European Medicines Agency
Evaluation of Medicines for Human Use

London, 8 October 2009
Doc. Ref No.: EMEA/712803/2009

ASSESSMENT REPORT FOR OPTISON

International non-proprietary name/Common name: perflutren

Procedure No. EMEA/H/C/166/Z/0032

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. BACKGROUND INFORMATION ON THE PROCEDURE

Optison Dispersion for Injection, (formerly known as Optison Suspension for Injection) is an intravenous diagnostic agent for ultrasound imaging. Optison (Perflutren) is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers, enhance left ventricular endocardial border delineation with resulting improvement in wall motion visualisation. Optison should only be used in patients where the study without contrast enhancement is inconclusive. Optison is a sterile, non-pyrogenic preparation comprising perflutren-containing microspheres suspended in a Human Albumin Solution (1%, w/v) (HSA). The microspheres are composed of an albumin shell encapsulating a perflutren (octafluoropropane, C_3F_8) gas core. In its non-resuspended form, Optison appears as a clear solution with a white microsphere top layer. After re-suspension, Optison appears as a homogenous white dispersion. The gas filled microspheres provide an interface that interacts with and reflects ultrasound signals in a manner to provide diagnostic images.

On 17th November 2005, the MAH for OPTISON (EU/1/98/) notified the EMEA that it was undertaking a global recall of all batches of OPTISON on the EU/EEA market that were within expiry date. The reason for the recall was a lack of sterility assurance of the product.

The US-FDA performed a general GMP inspection of the Mallinckrodt plant 31st October through 11th November 2005 and the inspection findings raised concerns about the manufacturer's compliance with GMP pertaining to OPTISON manufacture for USA and EU markets.

According to the MAH, no quality defects related to these observations have been found during testing and use of the product. Nevertheless, Amersham Health AS investigated the issues raised by FDA and decided on a voluntarily recall. The MAH concluded that based on the review of the global safety database for OPTISON for the last 12 months (6 reports, 4 non-serious, 2 serious (1 in USA and 1 in UK)), there was no evidence and no suspicion that there was any risk to public health.

The Norwegian Medicines Agency immediately suspended the manufacturing authorisation of the importer, Amersham Health AS, Oslo, Norway prohibiting further import of OPTISON into the EU/EEA.

In December 2007, the MAH of Optison submitted the 2nd Renewal of the Marketing Authorisation (MA) and the procedure started the same month. In the context of the re-assessment of the benefit-risk balance for Optison during the second renewal procedure of the product's marketing authorisation, the Committee for Medicinal Products for Human Use (CHMP) recommended that the marketing authorisation for Optison be suspended. On 12 June 2008, the European Commission issued a Decision to suspend the marketing authorisation for Optison.

On 12 June 2008, the EC issued a Decision to renew the MA for Optison and, at the same time, to suspend the MA. Annex IV of the CD outlined the conditions of the lifting of the suspension of the MA of Optison which are:

- A re-inspection by the Supervisory Authority (NOMA) of the manufacturing facilities at Mallinckrodt Inc., US, has taken place, confirming compliance with GMP principles and guidelines.
- The suspension of the section of the manufacturing authorisation of the EU/EEA site of batch release, GE Healthcare AS, which concerns import of Optison to the EU/EEA market, has been lifted.

On 30 April 2008, the MAH informed the EMEA that the improvement actions to the manufacturing process were completed and a re-inspection of Mallinckrodt Inc., USA, was carried out by NOMA in the week from 8 to 13 June 2008. The corrective measures to the manufacturing site, Mallinckrodt, USA, included the installation of a new filling line and changes to the manufacturing/production process. These changes have to be implemented in the MA before batches of the product for the EU/EEA market can be produced and the medicinal product can be replaced on the market.

This dossier is in support of an application to lift the suspension of the Marketing Authorisation (MA) in EU. Changes to the quality documentation related to the improvements works at Mallinckrodt Inc. which will be implemented at re-launch of Optison in EU are also included.

2. SCIENTIFIC DISCUSSION

2.1 Lifting of the suspension of the marketing authorisation of Optison

As already mentioned the lifting of the suspension of the marketing authorisation of Optison may be recommended provided that the MAH provides evidence that the following conditions are met:

- A re-inspection by the Supervisory Authority (NOMA) of the manufacturing facilities at Mallinckrodt Inc., US, has taken place, confirming compliance with GMP principles and guidelines.

- The suspension of the section of the manufacturing authorisation of the EU/EEA site of batch release, GE Healthcare AS, which concerns import of Optison to the EU/EEA market, has been lifted.

In this context, the Applicant submitted the relevant documentation in support of an application to lift the suspension of the Marketing Authorisation (MA) in EU. It was noted that changes to the quality documentation related to the improvements works at Mallinckrodt Inc., which will be implemented at re-launch of Optison in EU have been also included.

A re-inspection by the Supervisory Authority (NOMA) of the manufacturing facilities at Mallinckrodt Inc., US, has been taken place. A GMP certificate dated 27 March 2009 issued by Norwegian authority has been submitted. The compliance with GMP principles and guideline has been certified by Norwegian authority.

The suspension of the section of the manufacturing authorisation of the EU/EEA site of batch release, GE Healthcare AS, which concerns import of Optison to the EU/EEA market, has been lifted.

A manufacturing licence date 27 March 2009 issued by Norwegian authority has also been submitted for the GE Healthcare AS site in Oslo (Norway). The authorisation includes also importation of medicinal products from countries outside the EEA, according to part 2.

The authorisation includes also importation of medicinal products from countries outside the EEA, according to part 2.

Conclusion and Benefit-Risk Assessment

The lifting of the suspension of the marketing authorisation of Optison is recommended. In addition, the quality changes related to improvements at the manufacturing site are also approvable and the changes do not affect the benefit-risk balance of this product.

2.2 Conclusions and Recommendation on lifting the suspension and Quality changes

In conclusion, the CHMP having assessed the documentation submitted by the MAH regarding the 2 conditions to lift the suspension (A re-inspection by the Supervisory Authority (NOMA) of the manufacturing facilities at Mallinckrodt Inc., US to confirm compliance with GMP principles and guidelines and to lift the suspension of the section of the manufacturing authorisation of the EU/EEA site of batch release, GE Healthcare AS, which concerns import of Optison to the EU/EEA market) considers that the MAH's proposals are now sufficient to guarantee the satisfactory quality of OPTISON active substance and finished products.

Therefore, the CHMP recommends the lifting of the suspension of the Marketing Authorisation of the medicinal product Optison on the basis of the MAH's having resolved the concerns raised that led to the suspension.

3. OVERALL DISCUSSION AND RECOMMENDATION

The CHMP, having reviewed the data submitted by the Marketing Authorisation Holder in the context of the suspension and having re-assessed the data submitted, recommended to lift the suspension of the medicinal product Optison.

4. CONCLUSION

The CHMP consequently, on 25 June 2009 recommended the lifting of the suspension of the Community Marketing Authorisation for the medicinal product Optison.