Nicorandil (Ikorel®): Advice on the Risk of Serious Ulcerations or Related Events

Ikorel Tablets 10mg PA 540/102/1 and Ikorel Tablets 20mg PA 540/102/2

7th August 2014

Dear Healthcare Professional,

Sanofi would like to inform you of new and strengthened warnings on the risk of ulcerations and perforations that may occur with the use of nicorandil (Ikorel®) and give guidance on how this risk can be managed. Ikorel is indicated for the prevention and management of angina pectoris. This letter is being sent to you as you may diagnose the related adverse events, even if you are not the prescriber of this drug.

This letter is sent in agreement with the Health Products Regulatory Authority (formerly known as the Irish Medicines Board).

Summary

- Gastrointestinal ulcerations, skin and mucosal ulcerations are known adverse reactions of nicorandil. In addition, conjunctivitis, corneal and conjunctival ulcerations have also been very rarely reported. Ulcerations may develop at different locations in the same patient.

- Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has also been reported with nicorandil. Patients taking concomitant acetylsalicylic acid (aspirin) or corticosteroids are at increased risk for severe complications such as gastrointestinal perforation and haemorrhage. Caution is advised when concomitant use of nicorandil with any of these medicines is considered.

- If advanced, ulcers may develop into perforation, fistula, or abscess formation. Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

- Nicorandil-induced ulcerations are refractory to treatment and generally only respond to withdrawal of nicorandil. Nicorandil treatment should therefore be permanently discontinued under the supervision of their doctor if these ulcerations occur.

The Summary of Product Characteristics (SmPC) and the Patient information leaflet has been updated accordingly (see Annex I).

Recommendations to healthcare professionals

- Patients should be informed of the risk of ulcerations and of the necessity to contact their healthcare professional in case of any associated symptoms.

- The occurrence of any ulceration in patients treated with nicorandil, regardless of the site, should lead to an immediate discontinuation of treatment under medical supervision in order to minimise the associated risks while ensuring continued management or prevention of of angina symptoms.

- Caution is advised when concomitant use of corticosteroids or acetylsalicyclic with nicorandil is considered.

- The benefits of nicorandil are considered to continue to outweigh any risks in the approved indications.

Further information on the safety concern and the recommendations:

This information is the result of a cumulative review of available data including post-marketing spontaneous reports, individual literature case reports, reports in clinical trials and post marketing surveillance since first launch in April 1984 up to October 2013.

The review concluded that the estimated frequency of nicorandil-induced gastrointestinal ulcerations and related events is rare and of nicorandil-induced conjunctival and corneal ulceration is very rare.
Although rare, approximatley two-thirds of the reported nicorandil-induced gastrointestinal ulcerations were serious. Most reported cases of perforations, fistula, abscess and haemorrhage required hospitalisation for treatment of these complications. Other locations of ulceration included the skin, genital area and eyes. There may be multiple locations in the same patient, involving the skin, mucous membranes and eyes, and these may develop simultaneously or sequentially. Post marketing data have shown that patients treated concomitantly with corticosteroids or acetylsalicyclic acid and nicorandil have an increased risk of gastrointestinal ulcerations, perforations and haemorrhage. Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Based on the available information, the time between initiation of nicorandil therapy and the onset of ulceration ranged from shortly after initiating nicorandil treatment to several years after starting nicorandil. In the absence of complications, the ulcerations usually heal once nicorandil treatment is discontinued. However, a delay in diagnosis may lead to a worsening of the ulcers and possible development of abscess, perforations, bleeding or fistulas.

The underlying pathogenesis of ulcerations remains unknown.

Please refer to the IPHA website (www.medicines.ie) for the current version of the Ikorel ® SmPC.

Call for Reporting
Any suspected adverse events experienced by your patients should be reported to Sanofi Ireland Ltd. directly or to the Pharmacovigilance Section of the HPRA using the on-line reporting function on the HPRA website (www.hpra.ie) or alternatively by contacting the HPRA at 01 6764971 or medsafety@hpra.ie.

Company Contact Point
For further information please contact:
Sanofi Ireland Ltd.
18 Riverwalk
Citywest Business Campus
Dublin 24
Telephone: 01-4035600
Email address: IEmedinfo@sanofi.com

We remain at your disposal for any further information you may need.

Yours sincerely,

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Dr Mark Toms
Medical Director UK and Ireland

Annex1

Relevant sections of the Product Information have been revised.

Underlined wording/statements are included in the SmPC.

Section 4.4 Special warnings and precautions for use

Gastrointestinal ulcerations, skin and mucosal ulcerations have been reported with nicorandil.

Gastrointestinal ulcerations
Nicorandil induced ulceration may occur at different locations in the same patient. They are refractory to treatment and most only respond to withdrawal of nicorandil treatment. If ulceration(s) develops, nicorandil should be discontinued (see section 4.8).

Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has been reported with nicorandil. The patients taking concomitantly acetylsalicylic acid are at increased risk for severe complications such as gastrointestinal haemorrhage. Therefore caution is advised when concomitant use of acetylsalicylic acid and nicorandil is considered (see section 4.5).
If advanced, ulcers may develop into perforation, fistula, or abscess formation. Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Eye ulcerations
Very rare conjunctivitis, conjunctival ulcer and corneal ulcer have been reported with nicorandil.
Patients should be advised of the signs and symptoms and monitored closely for corneal ulcerations. If ulceration(s) develops, nicorandil should be discontinued (see section 4.8).

Section 4.5 Interaction with other medicinal products and other forms of interaction

In patients receiving concomitantly acetylsalicylic acid there is an increased risk for severe complications such as gastrointestinal haemorrhage (see section 4.4).

Section 4.8 Undesirable effects

Gastrointestinal disorders
Rare: Gastrointestinal ulcerations (stomatitis, mouth ulcer, tongue ulcer, small intestine ulcer, large intestinal ulcer, anal ulcer) (see section 4.4)
Frequency unknown: gastrointestinal haemorrhage (see section 4.4)

Description of selected adverse reactions:
Weight loss has been reported in association with Nicorandil induced ulcers and fistulas.

Eye disorders
Very rare: Conjunctivitis, conjunctival ulcer and corneal ulcer (see section 4.4)

The Patient Information Leaflet is updated accordingly.