IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Busol 0.004 mg/ml solution for injection for cattle, horses, rabbits

PRODUCT SUMMARY

EU Procedure number	IE/V/0213/001/DC
Name, strength and pharmaceutical form	Busol 0.004 mg/ml Solution for Injection for cattle, horses, rabbits
Active substance(s)	Buserelin
Applicant	T.P. Whelehan & Son Ltd. Bracetown Business Park Clonee Co Meath Ireland.
Legal basis of application	"Well established use" application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of procedure	30th July 2008
Target species	Bovine, equine and rabbits
Indication for use	For the induction of ovulation in cows, mares and rabbits.
ATCvet code	QH01CA90
Concerned Member States	BE, BG, CY, CZ, EE, EL, ES, FI, HR, HU, IT, IS, LT, LV, PT, RO, SI, SK,

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended.Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A.Qualitative and Quantitative Particulars

The product contains Buserelin (as buserelin acetate) 0.004 mg/ml and the excipients benzyl alcohol, sodium dihydrogen phosphate dihydrate, sodium chloride, sodium hydroxide and water for injections.
The container/closure system is a clear type 1 glass vial closed with rubber stopper with PTFE foil and aluminium caps.The product is a well established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B.Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C.Control of Starting Materials

The active substance is Buserelin (as buserelin acetate)an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D.Control on Intermediate Products

Not applicable.

E.Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F.Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approvedconditions.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.ASafety Testing

Pharmacological Studies

Buserelin is a peptide hormone, the mode of action of whichcorresponds to the physiologic-endocrinological action of the naturally occurring gonadotrophin releasing hormone.
The applicant has provided bibliographical data which show thatGonadotrophin releasing hormone (GnRH, LH-RH) stimulates the secretion of FSH and LH from the pituitary gland. This release of FSH and LH is responsible for the subsequent production of gonadal sex steroids. In the male, LH acts to stimulate the Leydig cells to produce androgens (mainly testosterone), whereas FSH acts on Sertoli cells to control spermatogenesis. In females, FSH promotes ovarian growth, follicular maturation and subsequent secretion of oestradiol, whereas LH is essential for ovulation and development and release of progesterone by the corpus luteum.

The applicant has also provided bibliographical data which show that following intravenous administration buserelin is rapidly eliminated from blood circulation with an initial half life of 5 minutes (rats) or 12 minutes (guinea pigs). The compound accumulates in the pituitary gland, liver and kidneys, where it is enzymatically degraded into smaller peptide fragments with negligible biological activity. The main excretory route is through the urine.

Toxicological Studies

The applicant has provided bibliographical data which show that that toxic potential following acute dosing is low and that effects of repeat dosing are typically confined to effects on reproductive function relating to hormone secretion by the pituitary and gonads.
With respect to reproductive toxicity, there is no evidence for teratogenic effects. It has also been demonstrated that buserelin is not mutagenic.

Observations in Humans

The applicant has provided bibliographical data which show that appropriate precautions should be taken by women of child bearing age, in relation to the potential for effects on reproductive function. Such advice has been included in the product literature.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that when administering the product, care should be taken to avoid accidental self-injection. Furthermore, women of child bearing age should handle the product with caution and pregnant women should not administer the product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.BResidues Documentation

Residue Studies

The applicant has provided bibliographical data which show that
·Buserelin is rapidly eliminated from the circulation following parenteral administration.
·Buserelin was demonstrated to be orally inactive in man following high oral doses (due to digestion),
·Buserelin is included in Annex II of Council Regulation 2377/90 for use in all food-producing species.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for meat in bovines, equines and rabbits and zero days for milk are justified.

IV. CLINICAL ASSESSMENT

IV.APre-Clinical Studies

Tolerance in the Target Species of Animals

Target animal tolerance data specific for Busol have not been provided. However, giventhe fact that products containing buserelin have been in use in veterinary medicine for in excess of 20 years, Busol can be considered to have an acceptable safety profile.

None of the field data submitted in support of the application provides any indication of adverse effects in any of the proposed target species following buserelin therapy.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Field Trials

The applicant has provided bibliographical data which show that buserelin was found to be effective in the horse when administered by the intramuscular, subcutaneous and intravenous routes of administration for:

oInduction of ovulation in oestrus mares
Dose: 20-40 µg, at 12 hour intervals

oImprovement of pregnancy rate
Dose/protocol: 20 - 40 µg buserelin between 8 and 12 days after natural mating/insemination
The applicant has also provided bibliographical data which show that buserelin was found to be effective in cattle for:
oInduction of ovulation in cows with a dominant follicle
Dose: 10 µg, intramuscularly

oSynchronisation of oestrus and induction of ovulation
Dose/protocol: buserelin (10 µg, intramuscularly) administered on Day 0, followed by PGF2α on Day 7 and buserelin (10 µg, intramuscularly) on Day 9.

oTreatment of ovarian follicular cysts
Dose: 20 µg intramuscularly
The applicant has also provided bibliographical data which show that buserelin was found to be effective in rabbits for:
oInduction of ovulation for post-partum insemination
Dose: 0.8µg buserelin intramuscularly
oImprovement of conception rate
Dose: Dose: 0.8µg buserelіun intramuscularly.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:
None.