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**New contraindications and monitoring advice for
LUMIRACOXIB (▼PREXIGE®) following notification of serious hepatotoxicity**

Dear Healthcare Professional,

Novartis wishes to inform you of important new prescribing advice for lumiracoxib indicated only for the treatment of osteoarthritis of the hip and knee (daily dose 100mg).

Summary

Novartis has recently been notified of reports of serious hepatotoxicity, including cases resulting in death or liver transplantation in patients taking lumiracoxib, mostly with doses higher than the 100mg daily dose authorised in the EU.

Following an EU interim assessment led by the Medicines and Healthcare products Regulatory Agency (MHRA) of the latest safety evidence, you are provided with the following new prescribing advice:

- Lumiracoxib is now contraindicated in patients
 - with any current hepatic disease;
 - with prior drug-induced significant (>3xULN) elevations of transaminases;
 - with liver transaminases >1.5xULN before treatment, or >3xULN during treatment (see below); or
 - taking other medicines associated with clinically significant hepatotoxicity.
- The new Liver Function Test (LFT) monitoring advice is:
 - Perform baseline LFTs before starting treatment (lumiracoxib is contraindicated if transaminases >1.5xULN).
 - Where treatment is needed for longer than 1 month, repeat LFTs (monthly).
 - Stop treatment if transaminases >3xULN, repeat in 7 days if transaminases >2xULN.
 - Conduct LFTs for patients reporting any systemic illness whilst taking lumiracoxib.
- Patients already taking lumiracoxib should be reviewed at their next routine appointment. If continued treatment is considered appropriate (after consideration of overall benefit and risks, and after taking new contraindications into account), then LFTs should be taken.

Reminder: Treatment should be limited to the shortest duration necessary and should not exceed the recommended 100mg daily. The need for continued treatment should be frequently reassessed.

Advice to Patients: Physicians should counsel their patients for possible signs and symptoms of hepatic injury such as nausea, vomiting, anorexia, malaise, fatigue, dark urine and right upper abdominal discomfort, as well as specific symptoms such as itching or jaundice. Patients should be advised to stop treatment in the event of any symptoms and seek urgent advice from their doctor.

Background information on safety concern

Lumiracoxib is a selective COX-2 inhibitor indicated only for the treatment of osteoarthritis of the hip and knee (daily dose 100mg).

Liver injury and fatalities have been reported rarely (incidence >1/10,000, <1/1,000) with exposure to lumiracoxib. Worldwide there have been 11 cases of severe* hepatotoxicity (including 9 cases of liver failure) with a suspected causal relationship with lumiracoxib, mostly with doses higher than the 100mg daily dose authorised in the EU, leading to 2 fatalities and 3 liver transplants. *The criteria applied were hepatic failure or Hy's case (transaminases > 3ULN and bilirubin >2ULN) or a fatal outcome or liver transplantation.

Reporting suspected adverse reactions

As PREXIGE is a black triangle drug, please report all suspected adverse drug reactions via a Yellow Card (www.yellowcard.org.uk).

Annexes

Relevant changes to the Summary of Product Characteristics (SPC) are annexed. A full copy of the updated SPC and updated Patient Information Leaflet for Prexige is available at www.emc.medicines.org.uk.

Clinically significant hepatotoxicity of concomitant medicines can be determined in the respective product information for medicines and a reference source such as British National Formulary Appendix 2.

Additional prescribing advice may be issued in September following further assessment.

If you require more information, please call Novartis' Medical Information Service on 01276 698370.

Yours sincerely,

Dr Tim Cave
Novartis Medical Director

ANNEX – ▼PREXIGE® (lumiracoxib)

UPDATED PRESCRIBING ADVICE:

The additional text below reflects the additional text and/or amended text for the Prexige Summary of Product Characteristics:

4.2 Posology and method of administration:

As the cardiovascular and hepatotoxic risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used.

Hepatic impairment:

Lumiracoxib is contraindicated in: patients with any current liver disease, those with prior drug-induced significant (>3xULN) elevations of transaminases, and those with baseline of >1.5xULN or >3xULN during treatment (see also sections 4.3 and 4.4).

4.3 Contraindications:

- Patients with any current hepatic disease.
- Patients with prior drug-induced significant (>3xULN) elevations of transaminases
- Patients with liver transaminases >1.5xULN before treatment, or >3xULN during treatment (see section 4.4)
- Patients taking other drugs known to cause clinically significant hepatotoxicity

4.4 Special warnings and precautions for use:

Hepatic effects:

It is equally important to remain vigilant for symptoms of hepatic injury at any time during treatment.

Liver damage has been reported following exposure to lumiracoxib. Although most cases of serious hepatotoxicity have occurred at doses higher than 100mg daily, patients should be advised to remain vigilant for any symptoms compatible with hepatic injury during treatment with lumiracoxib (e.g. anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, jaundice, pruritis). Patients should stop lumiracoxib if any such symptoms occur, and should seek medical advice urgently.

Patients should be reminded of normal limits for safe alcohol consumption whilst taking lumiracoxib. Excessive alcohol consumption could aggravate any drug-related liver reaction.

Liver function Monitoring

The following precautionary monitoring is advised:

Baseline monitoring

All patients should have baseline liver function tests prior to commencing treatment. Patients with transaminases > 1.5 x ULN should not commence therapy with lumiracoxib.

Periodic monitoring

Treatment duration should be kept to a minimum; however if treatment for more than 30 days is required liver function tests should be repeated at monthly intervals (see actions to be take below).

Intercurrent illness

Any patients reporting systemic illness (see above for symptoms that are mostly likely to be relevant) during lumiracoxib therapy should have liver function testing (see actions to be taken below)

Actions to be taken in the event of elevated liver transaminase results (AST or ALT) during treatment:

In the event of any elevation of transaminases >3x ULN, lumiracoxib should be withdrawn immediately. If transaminase levels > 2xULN are detected, then lumiracoxib may be continued, but the liver function tests should be repeated in 7 days.

Undesirable effects:

Hepatobiliary disorders

Rare: Cholecystitis, Cholelithiasis, (Acute) hepatitis, hepatic failure (sometimes fatal), jaundice