01/08/2016
EMA/353887/2016
EMEA/H/A-13/1427

Questions and answers on Levonelle and associated names (levonorgestrel, 1500 microgram tablets)

Outcome of a procedure under Article 13 of Regulation (EC) 1234/2008

On 26 May 2016, the European Medicines Agency completed a review for the emergency contraceptive Levonelle (levonorgestrel, 1500 microgram tablets) and associated names. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that when Levonelle is taken together with certain interacting medicines (including the HIV medicine efavirenz and ritonavir, certain medicines for tuberculosis and epilepsy and herbal medicines containing St John's wort) the dose of Levonelle should be doubled. However, Levonelle should only be used with these medicines when a non-hormonal emergency contraceptive (i.e. a copper intrauterine device) is not an option. In order to ensure the correct use of Levonelle, the CHMP recommended including advice on when to take a double dose on the medicine's outer carton as well as in the package leaflet.

What is Levonelle?

Levonelle is an emergency contraceptive used to prevent unintended pregnancy when taken within 72 hours (3 days) of unprotected intercourse or failure of a contraceptive method. Levonelle contains levonorgestrel, which works mainly by preventing or delaying ovulation. The sooner it is taken after having unprotected sex the more effective it will be. It is available as a single tablet containing 1500 microgram levonorgestrel or as two tablets each containing 750 microgram levonorgestrel. This review only covered the 1500 microgram tablets.

In most EU Member States Levonelle and associated names can be obtained without a prescription. The company that markets these medicines is Gedeon Richter Plc.

Why was Levonelle reviewed?

Levonelle has been authorised in the EU under a mutual recognition procedure based on an initial authorisation granted by the United Kingdom on 15 June 2004. On 17 September 2014, the company for Levonelle applied for a change to the marketing authorisation to include the HIV medicine efavirenz as an interacting medicine in the product information. The company wanted this change to be recognised in Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain and Sweden. The application was based on a study that showed that blood levels of levonorgestrel were reduced by

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around 50% in women taking efavirenz, which is known to increase the activity of a particular liver enzyme (CYP3A4) which is involved in the breakdown of levonorgestrel. This could mean that the contraceptive effects of Levonelle are reduced.

Although the Member States agreed that efavirenz interacts with levonorgestrel and that this information should be included in the product information, the Member States were unable to reach an agreement on how this interaction should be managed and whether specific recommendations such as dose adjustment were required for women taking Levonelle while on efavirenz or other medicines which also reduce levonorgestrel levels. On 1 October 2015, the UK referred the matter to the CHMP for arbitration.

The grounds for the referral were concerns from Italy that there are insufficient clinical data to support doubling the dose of Levonelle in cases where the woman is also taking a medicine that interacts with Levonelle. In addition there were concerns that, since Levonelle is available without prescription in many EU Member States, any new advice issued could lead to medication errors as there may not always be a consultation with a healthcare professional prior to taking the medicine.

What are the conclusions of the CHMP?

The CHMP noted that the reductions in blood levels of levonorgestrel seen with efavirenz were similar to those seen with other medicines (so-called liver enzyme inducers) that interact with levonorgestrel (including certain medicines for tuberculosis and epilepsy and herbal medicines containing St John's wort). Based on data on interactions with these medicines, which all increase the activity of the liver enzyme CYP3A4, as well as data on combined hormonal contraceptives, the CHMP concluded that interactions between these medicines and Levonelle may prevent Levonelle from working effectively and could lead to contraceptive failure. The CHMP recommended that women who use liver enzyme inducers should instead use a non-hormonal emergency contraceptive (i.e. a copper intrauterine device) which is not affected by liver enzyme inducing medicines. However, when this is not an option, the CHMP considered that doubling the dose of Levonelle from 1500 to 3000 microgram is recommended to compensate for the reduction in blood levonorgestrel levels. No increased risk of side effects is expected from the higher dose. In order to ensure the correct use of Levonelle, the CHMP also recommended including advice on when to take a double dose on the medicine's outer carton as well as in the package leaflet. Feedback was sought from patients and relevant healthcare professionals to ensure that women could identify when to use a double dose versus a single dose based on the information provided.

Although the review did not cover the 750 microgram Levonelle tablets, the CHMP recommended that similar changes should be considered for these medicines.

The European Commission issued an EU-wide legally binding decision to implement the CHMP recommendations on Levonelle on 01/08/2016.