Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Procapen, 300 mg/ml, Suspension for injection for cattle, pigs and horses
(BG, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IT, LV, LT, MT, NL, PL, PT, RO, SK)

Livipen, 300 mg/ml, Suspension for injection for cattle, pigs and horses
(AT, SI)

Date: 20 December 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0126/001/DC
Name, strength and pharmaceutical form	Procapen, 300 mg/ml, Suspension for injection for cattle, pigs and horses
Applicant	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany
Active substance(s)	Benzylpenicillin, procaine 1 H_2O
ATC Vetcode	QJ01CE09; Beta-lactamase sensitive penicillins
Target species	Cattle, pigs (adult pigs) and horses
Indication for use	For the treatment of bacterial infectious diseases, caused by benzylpenicillin sensitive pathogens. Cattle, calves, and horses: General bacterial infections (septicaemias) Infections of the - respiratory system - urinary and genital apparatus - skin and the claws - joints Pigs (adult pigs): Infections of the - urogenitary tract (infections with ß-haemolytic *Streptococcus spp*.) - musculoskeletal system (infections with *Streptococcus suis*) - skin (infections with *Erysipelotrix rhusiopathiae*) The use should be based on the result of an antibiogram.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the Decentralised procedure	26 May 2009
Date product first authorised in the Reference Member State (MRP only)	15 July 2009
Concerned Member States for original procedure Concerned Member States for the repeat use procedure	Denmark, Finland, Hungary, Poland, Romania, The Netherlands, Spain, Sweden Austria, Bulgaria, Czech Republic, Cyprus, Estonia, Greece, Italy, Latvia, Lithuania, Malta, Portugal, Slovakia, Slovenia

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 risk/benefit analysis is in favour of granting a marketing authorisation.
The safety aspects and with regard to the target species cattle and horse the efficacy aspects of this product are identical to Procain-Penicillin-G ad us. vet. The initial application for Procain-Penicillin-G ad us. vet. was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

II. QUALITY ASPECTS

A. Composition

The product contains Benzylpenicillin, procaine $1H_2O$ 300.00 mg/ml and Methyl-4-hydroxybenzoate 2.84 mg/ml, Propyl-4-hydroxybenzoate 0.32 mg/ml, (3-sn-Phosphatidyl)cholin (Lecithin), Povidone K 25, Sodium citrate 2 H_2O, Sodium thiosulphate 5 H_2O, Propylene glycol, Disodium edetate 2 H_2O, Potassium-dihydrogen phosphate and Water for injections.

The product is packed in 100 ml siliconised PP or glass bottles (glass type II) with a bromobutyl rubber stopper and an aluminium flip-off seal in a cardboard box.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of the preservatives are justified.

The product is an 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 from 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 Benzylpenicillin, procaine $1H_2O$, 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.

A copy of the valid CEP “Benzylpenicillin, procaine, lecithin coated (1%), sterile” has been provided by the manufacturer.

D. 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.

E. Control on intermediate products

Not applicable

F. 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.

G. 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 approved conditions.

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.

The claim of a 28 day stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at 2 - 8°C.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

The product contains qualitatively and quantitatively the same active ingredients as the reference product Procain-Penicillin G with procaine benzylpenicillin as active substance. The pharmaco- toxicological properties apply to Procapen likewise. Data on toxicological tests are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that that the risks for the user of the product are not greater compared to the reference product Procain-Penicillin G ad us.vet.
The detailed warnings of the SPC section 4.5. *Special precautions to be taken by the persons administering the veterinary medicinal product to animals* and further product literature are considered adequate to ensure safety to users of the product.

Ecotoxicity

A first phase environmental risk assessment for the target species cattle, pigs (adult pigs) and horses, led to the conclusion that the recommended use of the medicinal product does not pose a risk for the environment.

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.B Residues documentation

Residue Studies

Cattle and horse:
Procapen and the reference product “Procain-Penicillin G ad us. Vet.” are completely identically composed. The reference product “Procain-Penicillin G ad us. Vet.” is authorised for cattle and horse. Therefore, no new studies for residue depletion were provided by the applicant.

Pigs:
The applicant has conducted two new GLP-residue depletion studies in the new target species pigs. It was shown that in adult sows 11 days after treatment benzylpenicillin concentrations measured in all samples were below the MRL of 50 µg/kg and the limit of quantification (12.5 µg/kg) respectively. After adding a maximum safety span of 30% (= 3.3 days) a withdrawal period of 15 days is determined for edible tissues of pigs.

The analytical method which was used for the detection of benzylpenicillin in edible tissues of pigs was a solid phase extraction followed by a LC-method with MS/MS-detection. The method was fully validated. The LOQ of the method was estimated as 12.5 µg benzylpenicillin/kg for all tissues.

MRLs

Benzylpenicillin and Procaine are listed in Table 1 of the Annex of Commission Regulation (EU) No 37/2010 of 22 December 2009 as amended for all food producing species . The marker substance is benzylpenicillin.

MRLs are listed below:

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification
Benzylpenicillin	Benzylpenicillin	All food producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 4 µg/kg	Muscle Fat Liver Kidney Milk	For fin fish the muscle MRL relates to 'muscle and skin in natural pro-portions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which eggs are produced for human consumption.	Anti-infectious agents/Antibiotics
Procaine	Not applicable	All food producing species	No MRL required	Not applicable	No entry	No entry

All excipients are included either in Table 1 of the Annex of Commission Regulation (EU) No 37/2010 with a "No MRL required" status for all food producing species or in the "Out of scope list".

Withdrawal Periods

Based on the data provided above and comments of some CMS, the following withdrawal periods are justified:

Cattle: meat and offal: 14 days

Milk: 6 days

Horse: meat and offal: 14 days

Not permitted for use in lactating mares producing milk for human consumption.

Pigs (adult pigs): meat and offal: 15 days

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a hybrid-type application according to Article 13(3) of Directive 2001/82/EC as amended. As Procapen is identical with a product already approved for the indications related to the target species cattle and horse no target animal safety and efficacy studies are requested for the species. For the new target species “adult pig” and the indications proposed for this species new studies have been presented.

These indications are primary and secondary infections of the urogenitary tract (infections with ß-haemolytic *Streptococcus spp*.), of the musculoskeletal system (infections with *Streptococcus suis*) and of the skin (infections with *Erysipelothrix rhusiopathiae*). In pigs, Procapen has to be injected intramuscularly at daily doses of 20 mg/kg bw corresponding to 1 ml per 15 kg bw over 3 days. The injection volume to be administered per site should not exceed 10 ml.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that *in vitro* the target bacteria, such as ß-haemolytic *Streptococci spp*., *Streptococcus suis* and *Erysipelothrix rhusiopathiae* are highly susceptible to benzylpenicillin procain, the active ingredient of Procapen. This has been demonstrated in a sufficient number of bacterial strains isolated from infections in pigs in several European countries within the last decade.

Genuine pharmacokinetics studies in pigs carried out in compliance with Good Laboratory Practice (GLP) demonstrated that when administered according to the recommended treatment scheme, Procapen will provide plasma concentrations of penicillin that exceed the minimum inhibitory concentrations (MICs) of the target bacteria for the entire dosing interval.

Tolerance in the Target Species of Animals

The applicant has conducted a GLP-compliant controlled target animal tolerance study, using multiples of the recommended dose in the target species pig. A saline solution was used as a control. All doses were administered by intramuscular route on three occasions into the right or left neck.

The systemic and local tolerance of treatment was evaluated by clinical and laboratory investigation.

Minor adverse effects consisting of vomitus, coughing and small injection site swellings were seen following doses up to three times the recommended dose.

Resistance

The bibliography provided suggests that the resistance rate of the target bacteria is low. Adequate precautions that treatment should be based on susceptibility tests of isolates taken from the infection sites appear on the product literature.

IV.B Clinical Studies

The applicant provided bibliographical data, which show that benzylpenicillin procain at the dose regime proposed for Procapen is effective in the treatment of the infections claimed for pigs. In combination with the pre-clinical data the clinical data were considered sufficient to support the approval of the product for these indications.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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.

12 May 2020	Addition of a manufacturer responsible for batch release Introduction of 250 ml package size
30 October 2019	Harmonisation of the SPC, labelling and package leaflet between former and new concerned Member States after the repeat-use procedure
12 September 2019	Replacement or addition of a supplier of packaging components
13 March 2019	Repeat Use procedure
06 September 2018	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient.
23 November 2017	ASMF Update
22 February 2018	Change in the batch size (including batch size ranges) of the finished product
01 September 2015	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:
24 September 2015	Change to importer, batch release arrangements and quality control testing of the finished product
01 September 2015	Introduction of a new ASMF

18 December 2014	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product Change to importer, batch release arrangements and quality control testing of the finished product
26 July 2013	Change in immediate packaging of the finished product
23 April 2013	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:
17 October 2012	Change(s) to an existing pharmakovigilance system as described in the detailed description of the pharmakovigilance system
25 February 2010	Change in pack size of the finished product
22 October 2009	Addition of a new API manufacturer