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

Ammonaps may still be supplied where no alternatives are available

The European Medicines Agency (EMA) has 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 to be critical for public health.

The recommendation is the outcome of a review into issues with good manufacturing practice 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 is no evidence of a defect in any of the medicines produced at the site or of harm to patients, EMA's Committee for Medicinal Products for Human Use (CHMP) concluded, as a precaution, that supply of non-critical medicines should be stopped. In addition, CHMP requested the site to implement corrective measures to ensure compliance with GMP standards.

The Committee's recommendation will have 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., will remain 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 can only 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 manufactured at alternative registered manufacturing sites. The medicines from these alternative

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sites will therefore remain available in the EU. For Lutigest/Lutinus, some batches produced at the US site are still available on the EU market and will be recalled.

The CHMP's recommendation concerning these medicines will now be sent to the European Commission for 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 is no evidence of harm or lack of effectiveness with any of the medicines, as a precaution, non-critical medicines from this site will no longer be available in the EU.
- One of the medicines affected, Ammonaps (sodium phenylbutyrate), used to treat inherited metabolic disorders, is considered a critical medicine and will remain 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 medicines that are produced at the site 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), as well as problems with the way data were generated and checked and deficiencies in the systems for ensuring medicines' quality (quality assurance).
- There is 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 should no longer 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 as an alternative. 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 will be recalled in countries where alternatives are available.
- Healthcare professionals will be informed in writing about these recommendations.
- Other medicines (Dutasteride Actavis (dutasteride), Lutigest/Lutinus (progesterone), and associated names) that are 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 (cholecalciferol). 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 has been 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 will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

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