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## Safety and efficacy of Belfeed B MP/ML (endo-1,4- $\beta$ -xylanase) as a feed additive for sows, in order to have benefits in piglets, and for all porcine species

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Noël Albert Dierick, Guido Rychen and Montserrat Anguita

### 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 Belfeed B MP/ML as a feed additive for sows in order to have benefits in piglets and for all porcine species. This additive contains endo-1,4- $\beta$ -xylanase produced by a genetically modified strain of *Bacillus subtilis* and it is authorised in the European Union as a feed additive for poultry for fattening, weaned piglets and pigs for fattening. The applicant requested the extension of use of the additive to sows in order to have benefits in piglets and to all porcine species at any developmental stage at 10 IU/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 Belfeed B MP/ML in all *Suidae* species. The additive is not irritant for skin or eye but it should be considered a potential respiratory sensitiser for the users, the Panel could not conclude on the potential of the additive as a potential dermal sensitiser. Considering the results from a tolerance trial done in weaned piglets, those in a subchronic oral toxicity study and the nature/origin of the product under assessment the Panel concluded that the additive is safe for all porcine species at any developmental stage. The data previously assessed in piglets and pigs for fattening allowed to conclude that the additive is efficacious at 10 IU/kg feed in suckling piglets and all *Suidae* species from suckling to slaughter. The data submitted to support the efficacy for sows was considered insufficient and therefore the Panel could not conclude on the efficacy in sows.

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**Keywords:** Zootechnical additives, digestibility enhancers, xylanase, safety, efficacy, sows

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**Correspondence:** feedap@efsa.europa.eu

**Panel members:** Giovanna Azimonti, Vasileios Bampidis Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Maryline Kouba, Mojca Kos Durjava, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa and Ruud Woutersen.

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## 1. Introduction

### 1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003<sup>1</sup> 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 Beldem<sup>2</sup> for authorisation of the product Belfeed B MP/ML (endo-1,4- $\beta$ -xylanase), when used as a feed additive for sows in order to have benefit in piglets and all porcine species and life stages (category: zootechnical additive; 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 3 May 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 Belfeed B MP/ML (endo-1,4- $\beta$ -xylanase), when used under the proposed conditions of use.

### 1.2. Additional information

The additive is a preparation of endo-1,4-beta xylanase produced by a genetically modified strain of *Bacillus subtilis* (LMG-S 15136). The additive is authorised in the European Union for poultry, weaned piglets and pigs for fattening.<sup>3</sup>

In 2016, the FEEDAP Panel assessed the safety and efficacy of the additive for poultry, piglets and pigs for fattening (EFSA FEEDAP Panel, 2016).

## 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<sup>4</sup> in support of the authorisation request for the use of product Belfeed B MP/ML (endo-1,4- $\beta$ -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.

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 Belfeed B MP/ML (endo-1,4- $\beta$ -xylanase) in animal feed are valid and applicable for the current application.<sup>5</sup>

### 2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of Belfeed B MP/ML (endo-1,4- $\beta$ -xylanase) is in line with the principles laid down in Regulation (EC) No 429/2008<sup>6</sup> and the

<sup>1</sup> 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.

<sup>2</sup> Beldem, a division of Puratos NV, rue Bourrie 12, 5300 Andenne, Belgium.

<sup>3</sup> Commission implementing Regulation (EU) 2017/2011 of 7 February 2017 concerning the authorisation of a preparation of endo-1,4-beta-xylanase (EC 3.2.1.8) produced by produced by *Bacillus subtilis* (LMG-S 15136) as a feed additive for poultry, weaned piglets and pigs for fattening, and amending Regulations (EC) No 259/2004, (EC) No 1206/2005, and (EC) No 322/2009 and repealing Regulation (EC) No 516/2007 (holder of authorisation Beldem, a division of Puratos NV).

<sup>4</sup> FEED dossier reference: FAD-2018-0007.

<sup>5</sup> The full report is available on the EURL website: [https://ec.europa.eu/jrc/sites/jrcsh/files/corrected-finrep-fad-2010-0285\\_belfeed\\_b\\_ml\\_mp.pdf](https://ec.europa.eu/jrc/sites/jrcsh/files/corrected-finrep-fad-2010-0285_belfeed_b_ml_mp.pdf)

<sup>6</sup> 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.

relevant guidance documents: Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018). and the Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017).

### 3. Assessment

The product Belfeed B MP/ML is a feed additive that contains endo-1,4-  $\beta$ -xylanase (EC 3.2.1.8; xylanase) and it is intended to be used in sows, in order to have benefits in piglets, and in all porcine species and life stages as a zootechnical additive (functional group: digestibility enhancers).

#### 3.1. Characterisation

The xylanase present in the additive is produced by a genetically modified strain of *B. subtilis* deposited at the Belgian Co-ordinated Collections of Microorganisms with deposition number LMG S-15136. The additive is available in two formulations, solid (Belfeed B MP) and liquid (Belfeed B ML). The two formulations of the additive ensure a guaranteed minimum xylanase activity of 400 IU<sup>7</sup>/g.

In a previous opinion, the Panel described the additive and its manufacturing process including the production strain (EFSA FEEDAP Panel, 2016). The data pertaining to composition, physical properties and stability submitted in the previous assessment still apply.

The additive is to be used in feed for sows, in order to have benefits in the piglets, and in all porcine species at a level of 10 IU/kg feed.

#### 3.2. Safety

The 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 user and for the environment have been previously assessed (EFSA FEEDAP Panel, 2016). The Panel concluded that the use of the product as a feed additive raises no concerns for consumer safety and for the environment. Regarding the safety for the user, the Panel concluded that the additive is not irritant for skin or eye but it should be considered a potential respiratory sensitiser, the Panel could not conclude on the potential of the additive as a dermal sensitiser. The applicant did not submit any information that would lead it to reconsider the conclusions drawn previously and considers that the extension of use to the new species for which the application is made would not have an impact on the safety aspects already considered. However, the safety for the new target species, sows, suckling piglets and minor porcine species, needs to be assessed.

##### 3.2.1. Safety for the target species

In the previous assessment, the Panel evaluated a tolerance trial in weaned piglets in which the animals tolerated well 100-fold the level of 10 IU/kg feed (EFSA FEEDAP Panel, 2016). The conclusions from that study and the wide margin of safety identified allows the Panel to extrapolate the conclusions to all porcine species from suckling to slaughter age at the recommended dose.

The applicant did not provide any specific study to address the safety for sows but referred to a subchronic oral toxicity study conducted in rats. This subchronic oral toxicity study has been evaluated by the FEEDAP Panel previously (EFSA FEEDAP Panel, 2016) and the no-observed-adverse-effect-level (NOAEL) identified was 3,000 IU/kg body weight per day. The Panel considers that the test item used in that study, albeit it is not exactly the same fermentation product as the one that it is currently produced, may reflect the characteristics of the one currently produced and therefore be a valid test item for the assessment.<sup>8</sup> Using the NOAEL identified in the study, and applying the procedure detailed in the guidance on the safety for the target species (EFSA FEEDAP Panel, 2017), the maximum safe level in feed for sows is calculated to be 880 IU/kg feed. This value is approximately 90 times higher than the proposed use level in sows. The Panel notes that the enzyme is obtained from a production strain that belongs to a species that qualifies for the QPS approach to safety assessment and the qualifications were met (EFSA, 2007; EFSA BIOHAZ Panel, 2017). Considering this fact, no concerns for the target species would raise from the fermentation product, with the exception of the xylanase.

<sup>7</sup> One International Unit (IU) is defined as the amount of enzyme which liberates one micromole of reducing sugars (xylose equivalents) from birchwood xylan per minute at pH 4.5 and 30°C.

<sup>8</sup> Technical dossier/Supplementary information July 2019.

However, no adverse effects on the reproductive parameters of the sows are expected from the xylanase present in the additive, and other adverse effects could have been identified already in the tolerance trial in weaned piglets (EFSA FEEDAP Panel, 2016). In that study, there were no indications of a detrimental effect of the xylanase in weaned piglets and consequently no adverse effects are expected in sows. Therefore, considering all the above, the Panel concludes that the additive is also safe for sows at the recommended level of 10 IU/kg feed. This conclusion is extrapolated to all *Suidae* in the reproductive stage.

Considering all the above, the Panel concludes that the additive is safe for the new target species/categories at a recommended level of 10 IU/kg feed.

### 3.3. Efficacy

In the previous opinion, the FEEDAP Panel assessed the efficacy of the additive when used in weaned piglets and pigs for fattening. The Panel concluded that the additive has the potential to be efficacious as a zootechnical additive in weaned piglets and pigs for fattening when added at 10 IU/kg feed. Considering that the mode of action is well known and similar between categories of the porcine species and between porcine species the Panel concludes that the conclusions reach in weaned piglets and pigs for fattening can be extrapolated to *Suidae* species in all growing stages, from suckling to slaughter.

The applicant has also requested to extend the use in sows, including minor porcine species, in order to have benefits in piglets. To support the efficacy the applicant submitted four trials, two presented as digestibility trials and two as long-term trials.

#### 3.3.1. Digestibility trials

The digestibility trials were conducted in the same trial site and shared a common design.<sup>9</sup> In each trial, a total of 32 sows (Large White x Landrace) were blocked according to parity number and body condition/weight and were allocated to two treatments (16 replicates per treatment). Sows were under study for 28 days, starting from 7 days prior to farrowing. Basal diets based on wheat, barley and soybean meal were either not supplemented or supplemented with Belfeed to provide 10 IU/kg feed (confirmed by analyses). Feed contained titanium dioxide as an external marker and was offered in pelleted form for 28 days. Body weight and back fat thickness of the sows were evaluated at the beginning and at the end of the study. Feed intake of the sows was registered throughout the study. Farrowing performance including litter size, number of piglets born alive, number of stillborns and body weight of the piglets were registered. The performance of the litters was also measured, and the parameters included litter size and body weight of the piglets, mortality was recorded. From day 16 to 19, faeces were collected from the sows in order to study the total apparent faecal digestibility of dietary components as well as the energy. An analysis of variance (ANOVA) was done with the data obtained considering the treatment, for the performance parameters the parity number of the sow was used as a covariate. Group means were compared with Tukey test.

In trial 1, there were no differences identified between the treatments regarding the parameters measured in the sows (body weight loss 16.2 and 18.6 kg; back fat loss 11.8% or 5.7%; feed intake 5.32 or 5.45 kg/day) or their litters (final number of piglets 10.7 and 11.1; body weight 5.6 and 5.5 kg). The apparent faecal digestibility of the energy was significantly improved in sows that received the additive compared to control, from 80.9% to 82.7%. In trial 2, there were no differences identified between the treatments regarding the parameters measured in the sows (body weight loss 30.5 and 30.8 kg; back fat loss 14.6% or 11.7%; feed intake 5.28 or 5.18 kg/day) or their litters (final number of piglets 10.8 and 11.0; body weight 6.1 and 6.2 kg). No differences were observed in the apparent faecal digestibility of the energy between treatments.

#### 3.3.2. Performance trials

Regarding the performance trials, in the first a total of 38 sows (Belgian Landrace × (Belgian Landrace × Irish Landrace)) were allocated to two treatments (considering also parity number) and were kept under study from one week prior to farrowing until the weaning of the piglets on day 28 of age.<sup>10</sup> A basal diet based on wheat, corn, barley and protein sources (soybean, rapeseed and

<sup>9</sup> Technical dossier/Section IV/Annex IV.02.02 and IV.02.03.

<sup>10</sup> Technical dossier/Section IV/Annex IV.02.01 and supplementary information January 2019/Annex 2.

sunflower meals) was either not supplemented or supplemented with Belfeed to provide 10 IU/kg feed (confirmed by analysis). Diets were offered in pelleted form and on *ad libitum* basis for 35 days. Sows were weighed and back-fat thickness and muscle thickness at P2 were measured on days 1 and 35. Feed intake of the sows was measured individually. Return into oestrus after weaning and insemination success rate were also measured. Cross-fostering of piglets was applied on day 1. The number of piglets was recorded and weight was measured at farrowing, after cross-fostering and at weaning, mortality was recorded. An ANOVA was done with the data considering the treatment, sow genetics (and father genetics for piglets) and parity class as fixed effects, and the initial number of piglets as a covariate.

The results on the body weight/condition and feed intake of sows of the two studies are given in Table 1. No effects of the additive were observed in the parameters measured in the sows regarding the body weight/condition, the feed intake or the return to oestrus (data not shown, all returned to oestrus 1 week after). The piglets from sows fed with the additive showed a significantly higher body weight at the end of lactation and a higher daily weight gain compared to the litters from sows that received the control diet.

The second performance trial at total of 24 sows (Large White  $\times$  Landrace, from two batches) that were allocated to two treatments (12 replicates per treatment).<sup>11</sup> Sows were under study for 37 days,<sup>12</sup> starting from around 14 days prior to farrowing. Basal diets based on wheat, barley and soybean meal were either not supplemented or supplemented with the xylanase form Belfeed B to provide 10 IU/kg feed (confirmed by analyses). Feed contained titanium dioxide as an external marker and was offered in pelleted form for 37 days. Body weight and back fat thickness of the sows were evaluated at the beginning and at the end of the study. Feed intake of the sows was registered throughout the study. Farrowing performance including litter size, number of piglets born alive, number of stillborns and body weight of the piglets were registered. Cross-fostering of piglets was done but no details were given. The performance of the litters was also measured, and the parameters included litter size and body weight of the piglets, mortality was recorded. On the last 4 days under study, faeces were collected from the sows in order to determine the total apparent faecal digestibility of dietary components as well as the energy. An ANOVA was done with the data obtained considering the treatment as a fixed effect and the batch of the sows as a random effect. The Panel noted the following limitations in the reporting/design of the study: (i) initial number of the piglets per sow after cross-fostering was different between the groups (13 in control and 12 in the Belfeed B group), (ii) duration of the lactation not given and probably different between litters, (iii) final number of piglets not reported, and (iv) no indication on the use of creep feeding during the lactation.

No differences were observed in the digestibility of the energy of the diets between the two groups. The results on the performance (Table 1) showed no differences in the initial and final body weight of the piglets, but a significantly improved average daily weight gain of the piglets during the lactation. The Panel notes that although the average daily weight gain of the litters was higher in the piglets from sows that received Belfeed B, this would be in contrast with the total body weight gain of the piglets during the lactation (final body weight minus initial body weight), which was similar between the groups (4.7 vs. 4.6 kg). A difference in the average daily weight gain could only be explained by an error in the reporting or by a different duration of the lactation period between treatments, but this fact has not been indicated in the study report. Moreover, numerically higher number of piglets after cross-fostering (control had 13 and Belfeed B 12) could also play a role on the effect seen in the average daily weight gain, since a lower gain per piglet with higher number of piglets per litter can be expected.

In a similar way, the results showed a significantly lower body weight loss and back-fat loss in sows receiving Belfeed B. However, these results could have been due to the lower total weight gain of the litter in the sows receiving Belfeed B, but no data has been provided at this regard.

Considering the limitations identified in the reporting of the study and on the results, the Panel considers the significant effects seen in different parameters in trial 2 cannot only be ascribed to the addition of Belfeed B to the diets.

<sup>11</sup> Technical dossier/Supplementary information February 2019/Annex 3.

<sup>12</sup> Technical dossier/Supplementary information February 2019/TPDS.

**Table 1:** Effect of Belfeed B on the sow's body condition and feed intake and litter performance during the lactation

	Trial 1		Trial 2	
	Control	Belfeed B	Control	Belfeed B
<b>Sow parameters</b>				
Body weight loss (kg)	40	43	32 <sup>b</sup>	23 <sup>a</sup>
Back fat loss (mm in trial 1 or % in trial 2)	6.95	6.32	21.5 <sup>b</sup>	7.8 <sup>a</sup>
Back muscle loss (mm)	5.0	2.47	–	–
Total/daily feed intake in lactation (kg)	160	151	4.85	4.94
<b>Litter parameters</b>				
Initial number of piglets	13.4	12.9	13	12
Final number of piglets	11.0	11.1	Not reported	Not reported
Initial body weight (kg)	1.44	1.42	1.48	1.48
Final body weight (kg)	7.23 <sup>a</sup>	7.71 <sup>b</sup>	6.20	6.11
Daily weight gain (g/day)	209 <sup>a</sup>	228 <sup>b</sup>	211 <sup>a</sup>	235 <sup>b</sup>
Mortality (%)	16.1	13.1	8.4	9.3

<sup>a,b</sup>: Values within a row and study with different superscript are significantly different ( $p < 0.05$ ).

### 3.3.3. Conclusions on the efficacy

Based on previously evaluated data, the Panel concludes that the additive, in either form, has the potential to be efficacious as a zootechnical additive at 10 IU/kg feed in *Suidae* species from suckling to slaughter.

The data provided in sows showed a better utilisation of the energy in the diets in one trial and a better performance of the piglets when the additive was added to the diets of lactating sows in another trial. However, due to the insufficient data the Panel cannot conclude on the efficacy of the additive when administered to the sows. Consequently, no conclusion can be reached with other porcine species for reproduction.

### 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<sup>13</sup> and Good Manufacturing Practice.

## 4. Conclusions

The additive, in either form, is safe for all porcine species at any developmental stage at 10 IU/kg feed.

The FEEDAP Panel concludes that there are no concerns for consumer safety and no risks for the environment are expected from the use of the additive in all porcine species. The additive is not irritant for skin or eye but it should be considered a potential respiratory sensitiser, the Panel cannot conclude on the potential of the additive as a potential dermal sensitiser.

The Panel concludes that the additive, in either form, has the potential to be efficacious in porcine species from suckling to slaughter. However, the Panel cannot conclude on the efficacy of the additive when administered to *Suidae* species for reproduction.

## Documentation as provided to EFSA/Chronology

Date	Event
19/02/2018	Dossier received by EFSA. Belfeed B MP/ML for sows in order to have benefits in piglets and all porcine species and life stages. Submitted by Puratos

<sup>13</sup> Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 October 2003 laying down requirements for feed hygiene. OJ L 31, 8.2.2005, p. 1.



Date	Event
16/03/2018	Reception mandate from the European Commission
03/05/2018	Application validated by EFSA – Start of the scientific assessment
21/06/2018	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: safety and efficacy for the target species</i>
19/02/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
03/08/2018	Comments received from Member States
10/05/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: safety for the target species</i>
03/07/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
07/10/2019	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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## Abbreviations

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