

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Carprofen Norbrook 50 mg/ml solution for injection for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0612/001/DC
Name, strength and pharmaceutical form	Carprofen Norbrook 50 mg/ml solution for injection for cattle
Active substance(s)	Carprofen
Applicant	Norbrook Laboratories Ireland Limited Rossmore Industrial Estate Monaghan
Legal basis of application	Generic application in accordance with Article 18 of Regulation (EU) 2019/6.
Date of completion of procedure	17/12/2025
Target species	Cattle
Indication for use	This product is indicated as an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle.
ATC vet code	QM01AE91
Concerned Member States	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HR, IT, NL, NO, PT, RO, SI, SK, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 the relevant articles of Regulation (EU) 2019/6. 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, 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 50 mg/ml carprofen and the excipients ethanol anhydrous, sodium formaldehyde sulphonylate, macrogol 600, macrogol 40000, arginine, sodium hydroxide and water for injections.

The container/closure system is a 50 ml multidose amber type I glass vial with 20 mm bromobutyl rubber stopper and 20 mm aluminium seals in a cardboard box

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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is carprofen, 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 has 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 has been provided.

Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has 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)

This application for 'Carprofen Norbrook 50 mg/ml solution for injection', containing the active substance carprofen, was submitted in accordance with the requirements of Article 18 of Regulation (EU) 2019/6 (that is, a generic application). The reference product cited is 'Rimadyl Cattle 50 mg/ml Solution for Injection' (IE/V/0140/001) which is authorised through the decentralised procedure and is accepted as a suitable reference product.

Waivers from bioequivalence study requirements (to demonstrate *in vivo* bioequivalence) were claimed based on compliance with the conditions set out in sections 7.1.a) and b) of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4) for the intravenous and subcutaneous routes of administration respectively.

The claim for exemption from conducting an *in vivo* bioequivalence study for the intravenous route of administration was accepted, based on fulfilment of the criteria set out under Section 7.1 a) of the bioequivalence guideline.

Regarding compliance with the conditions set out under Section 7.1 b) of the aforementioned guideline, the candidate product and the reference product are of the same qualitative and quantitative composition in terms of the active substance. The candidate product is of the same pharmaceutical form (solution for injection), is intended to be used for the same indications, in the same target species, via the same routes of administration and same posology as the reference product. The results of an *in vivo* bioequivalence study were provided which were considered suitably supportive to demonstrate that the difference in excipient profiles between the candidate and reference product does not influence the rate and /or extent of absorption of the active substance. Based on the totality of the data presented, bioequivalence between the candidate and reference product formulations was also accepted for the subcutaneous route of administration.

As this is a generic application (according to Article 18), and bioequivalence with a reference product has been accepted, results of safety tests are not required. The safety aspects of this product are identical to the reference product.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III. SAFETY ASSESSMENT

III.A Safety Testing

Pharmacological Studies

As this is a generic application (according to Article 18), and bioequivalence with the reference product has been accepted, results of pharmacological tests are not required. See Part IV for assessment of the *in vivo* bioequivalence study provided.

Toxicological Studies

As this is a generic application (according to Article 18), and bioequivalence with a reference product has been accepted, results of toxicological tests are not required. However, in support of this application an overview of the toxicological profile of carprofen as available from bibliographic data, in addition to proprietary toxicological studies, was presented.

The pharmacological and toxicological data on the active substance were reviewed previously by the CVMP in the context of an application to establish an MRL. Based on those data, carprofen is listed in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010, indicating that the product has been approved for use in food-producing species. The CVMP concluded that carprofen has low toxic potential following single (acute) administration. The oral LD₅₀ in mice was determined to be 282 mg/kg and in rats 149mg/kg. A NOEL of 1 mg/kg/bw/day was established based on a 2 year oral toxicity study in rats. An ADI of 0.01 mg/kg (0.6 mg/person) was thus established using a safety factor of 100. The CVMP also concluded that carprofen is not considered to be teratogenic, foetotoxic, carcinogenic or mutagenic. The data provided by the applicant support the conclusions of the CVMP summary report.

User Safety

A brief user safety assessment was provided. It is accepted that the candidate product does not pose any greater risk to the user than the reference product, and as such, the user safety warnings as accepted by CVMP for the reference product may also be considered applicable for 'Carprofen Norbrook 50 mg/ml solution for injection.'

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, as follows:

'Carprofen, in common with other NSAIDs, has been shown to exhibit photosensitising potential in laboratory studies. Avoid skin contact with the veterinary medicinal product. Should this occur, wash the affected areas immediately.

Administer the veterinary medicinal product with caution to avoid accidental self-injection. In case of accidental self-injection, seek medical advice and show the package leaflet or the label to the physician.'

Environmental Risk Assessment

Phase I

An environmental risk assessment that is compliant with relevant guidance was submitted. The environmental risk assessment can stop in Phase I, and no Phase II assessment is required because the VMP is intended for use in individual animals.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies

A GLP-compliant residue depletion study was conducted using the final formulation as intended for marketing. Samples of tissues were taken from animals at several time points (4 animals per time point) following administration of the product in accordance with the recommended dosing regimen. Quantifiable residues were not detected in any tissues (including injection site) sampled 7 to 21 days following administration of the product.

The proposed meat withdrawal period of 21 days is therefore considered acceptable and also in line with that approved for the reference product.

The analytical method was HPLC with UV detection. The method was fully validated.

A milk residue study was not conducted. However, based on available data, bioequivalence (when administered by either the subcutaneous or intravenous routes) with the authorised reference product, 'Rimadyl Cattle 50 mg/ml Solution for Injection', is accepted. Consequently, it can be accepted that depletion from milk will be similar for both products and that the zero day

milk withdrawal period for the reference product can also be applied to the 'Carprofen Norbrook 50 mg/ml solution for injection.'

Maximum Residue Limits (MRLs)

The active substance carprofen (marker residue: "Sum of carprofen and carprofen glucuronide conjugate") is listed in Table 1 of the Annex to Commission Regulation (EU) No. 37/2010 with the following MRLs for bovines:

Muscle – 500 µg/kg

Fat, liver and kidney – 1000 µg/kg

Milk – "No MRL required"

The MRL status of the excipients of the product 'Carprofen Norbrook 50 mg/ml solution for injection' is indicated in the following table:

Qualitative composition of excipients and other constituents	MRL status
Ethanol anhydrous	Table 1, no MRL required
Sodium formaldehyde sulfoxylate (SFS)	Table 1, no MRL required
Macrogol 600	Table 1, no MRL required
Macrogol 4000	Table 1, no MRL required
Arginine	Table 1, no MRL required
Sodium Hydroxide (E 524)	Table 1, no MRL required

The excipients are approved as additives in foodstuffs for human consumption and are therefore allowed substances for which Table I of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required.

Withdrawal Periods

Meat and offal: 21 days.

Milk: Zero days.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 18, and bioequivalence with a suitable reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

In order to demonstrate that any difference in formulation between the candidate and reference products does not influence the rate and/or extent of absorption of the active substance, a GLP-compliant *in vivo* bioequivalence study was presented. The reference product used in the study was 'Rimadyl Large Animal Solution.' The choice of reference product used was sufficiently justified through the provision of additional information, including the results of physicochemical analysis. Plasma concentrations of carprofen were measured following single administration of the candidate and reference items to cattle by the subcutaneous route at a dose of 1.4 mg carprofen/kg bodyweight, with blood samples collected at appropriate timepoints.

The results of this study indicated that the 90 % confidence intervals for the test to reference mean ratio of C_{max} and AUC_t for carprofen fell within the pre-defined acceptance criteria for C_{max} and AUC_t .

The bioequivalence study was considered suitably supportive to demonstrate that any differences in formulation between the candidate and reference products should not influence the rate and/or extent of absorption of the active substance.

No data were provided to characterise the pharmacokinetic profile of the test product following intravenous administration to cattle at the recommended treatment dose of 1.4 mg carprofen/kg. The absence of pharmacokinetic data following intravenous use in cattle was accepted based on the biowaiver claimed under section 7.1.a) of the bioequivalence guideline.

Tolerance in the Target Species of Animals

As this is a generic application (according to Article 18), and bioequivalence with a reference product has been accepted, results of target animal safety tests are not required. Notwithstanding the legal basis of the application, the applicant presented a literature review and carried out two GLP compliant target animal safety studies in cattle (the proposed target

species), following administration of the veterinary medicinal product either subcutaneously or intravenously at the maximum recommended dose rate (1.4 mg/kg bw) at three times the maximum recommended dose rate (4.2 mg/kg bw) by the recommended subcutaneous or intravenous routes of administration once daily for two consecutive days. It was concluded that, when administered at the proposed recommended single dose rate of 1.4 mg carprofen/kg bodyweight intravenously, 'Carprofen Norbrook' is well tolerated in cattle. The veterinary medicinal product is well tolerated systemically when administered by the intravenous or subcutaneous route at up to three times the recommended treatment dose on two occasions with a between treatment interval of 24 hours.

Based on proprietary data presented, it is noted that the product may cause mild, transient swelling at the injection site after subcutaneous injection – a statement to this effect has been included in the SPC.

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

IV.B Clinical Studies

No proprietary data were submitted. As this is a generic application (according to Article 18), and bioequivalence with a reference product has been accepted, results of efficacy tests are not required.

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.