05/12/2016
EMA/826770/2016 Corr.*

Pharmaceutics International Inc, US: supply of non-critical medicines to EU stopped due to manufacturing failings

Ammonaps may still be supplied where no alternatives are available

On 15 September the European Medicines Agency (EMA) recommended that medicines manufactured by Pharmaceutics International Inc, located in the United States, should no longer be available in the EU, except Ammonaps (sodium phenylbutyrate), which is considered critical for public health.

The recommendation was the outcome of a review of good manufacturing practice (GMP) at Pharmaceutics International Inc. The review was started after a follow-up inspection of the site by the UK medicines regulatory agency (MHRA) and the US FDA. This inspection found that corrective measures previously agreed had not been appropriately implemented. In particular, several manufacturing shortcomings had not been resolved. These related to the risk of cross-contamination (the possible transfer of one medicine to another) and deficiencies in the systems for ensuring medicines' quality (quality assurance).

Although there was no evidence of a defect in any of the medicines produced at the site or of harm to patients, the site was required to implement corrective measures to ensure compliance with GMP standards.

The recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) has the following impact on availability of medicines from Pharmaceutics International Inc:

- Ammonaps, a medicine for treating urea cycle disorders which is exclusively manufactured at Pharmaceutics International Inc, remains available where there are no treatment alternatives. In EU countries where treatment alternatives exist, Ammonaps will be recalled.
- SoliCol D3 (cholecalciferol), a medicine for vitamin D deficiency which is also exclusively produced at Pharmaceutics International Inc but has not yet been marketed in the EU, will not be made available in the EU. The medicine is only to be marketed once evidence is provided that its manufacturing is compliant with GMP standards.
- The medicines Dutasteride Actavis (dutasteride), Lutigest/Lutinus (progesterone), and associated names, are registered to be produced at Pharmaceutics International Inc, but are now

* This document was revised on 14 October 2016 in line with an updated CHMP opinion clarifying recommendations concerning prohibition of supply. The Committee noted that recommendations on prohibitions of supply have been issued by the national supervisory authority.

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manufactured at alternative registered manufacturing sites. The medicines from these alternative sites therefore remain available in the EU. For Lutigest/Lutinus, some batches produced at the US site were still available on the EU market and were to be recalled.

The CHMP's recommendation concerning these medicines were sent to the European Commission, which issued a legally binding decision valid throughout the EU.

Information for patients

- Failings have been found at a manufacturing site in the United States that produces medicines marketed in the EU. Although there was no evidence of harm or lack of effectiveness with any of the medicines, as a precaution, non-critical medicines from this site are no longer available in the EU.
- One of the medicines affected, Ammonaps (sodium phenylbutyrate), used to treat inherited metabolic disorders, is considered a critical medicine and remains on the market where there are no alternatives. In countries where alternatives are available, your doctor will consider putting you on another treatment.
- If you have any questions about your treatment with Ammonaps, speak to your doctor or pharmacist.
- Other Pharmaceutics International Inc medicines have alternative manufacturing sites and therefore their availability is unaffected.

Information for healthcare professionals

- The manufacturing site Pharmaceutics International Inc in the United States which makes a number of medicines has been found to have several shortcomings in its good manufacturing practice. The manufacturing site had insufficient measures in place to reduce the risk that traces of one medicine could be transferred to another (cross-contamination). There were also problems with the way data were generated and checked and deficiencies in the systems for ensuring medicines' quality (quality assurance).
- There was no impact on the quality of the medicines produced at this site and corrective measures are currently being taken at the site to address these issues.
- However, as a precautionary measure, medicines manufactured by Pharmaceutics International Inc that are not considered critical to public health are no longer to be used in the EU.
- One of the medicines manufactured at this site is Ammonaps (sodium phenylbutyrate), a medicine to treat urea cycle disorders. Ammonaps should only be used in patients when no alternative treatment is available.
- In patients receiving Ammonaps orally (either as tablets or granules), other phenylbutyrate-containing medicines should be considered instead. Ammonaps granules should only be used in patients who have a feeding tube such as a nasogastric tube or gastrostomy and require the medicine. Ammonaps has been recalled in countries where alternatives are available.
- Healthcare professionals have been informed in writing about these recommendations.
- Other medicines (Dutasteride Actavis (dutasteride), Lutigest/Lutinus (progesterone), and associated names) produced at the site have alternative manufacturing sites and the availability of these medicines is unaffected.

More about the medicines

The medicines that are produced at the Pharmaceutics International Inc site in the United States are: Ammonaps (sodium phenylbutyrate), Dutasteride Actavis (dutasteride), Lutigest/Lutinus (progesterone) and SoliCol D3 (colecalciferol). Ammonaps is a medicine authorised in the EU through the centralised procedure, whereas the other medicines have been authorised through national procedures. More information on Ammonaps can be found here.

More about the procedure

The review of medicines manufactured by Pharmaceutics International Inc, US, was initiated on 23 June 2016 at the request of the European Commission under Article 31 of Directive 2001/83/EC.

The review was carried out by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's opinion. The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States on 29/11/2016 (Ammonaps) and 5/12/2016 (Dutasteride Actavis and associated names, Lutinus and associated names and SoliCol D3).

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