European Medicines Agency
Evaluation of Medicines for Human Use

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Questions and answers on the recommendation to suspend the marketing authorisation of Ionsys

The European Medicines Agency (EMEA) has completed a review of Ionsys at the request of the European Commission, following concerns over a defect in the medicine that could have an impact on its safety. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Ionsys no longer outweigh its risks, and that its marketing authorisation should be suspended across the European Union (EU). The review was carried out under an 'Article 20' referral[1].

What is Ionsys?
Ionsys is a system that delivers the active substance fentanyl hydrochloride into the body through the skin. Fentanyl is an opioid analgesic (a strong painkiller that is related to morphine). Ionsys should only be used in hospital to control pain after an operation.

The system is applied to the patient's skin on the chest or upper arm by a doctor or nurse. When in pain, the patient uses a button on the Ionsys system to start the delivery of a dose of fentanyl. The system is programmed to allow up to six doses to be given in a one-hour period, but it will stop working 24 hours after the first dose or when a total of 80 doses have been given.

Ionsys has been authorised in the EU since January 2006 and has been marketed in 12 EU Member States[2].

What is the issue with Ionsys?
In September 2008, the marketing authorisation holder (MAH) for Ionsys, Janssen-Cilag International NV, found a defect in one batch of Ionsys. The defect involved corrosion of a component within the system that could result in it releasing fentanyl without being activated by the patient. This could expose patients to more fentanyl than expected, putting them at risk of overdose. The potential risks of fentanyl overdose include respiratory depression (inhibition of breathing), which could be life-threatening.

There were no complaints linked to this defect and there is no evidence that any patients have been harmed as a result of it. However, as a precautionary measure, the MAH recalled all batches of the medicine while it investigated the root cause of the defect. This recall involved a total of over 13,000 systems, both from wholesalers and hospitals.

Ionsys is currently unavailable and patients have been switched to alternative treatments, such as opioid treatment given by mouth or injection, or by using patches. The MAH agreed that it would not resume marketing of Ionsys until its investigations had finished, and any corrective actions had been agreed and put in place.

As the root cause of the defect could not be identified, the European Commission issued a formal request under Article 20 of Regulation (EC) 726/2004. This enabled the CHMP to prepare an opinion

[1] Article 20 of Regulation (EC) No 726/2004.
[2] Ionsys has been marketed in Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Luxembourg, the Netherlands, Slovenia, Sweden and the United Kingdom.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 71 29
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

on whether the marketing authorisation for Ionsys should be maintained, changed, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?
The CHMP has reviewed the information provided by the MAH from its investigations into the root cause of the defect. This included a review of the way the product is made, tested and released, its stability, and how the electronic circuit board that controls the release of the medicine is assembled. The MAH also supplied information on the side effects reported in patients using Ionsys since it was launched.

What were the conclusions of the CHMP?
The CHMP noted that the root cause of the defect in Ionsys had not yet been identified. Corrosion was seen within the circuit boards of some of the recalled Ionsys systems. The type of corrosion seen on the circuit boards is a known cause of self-initiation of the units, which may lead to the release of fentanyl without the product's button being pressed, putting patients at risk of overdose.

The CHMP was concerned that the MAH could not identify the root cause of this corrosion. In addition, the quality controls put in place by the company at the manufacturing and the testing sites were unable to identify the Ionsys systems that contain corroded components.

The CHMP was also concerned that the company's quality systems have not been able to resolve the problems with Ionsys or prevent this quality defect from occurring. At this point in time, it is not clear whether the defect only affects one batch of Ionsys, or whether it could also affect other batches.

The CHMP noted that, of the 13 cases of overdose or respiratory depression reported up to the end of September 2008, none were reported to be serious by the MAH. In addition, none of these cases were linked to a defect with Ionsys.

Because of the failure to find a cause of the defect, the inability of the MAH to identify corroded circuit boards reliably and the potential risks of overdose, respiratory depression and even death, the CHMP has concluded that the benefits of Ionsys no longer outweigh its risks, and that the marketing authorisation should be suspended. This suspension should remain in force until the MAH has identified the cause of the defect, has taken appropriate corrective measures and has reassured the CHMP that it can manufacture the product in a safe manner.

What is the advice to patients and prescribers?
- Following the recall by the MAH, Ionsys has not been available for use since September 2008.
- Prescribers should continue to treat patients with alternative pain-killing medicines after surgery.
- Patients who have any concerns should speak to their doctor or pharmacist.

A European Commission decision on this opinion will be issued in due course.
Full information on the current regulatory status of Ionsys can be found in the European public assessment report (EPAR) here.