European Medicines Agency

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Questions and answers on the withdrawal of the marketing authorisations for medicines containing dextropropoxyphene

On 25 June 2009, the European Medicines Agency completed a review of the safety and effectiveness of dextropropoxyphene-containing medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of dextropropoxyphene do not outweigh its risks, and recommended that all marketing authorisations for dextropropoxyphene-containing medicines should be withdrawn throughout the European Union (EU).
At the request of the marketing authorisation holders, the CHMP re-examined its opinion. On 21 October 2009, the Committee confirmed its original recommendation that the marketing authorisations for the non-parenteral (tablets, capsules and suppositories) forms of dextropropoxyphene-containing medicines should be withdrawn. However, for the parenteral form (solution for injection), the CHMP recommended that the marketing authorisations be suspended until further data are available.
The Committee recommended that the withdrawals and suspensions should be gradual in line with national recommendations.
The review was carried out under an 'Article 31' referral[1].

What is dextropropoxyphene?

Dextropropoxyphene is a painkiller that is used to treat short- and long-term (chronic) pain. It is a weak opioid (opioids are medicines related to morphine) that relieves pain by acting on receptors in the brain and spinal cord. It has been available as a prescription-only medicine for about 40 years, both on its own and in combination, as tablets, capsules, suppositories and solutions for injection.
Medicines containing dextropropoxyphene on its own are authorised in 10 Member States (Belgium, Denmark, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Spain and Sweden) and medicines containing dextropropoxyphene combined with paracetamol (sometimes with caffeine) are authorised in six Member States (Belgium, Cyprus, France, Luxembourg, Malta and Portugal) as well as Norway.

Why was dextropropoxyphene reviewed?

There have been concerns for some years over the risk of death from overdose – both intentional and accidental – in patients taking medicines containing dextropropoxyphene and paracetamol. Because of this, a number of Member States have carried out safety reviews of this combination, but these have led to different conclusions. In the United Kingdom and Sweden, the marketing authorisations for these medicines were withdrawn from 2005.
In November 2007, the European Commission asked the CHMP to carry out a full assessment of the benefit-risk balance of combination products containing dextropropoxyphene and paracetamol and to issue an opinion on whether the marketing authorisations for these medicines should be maintained, varied, suspended or withdrawn across the EU. Because the Committee was also concerned about the safety of medicines containing only dextropropoxyphene, in March 2009, the assessment was widened, in agreement with the Commission, to include all dextropropoxyphene-containing medicines, either on its own or in combination.

[1] Article 31 of Directive 2001/83/EC as amended, referral under Community interest.

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Which data has the CHMP reviewed?
The CHMP initially reviewed data presented by the companies that market dextropropoxyphene-containing medicines, providing information on the efficacy and the safety of their medicines. The Committee also reviewed data from published literature including analyses comparing the results of different studies (meta-analyses) in short-term pain relief.
In light of differences between Member States in terms of the number of fatal overdoses reported, the Committee also sought data from other sources available in Member States, including case reports of fatal overdose, data from poison centres, data from coroners' services, hospital statistics, national mortality statistics, and toxicology data from forensic services, from both published and unpublished research.
The CHMP noted that data from case reports of fatal overdose and from national poison centres under-estimate the number of deaths from overdose with dextropropoxyphene-containing medicines. The full extent of the risks of dextropropoxyphene-containing medicine only became apparent when looking at complete forensic data and national mortality statistics, including toxicology data.

What were the conclusions of CHMP after the initial review?
The CHMP concluded that the available data showed that dextropropoxyphene-containing medicines were weak painkillers, and only have limited effectiveness in the treatment of pain. The available evidence suggests that the combination of dextropropoxyphene and paracetamol is no more effective than paracetamol on its own, or ibuprofen, for short-term pain. For long-term pain, the Committee noted that there is no evidence that dextropropoxyphene and paracetamol is more effective than alternative painkillers.
In terms of safety, the major concern of the Committee was the 'narrow therapeutic index' of dextropropoxyphene. This means that the difference between the dose needed to treat the patient and the dose that could harm the patient is small. Patients may easily take too much dextropropoxyphene and risk a fatal overdose, as dextropropoxyphene can be rapidly fatal. Data assessed by the Committee highlighted that many of the cases of fatal overdoses seen have been accidental. Quite often, the patients had taken medicines prescribed for someone else.
The CHMP also concluded that data from several Member States, specifically those from forensic centres and national mortality statistics, showed a significant number of deaths associated with overdose in patients taking dextropropoxyphene. Proposed activities to reduce this risk, such as including further warnings or restrictions, or limiting the size of packs, were not considered to be adequate to protect public health.
Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of all medicines containing dextropropoxyphene, either on its own or in combination, do not outweigh their risks. Therefore, the Committee recommended that the marketing authorisations for these medicines be withdrawn across the EU.
The Committee acknowledged that it is important that patients continue to receive adequate pain relief, and that it is necessary to allow for those who currently take dextropropoxyphene-containing medicines to be transferred to alternative treatments. To ensure prescribers have enough time to determine the most appropriate treatments for individual patients, the Committee recommended that the withdrawal of the medicines from the market be carried out gradually. It will be the responsibility of each Member State to set the timeframe for this withdrawal and assess the need for other activities such as recommendations for prescribers and patients on safe and effective pain relief.

What happened during the re-examination?
During the re-examination, the CHMP looked again at the data it had previously received, taking into consideration the different forms of dextropropoxyphene-containing medicines. The CHMP also considered the views received from patient organisations.

What were the conclusions of the CHMP following the re-examination?
Following the re-examination, the Committee confirmed that the benefits of non-parenteral forms of dextropropoxyphene-containing medicines do not outweigh their risks and recommended their withdrawal.
The CHMP noted that safety was less of a concern for the parenteral form, because these medicines are only given in a hospital setting where there is a lower risk of overdose. However, there were insufficient data on their effectiveness. The CHMP therefore recommended that the marketing

authorisations for the parenteral form of dextropropoxyphene-containing medicines be suspended until further data are available to show that the benefits outweigh the risks.

What are the recommendations for patients?

- Patients who are currently receiving dextropropoxyphene-containing medicines should speak to their doctor at their next appointment to review their treatment.
- Patients who have any dextropropoxyphene-containing medicines that they are no longer using are encouraged to take them to their pharmacist for safe disposal.

What are the recommendations for prescribers?

- Prescribers should carefully consider the best alternative treatments for patients currently taking dextropropoxyphene-containing medicines in line with national recommendations.
- Prescribers should be aware that the availability of dextropropoxyphene-containing medicines will decrease as the withdrawal takes place according to national timeframes. In the meantime, it is recommended that no new patients are started on dextropropoxyphene-containing medicines.

The European Commission issued a decision on 14 June 2010.