

12th July, 2013

Direct Healthcare Professional Communication

Diclofenac - new contraindications and warnings after a Europe-wide review of cardiovascular safety

Dear Healthcare professional,

This letter is sent in agreement with European Medicines Agency (EMA) and Medicines Authority of Malta to inform you of important restrictions to the use of diclofenac-containing medicines (systemic formulations), following completion of a Europe-wide review of its cardiovascular safety.

Summary

- **The benefits of diclofenac outweigh the risks, however, currently available data indicate an increase in arterial thrombotic risks associated with diclofenac, similar to that for selective COX-2 inhibitors.**
- **Diclofenac is now contraindicated in patients with established congestive heart failure (New York Heart Association, NYHA, classification II–IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease. Patients with these conditions should have their treatment reviewed.**
- **Diclofenac treatment should only be initiated after careful consideration for patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).**
- **The lowest effective dose of diclofenac should be used for the shortest duration necessary to control symptoms in all patients.**

Further information

Diclofenac is a widely used NSAID for relief of pain and inflammation. In 2012, the European Committee on Medicinal Products for Human Use (CHMP) considered the latest available data for the risk of cardiovascular side effects (such as heart attack or stroke) with non-selective NSAIDs. The Committee concluded that these data provided further evidence on the known risk with these medicines. Overall, the studies consistently indicated a small increased risk of cardiovascular side effects with diclofenac, similar to that seen with the COX-2 inhibitors.

As this conclusion raised safety concerns for diclofenac, the European Pharmacovigilance Risk Assessment Committee (PRAC) began an in-depth review on the cardiovascular safety of diclofenac in October 2012.

Academic research has been a central element of the reviews of NSAIDs and diclofenac. This includes an independent research project called 'safety of non-steroidal anti-inflammatory drugs' (SOS)¹, set up and funded by the European Commission's Seventh Framework Programme. Other groups have also been investigating the cardiovascular safety of NSAIDs, notably the Coxib and traditional NSAID Trialists' (CNT) collaborative group², who shared their results from a large meta-analysis of more than 600 randomised clinical trials with the Agency, and these were included in the PRAC's assessment of diclofenac. The group found that of 1000 patients allocated to diclofenac for a year, three more had major vascular events, compared to placebo.

Considering all evidence available, the PRAC supported the conclusions of the previous CHMP review and concluded that the benefits of diclofenac are considered to outweigh the risks. However, there is an increase in the risk of arterial thrombotic events associated with diclofenac, similar to that for selective COX-2 inhibitors. Therefore, new contraindications have been recommended in the product information for diclofenac, in line with measures in place for COX-2 inhibitors to help minimise cardiovascular risk.

The Summary of Product Characteristic (SmPC) and Package leaflet (PL) will be updated accordingly.

Call for reporting of adverse reactions

Healthcare professionals should report any suspected adverse reactions associated with the use of diclofenac in accordance with the national spontaneous reporting system:

Healthcare Professionals are hence requested to submit ADR reports using the ADR report card which can be found at <http://medicinesauthority.gov.mt/reportingadversereactions?l=1> and submit it electronically to postlicensing.medicinesauthority@gov.mt or by post to 'Medicines Authority, 203, Level 3, Rue D'Argens, GZIRA GZR 1368'.

Company contact point

Adverse events should also be reported to Remedica Ltd on +357 25 553251 or drugSafety@remedica.com.cy and/ or to Vivian Corporation Ltd. on +356 21320338/21344610/21344616 or pv@viviancorp.com

Pharmaceutical products of Remedica Ltd that contain Diclofenac

Trade name	Strength	Pharmaceutical form
Remethan	25mg	Enteric Coated Tablets
Remethan	100 mg	Suppositories

Yours sincerely,



Christina Cachia

Medical Representative
Vivian Corporation



Andreas Vasiliou

European Union Qualified Person Responsible for Pharmacovigilance
(EU QPPV), Remedica Ltd.

¹ See www.sos-nsaids-project.org.

² See [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)60900-9/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)60900-9/abstract)