporting a suspected adverse reaction to a biological medicinal product, the brand name, batch number and expiry date should be included.

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

PRODUCT	SAFETY ISSUE
Granulocyte colony-stimulating factors *(G-CSFs)*	New warning regarding aortitis
Tivicay *(dolutegravir)*, Triumeq (dolutegravir, abacavir, lamivudine), Juluca (dolutegravir, rilpivirine)	Neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception.
Xgeva (denosumab)	Risk of new primary malignancy with Xgeva
Epilim (sodium valproate) *DHPC for prescribers* *DHPC for pharmacists*	New restrictions on use. Pregnancy Prevention Programme to be put in place.

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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