16 September 2011
EMA/683085/2011
Patient Health Protection

Assessment report for Novosis Goserelin 3,6 mg Implantat and associated names

Pursuant to article 36 of directive 2001/83/ec, as amended

International Non-proprietary Name: goserelin

Decentralized procedure no: DE/H/0733/01/DC

Procedure number: EMEA/H/A-36/1295

Referral under Article 36 of Directive 2001/83/EC, as amended

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

1.1. Referral of the matter to the CHMP

On 16 March 2011, Germany triggered a referral under Article 36 of Directive 2001/83/EC, as amended. The CHMP was requested to give its opinion on whether the marketing authorisations for the medicinal product Novosis Goserelin 3,6 mg Implantat and associated names containing goserelin should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Goserelin is among others, authorised for patients with advanced prostate cancer where an endocrine treatment is indicated. It is an LHRH agonist (analogue of the natural luteinizing hormone-releasing hormone) and suppresses the serum testosterone to castration level to inhibit the growth of hormone-depending prostate carcinoma.

During the evaluation of the marketing authorisation application of some goserelin-containing medicinal products inconsistencies were recognised (e.g. assignment of patients to blood samples unclear). These inconsistencies led to a Good Clinical Practice (GCP) inspection of the contract laboratory, by the German authority (BfArM). The contract laboratory performed the analysis of the plasma samples for the clinical studies GOS/001/C and GOS/002/C. The results of these studies were submitted in a number of marketing authorisation applications of goserelin-containing generic medicinal products to demonstrate therapeutic equivalence with the reference product Zoladex in the course of a MAA under Article 10(3), i.e. hybrid application. It was the aim of the inspection to verify whether the clinical studies GOS/001/C and GOS/002/C were conducted in compliance with GCP and applicable regulations and whether the validity and quality of the submitted data are adequate.

During the GCP inspection 19 findings were identified, of which 9 were classified as critical, 7 as major, and 3 as minor. Critical violations of fundamental standards of ICH GCP and internationally accepted laboratory standards during the bioanalytical analyses of the blood samples from both GOS/001 (1-month depot formulation) and GOS/002 (1 and 3-month depot formulation) were uncovered. These included insufficient validation of the bioanalytical methods, deletion of raw data by re-injection of samples, inconsistent manual reintegration of chromatograms, lack of crucial acceptance criteria for analyses and an insufficient quality management by the sponsor. In view of the number and the seriousness of the deficiencies, the extent of deviations of the measured serum concentrations of both, goserelin and testosterone from the actual concentrations, cannot be estimated. Due to the observed critical and major findings in the studies GOS/001/C and GOS/002/C, a GCP compliant conduct could not be confirmed. Data generated and reported in connection with these two studies had to be classified as not credible.

BfArM considered that a suspension of the marketing authorisations (MAs) was necessary for the protection of public health due to the GCP finding and the uncertainty is raised on the robustness and GCP compliance of the pivotal studyiesGOS/001/C and GOS/002/C for these applications and therefore requested the CHMP/EMA to give its Opinion under Article 36 of Directive 2001/83/EC.

The MA has been suspended in Germany. The MAHs also applied for suspension of the MA in all MSs where authorised. In addition, the product has been recalled from the market in the MS where it was marketed.

2.2. Discussion

Having considered the grounds for the referral triggered by Germany the CHMP requested the MAHs to provide answers on the following:

In view of the critical outcome of the GCP inspection performed, of the bioanalytical part of the pharmacodynamic study GOS/001/C pertaining to Novosis Goserelin 3,6 mg Implantat (ACINO AG) (DE/H/0733/001/DC) (inspection report previously provided to the MAH by the German Competent Authority) the MAHs are asked to address its impact on the quality and reliability of the documentation submitted in support of the MAs granted, considering that for these kind of products a pharmacodynamic study is substituting a full clinical development. The MAHs should seek to provide assurance that the legal requirements for an application for a MA were nevertheless fulfilled and satisfactorily established in accordance with Art. 10 (3) of Directive 2001/83/EC, as amended, and therefore justify the maintenance of the MA for Novosis Goserelin 1 month implant and associated names.

MAH's responses

The MAH agreed with the authorities that GCP violations have happened at the bioanalytical testing facility and has taken extensive measures to correct these facts for future clinical trials. However, the MAH supported that the GCP findings do not fundamentally compromise the validity of the studies and that the products are safe and efficacious.

Goserelin suppresses testosterone function in patients with prostate cancer. In the concerned studies its efficacy was measured mainly by determining testosterone levels and ensuring that they were below the castration level (castration level was defined as 2.5 nmol/ml corresponding to 0.72 ng/ml in study GOS/001/C; in study GOS/002/C castration level was defined as 2 nmol/ml corresponding to 0.58 ng/ml).

In nearly all plasma samples of patients treated with the MAH's product or Zoladex®, testosterone levels were close to or below the analytical limit of quantitation of 0.1 ng/ml in the relevant time frame between days 28 and 56 for the GOS/001/C study and between days 28 and 84 for the GOS/002/C study, i.e. way below the castration level of 0.5 ng/ml.

Due to the fact that testosterone levels were very close to or below the lower limit of quantitation of 0.1 ng/ml analytical errors in a larger percentage than normally allowed would not affect the results (below limit of quantitation remains as such even if the precision of the analytical method is not satisfactory). The difference between the actual level of testosterone measured and the castration level was large enough to compensate potential analytical shortcomings identified by the inspectors.

The analytical errors, if present, would be the same for the comparator drug and the MAH's implant, testosterone levels and Areas under the Curve would be affected in the same way for both the originator and MAH's products.

The inspectors assessed the HPLC / MS analytical data measured, which was one of the methods used to determine testosterone in the studies evaluated. However, efficacy of both comparator and MAH's product were assessed with further parameters such as the results of the clinical examination of the prostate including PSA. The MAH reported the decrease of PSA concentration in both groups (the comparator group and the MAH's product group) as obtained by local measurements 3 time points after administration of the first implant.

Due to GCP deficiencies, the inspectors did not accept the validity of the analytical method for goserelin. However, the MAH supported that goserelin measurements have no impact on the efficacy conclusions of the clinical study GOS/001/C and GOS/002/C since goserelin release rates from the originator Zoladex® and from the MAH's implant are not identical. Goserelin plasma levels do not allow any conclusion for product efficacy as different goserelin plasma levels over time may lead to the same testosterone suppression. Analytical inadequacies for goserelin concentration in this very special case do not have any significant impact on clinical efficacy and safety conclusions.

The MAH took extensive measures to correct the GCP deficiencies identified during the inspection. The testosterone method used in GOS/001/C and GOS/002/C was re-validated after the inspection taking into account all findings of the inspection. This re-validation confirms that the method per se is valid in spite of shortcomings in the initial validation.

The MAH decided to clinically reinvestigate the current goserelin 1-month product using an adapted study design.

CHMP's position

Any argumentation based on the data generated is inappropriate in view of the number and seriousness of deficiencies. The magnitude of deviation of results from actual serum concentration cannot be estimated. Therefore, neither the comparative study design nor the cited results of the study can compensate for the breach of the legal requirements to provide GCP-compliant studies in support of a MAA. It needs to be emphasized that the unique small (n=40) pharmacodynamic study performed by the sponsor is meant to substitute for a full clinical development.

The CHMP agrees that the decrease in PSA is supportive of an efficacious product. However, the two PSA measurements at day 28 and day 56 demonstrating a reduction in the concentration cannot substitute for a valid pharmacodynamic study assessing the primary endpoint of successfully reaching and maintaining castration during treatment.

The CHMP does not agree that the valid goserelin measurements are dispensable. Even though the actual release from the MAH's implant may differ from the release from the reference product in the course of a hybrid application, important information is gained from goserelin measurements, e.g. the plausibility of the adequacy of the dosing interval compared to the reference product.

The main objective of a method validation is to demonstrate the reliability of a particular method for the determination of an analyte concentration in a specific bioanalytical matrix and should appropriately be performed before analysis of study/subject samples. Important aspects such as the difficulty of endogeneous testosterone levels in female blank plasma were only considered in the retrospective validation report with additional testing on either pre-treated or pre-selected matrix. Overall, the value and reliability of a retrospective method-validation more than five years after end of GOS/001 and more than two years after end of GOS/002 is highly questionable.

The performance of a GCP-valid clinical and bioanalytical study is required to support application under such legal basis.

The synopsis of the planned study is currently assessed by the German Competent Authority (BfArM) in an informal national scientific advice procedure.

Whilst it was recognised that only a brief study synopsis with limited information was provided, the following comments were made:

a. The proportion of patients achieving and maintaining castrate levels of testosterone is an accepted primary endpoint. A high efficacy (98-100%) is expected in view of the therapeutic aim of LHRH analogues.
b. Documentation and comparison of PK parameters for both goserelin and testosterone as supportive information using an appropriate blood sampling scheme is considered necessary.
b. The company should provide a clear proposal as to how they plan to handle testosterone breakthroughs (including transient escapes from castration levels, acute-on-chronic phenomenon) and the significance of these in terms of defining treatment failure and success.
c. LH and FSH monitoring is considered relevant.
d. The criteria for the study being regarded as successful are unclear and should be agreed in advance. A lower confidence bound for the "percentage of patients who have reached castration by day 28 and who maintained castration until the end of the study" should be stated in the protocol and the sample size required should be calculated accordingly. A lower confidence bound less than 5% from the expected response on the reference treatment could be discussed (e.g. LCL > 93% if expected response to reference is 98%).

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing, the CHMP concluded that:

1. The bioanalytical studies submitted by the MAHs were not conducted in accordance with GCP as required by Annex I of Directive 2001/83/EC as amended and the nature of the findings is such

that the conduct of the studies and their results cannot be relied on to maintain the marketing authorisation.

Considering the above, the CHMP is of the opinion that the particulars submitted in support of the application do not comply with article 10 of Directive 2001/83/EC as amended. The Committee further considers that it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product and that, in these circumstances, the marketing of the product constitutes a risk to public health.

Therefore, the CHMP recommended the suspension of the marketing authorisations for the medicinal products referred to in Annex I.

The conditions for lifting the suspension of the marketing authorisations are set out in Annex III to the opinion.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.