Annex II

Scientific conclusions and grounds for suspension of the marketing authorisation(s) presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of Goserelin cell pharm 3,6 mg Implantat and associated names (see Annex I)

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.

2. Discussion

MAH's position

The MAH agreed with the authorities that GCP violations have happened at the bioanalytical testing facility of the contract laboratory and has taken extensive measures to correct these facts for future clinical trials.

The MAH believes that the impact of these analytical findings on the conclusions of the clinical studies is limited, because clinical efficacy in both studies is based on a comparison of testosterone levels attained during treatment for the MAH's product and the comparator drug. The two important criteria were:

- comparable AUC of testosterone after sufficient treatment days for MAH's product and comparator
- testosterone levels below castration for both products.

Since testosterone levels measured were either below or close to limit of quantitation (0.1 ng/ml) and clearly below the castration level of 0.5 ng/ml clinical efficacy is ensured even if the analytical method is not sufficiently precise.

Revalidation of the testosterone method confirmed the confidence in the reliability of the results obtained earlier.

Analytical inadequacies would affect comparator and MAH's product in the same way:
Since the clinical efficacy was based on a comparison between two products analytical errors would

be expected to affect both products in the same way. Therefore the clinical conclusions should remain the same.

In view of all these facts the MAH requested the CHMP to confirm the acceptability of the existing clinical package for goserelin and maintain the marketing authorization for the concerned products.

CHMP's position

Any argumentation based on the data generated at the contract laboratory 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 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.

Based on the totality of data submitted, the CHMP considered that therapeutic equivalence with Zoladex had not been demonstrated and as such the benefit risk ratio for this generic product was considered negative until the MAH can demonstrate therapeutic equivalence with the reference product.

Grounds for suspension of the marketing authorisations

Whereas,

- The Committee considered the referral triggered under Article 36 of Directive 2001/83/EC for Goserelin cell pharm 3,6 mg Implantat and associated names as listed in Annex I.

- The Committee agreed that 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 Committee recommends the suspension of the marketing authorisations, subject to the conditions outlined in Annex III of the Opinion.