4 December 2025
EMA/CVMP/330013/2025 Corr.1[1]
Veterinary Medicines Division

Opinion and EPMAR of the Committee for Veterinary Medicinal Products on the establishment of maximum residue limits

Procedure no: EMEA/V/MRL/003649/MODF/0004

Name of the substance: Lidocaine (INN)

Basis for the opinion

Pursuant to Article 3 of Regulation (EC) No 470/2009, Scanvet Animal Health A/S submitted to the European Medicines Agency, on 9 February 2024, an application for the modification of the maximum residue limits for lidocaine in porcine.

On 18 July 2024, the Committee for Veterinary Medicinal Products adopted a list of questions to be addressed by the applicant. The response to the list of questions was submitted to the CVMP on 28 November 2024.

On 15 May 2025, the Committee for Medicinal Products for Veterinary Use adopted an opinion recommending by consensus the modification of maximum residue limits for lidocaine to include a provisional 'No MRL required' status in porcine with restrictions to the route of administration and the time until slaughter.

On 5 June 2025, the European Commission requested the Committee to reconsider its opinion of 15 May 2025, as a classification of 'provisional No MRL required' is not foreseen in Article 14(2) of Regulation (EC) No 470/2009.

Recommendation

The Committee, having considered the application, having evaluated the responses submitted by the applicant, and having considered the request from the Commission, recommends, by consensus, the modification of maximum residue limits for lidocaine in porcine, in accordance with the following table:

[1] The unit for the numerical MRL for bovine fat tissue in the MRL tables was corrected to read µg/kg instead of g/kg.

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Lidocaine	NOT APPLICABLE	Equidae	No MRL required	NOT APPLICABLE	For local/regional anaesthesia only.	Local anaesthetic
		Porcine	No MRL required	NOT APPLICABLE	For cutaneous and epilesional use in piglets up to 7 days of age only. For injection into scrotum, testicles and spermatic cord in piglets up to 7 days of age only.	
	Lidocaine	Bovine	150 µg/kg 200 µg/kg 1 µg/kg 200 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk	NOT APPLICABLE	

The Norwegian CVMP member agrees with the above-mentioned recommendation of the Committee.

The scientific conclusions of the Committee are presented in the revised European public MRL assessment report (EPMAR), provided in Annex I of this opinion.

The present opinion is forwarded to the European Commission and to the applicant together with its appendices.

Annex I

European public MRL assessment report (EPMAR)

Lidocaine (porcine)

Summary of the scientific discussion for the establishment of MRLs

Substance name:	Lidocaine
Therapeutic class:	Local anaesthetic
Procedure number:	EMEA/V/MRL/003649/MODF/0004
Applicant:	Scanvet Animal Health A/S
Target species:	Porcine
Intended therapeutic indication:	Local anaesthesia
Route(s) of administration:	Injection

1. Introduction

Lidocaine is a local anaesthetic of the amino-amide type. It induces local pain relief by preventing signal transmission in neuronal cells through the inhibition of voltage-gated sodium channels. In veterinary medicine, lidocaine is authorised for use in companion animals, horses and calves. Lidocaine is also authorised as a local anaesthetic for human use.

The aim of the present application is to modify the currently established 'Other provisions' for porcine species by removing the restriction on the route of administration ('For cutaneous and epilesional use only'), to allow for the administration of lidocaine via the injection route in piglets for pain relief prior to castration.

Lidocaine was previously assessed by the CVMP and an overall (toxicological) ADI of 0.1 mg/kg bodyweight (bw)/day, i.e. 6 mg/person/day, was established as well as an acceptable exposure level of 1728 µg/person/day for 2,6-xylidine (also known as 2,6-dimethylanaline or 2,6-DMA).

Currently, lidocaine is listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 with the following specifications:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Lidocaine	NOT APPLICABLE	Equidae	No MRL required	NOT APPLICABLE	For local/regional anaesthesia only.	Local anaesthetic
		Porcine			For use in piglets up to 7 days of age only.	

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
					For cutaneous and epilesional use only.	
	Lidocaine	Bovine	150 µg/kg 200 µg/kg 1 µg/kg 200 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk	NOT APPLICABLE	

Based on the evaluation of the data submitted by Scanvet Animal Health A/S, the Committee adopted an opinion on 15 May 2025, recommending the modification of maximum residue limits for lidocaine to include a provisional 'No MRL required' status in porcine with restrictions to the route of administration and the time until slaughter. On 5 June 2025, the European Commission requested the Committee to reconsider its opinion, as a provisional classification of 'No MRL required' does not align with the classifications foreseen in Article 14(2) of Regulation (EC) No 470/2009.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of lidocaine and established an ADI of 0.1 mg/kg bw/day, i.e. 6 mg/person/day, based on the systemic NOAEL of 1 mg/kg/day in human subjects and applying a 10-fold factor for individual variation. The CVMP also established an acceptable exposure level of 1728 µg/person/day for 2,6-xylidine, a genotoxic metabolite, based on a $BMDL_{10\ corrected}$ range of 28.8–46.8 mg/kg bw/day from a carcinogenicity study, and using an interspecies factor of 10, an intraspecies factor of 10 and a 'severity of effect and data quality' factor of 10. No further assessment regarding the consumer safety of the substance is required for the purpose of this modification application.

2.2. Residues assessment

In May 2022, the applicant received scientific advice from the CVMP on the intended approach, the planned residue depletion study, and the protocol for fulfilling the requirements for this application.

The applicant provided a residue depletion study in the target animal species in accordance with the scientific advice received. The estimation of 4-OH-xylidine residues was also taken into account, as 4-OH-xylidine is considered to be a precursor of the genotoxic metabolite 2,6-xylidine.

2.2.1. Pharmacokinetics in target species

No study on the pharmacokinetics of lidocaine has been provided with the current application. Instead, the applicant makes reference to the pharmacokinetic data stated in the EPMAR published following the conclusion of the initial MRL application (EMA/CVMP/393160/2020).

In target animals, i.e. piglets up to 7 days of age, after topical administration of lidocaine, the parent compound and its metabolites were detected in plasma, faeces and urine until 24 hours post treatment. In plasma, the main analyte found was the parent compound followed by lidocaine-*N*-oxide and 2,6-xylidine. After 7 days of treatment, only the parent compound, monoethylglycinexylidide, lidocaine-*N*-oxide and glycinexylidide were detected.

In urine, the parent compound and the metabolites 3-OH lidocaine, monoethylglycinexylidide and lidocaine-*N*-oxide were found in high concentrations. Glycinexylidide and 2,6-xylidine were also found until 7 days and 24 hours, respectively.

In faeces, the pattern of excretion of lidocaine and its metabolites was similar to that seen in urine albeit in lower amounts.

Metabolism following injection is expected to be qualitatively similar to that after epilesional use, and there is not considered to be a need to investigate the presence of other metabolites than those already identified.

2.2.2. Residue depletion studies

Depletion in tissues

No radiometric residue depletion studies were submitted with the current application. The applicant provided results from one residue depletion study in edible tissues of piglets following injection of 'Lignovet 19 mg/ml' in order to demonstrate the residue depletion of lidocaine, 2,6-xylidine, monoethylglycinexylidide (MEGX), glycinexylidide (GX), 3-OH lidocaine (3-OH-LIDO) and lidocaine-*N*-oxide (LIDO-*N*-oxide). Residues of 4-OH-xylidine were estimated using the same approach as taken in the original application (based on literature data, 4-OH-xylidine was conservatively estimated to be present at levels equivalent to 20% of the levels of 2,6-xylidine).

In this study, 32 piglets up to 7 days of age prior to castration, were administered lidocaine by injection into the scrotum, testicles and spermatic cord. The dose volume was 0.5 ml per testicle (i.e. 20 mg lidocaine per piglet). Sixteen piglets were used for tissue analysis and were sacrificed at 12, 18, 24 and 48 hours after treatment.

Peak level residues of lidocaine and 2,6-xylidine were found at 12 hours after treatment. For lidocaine, the maximum values observed were 10.9, 9.19, 6.04 and 67.3 µg/kg in liver, kidney, muscle and skin/fat, respectively, while the maximum values observed for 2,6-xylidine were 107, 160, 149 and 906 µg/kg in liver, kidney, muscle and skin/fat, respectively. These residues decreased over the sampling points but still remained above the limit of quantification (LOQ; 0.2 µg/kg) at 48 hours after treatment. In muscle, liver and kidney, residues of MEGX, 3-OH lidocaine, GX and lidocaine-*N*-oxide were all below the LOQ/limit of detection (LOD; 0.2/0.07 µg/kg) at 48 hours after treatment. In skin/fat, residues of MEGX were above the LOQ (0.2 µg/kg) at all timepoints sampled, while 3-OH lidocaine, GX and lidocaine-*N*-oxide were found in quantities below the LOQ/LOD (0.2/0.07 µg/kg) at 48 hours after treatment. However, data relating to the stability of lidocaine residues during storage are inadequate, raising concerns over the reliability of these results (see section 2.2.4. 'Analytical method for measurement of residues' below).

Following the European Commission's June 2025 request to reconsider its opinion of 15 May 2025, the CVMP took account of information that had not previously been available.

Notably, in a new study, eight piglets up to 7 days of age were administered lidocaine by injection into the scrotum, testicles and spermatic cord prior to castration. A maximum volume of 0.5 ml of

lidocaine was applied (i.e. 1 ml per piglet), which translates to 10 mg lidocaine per testicle or 20 mg per piglet. The testicles were removed after 5 minutes, frozen and analysed for lidocaine content. Hence, the amount of remaining lidocaine in the piglet was calculated. The mean removed amount of lidocaine was 4.521 mg/piglet, so the systemically available dose estimated is 15.479 mg lidocaine per piglet after castration. The analytical method and the analytical laboratory were the same as for the original MRL application for lidocaine in porcine. As the analytical method was not previously validated for determination of residues in testes, limited validation data were generated to demonstrate its applicability in this tissue. The LOQ was determined to be 10 mg/kg. A two-week stability study confirmed that lidocaine is stable for at least two weeks at -18 °C, at the 500 mg/kg level.

Selection of marker residue and ratio of marker to total residues

The applicant applies for a 'No MRL required' classification and does therefore not propose a marker residue or a ratio of marker to total residues.

2.2.3. Monitoring or exposure data

No monitoring or exposure data were available.

2.2.4. Analytical method for measurement of residues

The analytical method and the analytical laboratory are the same as in the original MRL application for lidocaine (porcine) already assessed by the CVMP. The final determination of the residues is via reversed phase Ultra-High Performance Liquid Chromatography (UHPLC) with tandem mass spectrometry (MS/MS). Two different chromatography conditions were used, i.e. one for lidocaine, MEGX, 3-OH lidocaine and lidocaine *N*-oxide and one for 2,6-xylidine and GX. In the initial application, the applicant provided a validation report describing both chromatographic methods.

The method was developed and validated for the determination of residues of lidocaine and its metabolites in porcine tissues. The method was presented in an internationally recognised format and has been validated in line with the current requirements of Commission Regulation (EU) 2018/782.

Within the present application, the method was successfully newly validated for residues of lidocaine and its metabolite residues in porcine tissues at the LOQ of 0.2 µg/kg per analyte. The linearity has been shown with good correlation coefficients for concentrations from 0.06 to 40 µg/kg in porcine tissues and, where necessary, dilutions were performed. The applicant has provided information on the sample dilutions from the analysing laboratory. With regard to selectivity, quantitation and procedural recovery data, the analytical method was suitable for the measurement of residues in the samples of the residue depletion study.

According to the applicant, the maximum storage interval for porcine tissues at approximately -18 °C from sampling to extraction was 321 days in the current application, while long-term freezing stability was only demonstrated for 50 days for liver, 49 days for kidney, 48 days for muscle and 47 days for fat in the validation report of the initial MRL application. The applicant has provided literature data to justify the stability of lidocaine, but these data only refer to lidocaine in solutions and formulations. No data has been provided demonstrating the stability of lidocaine in biological matrices relevant for the current procedure. Furthermore, these data do not cover the 321-day storage period reported in the submitted dossier and no information on the stability of lidocaine metabolites has been provided. Therefore, the applicant has calculated correction factors

accounting for the potential degradation of analytes during the storage period, as described in section 3.2. ('Elaboration of MRLs') below.

2.2.5. Potential effects on the microorganisms used for industrial food processing

The substance is not intended for use in dairy animals and therefore potential effects in dairy products were not investigated.

2.2.6. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

3. Risk management recommendations

3.1. Availability of alternative medicines and other legitimate factors

Availability of alternative medicines

The intended use of lidocaine in porcine species is for local anaesthesia during and after castration of piglets. This would result in a potentially wide use in a major species.

There are limited options available which can be used for anaesthesia/treatment of pain associated with the castration of piglets. These include lidocaine for cutaneous and epilesional use, other local anaesthetic products for injection, anaesthetic products for inhalation and NSAIDs.

Technological aspects of food and feed production (potential effects on the microorganisms used for industrial food processing)

Piglet meat is not further processed to food or feed products using microorganisms.

Conditions of use

In its opinion of 15 May 2025, the CVMP considered that the use of lidocaine needs to be restricted to piglets up to 7 days of age because available data indicate that older pigs metabolise the substance in question more extensively, potentially resulting in higher concentrations of 2,6-xylidine. No numerical MRLs are needed when used as proposed for this category of animals, and no dose restriction is considered necessary, since there is a large margin of safety when estimating the residues in tissues.

However, since no residues data is available for other routes of administration (i.m./i.v./s.c.), no MRL recommendation can be made for injection routes other than those assessed within the current application. Besides, in view of the deficiencies already highlighted concerning the sample storage stability, the CVMP initially deemed it appropriate to put in place the following restriction: 'Not for use in animals intended for slaughter within 50 days'. Given the known rapid metabolism of lidocaine and its residues, this additional restriction provided ample assurance that residues will remain at safe levels.

However, following the European Commission's June 2025 request to reconsider its opinion of 15 May 2025, the CVMP took account of an additional study, in which lidocaine was administered by injection into the scrotum, testicles and spermatic cord of piglets up to 7 days of age. Based on this, the above-mentioned restriction (i.e. 'Not for use in animals intended for slaughter within 50 days') is not considered necessary anymore (see section 3.2. 'Elaboration of MRLs' below for details). It was noted by the applicant that, by this route, no more than 20% of the original dose (20 mg/kg vs 100 mg/kg) was necessary to achieve the required effect.

Other factors that should, if applicable, be taken into consideration in support of the MRL recommendation:

No other relevant factors were identified for consideration of the risk management recommendations.

3.2. Elaboration of MRLs

In its opinion of 15 May 2025, the CVMP considered the following:

The toxicological ADI of 0.1 mg/kg bw per day or 6 mg/person per day is considered to be the overall ADI to be used for the consumer risk assessment of lidocaine. It is considered appropriate to reserve 20% of the ADI for future uses of the substance that could result in residues in other food commodities, particularly in milk. Consequently, the maximum amount of lidocaine that can be accepted in relation to residues in tissues is 4.8 mg/person/day. Using the same reasoning, the maximum acceptable amount of the genotoxic metabolite 2,6-xylidine that may be present in edible porcine tissue is calculated to be 1382 µg/person per day (worst-case scenario). For the consumer residues intake estimation, the maximum values of the residue concentrations obtained in the residue depletion study are used. Total intake of residues (lidocaine plus all analysed metabolites plus 20% of 2,6-xylidine to account for the estimated portion of 4-OH-xylidine) has been estimated and compared to the acceptable amount of lidocaine in tissues (i.e. 4.8 mg/person/day) and, on the other hand, the risk assessment of the metabolite 2,6-xylidine has been done considering the acceptable exposure limit established for that substance (i.e. 1382 µg/person per day).

However, no information was provided on the long-term stability of the analytes. Therefore, the obtained residue values cannot be considered to be reliable since it has not been demonstrated that, at the time of analysis, the analytes were in fact not degraded. Thus, in order to account for the potential degradation of the analytes, the applicant presented correction factors, which were only applied to the residue of most concern, i.e. 2,6-xylidine. No correction factors were applied to the measured levels of the remaining metabolites. This was considered acceptable due to the low amount of these metabolites compared to the total residues intake (see Table 1 for details).

The applicant considered two different scenarios: (i) 12 mg of lidocaine remain in the piglet for systemic distribution after the removal of both testicles (this figure is based on the amount of the administered product that was estimated to be retained in the removed testicles); (ii) the whole dose of 20 mg lidocaine is distributed systemically. For the purpose of the elaboration of MRLs, only the latter scenario was considered by the CVMP and is hence described below. The applicant compared the total amount of 2,6-xylidine measured in liver, kidney, muscle and skin/fat at 12 hours with the amount of 2,6-xylidine that would be in the systemic circulation if the entire dose of circulating lidocaine were transformed into 2,6-xylidine. This yielded a correction factor that accounted for both the degradation of samples during storage, and metabolism and elimination in the target animal. The correction factor was then refined by adjusting it to take account of the amount 2,6-xylidine estimated to have been eliminated through metabolism and elimination in the

target animal. This was done using a calculated mean half-life for 2,6-xylidine of 3 hours.

Under the assumption that the entire systemically distributed dose of lidocaine is transformed to 2,6-xylidine, a correction factor of 78.1 was obtained when considering the systemic distribution of 20 mg lidocaine. When additionally refining this value by considering tissue half-life, a factor of 4.88 was obtained.

Therefore, considering the maximum values obtained from the residues depletion study and the correction factor derived based on the assumption that the entire 20 mg of administered lidocaine are systemically available, the intake of residues including lidocaine and metabolites (expressed as lidocaine equivalents) at 12 hours was calculated as 643.69 µg/person/day (see **Table 1** for details), based on the standard food basket. This would account for 13.42% of the proportion of the portion of ADI that can be accepted for lidocaine residues in tissues (4.8 mg/person/day). Detailed calculations are shown in **Table 1**.

Table 1: Estimated lidocaine residues intake (expressed as lidocaine equivalents) 12 hours after administration.

Analyte/ edible tissue	**Liver** (measured)	**Kidney** (measured)	**Skin/fat** (measured)	**Muscle** (measured)	**Daily consumption (µg/person/day)**
Lidocaine	10.9	9.19	67.3	6.04	6.7265
MEGX	0.07	0.082	1.34	0.15	0.1231
GX	0.218	0.326	0.489	0.193	0.12045
3-OH-lidocaine	0.079	0.504	0.162	0.07	0.0622
Lidocaine-*N*-oxide	0.645	0.243	0.198	0.07	0.10755
2,6-xylidine	107	160	906	149	108.7 x 4.88 = 530.4 56 (corrected value)
Sum of residues intake excluding 4-OH-xylidine					537.60
Estimated 4-OH-xylidine intake (20% of 2,6-xylidine)					106.09
Total residues intake					643.69
Fraction of 80% of the ADI for lidocaine (0.644/4.8)					13.42%

For the risk assessment of the carcinogenic metabolite 2,6-xylidine, it was assumed that the proportion of lidocaine (and metabolites) that could give rise to 2,6-xylidine via metabolism in humans is 50% (each mole of lidocaine may maximally produce one mole of 2,6-xylidine). Based on molecular weights, each mg of lidocaine exposure may thus maximally produce 0.5 mg 2,6-xylidine via metabolism in humans. Therefore, half the intake of 'lidocaine and metabolites' (3.57 µg/person/day) was added to the intake of 2,6-xylidine estimated in the relevant tissues (530.46 µg/person/day) and the estimated intake of 4-OH-xylidine (106.09 µg/person/day). The resulting total potential human exposure was 640.12 µg/person/day, which represents 46.32% of the 80% acceptable exposure limit for 2,6-xylidine (1382 µg/person/day) at 12 hours after treatment. Detailed calculations are shown in **Table 2**.

Table 2: Estimated intake of residues giving rise to 2,6-xylidine (expressed as lidocaine equivalents) 12 hours after administration.

Analyte	Daily consumption (µg/person/day)
Lidocaine	6.7265
MEGX	0.1231
GX	0.12045
3-OH-lidocaine	0.0622
Lidocaine-*N*-oxide	0.10755
Sum of residues intake excluding 2,6-xylidine and 4-OH-xylidine	7.1333
50% of total lidocaine and metabolites excluding 2,6-xylidine and 4-OH-xylidine	3.56665
Estimated 2,6-xylidine intake	108.7 x 4.88 = 530.456 (corrected value)
Estimated 4-OH-xylidine intake (20% of 2,6-xylidine)	106.09
Total residues intake	640.12
Fraction of 80% of the acceptable exposure limit for 2,6-xylidine (640.12/1382)	46.32%

Using the same approach, the fraction of 80% of the acceptable exposure limit for 2,6-xylidine was estimated to be 34.19% 24 hours after administration.

Overall, considering the above estimations, the proposed injection into the scrotum, testicles and spermatic cord of 1 ml 'Lignovet 19 mg/ml' per piglet was shown to lead to residue levels that remain at safe levels (below 80% of the ADI for lidocaine and below the acceptable exposure level of 1382 µg/person/day for 2,6-xylidine) in relevant tissues 12 and 24 hours after administration, respectively, even if the worst-case assumptions (i.e. the entire 20 mg dose is available for systemic circulation combined with maximum measured levels of residues) are considered, representing a substantial margin of safety.

However, the correction factors proposed were based on theoretical considerations and data to demonstrate their suitability were not available. No stability data were submitted for the 321-day storage period and stability of the analytes in tissues should have been demonstrated as part of the validation of the analytical method, and to demonstrate the suitability of the correction factors. In view of these deficiencies, it was considered appropriate to include an additional safety provision, i.e. that treated piglets should not be slaughtered within 50 days of treatment.

Therefore, although no stability data were available, and considering all the information available, it was concluded that there would be no risk for consumers when lidocaine is used in piglets up to 7 days of age that are not intended for slaughter within 50 days after treatment. Thus, a provisional recommendation was made to keep the current restriction (i.e. 'for use in piglets of up to 7 days of age only'), and to include both the new route of administration as well as a restriction pertaining to the time to slaughter in the 'Other provisions' section while maintaining the 'No MRL required' status. The missing stability data were to be generated and provided in order to definitively modify the entry for lidocaine in Table 1 of the Annex to Commission Regulation (EU) 37/2010. The CVMP considered that these data would have possibly allowed for the removal of the restriction to animals not intended for slaughter within 50 days. The provisional MRL provisions were proposed to expire on 31 December 2027.

Following the European Commission's June 2025 request to reconsider its opinion of 15 May 2025, the CVMP took account of information that had not previously been available (see section 2.2.2. 'Residue depletion studies' for details)

Based on this new information, the applicant proposed to refine the correction factor that accounted for the degradation of samples during storage. Considering the new systemically available dose estimated (15.479 mg lidocaine/piglet), and the same approach as detailed above, a correction factor for storage degradation of 3.78 was derived.

Considering the maximum values obtained from the residues depletion study and the new correction factor, the intake of residues including lidocaine and metabolites (expressed as lidocaine equivalents) at 12 hours is calculated as 500.21 µg/person/day (418.03 + 82.18; see the **Table 3** for details), based on the standard food basket, which corresponds to 10.42% of the proportion of the ADI that can be considered in relation to lidocaine in tissues (4.8 mg/person/day). Detailed calculations are shown in **Table 3**.

Table 3: New estimated lidocaine residues intake (expressed as lidocaine equivalents) 12 hours after administration.

Analyte/edible tissue	Liver	Kidney	Skin/fat	Muscle	Daily consumption (µg/person/day)
Lidocaine	10.9	9.19	67.3	6.04	6.7265
MEGX	0.07	0.082	1.34	0.15	0.1231
GX	0.218	0.326	0.489	0.193	0.12045
3-OH-lidocaine	0.079	0.504	0.162	0.07	0.0622
Lidocaine-*N*-oxide	0.645	0.243	0.198	0.07	0.10755
2,6-xylidine	107	160	906	149	108.7 x 3.78 = 410.89 (corrected value)
Sum of residues intake excluding 4-OH-xylidine					418.03
Estimated 4-OH-xylidine intake (20% of 2,6-xylidine)					82.18
Total residues intake					500.21
Fraction of 80% of the ADI for lidocaine (0.500/4.8)					10.42%

For the risk assessment of the carcinogenic metabolite 2,6-xylidine, the same assumptions as outlined above apply. The resulting total potential human exposure is 496.63 µg/person/day, which represents 35.9% of the 80% acceptable exposure limit for 2,6-xylidine (1382 µg/person/day) at 12 hours after treatment. Detailed calculations are shown in **Table 4**.

Table 4: Estimated intake of residues giving rise to 2,6-xylidine (expressed as lidocaine equivalents).

Analyte	Daily consumption (µg/person/day)
Lidocaine	6.7265

MEGX	0.1231
GX	0.12045
3-OH-lidocaine	0.0622
Lidocaine-*N*-oxide	0.10755
Sum of residues intake excluding 2,6-xylidine and 4-OH-xylidine	7.1333
50% of total lidocaine and metabolites excluding 2,6-xylidine and 4-OH-xylidine	3.56665
Estimated 2,6-xylidine intake	108.7 x 3.78 = 410.89 (corrected value)
Estimated 4-OH-xylidine intake (20% of 2,6-xylidine)	82.18
Total residues intake	496.63
Fraction of 80% of the acceptable exposure limit for 2,6-xylidine (496.63/1382)	35.90%

The applicant also provided an estimation of a theoretical worst-case exposure scenario in order to support the new corrected calculations. In this scenario, it is assumed that the entire available lidocaine dose is metabolised into 2,6-xylidine and distributed between the edible tissues at 12 hours after administration, with calculations performed using the relative tissue distribution at 12 hours seen in the residue depletion study. The available lidocaine dose is 15,479 µg, which corresponds to 8,004 µg 2,6-xylidine. In order to obtain the concentrations at 12 hours after administration, a half-life of 3 hours is used. Detailed calculations are shown in **Table 5**.

Table 5: Estimated intake of 2,6-xylidine considering a theoretical worst-case scenario.

Tissue	Relative tissue distribu-tion at 12 h (2,6-xylidine)	Amount per organ (µg)	Organ weight in piglet (kg)	Concent-ration in organ at 0 h (µg/kg)	Concent-ration in organ at 12 h (µg/kg)	Food basket (kg/person/day)	Consumer intake (µg/person/day)
Liver	0.09	720	0.0973	7399.8	462.5	0.1	46.2
Kidney	0.15	1201	0.0217	55345.6	3459.1	0.05	173.0
Skin/ fat	0.61	4882	0.223	21892.4	1368.3	0.05	68.4
Muscle	0.15	1201	1.376	872.8	54.6	0.3	16.4
Sum	1	8004	1.718			0.5	304.0

From these worst-case calculations it can also be concluded that consumer safety is ensured, since the consumer intake of 2,6-xylidine equals to 304 µg/person/day, which represents 21.99% of the 80% acceptable exposure limit for 2,6-xylidine (1382 µg/person/day) at 12 hours after treatment.

In conclusion, the additional data enables the estimation of the remaining lidocaine dose in the piglet after castration. These additional data allow the refinement of the correction factor to account for the potential loss of residues during storage. The new calculations provided result in large margins of safety for consumer exposure to lidocaine and 2,6-xylidine residues, using the maximum residue values obtained in the animal study, as do the calculations performed with the full dose of 20 mg lidocaine per piglet (see **Table 1** and **2** for details). Therefore, a new residues depletion study is not deemed necessary. It is also noted that administration by injection into scrotum, testicles and spermatic cord achieves the required anaesthetic effect with only 20% of the dose used for cutaneous and epilesional administration. No dose restriction is considered necessary since there is a large margin of safety when estimating the consumer exposure even when maximum residue values are used.

Overall, considering all the information provided, it can be concluded that there is no risk for the consumer when lidocaine is used by injection into scrotum, testicles and spermatic cord in piglets up to 7 days of age. Thus, a recommendation can be made to maintain the current restriction for lidocaine in relation to porcine listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 ('For cutaneous and epilesional use in piglets up to 7 days of age only') and to further add the new route of administration of lidocaine for porcine (notably 'For injection into scrotum, testicles and spermatic cord in piglets up to 7 days of age only'). With the additional data demonstrating that a portion of the administered drug is removed with the testicles and so does not enter the wider systemic circulation, the previously proposed provision 'Not for use in animals intended for slaughtered within 50 days' is no longer considered necessary.

Injection Site Residues Reference Value (ISRRV)

In accordance with the scientific advice from the CVMP, the scrotal tissue, testicles and the spermatic cord are not considered to be edible tissue and thus the establishment of an ISRRV is not considered necessary.

4. Considerations on possible extrapolation of MRLs

In the frame of the initial MRL application, the CVMP considered the possibility of extrapolating the maximum residue limits established for lidocaine on the basis of residue data in piglets, to other food-producing species, in line with Article 5 of Regulation (EU) No 470/2009. However, since it was demonstrated that lidocaine can be metabolised to different extents in pigs of different ages and can be metabolised to a genotoxic metabolite, extrapolating the MRL recommendation to species other than pigs was considered to be associated with excessive uncertainty and thus could not be recommended.

For the current application, no new studies have been performed and no new data on pharmacokinetics are available in other food-producing species. Therefore, the high degree of uncertainty previously referred to, remains and extrapolation of MRLs from piglets to other food-producing species is therefore not recommended.

5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the toxicological ADI of 0.1 mg/kg bw/day (i.e. 6 mg/person/day) has been established as the

overall ADI for lidocaine, albeit only 4.8 mg/person/day are considered available for use in the context of the current evaluation, as the CVMP considered it appropriate to reserve 20% of the ADI for future uses of the substance,

- an acceptable exposure level for 2,6-xylidine of 1728 µg/person/day has been established, albeit only 1382 µg/person per day are considered available for use in the context of the current evaluation as the CVMP considered it appropriate to reserve 20% of the acceptable exposure level for future uses of the substance,
- the quantitative risk assessment based on lidocaine residues in piglet tissues resulted in a worst-case consumer exposure estimate well below the toxicological ADI (10.42% of the available proportion of the ADI for lidocaine residues in tissues, i.e. 4.8 mg/person/day) when using maximum residue values at all timepoints investigated (i.e. from 12 hours after dosing),
- the quantitative risk assessment based on levels of 2,6-xylidine in piglet tissues plus levels of 2,6-xylidine produced by metabolism of lidocaine in humans resulted in a worst-case consumer exposure estimate below the acceptable exposure level (35.90% when using maximum residue values) at all timepoints investigated (i.e. from 12 hours after dosing),
- metabolism of lidocaine in neonatal piglets is considerably lower than that in older pigs and the restriction to use in neonatal animals therefore remains appropriate,

the Committee recommends the modification of maximum residue limits for lidocaine in relation to porcine to also allow the injection into the scrotum, testicles and spermatic cord in piglets up to 7 days of age only, in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Lidocaine	NOT APPLICABLE	Equidae	No MRL required	NOT APPLICABLE	For local/regional anaesthesia only.	Local anaesthetic
		Porcine	No MRL required	NOT APPLICABLE	For cutaneous and epilesional use in piglets up to 7 days of age only. For injection into scrotum, testicles and spermatic cord in piglets up to 7 days of age only.	
	Lidocaine	Bovine	150 µg/kg 200 µg/kg	Muscle Fat	NOT APPLICABLE	

			1 µg/kg 200 µg/kg 30 µg/kg	Liver Kidney Milk		

The theoretical worst-case intake of residues from porcine tissues, represents 10.42% of the available proportion of the ADI for lidocaine and 35.90% of the acceptable exposure limit for 2,6-xylidine at 12 hours after treatment.

Background information on the procedure

Submission of the dossier	9 February 2024
Steps taken for assessment of the substance	
Application validated:	20 March 2024
Clock started:	21 March 2024
List of questions adopted:	18 July 2024
Consolidated response to list of questions submitted:	28 November 2024
Clock re-started:	16 December 2024
List of outstanding issues adopted:	12 February 2025
Consolidated response to list of outstanding issues submitted:	15 April 2025
Clock re-started:	16 April 2025
CVMP opinion adopted:	15 May 2025
European Commission request for reconsideration of CVMP opinion	5 June 2025
Revised CVMP opinion adopted:	4 December 2025