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## Safety and efficacy of a feed additive consisting of endo-1,4- $\beta$ -xylanase produced by *Bacillus subtilis* LMG S-27588 (Beltherm MP/ML) for laying hens, minor poultry species and all avian species (Puratos NV)

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, Mojca Fašmon Durjava, Maryline Kouba, Marta López-Alonso, Secundino López Puente, Francesca Marcon, Baltasar Mayo, Alena Pechová, Mariana Petkova, Fernando Ramos, Yolanda Sanz, Roberto Edoardo Villa, Ruud Woutersen, Noël Dierick, Lieve Herman, Giovanna Martelli, Jaume Galobart and Montserrat Anguita

### Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of an endo-1,4- $\beta$ -xylanase (Beltherm MP/ML), produced by a genetically-modified *Bacillus subtilis* strain, as a zootechnical additive for laying hens, minor poultry species and all avian species. The additive is authorised for use in feed for poultry species for fattening or reared for laying/breeding, weaned piglets, pigs for fattening and minor porcine species for fattening. The safety and efficacy of the additive for those species have been evaluated previously by the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel). The current application is for an extension of use of the additive. No viable cells were detected in the additive, but the data provided to support the absence of DNA in the additive was not sufficient to conclude on the absence of recombinant DNA in the additive. However, the Panel concluded that no safety concerns would arise from the presence of DNA from the production strain in the additive. In the current assessment, the FEEDAP Panel concluded that the additive is safe for all avian species at the recommended level of 100 ADXU/kg feed. Similarly, the FEEDAP Panel concluded that Beltherm MP/ML is safe for the consumer and the environment. Concerning the user safety, the FEEDAP Panel concluded that the additive is not toxic by inhalation or irritant for skin or eyes, but it is considered a potential dermal and a respiratory sensitiser. In a previous opinion, the efficacy of the additive in poultry species for fattening was shown. However, owing to the insufficient data submitted in previous and current assessments, the Panel could not conclude on the efficacy of the product for the target species for which the application was made.

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

**Panel members:** Vasileios Bampidis, Giovanna Azimonti, Maria de Lourdes Bastos, Henrik Christensen, Birgit Dusemund, Mojca Fašmon Durjava, Maryline Kouba, 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 feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from Puratos NV<sup>2</sup> for the authorisation of the additive consisting of endo-1,4- $\beta$ -xylanase (EC 3.2.1.8) produced by *Bacillus subtilis* LMG S-27588 (Beltherm MP/ML), when used as a feed additive for laying hens, minor poultry species and all avian species (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 29 April 2020.

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 endo-1,4- $\beta$ -xylanase produced by *Bacillus subtilis* LMG S-27588 (Beltherm MP/ML), when used under the proposed conditions of use (see Section 3.1.3).

### 1.2. Additional information

The subject of the assessment is the additive consisting of endo-1,4- $\beta$ -xylanase, intended for use as a zootechnical additive (functional group: digestibility enhancer) for laying hens, minor poultry species and all avian species.

EFSA issued three opinions on the safety and efficacy of this product when used in feed for chickens for fattening, chickens reared for laying, turkeys for fattening, turkeys reared for breeding, turkeys for breeding purposes, minor poultry species, piglets, pigs for fattening and other porcine species (EFSA FEEDAP Panel, 2017a, 2019a,b). The additive is currently authorised (4a30) for use in feed for chickens for fattening or reared for laying, turkeys for fattening or reared for breeding, minor poultry species for fattening or reared for laying or breeding, weaned piglets, pigs for fattening and minor porcine species for fattening.<sup>3</sup>

## 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 endo-1,4- $\beta$ -xylanase produced by *B. subtilis* LMG S-27588 (Beltherm MP/ML) 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 1,4- $\beta$ -xylanase produced by *B. subtilis* LMG S-27588 in animal feed are valid and applicable for the current application.<sup>5</sup>

<sup>1</sup> Regulation (EC) N° 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

<sup>2</sup> Puratos NV, Industrialaan 25, 1702 Groot-Bijgaarden, Belgium.

<sup>3</sup> COMMISSION IMPLEMENTING REGULATION (EU) 2019/1324 of 5 August 2019 concerning the authorisation of a preparation of endo-1,4- $\beta$ -xylanase produced by *Bacillus subtilis* LMG S-27588 as a feed additive for chickens for fattening or reared for laying, turkeys for fattening or reared for breeding, minor poultry species for fattening or reared for laying or for breeding, weaned piglets, pigs for fattening and minor porcine species (holder of authorisation Puratos), OJ L 206, 6.8.2019, p. 18.

<sup>4</sup> FEED dossier reference: FAD-2019-0080.

<sup>5</sup> The full report is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/finirep-fad-2016-0010-beltherm.pdf>

## 2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance (trade name of the product) is in line with the principles laid down in Regulation (EC) No 429/2008<sup>6</sup> and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017b), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017d), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018a), Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA FEEDAP Panel, 2018b) and Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019c).

## 3. Assessment

The additive that contains an endo-1,4- $\beta$ -xylanase (xylanase; EC Number 3.2.1.8) produced by *B. subtilis* LMG S-27588, hereinafter referred to as Beltherm MP/ML, is intended to be used as a zootechnical additive (functional group: digestibility enhancers) in feed for laying hens, minor poultry species and all avian species. The additive is currently authorised for use in feed for poultry species for fattening or reared for laying/breeding and for pig species for growing.

### 3.1. Characterisation of the additive

The additive and the production strain were assessed in previous opinions (EFSA FEEDAP Panel, 2017a, 2019a,b). New data has been provided in the current application in view of the new requirements established in the relevant guidance documents. The newly submitted information included data on the characterisation of the production strain and on the characteristics of the additive.

#### 3.1.1. Characterisation of production strain

The production strain of the enzyme present in the product is a genetically modified *B. subtilis* strain, which is deposited at the Belgian Co-ordinated Collections of Microorganisms with the deposition number of LMG S-27588.<sup>7</sup> The strain was characterised in full in the first assessment by the FEEDAP Panel (EFSA FEEDAP Panel, 2017a, 2019a,b). The applicant has provided new data on the characterisation of the strain using whole genome sequence (WGS) based analysis.<sup>8</sup>



<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.

<sup>7</sup> Technical dossier/Section II/Annex II.09.

<sup>8</sup> Technical dossier/Supplementary information February 2021/Annex 1.

[REDACTED]

These genetic modifications in the production strain do not raise concerns in comparison with the recipient strain.

### 3.1.2. Characterisation of the additive

Data on the batch-to-batch variation of the enzyme activity was provided for five batches of each form of the additive.<sup>9</sup> The mean xylanase activity expressed in xylanase Units/g (ADXU<sup>10</sup> /kg) was 548 ADXU/g additive (range from 533 to 559) in the solid formulation and was 563 (ranging 540 to 583) in the liquid formulation. These data would support the minimum enzyme activity specified by the applicant of 500 ADXU/g.

Data on the chemical and microbiological contaminants as well as for the presence of antimicrobial activity were provided for three batches of each form of the additive.<sup>11</sup> The results showed coliforms  $\leq$  280 colony forming units (CFU) per gram, Enterobacteriaceae  $\leq$  70 CFU/g, *Escherichia coli*  $<$  10 CFU/g, presumptive *B. cereus*  $<$  400 CFU/g, moulds  $\leq$  160 CFU/g and yeasts  $<$  40 CFU/g and absence of *Salmonella* in 25 g. The content of lead was  $<$  0.005 mg/kg, cadmium  $\leq$  0.026 mg/kg, mercury  $\leq$  0.001 mg/kg and arsenic  $\leq$  0.005 mg/kg. Mycotoxins were only measured in the solid formulation and included, ochratoxin A, aflatoxins B1, B2, G1 and G2, deoxynivalenol, zearalenone, T-2 toxin, HT-2 toxin and were all below the respective limits of quantification.<sup>12</sup> No antimicrobial activity was found in the batches tested.

The applicant provided three data sets regarding the presence of viable cells in the additive, the first two were not considered further due to the limitations identified in the methodology and the batches tested.<sup>13</sup> In the third data set, the presence of viable cells was tested in three batches of the intermediate product that is used to formulate the additive [REDACTED]

[REDACTED] The samples incubated showed no growth.

The presence of recombinant DNA was provided in two data sets. One data set was not considered further because it was tested in pilot scale batches,<sup>15</sup> and the analysis should be done in production batches. In the second data set, the applicant provided data from three batches of the non-stabilised fermentation product produced at industrial scale.<sup>16</sup> [REDACTED]

[REDACTED] After production, the batches showed

<sup>9</sup> Technical dossier/Supplementary information February 2021/annex II.a.01 and II.a.02.

<sup>10</sup> One ADXU is defined as the amount of enzyme which liberates one micromole of reducing sugars (xylose equivalents) from beechwood xylan per minute at pH 6.0 and at 70°C.

<sup>11</sup> Technical dossier/Supplementary information February 2021/annex IIb.01, Iib.02 and Iib.03.

<sup>12</sup> The limits of quantification were as follows: ochratoxin 0.2 µg/kg, aflatoxins B1, B2 and G1 0.1 µg/kg, aflatoxin G2 0.2 µg/kg, deoxynivalenol 50 µg/kg, and zearalenone, T-2 toxin and HT-2 toxin 20 µg/kg.

<sup>13</sup> Technical dossier/Section II/Annex II.20 and supplementary information February 2021/Annex II.c.01.

<sup>14</sup> Technical dossier/Supplementary information June 2021/Annexes I.01 and Annex I.02.

<sup>15</sup> Technical dossier/Section II/Annex II.22.

<sup>16</sup> Technical dossier/Supplementary information February 2021/Annex III.01 and Supplementary information June 2021.

enzyme activities [REDACTED]. However, two of the batches showed a reduction in the enzyme activity with time (analysis done approximately 14 months after production). The reduction in the enzyme activity shown in the batches generates doubts on the stability of the product and therefore on that of the DNA that could be present at the time of production. Consequently, the data cannot be further considered and there is not sufficient data to conclude on the absence of DNA in the final product.

### 3.1.3. Conditions of use

Beltherm MP/ML is proposed to be used as a zootechnical additive, functional group of digestibility enhancers, in feed for laying hens, poultry species and all avian species at a recommended level of 100 ADXU/kg feed.

## 3.2. Safety

### 3.2.1. Safety of the production strain

The safety of the production strain and the resulting product was assessed in previous opinions (EFSA FEEDAP Panel, 2017a, 2019a,b). In those assessments, the data available supported the unequivocal identification of the production strain as *B. subtilis*; the absence of toxigenicity was shown on Vero cells and the strain is susceptible to all relevant antibiotics. The inserted traits do not raise safety concerns.

[REDACTED] Moreover, no cells or DNA were detected in the samples analysed and, therefore, the Panel concluded in 2019 that 'the additive raises no safety concern with respect to the production strain and its genetic modification'.

In the context of the current application, new data have been provided supporting the previous identification and characterisation of the production strain and confirming the qualifications for the presumed safety status (QPS, EFSA 2007 and EFSA BIOHAZ Panel 2021) of the production strain (see Section 3.1.1). The applicant also provided new data on the presence of viable cells that would confirm the absence of viable cells in the additive, but insufficient data was submitted to conclude on the absence of DNA. However, considering the characteristics of the production strain, the presence of its DNA would not raise safety concerns.

### 3.2.2. Safety for the target species

Based on results from tolerance trials in chickens and turkeys for fattening, the FEEDAP Panel concluded in 2017 that the additive is safe for chickens, turkeys and minor poultry species for fattening at the recommended level of 100 ADXU/kg feed (EFSA FEEDAP Panel, 2017a, 2019a,b).

The applicant submitted a tolerance study in laying hens, which has been previously evaluated by the FEEDAP Panel (EFSA FEEDAP Panel, 2017a, 2019a,b). Based on the results from that tolerance trial, the Panel concluded that the additive is safe for laying hens at 100 ADXU/kg feed with a wide margin of safety, and that the additive is safe for turkeys for breeding purposes and for minor poultry species at the same level (EFSA FEEDAP Panel, 2017a, 2019a,b).

The xylanase present in the additive is produced by a production strain for which the qualifications for the qualified presumption of safety (QPS) status have been met and consequently, no concerns for the target species are expected from the production strain.

Taking into consideration all the above, the Panel considers that the additive is safe for all avian species at the recommended use level of 100 ADXU/kg.

### 3.2.3. Safety for the consumers, users and the environment

The safety of the product for the consumers, users and the environment were assessed in previous opinions (EFSA FEEDAP Panel, 2017a, 2019a,b). The Panel concluded that the use of the additive in animal nutrition under the conditions of use proposed would raise no concerns regarding the safety for consumers and environment. Concerning the safety for the users, the FEEDAP Panel considered that the additive, in either form, is not toxic by inhalation or irritant for skin or eyes but is considered a respiratory sensitiser, however, no conclusions could be reached for its potential to be a dermal sensitiser.

The FEEDAP Panel considers that the previous conclusions on safety for the consumers, environment, and users can be retained. In addition, the FEEDAP Panel notes that the new use of the additive requested by the applicant and the data regarding the presence of DNA would not introduce



risks not considered previously. Consequently, the FEEDAP Panel retains the conclusions drawn in previous assessments.

### 3.3. Efficacy

The FEEDAP Panel concluded in previous opinions (EFSA FEEDAP Panel, 2017a, 2019a) that the additive is efficacious for poultry species for fattening or reared for laying/breeding at the recommended dose of 100 ADXU/kg feed.

In the current application, the applicant submitted three studies in laying hens. In two of them, the body weight of the hens (at start and end of the study) was not measured. The Panel considers that this measurement is needed for such type of studies and therefore the studies are not be considered further in this assessment.<sup>17</sup>

In the third study,<sup>18</sup> a total of 384 22-week-old hens (ISA Brown) were distributed in 48 enriched cages of 8 hens each and allocated to 4 dietary treatments (12 replicates (cages) per treatment). A basal diet based on wheat, rye, soya bean meal was either not supplemented (control) or supplemented with Beltherm to provide 100, 200 or 400 ADXU per kg feed (confirmed by analysis). The feed was offered in mash form and *ad libitum* for 24 weeks. Mortality and general health were monitored throughout the study. Body weight of the hens was measured at the beginning and at the end. Feed consumption was recorded throughout the study. Egg production and egg weight was recorded every second day per cage. Feed to egg mass ratio was calculated. The number of broken, shell-less, and dirty eggs was recorded. An analysis of variance was done with the performance data (cage basis) and considering the treatment as the main effect and the significance level was set at 0.05. The treated group means were compared against the control with Dunnett's test.

The results showed a low mortality of the hens. No significant differences were identified between the control group and the groups supplemented with the additive in any of the parameters measured except for the feed to egg mass ratio. Hens that received the additive at the recommended level of 100 ADXU/kg feed showed a better feed to egg mass ratio as compared to the control. However, no such differences were identified at higher levels of the additive (Table 1).

**Table 1:** Effects of Beltherm MP on the weight gain, daily feed intake and laying performance of laying hens under study for 24 weeks

Groups (ADXU/kg feed)	Weight gain (g)	Daily feed intake (g)	Laying rate (%)	Daily egg mass per hen (g)	Egg weight (g)	Feed to egg mass	Mortality (n)
0	347	109	92.4	55.8	60.4	1.96	1
100	352	108	94.0	57.3	61.0	1.89*	0
200	344	110	94.5	57.2	60.6	1.92	1
400	309	110	94.2	57.1	60.7	1.92	2

\*: Means within a column with an asterisk are significantly different from the control group.

As only one valid study showing positive effects of the supplementation with the additive in the performance of laying hens was available, the Panel cannot conclude on the efficacy of the additive for laying hens, and consequently for other minor poultry species or avian species for laying/breeding or other avian species at the same physiological stage.

### 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>19</sup> and Good Manufacturing Practice.

<sup>17</sup> Technical dossier Annex IV.02 and IV.03 and supplementary information February 2021.

<sup>18</sup> Technical dossier Annex IV.04 and supplementary information February 2021/Annex VI.01.

<sup>19</sup> Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.



## 4. Conclusions

The production strain is considered safe and no cells of the production strain were detected in the samples tested. Uncertainty remains as to whether the final product is free from recombinant DNA, however, such presence would not pose any safety concerns.

The additive is safe for all avian species at the recommended use level of 100 ADXU/kg feed.

The use of the additive in animal nutrition under the proposed conditions of use is of no concern for consumers and the environment.

The additive, in either form, is not toxic by inhalation or irritant for skin or eyes but is considered a respiratory sensitiser. No conclusions can be reached on its potential to be a dermal sensitiser.

The FEEDAP Panel cannot conclude on the efficacy of the additive for the target species for which the application was made.

## 5. Documentation provided to EFSA/Chronology

Date	Event
05/12/2019	Dossier received by EFSA. Beltherm MP/ML for poultry species Submitted by Puratos
08/01/2020	Reception mandate from the European Commission
29/04/2020	Application validated by EFSA – Start of the scientific assessment
15/07/2020	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: Characterisation of the additive and efficacy</i>
17/02/2021	Reception of supplementary information from the applicant - Scientific assessment re-started
29/07/2020	Comments received from Member States
26/02/2021	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: characterisation</i>
07/06/2021	Reception of supplementary information from the applicant - Scientific assessment re-started
30/09/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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## Abbreviations

ADXU	Xylanase Units
CFU	colony-forming unit
EURL	European Union Reference Laboratory
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed

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