EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Referral under Article 31 of Directive 2001/83/EC

Medicinal products for which Pharmaceutics International Inc, Maryland, USA, is included in the marketing authorisation as manufacturing site

Procedure number: EMEA/H/A-31/1444

Ammonaps EMEA/H/A-31/1444/C/000219/0048

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 15 June 2016, the Medicines and Healthcare Products Regulatory Agency (MHRA), the competent authority in the United Kingdom, issued a good manufacturing practice (GMP) non-compliance statement for the manufacturer Pharmaceutics International, Inc. (PII), located in Maryland, USA.

The statement of non-compliance (SNC), limited to products considered non-critical to public health, was entered in the Community database by the UK in accordance with Article 111(7) of Directive 2001/83/EC. In addition, on 15 June 2016 the MHRA issued a corresponding certificate of GMP compliance of Pharmaceutics International Inc. limited to medicinal products confirmed by national competent authorities (NCAs) as critical to public health valid until 30 June 2017.

On 17 June 2016, the European Commission (EC) initiated a referral procedure under Article 31 of Directive 2001/83/EC, and requested the Agency to assess the potential impact of the deficiencies on the quality, safety and the benefit risk balance of the medicinal products which have been authorised by the European Commission and the Member States. The Committee for Human Medicinal Products (CHMP) was requested to give its opinion as to whether marketing authorisations of the medicinal products that include the above mentioned site should be maintained, varied, suspended, or revoked.

2. Scientific discussion

2.1. Introduction

Pharmaceutics International Inc. (PII) manufactures non-sterile products (solid, semi-solid and liquid dosages forms) and sterile products at a separate facility. No commercial sterile medicines are supplied to the EU from this facility.

Some of the active ingredients handled at the non-sterile and sterile facilities are high risk such as high potency, teratogens or cytotoxic.

PII was inspected in June 2015 and September 2015 by the MHRA and several deficiencies were identified. A follow-up inspection was recommended to review the implementation of the agreed corrective and preventive measures.

The follow-up inspection, conducted jointly by the MHRA and the US FDA in February 2016, found that the corrective and preventive measures had not been appropriately implemented and PII was found to be non-compliant with the legal requirements and/or the principles and guidelines of GMP as provided for by Union law as critical and major GMP deficiencies remained.

The following deficiencies were identified:

- Critical deficiencies relating to the failure of organisational and technical measures to minimise the risk of cross-contamination between hazardous and non-hazardous products manufactured in the same manufacturing facilities using shared equipment, as well as failures of the quality unit to ensure the effective operation of the quality system;
- Major deficiencies relating to organisational data governance failures, sterilisation and depyrogenation processes, and insufficient control of aseptic operations to provide the required level of sterility assurance.

Consequently, the UK supervisory authority (MHRA) issued a statement of non-compliance for this manufacturer, recommending a restriction of supply in the EU and the recall of the medicinal products

manufactured at this site unless considered critical to public health. The MHRA issued a corresponding certificate of GMP compliance for the site, limited to medicinal products confirmed by NCAs as being critical to public health. This certificate of GMP compliance is valid until 30 June 2017.

A medicinal product may be considered critical based on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective Member State(s) and, as appropriate, the nature of the disease to be treated.

Pharmaceutics International Inc. (PII), Maryland, USA is listed as manufacturer in the marketing authorisation of four products authorised in the EU, including the centrally approved product Ammonaps and three nationally approved products: Lutinus, Dutasteride Actavis and SoliCol D3.

Another medicinal product, Duexis, was initially identified as having PII named in their approved marketing authorisation. This product was authorised in the UK via a national procedure only and it was clarified that the marketing authorisation holder had voluntarily allowed the national marketing authorisation of Duexis to lapse under the Sunset provision. Duexis therefore does not fall under the scope of this review.

2.2. Ammonaps

Ammonaps is a centrally authorised product containing the active substance sodium phenylbutyrate that was first authorised in the EU in 1999. Ammonaps is indicated to treat the patients who have urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase. It is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

Ammonaps is available as white oval tablets (500 mg) and as granules (940 mg/g). PII is the only manufacturing site registered on the marketing authorisation for the manufacture of the finished products.

2.2.1. Quality aspects

After the initial MHRA inspection in June 2015, some measures have been taken to address the deficiencies identified, including the manufacture of Ammonaps in segregated rooms with dedicated equipment trains from September 2015. However other quality systems failures, including failure of quality oversight, failure to qualify the equipment, and data integrity failures remained.

As part of this referral procedure, the MAH has presented details of corrective actions that have been implemented at the PII manufacturing site and of the provided timelines and steps intended to be undertaken to ensure that the manufacturing of Ammonaps will be performed under good manufacturing practice.

In addition to the measures already implemented following the initial MHRA inspection in June 2015, further quality actions are currently on-going to improve the quality systems in place at the manufacturing site. These measures include the use of assistance from experienced external specialists specialised in quality management and an enhanced control of the batch documents by the qualified person (QP) at the EEA site responsible for batch release. Further testing of the product on importation in the EU was also put in place with a new set of analytical results being generated prior to the release.

A further surveillance inspection of PII was conducted by the MHRA in August 2016, to assess the effectiveness of these corrective measures. This inspection concluded that the deficiencies previously identified at the site were still present but acknowledged that corrective measures were being put in place. In addition, an audit to follow-up the corrective and preventive actions relevant to Ammonaps is planned to be performed by the QP in November 2016 after the measures have been completed. The MAH has committed to provide a progress report to inform on the progression of the actions to restore GMP compliance after each of these milestones, as follows:

Milestones	**Submission date of progress report**
Results from the August 2016 MHRA inspection	14 October 2016
Full audit by Qualified Person in November 2016	23 December 2016

Overall, although some significant measures have been implemented to prevent cross-contamination of Ammonaps, there are still significant issues with regard to assurance on the quality standards of Ammonaps which is below the expected standards. A further follow-up inspection is planned for early 2017.

2.2.2. Clinical aspects

The benefits of Ammonaps in urea cycle disorders is established and it is acknowledged that there is a need for continuous treatment with Ammonaps in conjunction with other treatments to manage these severely ill patients.

Neonatal-onset presentation of urea cycle disorders was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogues. With haemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in new-borns diagnosed after birth (but within the first month of life) increased to almost 80 % with most deaths occurring during an episode of acute hyperammonaemic encephalopathy. Patients with neonatal-onset disease had a high incidence of mental retardation. In patients diagnosed during gestation and treated prior to any episode of hyperammonaemic encephalopathy, survival was 100 %, but even in these patients, many subsequently demonstrated cognitive impairment or other neurologic deficits.

In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency that recovered from hyperammonaemic encephalopathy and were then treated chronically with dietary protein restriction and sodium phenylbutyrate, the survival rate was 98 %. The majority of the patients who were tested had an IQ in the average to low average/borderline mentally retarded range. Their cognitive performance remained relatively stable during phenylbutyrate therapy.

Other treatment options include Pheburane granules 483mg/g that contains sodium phenylbutyrate, and Ravicti 1.1g/ml oral liquid glycerol phenylbutyrate, both centrally approved. Availability of alternatives is limited and diverges between Member States. Also, Pheburane cannot be administered by naso-gastric or gastrostomy tubes and can therefore not be administered to patients who are unable to swallow.

A search in the MAH's safety database for case reports during the period 1 January 2011-31 May 2016 was performed. Search criteria were selected to cover any potential reports associated with potent substances as hormones, cytotoxic and teratogenic drugs as well as for adverse events that could be associated with improper cleaning procedures during manufacturing. These searches revealed ten relevant unique case reports during the period. Nine of the case reports identified were infections within the system organ class (SOC) "infections and infestations". In addition to the reports of infections, there was one mother/child report within the SOC "pregnancy, puerperium and perinatal conditions". The child was growth retarded and according to the reporting physician this was due to the mother´s severe liver disease and the reporter stated that the child had "no malformations or abnormalities".

Effects of exposure to hormones, cytotoxic and teratogenic substances have not been identified and may not be expected within the short time period of approximately five years; these effects may arise in a long time scenario. It is also acknowledged that occasional case reports concerning infections during a time period of five years could be expected, especially in this group of severely ill patients.

Based on the presented reports, there is insufficient evidence to support a causal relationship between the reports from the infections and infestation SOC and the current GMP issues.

The MAH should continue to routinely monitor neoplasms, congenital and genetic disorders, endocrine disorders as well as allergic reactions and infections.

2.2.3. Benefit-risk balance

The benefits of Ammonaps in its approved indication of urea cycle disorders are well established. This is a severe ill condition and a significant number of patients are treated with Ammonaps in the EU. Further, patients need life-long treatment and other available alternate treatment options appear limited, because of concerns over the supply of alternatives and the fact that some of these cannot be administered via naso-gastric/gastrostomy tubes, which is often needed in these patients. Based on the nature of the disease and the fact that therapeutic alternatives are not available in all Member States, the CHMP considers the product Ammonaps to be critical. The safety profile of Ammonaps in urea cycle disorders is well established. However the non-compliance with good manufacturing practice presents a degree of unquantifiable risk which cannot be detected reliably through post-marketing data, hence the lack of any significant concerns cannot provide sufficient reassurance over the safety of the batches manufactured at PII.

The additional risks due to non-compliance to GMP can potentially lead to potential cross-contamination with other drugs produced at the site, including hormones, cytotoxics and teratogens. Although no reports of cross-contamination have been reported in the post-marketing setting, taking into account the target population, that is severely ill and the small patient population (as the prevalence of the condition is very low), the absence of such reports only provides a low degree of reassurance. The reliability of the safety database to detect such an effect is very low. In addition, any significant safety events may only develop after a long period of time.

It is acknowledged that the shift of manufacturing of Ammonaps to a dedicated area using dedicated equipment provides some reassurance and the risk of cross-contamination following this change is considered low. Nevertheless, the quality system at the manufacturing site is still significantly lacking in terms of change control and quality oversight. The non-compliance with good manufacturing practice presents a degree of unquantifiable risk which cannot be detected reliably through post-marketing data; hence the lack of any significant concerns cannot provide sufficient reassurance over

the safety of the batches manufactured at PII. The consistent and continuous lack of adequate quality assurance since before 2015 is therefore of serious concern.

However, given the absence of reports of cross-contamination and taking into consideration the criticality of the product and the improvements in manufacturing which has reduced the risk of cross-contamination to low, it is recommended that the supply of Ammonaps from PII is maintained for the patient population for whom no other treatment option is available. In addition, Ammonaps should not be used if an alternative treatment is available and appropriate for the patient. Also, unless no alternative options are available for patients, the use of Ammonaps granules should be limited to patients requiring administration through a nasogastric tube or gastrostomy.

Concerning the GMP compliance of PII, it is noted that the current certificate of GMP compliance of PII will no longer be valid after 30 June 2017. The MAH should provide progress reports to inform on the progression of the actions taken to restore GMP compliance of the site no later than two weeks after each identified milestone. The MAH should provide evidence by 30 June 2017 that the manufacturing process complies with the requirements of Commission Directive 2003/94/EC (as amended) laying down the principles and guidelines of GMP as provided for in Article 8(3) of Directive 2001/83/EC, as this is a condition to the marketing authorisation.

Notwithstanding the above, the CHMP takes note of the statement of non-compliance with GMP of PII by the supervisory authority which recommends that in Member States where the product is not considered critical to public health, all batches of Ammonaps from Pharmaceutics Internationals Inc. should be recalled and the supply from this manufacturing site prohibited. The statement of non-compliance with GMP of PII clarifies that marketing authorisation holders are requested to contact the relevant NCAs to verify whether their products are considered medically critical to public health in their territory. According to this statement of non-compliance, NCAs should evaluate the criticality of products being supplied by PII and enact measures to ensure continued supply where appropriate.

Furthermore, the CHMP recommended that in due course, appropriate communications should be issued and proposed direct healthcare professional communications (DHPC) to inform on the outcome of the review and the conclusions reached concerning the use of Ammonaps.

The final version of the DHPCs and communication plan was agreed by the CHMP.

The MAH will agree the translations and local specificities of the DHPCs with NCAs. The DHPCs should be sent to paediatricians, neonatologists / neonatal intensive care units, hospital pharmacies including neonatal pharmacies, specialists in metabolic medicine, centres of (inherited) metabolic disorders and relevant scientific associations, as considered appropriate.

2.3. Lutinus (and associated names)

Lutinus is a vaginal tablet containing 100 mg progesterone, indicated for luteal support as part of treatment program for infertile women. This product was approved in the EU via a decentralised procedure including all 28 Member States, with Sweden acting as reference Member State (RMS). A second manufacturer is registered in the marketing authorisation of Lutinus which currently supplies all EU Member States.

No information on corrective actions has been provided. According to the MAH, there is no risk of cross-contamination of Lutinus at the PII site. To support this conclusion, the MAH provided a detailed assessment of all product complaint reports over the past five years which has not revealed any product complaint that can be linked to potential cross contamination. A detailed assessment of

cumulative safety data on Lutinus up to 31 May 2016 was also performed which did not raise any significant safety concerns related to GMP non-compliance.

However the non-compliance with good manufacturing practice presents a degree of unquantifiable risk which cannot be detected reliably through post-marketing data, hence the lack of any significant concerns cannot provide sufficient reassurance over the safety of the batches manufactured at PII.

A complete list of the batches distributed to the EU Member States provided by the MAH showed that the last batch manufactured by PII had been distributed in the EU in February 2015.

The CHMP noted the recommendations from the supervisory authority in the statement of non-compliance with GMP of PII that all batches of Lutinus from Pharmaceutics Internationals Inc. should be recalled and the supply from this manufacturing site prohibited. Given that all EU Member States are currently supplied with Lutinus manufactured at the alternative manufacturing site, no shortage is foreseen for this product.

Also, in view of the statement of non-compliance that was issued for Pharmaceutics International Inc. on 15 June 2016, the CHMP considered that the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC are incorrect and that the terms of the marketing authorisation of Lutinus should be varied to remove Pharmaceutics International Inc. as manufacturing site.

2.4. Dutasteride Actavis (and associated names)

Dutasteride Actavis is a medicinal product containing the active substance dutasteride, a triple 5α-reductase inhibitor. Dutasteride Actavis is indicated for the treatment of the benign prostatic hyperplasia.

This product was first approved in the EU on 3 June 2015 via a decentralised procedure, with Denmark acting as RMS.

No commercial batches of the product have been manufactured by PII, nor released in the EU market. All medicinal products Dutasteride Actavis (and associated names) currently available on the EU market were manufactured at an alternative manufacturing site already registered in the marketing authorisation at time of approval.

In view of the statement of non-compliance that was issued for Pharmaceutics International Inc. on 15 June 2016, the CHMP considered that the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC are incorrect and that the terms of the marketing authorisation of Dutasteride Actavis (and associated names) should be varied to remove Pharmaceutics International Inc. as manufacturing site.

2.5. SoliCol D3

SoliCol D3 20,000 IU tablets and SoliCol D3 50,000 IU tablets are medicinal products containing 20,000 or 50000 IU colecalciferol (vitamin D3 analogue) as active substance. SoliCol D3 was approved in the UK through a national procedure on 18 December 2015.

The product has not yet been launched on the market and the MAH, Pharmaceutics UK Limited, confirmed that no commercial batches of the product had been manufactured at PII.

No alternative manufacturer is registered in the marketing authorisation of SoliCol D3. In view of the certificate of non-GMP compliance issued for Pharmaceutics International, Inc., the CHMP considered that the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC are incorrect

and therefore, pursuant to Article 116 of Directive 2001/83/EC, the marketing authorisations of SoliCol D3 should be suspended.

For the suspension of SoliCol D3 to be lifted, the marketing authorisation holder shall provide evidence that the manufacturing process complies with the requirements of Commission Directive 2003/94/EC (as amended) laying down the principles and guidelines of GMP as provided for in Article 8(3) of Directive 2001/83/EC.

3. Grounds for opinion

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products for which Pharmaceutics International Inc, Maryland, USA, is included in the marketing authorisation as manufacturing site;
- The CHMP reviewed the inspection report provided by the Supervisory Authority, the (co–) rapporteur's assessment reports and the available data presented by the MAHs in writing in response to questions addressed by the CHMP;
- The CHMP considered the statement of non-compliance with GMP for Pharmaceutics International Inc. issued by the MHRA on 15th June 2016 recommending a restriction of supply in the EU and the recall of the medicinal products manufactured at this site unless considered critical to public health;
- The CHMP considered the GMP compliance certificate for Pharmaceutics International Inc. issued by the MHRA on 15th June 2016 restricted to medicinal products considered critical to public health and valid until 30 June 2017;

Ammonaps

- There is no alternative manufacturing site registered in the marketing authorisation of Ammonaps;

Based on the nature of the disease and the fact that therapeutic alternatives are not available in all Member States, the CHMP considers Ammonaps critical to public health The CHMP, as a consequence, considers that the benefit-risk balance of Ammonaps remains favourable for critical use and therefore recommends that the marketing authorisations be varied and subject to the condition that the marketing authorisation holder for Ammonaps provides evidence by 30 June 2017 that the manufacturing process complies with the requirements of Commission Directive 2003/94/EC laying down the principles and guidelines of GMP as provided for in Article 8(3) of Directive 2001/83/EC.

Lutinus (and associated names)

- Lutinus is currently manufactured at an alternative manufacturing site registered in their marketing authorisation;
- The CHMP noted that batches of Lutinus from Pharmaceutics international Inc. are currently available on the EU market.
- The CHMP considers that in the absence of GMP compliance of the manufacturing site Pharmaceutics International Inc., the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC for Lutinus are incorrect.

As a consequence, the CHMP recommends that the marketing authorisation for Lutinus (and associated names) should be varied to remove Pharmaceutical International Inc. as manufacturing site from their marketing authorisations.

Dutasteride (and associated names)

- Dutasteride Actavis is currently manufactured at an alternative manufacturing site registered in their marketing authorisation;
- The CHMP noted that there are no batches of Dutasteride Actavis from Pharmaceutics international Inc. on the EU market.
- The CHMP considers that in the absence of GMP compliance of the manufacturing site Pharmaceutics International Inc., the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC for Dutasteride Actavis are incorrect.

As a consequence, the CHMP recommends that the marketing authorisation for Dutasteride Actavis (and associated names) should be varied to remove Pharmaceutical International Inc. as manufacturing site from their marketing authorisations.

SoliCol D3

- There is no alternative manufacturing site registered in the marketing authorisation for SoliCol D3 and the CHMP noted that no batches of SoliCol D3 are currently available on the EU market;
- The CHMP considers that at present, the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC are incorrect.

As a consequence, the CHMP is of the opinion that pursuant to Article 116 of Directive 2001/83/EC, the marketing authorisations of SoliCol D3 should be suspended.

For the suspension of SoliCol D3 to be lifted, the marketing authorisation holder(s) shall provide evidence that the manufacturing process complies with the requirements of Commission Directive 2003/94/EC laying down the principles and guidelines of GMP as provided for in Article 8(3) of Directive 2001/83/EC.