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Questions and answers on the review of modified-release oral opioid medicines of the WHO level III scale for the management of pain

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

The European Medicines Agency has completed a review of the safety and effectiveness of modified-release oral opioid medicines of the WHO level III scale for the management of pain. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of most of these medicines continue to outweigh their risks, but that warnings on the use of these medicines together with alcohol should be made consistent across the class.

However, for modified-release medicines that contain a 'polymethacrylate-triethylcitrate controlled release system', the Committee concluded that the marketing authorisations should be suspended. These suspensions will remain in force until the companies that make these medicines have reformulated them so that they are more stable in alcohol.

What are modified-release oral medicines of the WHO level III scale for the management of pain?

Oral opioid medicines of the WHO level III scale for the management of pain are strong painkillers that are taken by mouth and used to treat intense pain that has not been controlled sufficiently with other medicines. They include morphine and the related medicines oxycodone and hydromorphone, all of which work by attaching to receptors in the brain and spinal cord to prevent pain. They are called 'WHO level III scale' medicines as they are on the highest step of the World Health Organization's three-step pain relief ladder. This ladder gives recommendations on the order in which painkillers of increasing strength should be used to control a patient's pain[1].

'Modified-release' forms of these medicines release the active substance slowly, often over many hours. This reduces the number of times a patient needs to take the medicine every day. Modified-release tablets and capsules are made by combining the active substance with other substances that

[1] See: http://www.who.int/cancer/palliative/painladder/en/.

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break down slowly in the body or limit the active substance's release, such as cellulose-based substances and polymers. These are called 'controlled-release systems'.

There are over 500 different medicines belonging to the WHO level III scale group authorised in European Union (EU) Member States.

Why were these medicines reviewed?

These medicines were reviewed following concerns that alcohol might have an effect on the way they release the active substance in the body. Because some of the chemicals used in the controlled-release systems dissolve in alcohol, there is a theoretical possibility that taking these medicines together with alcohol may cause the active substance to be released too quickly. This is called 'dose dumping' and could put patients at risk of exposure to large doses of the opioid, leading to side effects such as respiratory depression (an inhibition of breathing).

Consequently, the European Commission asked the CHMP to carry out an assessment of the benefit-risk balance of these medicines, concentrating on their interaction with alcohol, and to issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed the results of laboratory studies looking at the way that controlled-release systems act when they are placed in solutions containing alcohol. They looked at seven different systems used with morphine, two used with hydromorphone and four used with oxycodone. The CHMP used the results of these studies to predict what would happen if these medicines were taken with alcohol. Some information was also available from studies in human volunteers.

The CHMP also took information from studies looking at the drinking habits of patients with severe pain into account. These included patients with late-stage cancer.

What are the conclusions of the CHMP?

The CHMP concluded that around half of the controlled-release systems tested showed a slight increase in the amount of active substance they released when placed in an alcohol solution, but that this effect was mild and would only have a minor effect on the release of the active substance.

However, for one of the controlled-release systems tested - once-daily capsules using a polymethacrylate-triethylcitrate coating to control the release of morphine - there was a significant interaction with alcohol. When these capsules were put into a 20% alcohol solution, 80% of the active substance was released within 15 minutes. This means that almost a full day's dose of morphine would be released all at once if a patient were to take the capsule with large drink of neat strong liquor, such as whisky or vodka.

The CHMP noted that the use of this medicine in combination with alcohol is already contra-indicated. However, studies looking at the drinking behaviour of patients with severe pain show that many patients drink alcohol while being treated with strong opioids.

Therefore, the CHMP concluded that modified-release opioids using the polymethacrylate-triethylcitrate controlled-release system are highly sensitive to alcohol and that there is a risk of dose dumping if patients drink alcohol while taking them. Therefore, the Committee recommended that the marketing authorisations for these medicines should be suspended until the companies that make these medicines have reformulated the medicines so that they are more stable in alcohol.

For all other medicines in this class, the Committee concluded that their benefits continue to outweigh their risks, and therefore recommended that their marketing authorisations be maintained. However, the CHMP noted that all medicines in this class have the potential to interact with alcohol, such as increasing the opioids' sedative effects. Therefore, the Committee recommended that the warnings on this interaction be made consistent in the information for doctors and patients across all oral opioid medicines of the WHO level III scale. The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for patients and prescribers?

- Prescribers of modified-release opioids and their patients should be aware of the potential interaction between these medicines and alcohol. They should take note of the restrictions and warnings for the medicines that they are using.
- Prescribers are reminded that there are a large number of modified-release opioids available in each Member State. They should consider switching patients currently taking opioids containing the polymethacrylate-triethylcitrate controlled-release system to alternatives while the suspension is in force.
- 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.

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