European Medicines Agency

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Questions and answers on the outcome of the review of nimesulide-containing medicines[1]

The review of the liver-related safety of 'systemic formulations' of medicines containing nimesulide has been completed. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines still outweigh their risks, and that there is a need to restrict their use to ensure that the risk of patients developing liver problems is kept to a minimum. 'Systemic formulations' are medicines that are given as a treatment throughout the body, such as tablets, solutions and suppositories. The European Commission endorsed the CHMP opinion with a further restriction to limit the use of these medicines to 'second-line' (used when at least one other medicine has failed).

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 (swelling in the joints) and primary dysmenorrhoea (period pains). Products containing nimesulide have been available since 1985 and are authorised in a number of Member States[2]. They are only available with a prescription.

Why was nimesulide reviewed?
Nimesulide was reviewed by the CHMP in 2007 because of concerns with liver injury. The review was an article 107 procedure triggered by the decision of Ireland's medicines regulatory authority in May 2007 to suspend the marketing authorisation for systemic nimesulide-containing medicines, mainly because of liver problems. The European Commission asked the Committee to prepare an opinion on whether the marketing authorisations for products containing nimesulide should be maintained, changed, suspended or withdrawn across the EU.

At the end of the review in September 2007, the CHMP concluded that the available data did not support a suspension of all marketing authorisations in Europe. However, it recommended that some restrictions should be placed on the way these medicines are prescribed, including limiting the pack size to 30 doses, and that the information provided to doctors and patients be amended to limit the risk of liver injury[3].

The CHMP opinion adopted in September 2007 was transmitted to the European Commission so that it could issue a final decision. This process involves a consultation step with the Standing Committee for Medicinal Products for Human Use, a body of representatives from Member States. The Standing Committee could not reached an agreement, and, on 8 February 2008, the European Commission therefore asked the CHMP to further consider its opinion, taking new data on the risk of liver problems into account, in particularly new data supplied by Ireland, and looking at ways of minimising the risk associated with nimesulide.

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[1] Procedure under Article 107 of Directive 2001/83/EC, as amended.
[2] Nimesulide is available as branded and generic medicines in the following Member States: Austria, Bulgaria, the Czech Republic, Cyprus, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia. Until December 2007, it was also available in Belgium.
[3] The details on the actions taken by the EMEA and of their outcome can be found in the question-and-answer document published in September 2007.

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Which data has the CHMP reviewed?
In the latest review, the CHMP has looked at all the reports of side effects affecting the liver in patients taking nimesulide reported since April 2007, including those from Ireland. The Committee has also reviewed the results of an Italian 'simulation study', carried out by the Italian medicines regulatory authority. This study used existing reports of the rate of side effects with all NSAIDs to simulate the possible effect that a suspension of nimesulide would have on the rates of side effects affecting the stomach and gut. The simulation took the impact of patients switching to alternative painkiller medicines into account.
The Committed has also looked at whether Member States took additional measures to those proposed by the CHMP in September 2007, in order to minimise the risk of liver problems in patients using nimesulide-containing medicines.

What are the conclusions of the review?
Based on the additional information reviewed, the CHMP has not changed its conclusions from September 2007, namely that the benefits of systemic formulations of nimesulide still outweigh their risks, provided that the use of these medicines is restricted to ensure that the risk of patients developing liver problems is kept to a minimum.

The CHMP noted that the only additional measures taken by Member States were changes to the prescription status or reimbursement levels for nimesulide-containing medicines. This suggested that the measures recommended in September 2007, including the changes to the prescribing information, were appropriate to reduce the risk of liver problems associated with nimesulide.

However, the CHMP further concluded that the benefits and risks of nimesulide should be assessed in a wider context. This review should look at all of the potential risks of the medicine, especially the risk of side effects affecting the stomach and the gut, which were outside the scope of the original Article 107 procedure. This should be carried out in a separate 'Article 31' referral procedure. This type of referral is used when it is of 'Community interest' (for the benefit of all Member States) to have a common view on the benefit-risk balance of a medicine.

Because of the severity of the side effects, the European Commission recommended that further measures be taken to ensure that the risk of these side effects is lowered. The European Commission noted that, in some Members States, nimesulide was restricted to second-line treatment. The restriction was therefore added into the prescribing information for nimesulide-containig medicines. The Commission also made it clear that the companies that market nimesulide-containing medicines should inform doctors about the medicines' risks.

The European Commission issued a decision on 16 October 2009.