22 October 2015
EMA/746527/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

InductOs

International non-proprietary name: dibotermin alfa

Procedure number: EMEA/H/A-20/1422/C/0408/0082

Note

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

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1. Background information on the procedure

Referral of the matter to the CHMP

On the 20 July 2015, the Netherlands informed the European Medicines Agency (EMA) and the European Commission (EC), on the draft statement of GMP non-compliance issued at the beginning of July 2015 for the manufacturer (Integra LifeSciences Corporation) of the absorbable collagen sponge (ACS), an excipient of the centrally authorised product, InductOs.

The final statement of non-compliance was issued and entered in the Community database by the Netherlands (IGZ) in accordance with Article 111 (7) of Directive 2001/83/EC on 23 July 2015.

On 23 July 2015, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the Agency to assess the above concerns and their impact on the benefit-risk balance of InductOs and whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

The EC also asked the CHMP on 23 July 2015 to consider if there was a need to take provisional measures to be applied immediately, notably a withdrawal from the market and/or suspension of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

InductOs is a kit for implant authorised centrally since 2002 for single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition. InductOs is also indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

The kit consists of a powder containing the active substance, dibotermin alfa, a solvent and a matrix (absorbable collagen sponge, ACS). This has to be applied to the sponge which is thereafter implanted into patients. ACS has been classified as an excipient of InductOs. As such it is consequently inspected against EU-GMP guidelines.

The manufacturer of the ACS, Integra LifeSciences Corporation (ILS), located in a third country (i.e. USA), was inspected last in April 2015 by the Netherlands and Spain and found to be not compliant with the legal requirements and/or the principles and guidelines of GMP as provided for by Union law.

The main concern identified was potential for particulate contamination.

During the previous inspection (January 2014) a number of major deficiencies were already identified. It was decided that a re-inspection would be done after one year to assess the progress in eliminating the major deficiencies. At that time, following a corrective action plan, a restricted GMP certificate valid until January 2015 was issued. As mentioned above, the April 2015 inspection found that the corrective action plan failed and the contamination of ACS with particulate matter was not under control and the quality system not aiming for continuous improvement.

Consequently, the Netherlands issued a draft statement of GMP non–compliance for this manufacturer which is the only existent one.

The final statement of non-compliance was issued and entered in the Community database by the Netherlands (IGZ) in accordance with Article 111 (7) of Directive 2001/83/EC on 23 July 2015. This action determined that no new batches of InductOs could be produced nor released in the EU. A shortage of supply was expected from November 2015.

An Article 20 of Regulation (EC) No 726/2004 was initiated by the EC on 23 July 2015 for the above concerns and their impact on the benefit-risk balance of InductOs to be determined and to decide if the relevant marketing authorisation should be maintained, varied, suspended or revoked.

On 23 July, the CHMP considered the need to take provisional measures to be applied immediately, notably a withdrawal from the market and/or suspension of the marketing authorisation, as requested by the EC.

The CHMP noted that, following the inspection in April 2015, no batches of InductOs had been released in the EU as recommended by the inspectors. The latest batch was released in January 2015 into the EU market, thus prior to the above inspection.

From a public health perspective, there was no indication of risks to patients linked to the inspection findings. Therefore, and taking into account the assessment of the latest PSUR for InductOs dated April 2015 showing no signals in this regard, the CHMP was of the view that there was no need to adopt provisional measures for InductOs.

Healthcare professionals using InductOs were advised to follow the instructions in the product information as usual and a Direct Health Care Professional Communication (DHPC) was adopted and agreed to be distributed on 12 August by the MAH.

On 23 July 2015, the CHMP also adopted a list of questions to be addressed by the MAH. The summary of the MAH responses is hereafter presented.

2.2. Quality aspects

A qualitative analysis was done on the sponge (ACS) resulting in a list of potentially contaminating elements. The identified contamination of the sponge are hairs, fibres, salts and metal particles. This was supplemented by a quantitative analysis of the metal content of the sponge. A toxicological analysis of the results concluded that these particles do not represent a risk for the safety of patients.

The MAH submitted the results of the report regarding particulates and root cause analysis (Particulate and Root Cause Analysis for ACS Particulate Reduction R-NJ-2015-0120), the updated Failure Mode and Effect Analysis (FMEA) and the updated Corrective Actions and Preventive Actions (CAPA).

Based on the root cause analysis and FMEA, a set of actions have been defined to reduce risk and establish control with regard to particulate contamination for the manufacturing process of ACS in the current manufacturing facility.

The CAPA focusses on the equipment as a source of particulate matter (metal). Several pieces of the equipment (grinder, dispersion tank and cutting equipment) will be replaced before April 2016.

It is therefore expected that by April 2016, the majority of CAPAs identified by Integra to address the findings of the April 2015 GMP inspection will be implemented.

The CHMP noted that the conclusions of the inspection report are covered in the CAPA and their acceptability is to be assessed in a future GMP inspection.

2.3. Clinical aspects

The CHMP noted that adverse event reports from clinical trials and spontaneous reporting data analysed and submitted by the MAH are either not related to the contaminations or are expected reactions that can occur at the site of surgery and causality with InductOs cannot be ascertain.

Quality complaints reports (10) describing potential contamination of the ACS with particulate matter (6 mentioning human hair, 3 cases of a coloured spot and 1 case of a glue-like substance) were also noted.

No safety concerns have been identified associated with the potential contamination of ACS with particulate matter.

3. Conclusion and Grounds for the recommendation

The CHMP, having considered all the data provided by the MAH, considers that there is no apparent identified safety concern nor seems to be a risk to patients associated with the contamination of the ACS with particulate matter. However the CHMP also noted that although the findings may not pose a risk to the patients, the sponge should not include any other unwanted components/contaminants and the MAH must undertake efforts to remove these and comply with the legal obligations.

It was noted that alternative treatments are available, including the use of autogenous bone grafts, which are usually harvested from the iliac crest. No other 'morphogenetic proteins' (such as InductOs) are available in the EU but substances known as 'graft extenders' reduce the required amount of bone graft (but not completely replace the grafts). Several such products are available, both derived from human donor tissue and from ceramics.

For the treatment of tibia fractures, fixation with a reamed nail instead of InductOs plus unreamed nail fixation is an alternative option. Standard of care in the EU consists of surgical intervention using reamed or unreamed intramedullary nailing with locking screws.

Given the findings, the CHMP considered that the quality of InductOs cannot be assured at present due to the lack of GMP compliance of the ACS issued on 23 July 2015. Therefore, at present the positive benefit-risk cannot be confirmed.

On the basis of the above and taking into account that InductOs has no alternative ACS manufacturing site authorised:

- The CHMP considers that at present the particulars and documents provided for in Article 8(3) of Directive 2001/83/EC, are incorrect;

- The CHMP considers that the absence of GMP compliance of the manufacturing site of the absorbable collagen sponge, part of the medicinal product precludes at present the confirmation of the benefit-risk of InductOs;

As a consequence, the CHMP recommends the suspension of the marketing authorisation for InductOs in accordance with Article 116, second paragraph of the said Directive.

The CHMP also considers that no product is recommended to be recalled from the market, as the current product on the market was released under a valid GMP certificate in January 2015. No further

product was released after the GMP non-compliance certificate was issued and the latest information on stock indicates that InductOs will be available until end of December 2015.

4. Condition for lifting the suspension of the marketing authorisation

For the suspension to be lifted, the Marketing Authorisation Holder shall provide the following:

- A valid GMP compliance statement for the manufacturer of the ACS, fulfilling the requirements set out in Article 46 of Directive 2001/83/EC.