European Medicines Agency

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QUESTIONS AND ANSWERS ON THE CHMP RECOMMENDATION ON NIMESULIDE-CONTAINING MEDICINES

The European Medicines Agency (EMEA) has completed a review of the liver-related safety of nimesulide. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of 'systemic formulations' of medicines containing nimesulide still outweigh their risks, but that there is a need to restrict the use of these medicines to ensure that the risk of patients developing liver problems is kept to a minimum. 'Systemic formulations' are types of medicine that are given as a treatment throughout the body, such as tablets, solutions and suppositories.

What is nimesulide?

Nimesulide is a non-selective non-steroidal anti-inflammatory drug (NSAID). It is used to treat acute (short-term) pain, and the symptoms of painful osteoarthritis and primary dysmenorrhoea (period pains). Products containing nimesulide have been available since 1985 and are authorised in a number of Member States[1]. They are only available with a prescription.

When first put on the market, nimesulide was used to treat a wider range of conditions, but concerns arising in 2002 over the effects of the medicine on the liver led to a review by the CHMP[2]. As a result, in April 2004 its use was restricted to the three conditions listed above and the maximum daily dose of nimesulide limited to 100 mg twice a day. The use of nimesulide was also contra-indicated in patients with liver problems, and doctors and patients were warned of the risk of serious liver problems in patients taking the medicine. As for all painkillers, a warning was added stating that the medicine should be used for as short a duration as possible.

In addition, the companies that make nimesulide were obliged to submit regular reports on any side effects affecting the liver to medicines regulatory authorities in their Member State.

Why was nimesulide reviewed?

Following reports of serious side effects affecting the liver in Ireland, the Irish medicines regulatory authority decided to suspend the marketing authorisation for nimesulide-containing medicines in May 2007. As a result, these medicines were taken off the market in Ireland. The reports on which the Irish authority acted came from the period from nimesulide's authorisation in Ireland in 1995 up until February 2007.
As required by Article 107 of Directive 2001/83/EC as amended, the Irish authority informed the CHMP of its action so that the Committee could prepare an opinion on whether the marketing authorisations for medicines containing nimesulide should be maintained, changed, suspended or withdrawn across the European Union (EU).

Which data has the CHMP reviewed?

In the current review, the CHMP has looked at all available information on the safety of nimesulide, especially side effects affecting the liver, as well as information on the number of patients who had taken the medicine, and possible risk factors and mechanisms for liver damage. This information came from the companies that market nimesulide and from Ireland and other Member States, as well as from

[1] Nimesulide is available as branded and generic medicines in the following Member States: Austria, Belgium, Bulgaria, the Czech Republic, Cyprus, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Romania, Slovakia and Slovenia.
[2] This review was carried out as a referral under Article 31 of Directive 2001/83/EC as amended (referral under Community interest). See the opinion here.

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the scientific literature and EMEA databases. The information covered the periods before and after the introduction of the restrictions in April 2004.

The CHMP also looked at the results of a study simulating the possible effect that a suspension of nimesulide would have on the rates of various side effects in Italy. This simulation took into account the effects of patients switching to alternative painkilling medicines.

What are the conclusions of the CHMP?
Based on the information provided, the CHMP has concluded that:

- there is a risk of liver toxicity in patients taking nimesulide, but the overall safety profile of nimesulide has not changed since the previous review of the medicine,
- the suspension of nimesulide would lead to a fall in the number of patients needing to go into hospital because of liver problems, but it could also lead to an increase in the number of patients needing hospital treatment because of side effects affecting the stomach and gut, when treated with other painkilling medicines,
- since most liver-related side effects were noted after two weeks of treatment with nimesulide, its use should be limited to a maximum of 15 days,
- the benefits of systemic formulations of nimesulide still outweigh their risks, but their use should be restricted to limit the risk of liver injury,
- doctors should base their decision to prescribe nimesulide on an assessment of the individual patient's overall risks.

The CHMP concluded that the available data did not support a suspension of all marketing authorisations in Europe. However they recommended that, in view of the new maximum duration of treatment, all packs containing more than 30 doses (tablets or sachets) should be removed from the market. The Committee concluded that there was a need for the remaining marketing authorisations to be changed, with the information provided to doctors and patients amended to limit the risk of liver injury.

The CHMP acknowledged that there is no known mechanism behind the effects of nimesulide on the liver, and this makes it difficult to predict whether an individual patient may be at risk of developing liver reactions if he or she takes nimesulide. The Committee decided to make it clearer that nimesulide should not be used at the same time as other medicines that can also cause liver damage or in patients whose liver is already damaged. It also recommended further surveillance measures and studies to investigate the risk of liver injury in patients taking nimesulide, and a letter to healthcare professionals to increase their awareness of the correct way in which nimesulide should be used.

The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for patients and prescribers?

- Patients who are taking systemic formulations of nimesulide should make sure that they only use them for up to 15 days.
- Doctors should restrict their prescriptions of nimesulide-containing medicines to a maximum of 15 days and should base their prescription on an assessment of the patient’s overall risks.
- Doctors and patients should remain aware of the possibility of the development of liver problems when taking nimesulide.
- Patients who have any questions should speak to their doctor or pharmacist.

A European Commission Decision on this opinion will be issued in due course. The Decision will apply in all Member States.