Health Canada Santé Canada

NATURAL HEALTH PRODUCT

DIGESTIVE ENZYMES

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.

Notes

- Any ingredient in Table 1 may be formulated as single ingredient products, or two or more ingredients may be combined to form multi-ingredient products. In addition, multi- ingredient products may be formulated from one or more ingredients from these tables with ingredients from any one or more of the following single ingredient monographs: Alpha-amylase, alpha-galactosidase, Cellulase, Chymotrypsin, Fruit bromelain, Fungal protease, Lactase, Lipase, Pancreatic enzymes, Papain, Stem bromelain and/or Trypsin.
- The International Union of Biochemistry and Molecular Biology (IUBMB) enzyme nomenclature identification number (IUBMB No.) is not required on the PLA form but may be provided as additional information.
- The text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date June 3, 2019

Proper name(s), Common name(s), Source materials

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)	
		Proper name(s)	Part(s)
Group 1: Carbohydrases			
1,3-(1-3,1-4)-beta-D-glucan 3(4)-glucanohydrolase	▸ beta-1,3-glucanase ▸ beta-Glucanase	▸ *Aspergillus niger* ▸ *Trichoderma longibrachiatum* ▸ *Trichoderma reesei*	Whole
▸ 1,4-alpha-D-Glucan glucohydrolase ▸ 4-alpha-D-Glucan glucohydrolase	▸ Acid maltase ▸ Amyloglucosidase ▸ Glucoamylase	▸ *Aspergillus niger* ▸ *Aspergillus oryzae* ▸ *Rhizopus niveus* ▸ *Rhizopus oryzae*	Whole

▶ 1,3-beta-D-xylan xylanohydrolase ▶ 1,4-beta-D-mannan mannanohydrolase ▶ 1,5-alpha-L-arabinan arabinanohydrolase ▶ alpha-L-arabinofuranoside arabinofuranohydrolase	Hemicellulase	▶ *Aspergillus niger* ▶ *Aspergillus oryzae* ▶ *Trichoderma longibrachiatum* ▶ *Trichoderma reesei*	Whole
▶ beta-D-fructofuranoside fructohydrolase ▶ beta-Fructofuranosidase	▶ Invertase ▶ Sucrase	▶ *Aspergillus niger* ▶ *Saccharomyces cerevisiae*	Whole
4-alpha-D-Glucan glucanohydrolase	▶ 1,4-alpha-D-glucan glucanohydrolase ▶ alpha-Amylase ▶ Diastase ▶ Fungal diastase ▶ Taka-Diastase (Aspergillus)	▶ *Aspergillus niger* ▶ *Aspergillus oryzae*	Whole
Malt diastase	▶ Maltase ▶ Malt diastase	*Hordeum vulgare*	Seed
▶ (1-4)-alpha-D-galacturonan glycanohydrolase ▶ Pectin pectylhydrolase ▶ Poly(1,4-alpha-D-galacturonide) glycanohydrolase ▶ Poly(1,4-alpha-D-galacturonide) lyase ▶ Poly(methoxyl-L-galacturonide) lyase	▶ Pectinase ▶ Polygalacturonase	▶ *Aspergillus niger* ▶ *Aspergillus oryzae* ▶ *Trichoderma longibrachiatum* ▶ *Trichoderma reesei*	Whole
▶ 1,3-beta-D-xylan xylanohydrolase ▶ 1,4-beta-D-xylan xylanohydrolase	▶ beta-1,3-xylanase ▶ beta-1,4-xylanase ▶ Xylanase	▶ *Trichoderma longibrachiatum* ▶ *Trichoderma reesei*	Whole

Group 2: Proteases

Proper name(s)	Common name(s)	Source material(s)	
		Proper name(s)	Part(s)
Bacterial Protease	▶ Bacterial Protease ▶ Neutral protease	*Bacillus subtilis*	Whole
▶ Pepsin A ▶ Pepsin B	Pepsin	*Sus scrofa*	Stomach

Group 3: Other enzymes			
Proper name(s)	Common name(s)	Source material(s)	
		Proper name(s)	Part(s)
Hydrogen-peroxide: hydrogen-peroxide oxidoreductase	Catalase	▶ *Aspergillus niger* ▶ *Saccharomyces cerevisiae*	Whole
▶ myo-Inositol-hexakisphosphate 3-phosphohydrolase ▶ myo-Inositol-hexakisphosphate 4-phosphohydrolase ▶ orthophosphoric-mono ester phosphohydrolase	1-Phytase 3-Phytase 4-Phytase 6-Phytase Phytase	*Aspergillus niger*	Whole

References: Proper names: IUPAC-IUBMB 2012; Common names: IUPAC-IUBMB 2012; Source materials: FCC 8 2012, Justice Canada 2012, Enzyme Technical Association (no date).

Route of administration

Oral

Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

Digestive enzyme(s)

Dose(s)

Subpopulation(s)

Adults 18 years and older

Quantity(ies)

Table 2. Daily maximum of enzymatic activity unit

Medicinal ingredients	Daily maximum (enzymatic activity unit/day)
Bacterial protease	Not to exceed 490,000 FCC PC
Beta-glucanase	Not to exceed 210 FCC BGU
Catalase	Not to exceed 3,200 FCC Baker
Diastase	Not to exceed 6,000 FCC DP
Glucoamylase (Amyloglucosidase)	Not to exceed 300 FCC AGU[1]
Hemicellulase	Not to exceed 45,000 FCC HCU
Invertase	Not to exceed 3,000 FCC INVU or Not to exceed 4,200 FCC SU
Malt diastase	Not to exceed 6,000 FCC DP
Pectinase	Not to exceed 180 Endo-PG
Pepsin	Not to exceed 1,900,000 FCC Pepsin
Phytase	Not to exceed 75 FCC FTU
Xylanase	Not to exceed 3,300 XU

[1] For the FCC Glucoamylase Activity (Amylogucosidase Activity) assay, the Abbreviation "FCC AGU" is acceptable.

Notes

The Quantity per dosage unit must be the enzymatic activity (FCC unit). The quantity of the enzymatic preparation in mg or ml should also be included as additional quantity.

Direction(s) for use

Take with food/meal.

Duration(s) of use

Consult a health care practitioner/health care provider/health care professional/doctor/physician for prolonged use.

Risk information

Caution(s) and warning(s)

For all medicinal ingredients and ingredient combinations

Consult a health care practitioner/health care provider/ health care professional/doctor/physician prior to use if you are pregnant or breastfeeding.

For products containing one or more carbohydrases

Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have diabetes.

For products containing one or more proteases

- Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have gastrointestinal lesions/ulcers or are having surgery.
- Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking blood thinners or anti-inflammatory agents.

Contraindication(s)

No statement required.

Known adverse reaction(s)

For all medicinal ingredients and ingredient combinations

Stop use if hypersensitivity/allergy occurs.

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

No statement is required.

Specifications

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.
- Details of the manufacturing of the enzyme at the raw material stage should include fermentation medium and the isolation process of the medicinal ingredient.
- The specifications must include testing for enzymatic activity of the medicinal ingredient at appropriate stages of formulation and manufacturing using the assay outlined in the current Food Chemicals Codex (FCC):
    - beta-GLUCANASE ACTIVITY

- GLUCOAMYLASE ACTIVITY (AMYLOGLUCOSIDASE ACTIVITY)
- HEMICELLULASE ACTIVITY
- INVERTASE SUMNER UNIT ACTIVITY
- DIASTASE ACTIVITY
- PROTEOLYTIC ACTIVITY, BACTERIAL (PC)
- PEPSIN ACTIVITY
- CATALASE ACTIVITY
- PHYTASE ACTIVITY

- Testing for enzymatic activity of the medicinal ingredient must be done at the appropriate stages of formulation and manufacturing using the assay outlined in the Food Chemicals Codex (FCC 5): INVERTASE ACTIVITY
- Testing for Endo-Polygalacturonase Activity must be done at the appropriate stages of formulation and manufacturing as outlined in Blandino et al. (2002).
- Testing for Xylanase Activity must be done at the appropriate stages of formulation and manufacturing as outlined in Ghose and Bisaria (1987).
- Manufacturers are responsible for ensuring that activity assays that are used outside the conditions specified in the FCC have been sufficiently validated for their intended use in accordance with the requirements of good manufacturing practices.
- Where published assays are not suitable for use, manufacturers will use due diligence to ensure that the enzymes remain active to the end of the shelf life indicated on the product label.

References cited

Blandino A, Iqbalsyah T, Pandiella SS, Cantero D, Webb C. Polygalacturonase production by *Aspergillus awamori* on wheat in solid-state fermentation. Applied Microbiology and Technology 2002;58:164-169.

Ghose TK, Bisaria VS. Measurement of hemicellulase activities part 1: Xylanases. Pure and Applied Chemistry 1987;59(12):1739-1752.

ETA: Enzyme Technical Association. Enzyme Preparations used in Food Processing (as compiled by the ETA members). [Internet] [Accessed 2019 May 21]. Available from: https://www.enzymetechnicalassociation.org/enzymes/food/

FCC 8: Food Chemicals Codex. Eighth edition. Rockville (MD): The United States Pharmacopeial Convention; 2012.

FCC 5: Food Chemical Codex. Fifth edition. Washington (DC): The National Academy of Sciences; 2001.

IUBMB 2012: International Union of Pure and Applied Chemistry and International Union of Biochemistry (IUPAC) and Molecular Biology (IUBMB). IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN) [Internet]. [Accessed 2019 May 21]. Available from: https://www.qmul.ac.uk/sbcs/iubmb/nomenclature/

Justice Canada. *Food and Drug Regulations* (C.R.C., c. 870); B.16.100; Table 5. [Internet]. Ottawa (ON): Justice Canada. [Accessed 2019 May 21]. Available from: https://laws.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

References reviewed

United States Food and Drug Administration. GRAS Notice Inventory. [Internet]. [Accessed 2012 March 21]. Available from http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm

EFSA Panel on Biological Hazards. Scientific Opinion on the maintenance of the list of QPS microorganisms intentionally added to food or feed (2009 update). EFSA Journal 2009;7(12):1431.