Annex II

Scientific conclusions

Scientific conclusions

Pharmaceutics International Inc. (PII), located in 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.

In February 2016, a joint inspection by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) found critical and major deficiencies and concluded that PII was non-compliant with the legal requirements and/or the principles and guidelines of Good Manufacturing Practice (GMP) as provided for by Union law.

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.

On 15th June 2016 the MHRA issued a GMP Statement of Non-Compliance (SNC) for PII, 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 National Competent Authorities 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.

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 CHMP was requested to issue an opinion as to whether marketing authorisations of the medicinal products that include the above mentioned site should be maintained, varied, suspended, or revoked.

Overall summary of the scientific evaluation

Ammonaps

Ammonaps is a centrally authorised product containing the active substance sodium phenylbutyrate. It 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.

The benefits of Ammonaps in its approved indication of urea cycle disorders are well established. This is a severe condition and a significant number of patients are treated with Ammonaps in the EU. Further, patients need life-long treatment and other available 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. 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 lack 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.

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 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.

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 option 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.

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 after each identified milestone in accordance with the agreed timelines. 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 National Competent Authority (NCA) to verify whether their products are considered medically critical to public health in their territory. According to this statement of non-compliance, the NCA 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 DHPCs should be sent in accordance with the agreed communication plan.

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. The sourcing of Lutinus from PII has stopped in 2014 and the manufacturing of the product fully switched to an alternative site registered in December 2013.

A detailed assessment of all product complaint reports over the past 5 years provided by the MAH did not reveal any product complaint that could be associated 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.

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 (and associated names) should be varied to remove Pharmaceutics International Inc. as manufacturing site.

In addition to the above conclusions, 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.

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 and was first approved in the EU on 3 June 2015 via a decentralised procedure, with Denmark acting as Reference Member State.

No commercial batches of the product have been manufactured by PII, nor released in the EU market. All medicinal products Dutasteride Actavis 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, is 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.

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 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.

Grounds for CHMP 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;
- In view of the nature of the disease and the fact that 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.