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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for extension for DRAXXIN (EMEA/V/C/000077/X/0026)

International non-proprietary name: tulathromycin

Extension to 25 mg/ml solution for injection for pigs

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

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Introduction

On 26 June 2013 an application for an extension to the Community marketing authorisation for DRAXXIN was submitted by Zoetis Belgium SA to the European Medicines Agency (the Agency) in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

DRAXXIN 100 mg/ml solution for injection for cattle and pigs contains tulathromycin, a semi-synthetic macrolide antibiotic, and was authorised for use in the Community on 11 November 2003.

This extension application was to add a new strength DRAXXIN 25 mg/ml solution for injection for pigs only. The route of administration is intramuscular use. It is presented in packs containing one glass vial of 50 ml, 100 ml or 250 ml. The rapporteur appointed was C. Ibrahim and co-rapporteur C. Muñoz Madero.

The applicant applied for the following indication: treatment and prevention of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin.

The proposed withdrawal period is 33 days (meat and offal).

On 8 May 2014, the CVMP adopted an opinion and CVMP assessment report.

On 8 July 2014, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 14 March 2013) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse event or adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance is manufactured in line with good manufacturing practice (GMP) requirements, based on the last audit conducted at the site.

The finished product is manufactured and tested by Laboratórios Pfizer Ltda, Guarulhos, São Paulo, Brazil. A GMP certificate for this site was provided and specifies that the site is authorised for the manufacture of veterinary medicinal products; sterile products (aseptically prepared and terminally sterilised) are specifically listed, based on the latest inspection conducted at the site.

Batch release for the European Union (EU) will be carried out by Pfizer PGM, Pocé Sur Cisse, France. A GMP certificate confirming the date of the last inspection for this site, was provided and specifies that the site is authorised for the importation and quality control of veterinary medicinal products; sterile products are specifically listed.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

DRAXXIN 25 mg/ml is a clear colourless to slightly yellow solution which contains the active substance tulathromycin, a semi-synthetic macrolide antibiotic consisting of two isomers with company's internal codes CP-472,295 and CP-547,272.

The following excipients are used in the manufacture of the finished product: monothioglycerol, propylene glycol, citric acid anhydrous, hydrochloric acid, sodium hydroxide, and water for injections; nitrogen is added to provide an inert atmosphere during manufacture and in filled and sealed vials.

Container

The finished product is presented in cardboard boxes containing one type I glass vial of 50 ml, 100 ml or 250 ml with fluoro-resin coated chlorobutyl rubber stoppers and aluminium seal with flip-off disc.

Development pharmaceutics

DRAXXIN 25 mg/ml is proposed for the treatment and prevention of swine respiratory disease (SRD) in pigs and is primarily intended for use in small pigs that have bodyweights that make it difficult to accurately dose with the currently approved product containing 100 mg/ml tulathromycin.

Stability studies were performed with several formulations and those that resulted in an unstable product were discontinued. The formulation optimisation studies were focused on pH adjustment for ease of manufacture and process parameters to reach the required isomer ratio.

The final formulation is qualitatively the same as DRAXXIN 100 mg/ml. The choice of the excipients was adequately justified within the initial marketing authorisation application. The selection of the sterilisation process (aseptic filtration) was adequately justified within the initial marketing authorisation application.

The proposed formulation complies with Criteria A of the European Pharmacopoeia (Ph. Eur.) test on efficacy of antimicrobial preservation.

Method of manufacture

Conventional pharmaceutical equipment is used in the manufacture of the product. The manufacturing process is the same as that for DRAXXIN 100 mg/ml with the exception of the different amounts of raw materials used to accommodate the lower concentration of tulathromycin. The bulk product is sterilised by appropriate filtration methods. Results of three commercial size batches demonstrate that the current process performs well for the lower concentration product and the finished product consistently met the proposed specifications.

Validation studies will be conducted prospectively on four consecutive commercial size batches of

DRAXXIN 25 mg/ml. To date, no validation results are available. The applicant has committed to the completion of successful process validation at Guarulhos, Brazil prior to commercial distribution of the finished product.

An approved validation protocol has been provided and the applicant has confirmed that the regulatory authorities will be informed immediately if the validation results show significant deviations from the expected data. In this case, corrective actions will be proposed and any changes in the manufacturing process will be approved by way of a variation.

Control of starting materials

Active substance

The data for the active substance (tulathromycin) were assessed within the initial marketing authorisation application and variations to the marketing authorisation hereafter.

Updated stability data of batches stored at 25 °C/60% relative humidity (RH) were submitted by the applicant with this extension application. Stability data covering 24 months are provided for 2 batches of tulathromycin manufactured with the original manufacturing process (Gen I) and for 4 batches manufactured with the Gen II process (approved via variation). Additional data for 2 batches manufactured with the Gen II process were provided covering 12 months for one batch and 6 months for the other. All batches meet the acceptance criteria when stored at 25 °C/60% RH.

The proposed retest period of 24 months is acceptable.

Excipients

DRAXXIN 25 mg/ml contains the same excipients as DRAXXIN 100 mg/ml. The quality of the excipients used in the manufacture is controlled with compendia texts, Ph. Eur. or National Formulary (NF) monographs.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active substance tulathromycin or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Transmissible spongiform encephalopathy (TSE) compliance declarations from the manufacturers of each of the excipients and the active substance were submitted accordingly.

Control tests during production

Not applicable.

Control tests on the finished product

The specifications proposed at release and at the end of shelf life are appropriate to control the quality

of the finished product.

The finished product specification contains tests/limits for appearance, particle contamination, identity, assay, impurities, content of monothioglycerol, pH, sterility, bacterial endotoxins and extractable volume.

The limits for the specified impurities and the lower limit for the assay are set wider.and will be revised after completion of the stability studies and following the first year of routine production.

The analytical methods were well described and validated. This is acceptable.

Batch analysis data of three production scale batches show that the finished product is in compliance with the release specification.

Stability

Finished product stability data is presented for three batches of the finished product, each packaged as proposed for marketing in clear type I glass vials of 50 ml, 100 ml and 250 ml. The batches were stored under the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) long-term, intermediate and accelerated conditions. For the 3 batches 24 months data at 30 °C/75% RH and 6 months data at 40 °C/75% RH were presented. For two of the three batches 24 months data at 25 °C/60% RH are also available. This is sufficient to justify the proposed shelf life of 3 years according to Annex II of the CVMP Guideline on stability testing of existing active substances and related finished products (EMEA/CVMP/QWP/846/99-Rev.1). Therefore, the proposed shelf life of the finished product can be granted.

In-use stability has been confirmed on a batch within the first 5 months after manufacturing. The proposed in-use period of 28 days is acceptable. It has been confirmed that in-use stability testing will be repeated approaching the end of the shelf life with the same lot that has been tested initially, and the applicant should inform of any results that are out of specification or trending out of specification.

According to the CVMP Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products) (EMEA/CVMP/424/01-Final) “a minimum of two batches, at least pilot scale batches, should be subjected to the test”. Therefore, at the end of the shelf life a minimum of two batches of the finished product should be subjected to in-use stability testing and testing results should be provided for the 50 ml vials as projected and additionally for a second batch of 250 ml vials.

The test designs for photostability and for freeze/thaw stability testing have been described. All testing results comply with the product specification.

According to the stability data presented no special storage conditions are needed for medicinal product as proposed by the applicant.

Overall conclusions on quality

DRAXXIN 25 mg/ml is an extension to DRAXXIN 100 mg/ml with a closely related formulation compared to the approved veterinary medicinal product. Therefore, parts 2.A, 2.B, 2.E and 2.F of the dossier have been adapted to the new strength, whereas the control of the starting materials (2.C) and the analytical methods used for the control of the finished product (2.E) are identical for both strengths.

Data on the active substance were presented in the initial marketing authorisation application and subsequent variations.

Comprehensive information on the manufacture and characteristics of the active substance was provided. Routine tests and specifications are considered sufficient to assure its constant quality. The proposed re-test period of 24 months is acceptable.

The excipients used are considered acceptable, as well as the packaging materials. The quality of the excipients used in the manufacture is controlled with compendia texts. There are no concerns in relation to TSE with any of the ingredients of the product.

The rationale for the choice of the formulation is acceptable.

The specifications proposed at release and end of shelf life are considered acceptable. The limits for the specified impurities and the lower limit for the assay should be revised after completion of the stability studies and following the first year of routine production.

The stability data provided reflect the VICH recommendations. Data demonstrate stability at long term, intermediate and accelerated conditions. A shelf life of 3 years without special storage conditions can be granted.

Regarding in-use stability, the tests at the end of the shelf life should be performed on two batches, both on the 50 ml vials as projected and additionally on a second batch of 250 ml vials.

Under this provision, the extension of the marketing authorisation to include DRAXXIN 25 mg/ml solution for injection for pigs can be recommended. It is however necessary to recommend further as follows:

Finished product specification:

Both the specifications for specified degradation products and the lower assay limit during shelf life should be revised after completion of the initial stability studies of the registration batches and following the first year of routine production.

In-use stability testing:

At the end of the shelf life a minimum of two batches of the finished product should be subjected to in-use stability testing and testing results should be provided for the 50 ml vials as projected and additionally for a second batch of 250 ml vials.

Part 3 – Safety

Cross-reference was made to the DRAXXIN 100 mg/ml dossier for pigs, and no new data have been provided as regards to pharmacodynamics, toxicology including reproductive toxicity, mutagenicity/carcinogenicity and on other effects. Given the nature of this extension application, this is considered acceptable.

Pharmacokinetics

The applicant has conducted a bioequivalence study in pigs that demonstrated that the two strengths (25 mg/ml and 100 mg/ml) are bioequivalent when administered by intramuscular injection at a dose of 2.5 mg/kg bodyweight. For details please see Part 4.

Tolerance in the target species of animal

For details please see Part 4.

User safety

Since DRAXXIN 25 mg/ml is intended for use in small pigs for the same indications, dose and treatment duration as DRAXXIN 100 mg/ml, and the route of administration is the same as DRAXXIN 100 mg/ml, no changes in the likelihood and frequency of use are expected. Consequently, the precautions for DRAXXIN 100 mg/ml are also applicable to DRAXXIN 25 mg/ml and are adequately reflected in the summary of product characteristics (SPC) and other product information.

Environmental risk assessment

The applicant did not provide an environmental risk assessment for this application. This is considered acceptable because the new strength (25 mg/ml) is not expected to increase the overall use of the product as there will be no new target species nor indications, and the treatment recommendations (dose and duration of treatment) are the same as the existing DRAXXIN 100 mg/ml.

DRAXXIN 25 mg/ml solution for injection is not expected to pose a risk to the environment when used according to the SPC.

Overall conclusions on the safety documentation

Data in support of the safety part in pigs have previously been submitted and assessed and no new data have been presented for this application. A bioequivalence study in pigs demonstrated that the two strengths (25 mg/ml and 100 mg/ml) are bioequivalent. Cross-reference has therefore been made to data previously submitted and assessed, which is acceptable. Appropriate measures to ensure the safe use of the product are included in the SPC and other product information.

Residues documentation

Overall conclusions on the residues documentation

No new residue studies have been conducted for the new formulation, but cross-reference has been made to data previously submitted and assessed, which is considered acceptable.

According to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues. However, in this particular case, a new residue depletion study with DRAXXIN 25 mg/ml is not necessary, given that the dose regime is the same as for DRAXXIN 100 mg/ml, that bioequivalence with the established 100 mg/ml formulation has been shown and that local tolerance of the new formulation is acceptable (see Part 4). The applicant has provided thorough justification that the change in active substance concentration and/or the administration of different injection volumes is unlikely to affect the depletion of residues from the injection site.

The currently approved withdrawal period of 33 days for DRAXXIN 100 mg/ml is also applied for the new DRAXXIN 25 mg/ml formulation for pigs.

Part 4 – Efficacy

Pharmacodynamics

No new studies have been performed on the new strength DRAXXIN 25 mg/ml. Cross-reference was made to data submitted and assessed for the already authorised product of DRAXXIN 100 mg/ml. Supplementary information was provided in a microbial safety report.

With this extension application the susceptibility data of target pathogens over the past 10 years have been reviewed by a compilation of recent publications and different European surveillance programs and by data from North America. Despite the use of tulathromycin (and other macrolides) in pigs, there was no detected shift in susceptibility amongst the pathogenic target species since the launch of DRAXXIN in 2003.

Development of resistance

The applicant has not performed any new studies.

An assessment on antimicrobial resistance was provided taking into account the evolution of the susceptibility profile since DRAXXIN was first authorised.

The most common acquired resistance mechanism is the production of an enzyme that methylates an adenine residue in the 23S ribosomal RNA of the 50S ribosomal subunit. This results in reduced ribosomal binding to not only erythromycin and most other macrolides, including azithromycin and clarithromycin, but also to the lincosamide and streptogramin B antibiotics. This phenotype is referred to as macrolide-lincosamide-streptogramin B (MLSB). The *erm* genes (MLSB phenotype) can be expressed inducible or constitutively. Experiments have demonstrated that tulathromycin is only weakly inducing the *erm* gene.

Co-resistance to several antimicrobial classes and macrolides has been reported in different bacterial species including *Campylobacter* spp., *P. multocida* and methicillin-resistant *Stapylococcus aureus* (MRSA).

Using clinical breakpoints for swine respiratory disease pathogens (*P. multocida, Bordetella bronchiseptica, A. pleuropneumoniae*) as set by the Clinical and Laboratory Standards Institute (CLSI), resistance development to tulathromycin was limited or not observed in most of the data sets collecting isolates of respiratory porcine target pathogens since the launch of DRAXXIN in 2003.

In addressing the impact of tulathromycin on foodborne pathogens and commensals, emphasis was put in particular on *Campylobacter coli* as this organism is involved in foodborne diseases arising from contamination of retail pork products and because treatment in humans with macrolides may be necessary. Assessment of this issue led to the conclusion that the risk associated with veterinary use of macrolides in pigs for the human health is considered to be low.

As tulathromycin is administered by injection to individual animals it can be considered that the level of exposure to the animal population is low. Bacterial exposure to microbiologically active drug is transient due to the single dose, parenteral administration, and since tulathromycin activity against enteric organisms in the gastro-intestinal tract is attenuated due to abiotic factors such as pH and faecal binding.

The CVMP concluded that it is unlikely that this extension application for a lower strength (25 mg/ml) of DRAXXIN solution for injection would give considerable rise to animal or public health concerns.

Pharmacokinetics / bioequivalence

All pharmacokinetic information as provided in the dossier of the original application for the marketing authorisation of DRAXXIN 100 mg/ml solution for injection remains unchanged, since DRAXXIN 25 mg/ml will be used at the same dose (2.5 mg/kg bodyweight), administration route, and for the same treatment duration as DRAXXIN 100 mg/ml.

A good laboratory practice (GLP) compliant study was conducted in swine to demonstrate bioequivalence of the lower concentration (25 mg/ml) to the current formulation of DRAXXIN (100 mg/ml). The study complies with the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev 2). Both products were administered by intramuscular injection at a single dose of 2.5 mg/kg bodyweight to young pigs weighing 15–25 kg. Blood samples were collected at regular intervals after administration for the determination of tulathromycin concentrations by using a validated analytical method. In addition, the pigs were observed for injection site reactions and general adverse effects.

Results demonstrated that both formulations were bioequivalent on the basis of the area under the curve (AUC)-ratio, which was within the common acceptance limits. C_{max}, however, could not be accurately determined since maximum plasma concentrations of tulathromycin had already been reached in most animals in the first blood sample, i.e. within 20 minutes after administration. However, as C_{max} is of minor relevance for macrolide-type antibiotics, it was concluded that bioequivalence of DRAXXIN 25 mg/ml and the approved 100 mg/ml strength has been demonstrated sufficiently by AUC-comparison.

Target animal tolerance

The new strength DRAXXIN 25 mg/ml is expected to have equivalent systemic effects as DRAXXIN 100 mg/ml and will not change the current safety profile in the target animal when used in swine via the intramuscular route of administration and thus, no further systemic tolerance or margin of safety studies were considered necessary. Bioequivalence has been demonstrated between the two strengths.

A GLP-compliant local tolerance study was conducted using DRAXXIN 25 mg/ml injected intramuscularly in growing pigs. The study was well conducted and the design was adequate to assess the local tolerance of the new formulation. All animals received a single injection at the maximum volume of 4 ml, even if this exceeded the recommended dose of 1 ml per 10 kg bodyweight (2.5 mg/kg bodyweight) calculated according to their bodyweights (22–26.5 kg). Clinical observations at injection sites performed over 42 days were insignificant. As evident from post mortal examination, the intramuscular injection of the test-article induced gross and microscopic transient changes in skeletal muscle and fascia in the injection sites. The changes in injection sites at any day of the 42 days examination period were considered to be mild or moderate with normal progression to macroscopic resolution within 28 days post-injection.

In addition, from the pharmacokinetic bioequivalence study, findings on injection site observations were reported. Compared to animals investigated in the injection site tolerance study, animals had lower bodyweights (15–25 kg bodyweight vs 31–38 kg bodyweight) and received the actual dose volume calculated according to their bodyweights. Out of 31 piglets receiving DRAXXIN 25 mg/ml two animals showed transient swellings at the injection sites. From the results it could be concluded DRAXXIN 25 mg/ml was well tolerated at the injection site.

Findings on injection site reactions are adequately covered by the present wording of SPC section 4.6.

Field trials

Given that bioequivalence has been demonstrated in the GLP study comparing DRAXXIN 100 mg/ml and DRAXXIN 25 mg/ml following intramuscular injection of either formulation at a dose of 2.5 mg/kg bodyweight, it is expected that DRAXXIN 25 mg/ml will have equivalent efficacy to DRAXXIN 100 mg/ml. The efficacy of DRAXXIN 100 mg/ml was appropriately established in the original dossier.

The applicant claimed the same indications for DRAXXIN 25 mg/ml as those approved for DRAXXIN 100 mg/ml in pigs. This is considered acceptable.

Overall conclusion on efficacy

DRAXXIN 25 mg/ml has shown to be bioequivalent to the authorised product DRAXXIN 100 mg/ml in pigs. When administered at the approved dose regime, efficacy is considered proven in all indications authorised for the 100 mg/ml strength.

The new strength DRAXXIN 25 mg/ml is expected to have equivalent systemic effects as DRAXXIN 100 mg/ml. Local tolerance has been demonstrated in a new study with DRAXXIN 25 mg/ml in pigs when injected intramuscularly at the maximum recommended treatment volume of 4 ml per injection site.

Part 5 – Benefit-risk assessment

Introduction

This application is for the addition of a new strength (25 mg/ml) of DRAXXIN solution for injection which is approved for use in cattle and pigs at a strength of 100 mg/ml.

DRAXXIN 25 mg/ml solution for injection is for use in pigs only and primarily intended for the treatment of small pigs that have bodyweights that would make it difficult to accurately dose with the 100 mg/ml strength.

Benefit assessment

Direct therapeutic benefit

DRAXXIN 25 mg/ml solution for injection proved to be bioequivalent to the approved product, DRAXXIN 100 mg/ml, in a GLP-compliant bioequivalence study in pigs. The direct therapeutic benefit for the new strength against relevant respiratory pathogens in pigs is therefore expected to be the same as that established for DRAXXIN 100 mg/ml with the initial application procedure for marketing authorisation.

Additional benefits

The addition of a lower strength of 25 mg/ml enables to dose smaller pigs more accurately than with the currently authorised strength (100 mg/ml).

Risk assessment

Main potential risks:

Quality:

As regards quality, the formulation and manufacture of Draxxin 25 mg/ml is well described and controlled, and adequate specifications have been defined.

For the target species, the user and the environment:

The potential risks with regard to the target animal, the user and the environment have been adequately characterised during the initial application procedure for marketing authorisation of DRAXXIN 100 mg/ml, and appropriate information (as for the approved DRAXXIN 100 mg/ml) has been included in the SPC and other product literature for the new strength. In a study on local tolerance of DRAXXIN 25 mg/ml in growing pigs only mild and transient injection site reactions were recorded after intramuscular injection. It has therefore been demonstrated that the product is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings have been included in the SPC.

For the consumer:

Considering that DRAXXIN 25 mg/ml solution for injection proved to be bioequivalent to the approved DRAXXIN 100 mg/ml in a GLP-compliant pharmacokinetic bioequivalence study in small pigs and that the route of administration, the dose and the duration of treatment for DRAXXIN 25 mg/ml in pigs does not change compared to the approved DRAXXIN 100 mg/ml, a new residue depletion study is not considered necessary. It is considered unlikely that the different concentrations will affect residue depletion profiles from the site of administration and, therefore, the withdrawal period of 33 days (meat and offal) can be extrapolated to DRAXXIN 25 mg/ml.

Specific potential risks:

Antimicrobial resistance:

An antimicrobial resistance assessment taking into account the evolution of the susceptibility profile over the past 10 years (since DRAXXIN was first authorised) was provided. No significant increase in resistance of target pathogens or foodborne pathogens and commensal organisms was observed in the EU and the United States of America since the launch of DRAXXIN in 2003. It is unlikely that this extension application of a lower concentration formulation (25 mg/ml) of the DRAXXIN 100 mg/ml solution for injection gives considerable rise to animal or public health concerns.

Risk management or mitigation measures

Appropriate information (as for the registered DRAXXIN 100 mg/ml solution for injection) has been included in the SPC and other product information for the new strength 25 mg/ml to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product is expected to be efficacious for the indication treatment and prevention of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae* and *Haemophilus parasuis* sensitive to tulathromycin.

The formulation and manufacture of DRAXXIN 25 mg/ml is well described and specifications set will ensure that product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. A sufficient withdrawal period has been set.

The product DRAXXIN 25 mg/ml solution for injection has been shown to have a positive benefit-risk balance overall.

Conclusion on the benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of DRAXXIN, including the new strength (25 mg/ml), are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the extension to the marketing authorisation for the above mentioned medicinal product.