Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we inform you of updated advice that nicorandil for treatment of stable angina should only be used for 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 or calcium antagonists. A review by the UK's Commission on Human Medicine's Pharmacovigilance Expert Advisory Group and by EU medicines regulators has led to updated advice. Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess. Treatment should be stopped if ulceration occurs—see page 2.

Also this month, we advise you that levonorgestrel-releasing intrauterine systems should always be prescribed by brand name because products have different indications, durations of use, and introducers—see page 3.

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1 Nicorandil (Ikorel): now second-line treatment for angina; risk of ulcer complications

Note updated advice on use of nicorandil as second-line treatment for stable angina; some ulcers may progress to complications unless treatment is stopped.

Advice for healthcare professionals:

- Use nicorandil 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 or calcium antagonists
- Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess
- Stop nicorandil treatment if ulceration occurs—consider the need for alternative treatment or specialist advice if angina symptoms worsen
- Please continue to report suspected adverse drug reactions to nicorandil or any other medicines on a [Yellow Card](#)

Ulcers

*Occurring in more than 1 in 10 000 patients.

†Occurring in fewer than 1 in 10 000 patients.

Nicorandil-induced ulceration has been most frequently reported for the gastrointestinal tract (rarely*); very rarely†, the skin and mucosa are affected, including the eye.

A review by the UK's Commission on Human Medicine's Pharmacovigilance Expert Advisory Group and by EU medicines regulators has led to updated advice for the use of nicorandil.

Risk factors

Patients with diverticular disease may be at risk of fistula formation or bowel perforation. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs, or corticosteroids with nicorandil increases the risk of gastrointestinal ulceration, perforations, or haemorrhage.

Location and time to onset

Ulcers may develop at different sites in the same patient, at the same time or one after another. Ulceration can occur at any time during nicorandil treatment (including years after starting treatment).

Treatment

Almost two-thirds of reported gastrointestinal ulcerations are serious. Ulcers caused by nicorandil do not respond to conventional 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 severity.

Other updated advice

- Nicorandil is contraindicated in patients with hypovolaemia or acute pulmonary oedema, and it must not be used with soluble guanylate cyclase stimulators such as riociguat (see [Summary of Product Characteristics](#) for full list of additional warnings and precautions for use)
- Use nicorandil with caution in the following situations:
  - In patients with heart failure (New York Heart Association class III or IV)
  - In patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency (consider the risk of methemoglobinurea)
  - In patients who are taking dapoxetine (consider the risk of reduced orthostatic tolerance)
  - In combination with other medicines that increase potassium levels, especially in patients with moderate to severe renal impairment
- Depending on clinical response, patients may now be titrated upwards to a maximum dose of 40 mg twice daily. The usual therapeutic dose range remains 10–20 mg twice daily; a lower starting dose of 5 mg twice daily may be used in patients particularly prone to headache

Further information

[Letter sent to healthcare professionals](#) 10 November 2015

[EMA review of prescribing information for nicorandil containing products](#)

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2 **Levonorgestrel-releasing intrauterine systems: prescribe by brand name**

Levonorgestrel-releasing intrauterine systems should always be prescribed by brand name because products have different indications, durations of use, and introducers.

Products containing 52 mg levonorgestrel

A levonorgestrel-releasing intrauterine system (IUS) has been available as the brand Mirena for a number of years. Recently, a second product called Levosert was licensed for use in the UK.

Although Mirena and Levosert both contain 52 mg levonorgestrel, they differ in two important ways:

Indications for use

- Mirena is licensed for 5 years' use and Levosert is licensed for 3 years' use in the indications of contraception or heavy menstrual bleeding. Clinical data for long-term efficacy and safety of Mirena for contraception and heavy menstrual bleeding are available for 5 years of use, whereas 3 years of data are currently available for Levosert
- Mirena is also licensed for 4 years' use for endometrial protection as part of a hormone-replacement therapy regimen (Levosert is not licensed for this indication)

Introducer or insertion device

- Mirena and Levosert have different introducers, requiring different insertion techniques. Insertion (and removal) of any intra-uterine device (IUD) may be associated with pain, bleeding, and (in some cases) perforation of the uterus. Therefore, IUDs should only be inserted by healthcare professionals who are experienced in insertion or who have had training in the relevant insertion techniques

Product containing 13.5 mg levonorgestrel

A smaller IUS that contains 13.5 mg levonorgestrel (called Jaydess) has been marketed since 2014 and is licensed for 3 years' use for contraception only. Note the advice for insertion above also applies to this product.

Reporting of adverse drug reactions

Suspected adverse drug reactions to these medicinal products should be reported to us, using the brand name, on a Yellow Card.

Further information

The Faculty of Sexual & Reproductive Healthcare provides guidance on the differences between products for Mirena and Levosert, and for Jaydess

Summaries of Product Characteristics can be obtained here for Mirena, Levosert, and Jaydess

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3 **Letters sent to healthcare professionals in December 2015**

In December 2015, a letter was sent to healthcare professionals regarding galantamine hydrobromide (Reminyl) and the risk of serious skin reactions.