November 2015

Direct Healthcare Professional Communication

Nicorandil (Ikorel 10mg and 20mg Tablets and Nicorandil 10mg and 20mg Tablets): Do not use as first-line treatment for angina; risk of ulcerations and progression to complications – stop nicorandil treatment if ulceration occurs.

Dear Healthcare Professional,
In accordance with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA), Sanofi and the MHRA would like to inform you of important restrictions to the licensed indication, the modification of posology and additional contraindications and warnings for nicorandil (Ikorel Tablets / Nicorandil Tablets). The most important advice is summarised below:

Summary

- Nicorandil is now indicated for treatment of stable angina only in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers and/or calcium antagonists.
- Nicorandil can cause serious skin, mucosal, and eye ulceration, which persists unless treatment is discontinued.
- Stop nicorandil treatment if ulceration develops on any part of the body. If stopping nicorandil treatment worsens angina symptoms, consult a cardiologist.
- Gastrointestinal ulcers may progress to perforation, haemorrhage, fistula, or abscess.
- Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation compared with patients without diverticular disease.
- Taking aspirin, non-steroid anti-inflammatory drugs (NSAIDs) or corticosteroids concomitantly with nicorandil increases the risk of gastrointestinal ulceration, perforations, and haemorrhage compared with taking either medicine alone.
- Nicorandil is now contraindicated in hypovolaemia, acute pulmonary oedema and for use with soluble guanylate cyclase stimulators such as riociguat.
- Use nicorandil with caution in combination with medicines which increase potassium levels, especially in patients with moderate to severe renal impairment.

This letter follows reviews by European drug regulatory agencies of the risk of skin and mucosal ulceration with nicorandil and the indications for nicorandil use. The key recommendations from these reviews are outlined above and in the further information below.

Dose
Nicorandil should normally be used in the dose range 10 to 20mg twice daily (in the morning and in the evening preferably), starting at 10mg twice daily and titrating if necessary, in accordance with patient need, response and tolerance up to a maximum of 40mg twice daily. A lower starting dose of 5mg twice daily may be used in patients particularly prone to headache (a very common adverse reaction to nicorandil as a result of cerebral vasodilation).

Ulcers
There have been reports from clinical practice of ulceration and related complications following nicorandil use. Almost two-thirds of the reported gastrointestinal ulcerations were serious[1], the remaining events were non-serious. Almost all cases of perforations, fistula, abscess and haemorrhage were serious and hospitalisation may be required for treatment of these complications.

The data showed that nicorandil-induced gastrointestinal ulcerations and related events are rare and conjunctivitis, conjunctival ulceration, and corneal ulceration are very rare.[2] It is still not known how nicorandil causes ulceration.

Ulcer location and time to onset
Ulcers may develop on different parts of the body in the same patient. The ulcers may develop at the same time or one after another. Ulceration can occur at any time during nicorandil treatment (including years after starting treatment).

Ulcer treatment
Ulcers caused by nicorandil do not respond to conventional ulcer treatment, including surgery. The only way to cure these ulcers is to stop nicorandil treatment. It may take weeks or months for the ulcers to heal, depending on their severity.

Other advice
Use nicorandil with caution in the following situations:
- In patients with heart failure NYHA III or IV
- In patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency (consider the risk of methemoglobinurea)
- In patients taking dapoxetine (consider the risk of reduced orthostatic tolerance)

The updated summary of product characteristics (SmPC) and updated patient information leaflet are available on the Electronic Medicines Compendium (EMC) at the following locations:

http://www.medicines.org.uk/emc/medicine/28187

http://www.medicines.org.uk/emc/medicine/29898

http://www.medicines.org.uk/emc/PIL.28159.latest.pdf

http://www.medicines.org.uk/emc/PIL.28160.latest.pdf

[1] Source: cases spontaneously reported by health care professionals or consumers, as well as cases originating from regulatory authorities, literature, clinical trials and post marketing surveillance. A serious adverse reaction is an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect

[2] Rare = ≥1/10,000 to <1/1,000; very rare= <1/10,000. The frequency of GI ulceration is based on a frequency calculation from pooled studies with nicorandil (n=1,152 subjects). When combining upper GI ulcers (mouth) with lower GI ulcers (small intestine ulcer, large intestine ulcer and anal ulcer) under the single term gastrointestinal ulcerations, the frequency was adjusted from very rare to rare. The frequency of conjunctivitis, conjunctival ulceration, and corneal ulceration is based on the 'rule of three' applied to nicorandil clinical data also taking into account the reporting rate from spontaneous reports.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions with the use of Ikorel Tablets / Nicorandil Tablets via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

Company contact point
For further medical information on Ikorel Tablets / Nicorandil Tablets, please contact:
SANOFI
One Onslow Street, Guildford, Surrey, GU1 4YS, UK
Tel: 01483 505515, Fax: 01483 535432
Email: uk-medicalinformation@sanofi.com

To report suspected adverse reactions contact:
SANOFI
One Onslow Street, Guildford, Surrey, GU1 4YS, UK
Tel: 01483 554242, Fax: 01483 554806
Email: uk-drugsafety@sanofi.com

Yours faithfully

Dr Andrew HOCKEY FFPM
Associate Medical Director - UK & Ireland