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Safety and efficacy of RONOZYME® WX CT/L (endo-1,4-β-xylanase) as a feed additive for sows for reproduction

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Abstract

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of RONOZYME® WX CT/L as a feed additive for sows for reproduction. This additive contains endo-1,4-β-xylanase produced by a genetically modified strain of *Aspergillus oryzae* and it is authorised in the EU as a feed additive for poultry for fattening, weaned piglets and pigs for fattening. The applicant requests the extension of use of the additive to sows for reproduction at 200 FXU/kg feed. The FEEDAP Panel concluded that there are no concerns for consumer safety and no risks for the environment are expected from the use of RONOZYME® WX in sows. The FEEDAP Panel concluded that the additive is not a skin or eye irritant, but it should be considered a respiratory sensitiser, but could not conclude on the skin sensitisation potential of the additive. A tolerance trial in lactating sows and two toxicological studies were made available to support the safety of the target species. Based on the data available, the FEEDAP Panel concluded that the additive is safe for sows for reproduction at the recommended level with a wide margin of safety. Three efficacy studies in lactating sows were evaluated. Sows that received RONOZYME® WX showed improvements on the apparent faecal digestibility of the energy in the three trials. The enzyme activity in feed that showed efficacy ranged from 124 to 287 FXU/kg feed, and the FEEDAP Panel concluded that the additive has the potential to be efficacious as a zootechnical additive in lactating sows at a level of approximately 250 FXU/kg feed. No data has been provided in gestating sows, and consequently, the Panel could not conclude on this physiological stage of the productive cycle.

Keywords: zootechnical additive, digestibility enhancers, safety, efficacy, xylanase, sows

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Table of contents

1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from DSM Nutritional Products Ltd., Switzerland,[2] for authorisation of the product RONOZYME® WX CT/L (endo-1,4-β-xylanase) when used as a feed additive for sows for reproduction (category: zootechnical additives; functional group: digestibility enhancers).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 19 September 2018.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the product RONOZYME® WX CT/L (endo-1,4-β-xylanase), when used under the proposed conditions of use.

1.2. Additional information

The additive RONOZYME® WX CT/L (also known as BioFeed® Wheat) is a preparation of endo-1,4-β-xylanase which is produced by a genetically modified strain of *Aspergillus oryzae* (DSM 26372) and is authorised in the European Union (EU) as a feed additive for poultry for fattening, weaned piglets and pigs for fattening.[3]

The Panel on additives and Products or Substances used in Animal Feed (FEEDAP) delivered in 2012 an opinion on the safety and efficacy of RONOZYME® WX CT/L when used as a feed additive for poultry, piglets (weaned) and pigs for fattening (EFSA FEEDAP Panel, 2012) and in 2016 assessed the proposal made by the applicant in order to change the production strain to *A. oryzae* DSM 26372 (EFSA FEEDAP Panel, 2016). In 2017, EFSA issued an opinion on the efficacy of this product when used in laying hens (EFSA FEEDAP Panel, 2017a). The applicant has requested for an extension of use of the additive to sows for reproduction.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[4] in support of the authorisation request for the use of RONOZYME® WX CT/L (endo-1,4-β-xylanase) as a feed additive.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA, to deliver the present output.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment regarding the methods used for the control of the active substance in animal feed are valid and applicable for the current application.[5]

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] Represented in EU by Novozyme A/S, Krogshoejvej 36, 2880 Bagsvaerd, Denmark.
[3] Commission Implementing Regulation (EU) No 1006/2017 of 15 June 2017 amending Implementing Regulation (EU) No 1206/2012 as regards the change of the production strain of the preparation of endo-1,4-beta-xylanase, produced by *Aspergillus oryzae* (DSM 10287) as feed additive for poultry for fattening, weaned piglets and pigs for fattening (holder of authorisation DSM Nutritional Products Ltd). OJ L 339, 16.6.2017, p. 9.
[4] FEED dossier reference: FAD-2018-0043.
[5] The full report is available on the EURL website: https://ec.europa.eu/jrc/en/eurl/feed-additives/evaluation-reports

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of RONOZYME® WX CT/L (endo-1,4-β-xylanase) is in line with the principles laid down in Regulation (EC) No 429/2008[6] and the relevant guidance documents: Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017b) and Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018).

3. Assessment

This opinion deals with the extension of use of RONOZYME® WX CT/L as a zootechnical additive (functional group: digestibility enhancers) for sows for reproduction.

3.1. Characterisation

RONOZYME® WX CT/L is a feed additive based on endo-1,4-β-xylanase (xylanase; Enzyme Commission number 3.2.1.8) produced by a genetically modified strain of *A. oryzae* DSM (26372). The additive is presented in two different formulations: RONOZYME® WX (CT) is a coated thermostable formulation which ensures a minimum activity of xylanase of 1,000 FXU/g and RONOZYME® WX (L) is a liquid formulation which ensures a minimum activity of xylanase of 650 FXU/ml. These two formulations were fully characterised and described, including the manufacturing process and the production strain, in previous opinions (EFSA FEEDAP Panel, 2012, 2016). However, the applicant provided new data to support the shelf-life of the additive up to 2 years.[7,8] The shelf-life was studied in three batches of RONOZYME® WX (CT) and three batches of RONOZYME® WX (L) stored at temperatures ranging from 10 to 40°C. The solid formulation showed a mean recovery of the initial activity of 98% and 94% after 24 months at 10°C and 25°C, respectively; the mean recovery of the activity at 40°C after 12 months was 86%. RONOZYME® WX (L) showed 97%, 85% and 53% mean recovery of the initial activity after 24 months at 10, 25 and 35°C, respectively.

The additive is intended to be used in feed for sows at a recommended enzyme activity of 200 FXU/kg feed.

3.2. Safety

Safety aspects regarding the use of this additive in feed including the safety of the genetic modification of the production strain, the safety for the consumers, for the users and for the environment have been previously evaluated (EFSA FEEDAP Panel, 2012, 2016). The FEEDAP Panel concluded that there are no concerns for the consumers of food products obtained from animals receiving the additive and no risks for the environment are expected. Considering the safety for the user, the Panel concluded that the additive is not a skin or eye irritant but could not conclude on the skin sensitisation potential of the additive due to the lack of data. Because of the proteinaceous nature of the active substance the additive was considered a potential respiratory sensitiser. The dossier does not contain any new information that would lead the FEEDAP Panel to reconsider the conclusions drawn previously. Moreover, the FEEDAP Panel considers that the new use in sows for reproduction requested by the applicant would not introduce any risk/hazard that has not been already considered. However, there is the need to assess the safety of the additive for the new target species.

3.2.1. Safety for the target species

A tolerance trial in lactating sows and two toxicological studies were considered.

In the tolerance trial, a total of 47 sows (Landrace x Large White, non-primiparous) were allocated to three dietary treatments (representing 14–17 sows per treatment) and were kept under study from 2 to 3 weeks before the expected farrowing day to weaning of the piglets (day 27 of lactation).[9] Until 1 week before the expected farrowing, the sows were kept in groups and then were moved to the lactation barns where they were housed individually. During the experimental period, sows received a

[6] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.
[7] Technical dossier/Section II/Annex 2.30.
[8] Technical dossier/Section II/Annex 2.31.
[9] Technical dossier/Section III/Annex 3.2 and Supplementary information May 2019/Appendix 1.

commercial diet based on wheat and soybean meal either not supplemented (control) or supplemented with RONOZYME® WX CT to provide 200 (1x recommended level) or 2,000 (10x) FXU/kg feed (confirmed by analysis). The diet was offered in pelleted form. During the gestation period, sows received 3 kg feed per day, while during lactation feed was offered *ad libitum*. Sows' body weight was measured before the start, after farrowing and after weaning. Weight loss during lactation was calculated. The feed intake of the sows was monitored individually during the experimental period. Farrowing performance was measured and included the number of piglets born and body weight. At weaning, blood samples from sows were collected and analysed for haematological[10] and biochemical[11] parameters. Cross-fostering of piglets was performed among sows of the same group and during the first 24–48 h of life. Growth of the piglets during the lactation was also measured. Piglets received creep-feed during the lactation and intake was measured. An analysis of variance (ANOVA) was performed with the data, with the sow as the experimental unit and considering the treatment, the batch and parity number of the sow. The significance level was set at $p < 0.05$.

No significant effects were observed in any of the performance parameters measured in sows and litters. Sow's feed intake during the lactation was 5.8 kg/day and the mean body weight loss during the period was 26 kg. The number of piglets born per sow were 12.2 and the mean body weight was 1.6 kg. At the end of the lactation, the number of piglets per litter was 10.9 and the mean body weight was of 8.3 kg (average daily weight gain 249 g/day) with mortality of piglets amounting 10%. There were some significant differences in the haematological and biochemical parameters measured in sows which included an higher white blood cells count in the 200 FXU/kg group compared to control and 2,000 FXU/kg (16.3 vs 13.1 and 11.2 $\times$ 10^3/mm^3), lower eosinophils with the xylanase supplementation at 2,000 FXU/kg feed compared to control (0.30 vs 0.64 $\times$ 10^3/mm^3), lower lymphocytes at 2,000 FXU/kg feed compared to control and 200 FXU/kg (3.89 vs 4.71 and 5.06 $\times$ 10^3/mm^3) and a lower alanine aminotransferase in the 200 FXU/kg feed compared to control and 2,000 FXU/kg feed (24.1 vs 27.8 and 27.4 IU). The modifications did not show a pattern and were of limited biological relevance. Consequently, the data from this study would not indicate a safety concern of the additive for sows during the lactation.

The current application refers to sows for reproduction and this includes the whole reproductive cycle. The tolerance trial submitted was performed during the farrowing/lactation period and although it supports the safety of the additive during the lactation phase, it would not support the safety of the additive for the whole cycle of the sows.

In order to address this limitation, the Panel considered a subchronic oral toxicity study (OECD 408) and a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422).[12] These studies were assessed in a previous opinion (EFSA FEEDAP Panel, 2016). The Panel considers that the results of the reproductive study in rats are more relevant for the current assessment and identified a no observed adverse effect level (NOAEL) of 241,048 FXU/kg body weight/day. From this NOAEL, the maximum safe level for sows was calculated according to the guidance on the safety for the target species (EFSA FEEDAP Panel, 2017b). The result of the calculation was 70,700 FXU/kg feed, and this would support the results of the of the tolerance trials and indicate a wide margin of safety for sows, approximately 350.

3.2.1.1. Conclusions on safety for the target species

Based on the data available, the FEEDAP Panel concludes that the additive is safe for sows for reproduction at the recommended dose of 200 FXU/kg feed with a wide margin of safety.

3.3. Efficacy

Three studies have been submitted, all done in the lactation period.

The first study was a digestibility study that was conducted in sows during the late lactation.[13] A total of 17 first-parity sows (Danish Landrace x Yorkshire) were distributed to two experimental groups (8 sows in the control group and 9 sows in the RONOZYME® WX group) on day 28 of lactation and remained under study in individual pens for 10 days. The sows were fed a basal diet based on barley and wheat

[10] Including: red blood cells, packed cell volume, mean corpuscular volume, haemoglobin, mean corpuscular haemoglobin, corpuscular haemoglobin concentration, white blood cells, eosinophils, basophils, band neutrophils, segmented neutrophils, lymphocytes, monocytes, platelets.
[11] Including: aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase.
[12] Technical dossier/Section III/Annexes 3.5 and 3.12.
[13] Technical dossier/Section IV/Annex 4.1 and supplementary information May 2019/Annexes 2.1 and 3.

that was either not supplemented (control) or supplemented with RONOZYME® WX CT to provide 200 FXU/kg feed (analysed enzyme activity of 129 FXU/kg feed). The feed contained chromium oxide as an external marker, and a total up to 9.8 kg/day was offered to the sows (three feeding times and allowance was reduced in sows by 5% for each piglet below 14). Feed intake was measured, sows were weighed and the back-fat thickness was measured on days 28, 31 and 38 of lactation. Piglets were individually weighed on the same days and milk yield was calculated from the body weight gain of the piglets. Milk samples were collected on day 35 to be analysed for fat, protein and lactose content and were used to estimate the energy content of the milk. On the same day, blood samples were collected from sows and analysed for glucose, lactate, triacyl glycerides, non-esterified fatty acids and urea. On days 37 or 38, a faecal sample was collected from each sow (spot sampling) and was analysed for energy, dry matter, crude protein and chromium oxide. An ANOVA was done with all the data.

No differences were observed in any of the performance parameters measured in the sows or piglets. The milk yield (kg/d) and its composition (including calculated energy content) were not different between the groups. The apparent total tract digestibility of the energy was significantly higher in the sows that received the additive compared to control (82.9 vs 81.3%).

The second and third trials were done during the lactation and performance as well as digestibility measurements were reported.

The second trial was conducted in a total of 30 (Danish Landrace x Danish Yorkshire) multiparous sows that were distributed to two dietary treatments (15 sows per treatment).[14] Sows were housed in individual pens during the whole experiment. A basal diet based on wheat and barley was either not supplemented (control) or supplemented with RONOZYME® WX CT to provide 200 FXU/kg feed (analysed 124 FXU/kg feed). Feed was offered in pelleted form from day 108 of gestation to day 28 of lactation and contained chromium oxide. Sows received the feed restrictively until farrowing and then they followed a standard feeding curve. The feed intake was monitored throughout the experimental period. Farrowing performance of the sows was measured. Sows were weighed and the back-fat was measured on days 2, 7, 14, 21 and 28. Faeces were collected on days 3 and 17 of lactation for the determination of the digestibility of dietary components. Blood samples were collected weekly for the analysis of glucose, triglycerides, lactate, non- esterified fatty acids and urea. Litter size was standardised on day 2 of the lactation within treatment. Litter weight was measured weekly and milk production was calculated. Milk samples were collected also weekly and the composition was analysed to calculate the energy content. The statistical analysis included all time points measured and considered the sow as the experimental unit.

The third short-term trial was conducted in 32 lactating sows (German Landrace x Large White) that were distributed to two dietary treatments (16 sows per treatment).[15] Sows were housed in individual pens during the whole experiment. A basal diet (mash form) based on wheat, barley and rye was either not supplemented (control) or supplemented with RONOZYME® WX CT to provide 200 FXU/kg (analysed 287 FXU/kg feed). Sows were under study from day 108 of gestation until day 28 of lactation. Diets included titanium dioxide as an external marker. Feed intake of the sows was measured throughout the study period. Sows were weighed, and the back-fat thickness was measured at day 2 after farrowing and at the day 28 of lactation. Number of piglets and weight were measured on day 1 and day 28. Faecal samples were collected on day 17 of lactation (spot samples) and were analysed to determine the digestibility of dietary components. An ANOVA was performed with all data.

The results of the parameters measured in sows for trials 2 and 3 are presented in Table 1 and the results of the performance of the litters are presented in Table 2.

[14] Technical dossier/Section IV/Annex 4.2 and supplementary information May 2019/Annex 2.2
[15] Technical dossier/Section IV/Annex 4.3 and supplementary information May 2019/Annexes 2.3, 4.3 and main answer.

Table 1: Effect of RONOZYME® WX on the daily feed intake, body weight, back-fat loss of the sows from farrowing to weaning and the apparent faecal digestibility of the Energy of the diet

Trial	Group (FXU/kg feed)	Daily feed intake (kg)	Body weight (kg)			Back-fat loss (mm)	Apparent faecal digestibility of Energy (%)
			2 days post-Farrowing	Weaning	Loss		
2	0	6.6[b]	274	261	13.6[a]	3.4	83[b]
	200	6.9[a]	274	268	5.2[b]	2.5	84[a]
3	0	5.7	266	249	17	5.3	78[b]
	200	5.9	271	249	22	5.1	81[a]

[a,b]Values within one study and within one column with different superscript are statistically different ($p < 0.05$).

Table 2: Effect of RONOZYME® WX on litter size, piglets' weight and mortality(1)

Trial	Group (FXU/kg feed)	Litter size (n)		Piglets' weight (kg)		Mortality/culls (%)
		Initial	Final	Initial	Final	
2	0	13.9	12.9	1.62	8.21	7.7
	200	13.9	12.8	1.61	8.18	7.7
3	0	14.8	11.6	1.46	8.51	Not given
	200	13.8	11.8	1.47	8.47	Not given

1: Initial litter size and piglets' weight on day 2 post-farrowing in trial 2 and day 1 in trial 3.

In trial 2, sows that received the additive showed a higher daily feed intake during the lactation a lower body weight loss and a higher apparent faecal digestibility of the energy. Milk yield and composition did not differ between the two groups. Blood parameters showed that the sows that received the enzyme had a higher triglycerides concentration (0.23 vs 0.20 mM) compared to control. No other differences were found in the parameters measured regarding the performance of the sows/piglets.

In trial 3, no differences were observed in any of the parameters measured with the exception of the apparent faecal digestibility of energy, which was statistically higher in the sows receiving the additive compared to control.

In summary, lactating sows that received RONOZYME® WX showed improvements on the apparent faecal digestibility of the energy in the three trials assessed. The analysed enzyme activity that showed efficacy ranged from 124 to 287 FXU/kg feed. Therefore, the additive has the potential to be efficacious as a zootechnical additive in lactating sows at a level approximately 250 FXU/kg feed. No data has been provided in gestating sows.

3.3.1. Conclusions on the efficacy

The FEEDAP Panel concludes that RONOZYME® WX has the potential to be efficacious as a zootechnical additive in lactating sows at 250 FXU/kg feed. Owing to the lack of data, the Panel cannot conclude on the efficacy of the additive in physiological stages other than the lactation period.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[16] and Good Manufacturing Practice.

4. Conclusions

The additive is safe for sows for reproduction at the recommended dose of 200 FXU/kg feed with a wide margin of safety.

The FEEDAP Panel concludes that there are no concerns for consumer safety and no risks for the environment are expected from the use of RONOZYME® WX in sows. The additive is not a skin or eye

[16] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

irritant, but it should be considered a respiratory sensitiser. The Panel cannot conclude on the skin sensitisation potential of the additive.

The FEEDAP Panel concludes that the additive has the potential to be efficacious in lactating sows at the dose of 250 FXU/kg feed. No conclusion can be drawn for sows in other reproductive stages of the productive cycle.

5. Documentation as provided to EFSA/Chronology

Date	Event
05/07/2018	Dossier received by EFSA. RONOZYME® WX CT/L for sows for reproduction. DSM Nutritional Products Ltd.
07/08/2018	Reception mandate from the European Commission
19/09/2018	Application validated by EFSA – Start of the scientific assessment
05/09/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: safety and efficacy of target animals*
19/12/2018	Comments received from Member States
29/05/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
03/07/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances usedin Animal Feed), 2016. Scientific opinion on the safety and efficacy of RONOZYME®WX (endo-1,4-beta-xylanase) as a feed additive for chickens and turkeys for fattening, minor poultry species for fattening, weaned piglets and pigs for fattening. EFSA Journal 2016;14(9):4564, 14 pp. https://doi.org/10.2903/j.efsa.2016.4564

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Abbreviations

ANOVA analysis of variance
EURL European Union Reference Laboratory
FEEDAP EFSA Panel on Additives and Products or Substances used in Animal Feed
NOAEL no observed adverse effect level