NEW DIETARY INGREDIENT NOTIFICATION FOR DEGLUSTEROL POWDER

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New Dietary Ingredient Notification for Deglusterol Powder

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SECTION A – ADMINISTRATIVE INFORMATION

A.1 Description of the New Dietary Ingredient

The proposed new dietary ingredient (NDI) manufactured by Caregen Co., Ltd. ("Caregen") is Deglusterol. Deglusterol is a powdered ingredient containing a mixture of (b) (4) (b) (4) ratio without the use of any other excipients. The (b) (4) peptides are independently manufactured and (b) (4) The individually-manufactured peptides are then (b) (4) . Deglusterol powder can also be formulated into a liquid form, (b) (4) ; however, the subject of this notification is Deglusterol powder.

The term "dietary supplement" is defined in 21 U.S.C. 321 (ff) (U.S. FDA, 2021a) as, among other things:

> "*a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)*".

Deglusterol powder is a dietary ingredient that qualifies for addition to dietary supplements as a combination of amino acids, in accordance with 21 U.S.C. 321 (ff)(1)(D) and (F), and as a dietary substance for use by man to supplement the diet by increasing total dietary intake, in accordance with 21 U.S.C. 321 (ff)(1)(E) (U.S. FDA, 2021a). The classification of Deglusterol as a combination of amino acid is supported by the *in vitro* digestibility studies in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) (see Section C.3) indicating that the peptides, adiporin and deobetide, were fully digested by the enzymes and conditions common to the human digestive tract, and were broken down to their constituent amino acids.

A.2 Description of the Dietary Supplement Product Containing the New Dietary Ingredient

Caregen is the ingredient manufacturer of the Deglusterol powder ingredient. This ingredient is intended to be used in dietary supplement products (*e.g.*, pills, tablets, capsules, powdered sachets).

A.3 Identification of Trade Secret Information

The following information and their location(s) within the dossier, as indicated in Table A.3-1, are identified as confidential trade secret and/or confidential commercial information under 21 CFR §20.61(d) and 190.6(e) (U.S. FDA, 2021b,c). Caregen understands that this information will be kept confidential for 90 days after the filing date of this Notice; however, Caregen respectfully requests that certain information, as described in Table A.3-1 below, be kept confidential even after the 90-day date. The confidential and proprietary information is related to Deglusterol powder's chemical composition, manufacturing, specifications, certificates of analysis and test methods, along with product-specific safety data.

Table A.3-1 Confidential Chapters and Sections of the New Dietary Ingredient Notification

Confidential Chapters and Sections	Explanation
Sections B.1, B.2 (Identity of New Dietary Ingredient and Manufacturing Details), and Appendix A	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as Sections B.1, B.2, and Appendix A contain the proprietary compositional breakdown of Deglusterol powder, structural data on the individual peptide components, raw materials, manufacturing process, quality control steps, and a schematic diagram that should remain confidential to protect Caregen's commercial valuable and proprietary data. Confidential Commercial Information under 21 CFR §20.61(b) (U.S. FDA, 2021b), as Sections B.1, B.2, and Appendix A contain information used in Caregen's business that is customarily held in strict confidence. Disclosure of this information would allow competitors to replicate Caregen's ingredient which would, in turn, cause substantial harm to Caregen's competitive situation.
Sections B.3, B.4, B.5 (*i.e.*, Product Specifications, Product Analysis, and Additional Characterization), and associated appendices (*i.e.*, Appendix B, C, and D)	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as Sections B.3, B.4, B.5, and the associated Appendices contain the established product specifications of Deglusterol powder, batch analysis, internal methods of analysis, certificates of analysis, and pesticide reports that are requested to be kept confidential to protect the proprietary commercial value. These data contain trade secret compositional information that should not be disclosed. Confidential Commercial Information under 21 CFR §20.61(b) (U.S. FDA, 2021b), as Sections B.3, B.4, B.5, and the associated Appendices contain information used in Caregen's business that is customarily held in strict confidence. Disclosure of this information would allow competitors to replicate Caregen's ingredient which would, in turn, cause substantial harm to Caregen's competitive situation.
Sections C.3, C.4, C.5, C.6 (*i.e.*, Metabolic Fate, Studies to Support Safety, and Clinical Studies), and associated appendices (*i.e.*, Appendix F and G)	Trade Secret under 21 CFR §20.61(a) (U.S. FDA, 2021b), as Sections C.3, C.4, C.5, C.6, and the associated Appendices contain product-specific safety data related to Caregen's Deglusterol powder. These data are not publicly available and are therefore regarded as proprietary information. Substantial effort was required to generate the data necessary for these Sections and Appendices through research and innovation. As such, these data represent significant proprietary commercial value and should not be disclosed. Confidential Commercial Information under 21 CFR §20.61(b) (U.S. FDA, 2021b), as Sections C.3, C.4, C.5, C.6, and the associated Appendices contain information used in Caregen's business that is customarily held in strict confidence. Disclosure of this information would allow competitors to replicate Caregen's ingredient which would, in turn, cause substantial harm to Caregen's competitive situation.

SECTION B – CHEMISTRY AND IDENTITY [CONFIDENTIAL]

B.1 Description of the New Dietary Ingredient [CONFIDENTIAL]

Deglusterol powder is a (b) (4) without the addition of any other excipients. Each peptide is produced (b) (4) The general composition of the Deglusterol powder is summarized in Table B.1-1 below. No excipients are included in the final Deglusterol powder product.

Table B.1-1 General Composition of Deglusterol Powder [CONFIDENTIAL]

(b) (4)

N/A = not applicable.

B.1.1 Deobetide

Deobetide is an (b) (4). The identity of deobetide is further described in Table B.1.1-1.

Table B.1.1-1 Description of Identity of Deobetide [CONFIDENTIAL]

(b) (4)

B.1.2 Adiporin

Adiporin is an amino acid conjugate of alanine, methionine, tryptophan, glycine, threonine, serine, alanine, glycine, and lysine. The identity of adiporin is further described in Table B.1.2-1.

(b) (4)

B.2 Manufacturing Information [CONFIDENTIAL]

B.2.1 Raw Materials

All raw materials and processing aids used in the manufacturing of (b) (4)

Table B.2.1-1 Raw Materials Used in the Production of Peptides for Deglusterol Powder

(b) (4)

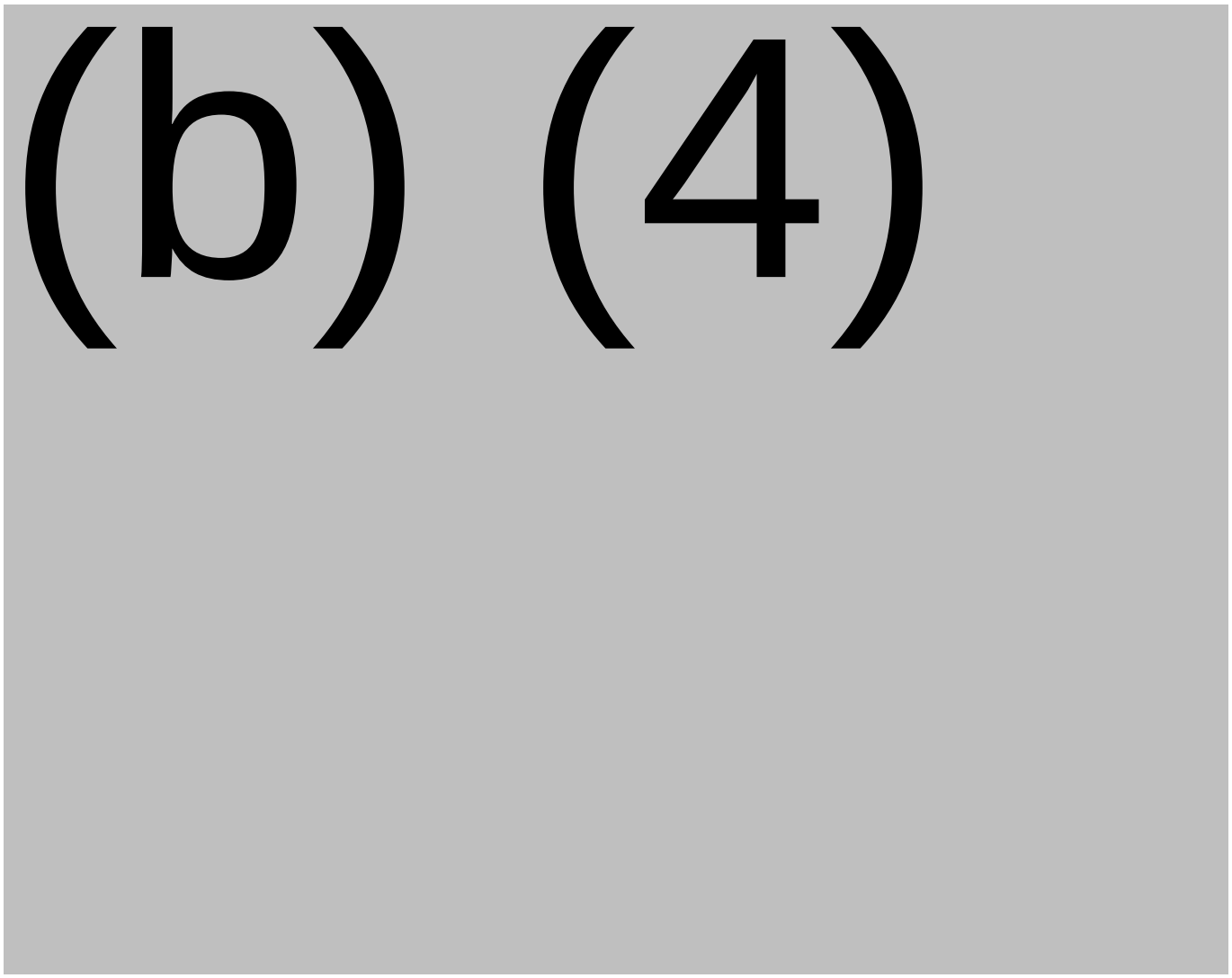
Table B.2.1-1 Raw Materials Used in the Production of Peptides for Deglusterol Powder

(b) (4)

B.2.2 Manufacturing Process

(b) (4)

Figure B.2.2-1 Schematic Overview of Peptide Synthesis for Use in Deglusterol Powder



B.3 Product Specifications [CONFIDENTIAL]

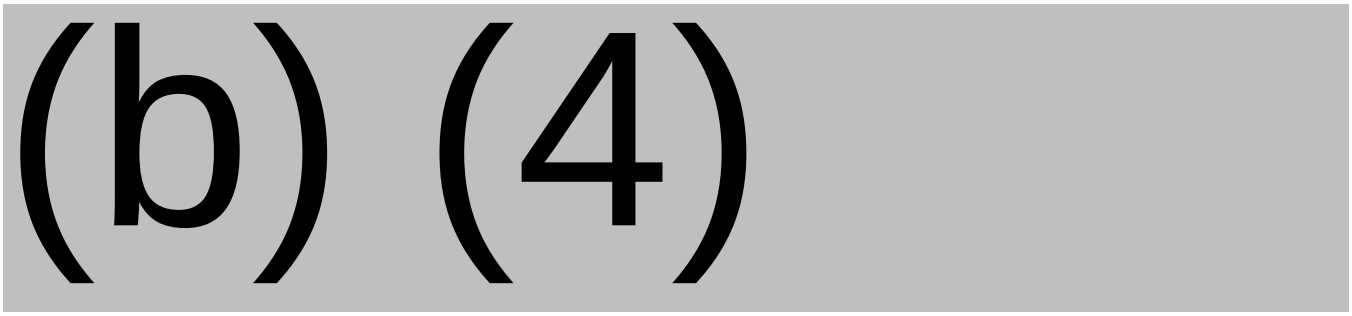


Table B.3-1 Specifications for Deglusterol Powder

(b) (4)

B.4 Product Analysis for Deglusterol Powder [CONFIDENTIAL]

(b) (4)

B.4.1 Product Analysis for the Individual Deobetide and Adiporin Peptide Components

(b) (4)

Table B.4.1-2 Specifications and Batch Analysis for 5 Production Batches of Adiporin

(b) (4)

Table B.4.1-2 Specifications and Batch Analysis for 5 Production Batches of Adiporin

(b) (4)

B.5 Additional Product Analysis [CONFIDENTIAL]

B.5.1 Proximate Analysis

(b) (4)

Table B.5.1-1 Proximate Analysis of Deglusterol Powder

(b) (4)

B.5.2 Pesticide Analysis

(b) (4)

B.6 Intended Use Level of the New Dietary Ingredient

Caregen is the bulk ingredient manufacturer of Deglusterol powder. The ingredient is intended to be used in dietary supplement products intended for use by adults at levels of up to 30 mg/day to support a healthy blood sugar level. Dietary supplement products containing Deglusterol powder are not intended for pregnant and lactating women or children, on the basis that appropriate studies for these demographic groups have not been carried out. A use level of 30 mg Deglusterol/day will provide a maximum daily exposure level of 15 mg deobetide and 15 mg adiporin.

Based on population reference intakes for protein[1], adults consume up to 0.80 g protein/kg body weight/day; therefore, a 70-kg adult would consume approximately 56 g protein/day. Daily intake of 30 mg Deglusterol powder corresponds to a total peptide content of 30 mg/day (15 mg/day for each peptide). At this level of intake, the amount of protein contributed from the proposed use of Deglusterol powder would be very small (0.06% of the reference daily intake) and is likely within the range of normal variation of protein intake among the general population.

[1] IOM (2005): https://www.nap.edu/read/10490/chapter/12

SECTION C – SAFETY AND TOXICOLOGY

C.1 Comprehensive Safety Profile for the New Dietary Ingredient

The safety of Caregen's Deglusterol powder is supported by a battery of product-specific toxicity studies conducted with the (b) (4) (*i.e.*, Deglusterol powder), including acute toxicity studies, 13-week repeated-dose toxicity studies in rodent and non-rodents (rats and dogs, respectively), toxicokinetic studies in rats and dogs, and genotoxicity studies, including an *in vivo* micronucleus test, bacterial reverse mutation test, and chromosomal aberration test. The safety of Deglusterol powder is further supported by its safe history of use in dietary supplements in Russia and the Philippines (see Section C.2).

The scientific evidence provided in the Sections below, along with the history of use in dietary supplements, collectively support that the use of Deglusterol powder as an NDI at levels of up to 30 mg/day will reasonably expected to be safe.

C.2 History of Safe Use

C.2.1 Russia

In 2017, Caregen received a declaration of conformity indicating that Deglusterol complies with the Russian Technical Regulation of the Customs Union 021/2011 "On Safety of Food Products" and 022/2011 "Food Products Marketing" (Customs Union Commission, 2011a,b). Within Russia, the recommended use level of Caregen's Deglusterol is 30 mg/day and is intended to be consumed on a chronic daily basis. The translated declaration of conformity document, for Deglusterol use in Russia, is provided in Appendix E, along with the relevant Export Declaration Certificates.

C.2.2 The Philippines

In 2020, the Philippines Food and Drug Administration approved Deglusterol powder (FDA Registration No.: FR-4000003590708) as a food supplement with no approved therapeutic claims, pursuant to the provisions of Republic Act No. 3720, otherwise known as the *Food, Drugs and Devices, and Cosmetic Act*, as amended by Executive Order No. 175, and Republic Act No. 9711, otherwise known as the *Food and Drug Administration Act of 2009*, and other applicable laws, rules, and regulations (Republic of the Philippines, 1963, 2009). Deglusterol is marketed in The Philippines in food supplement products that are to be consumed at levels of 30 mg Deglusterol/day on an ongoing, chronic, basis. The certificate of product registration is provided in Appendix E.

C.3 Metabolic Fate [CONFIDENTIAL]

(b) (4)

(b) (4)

C.4 Studies to Support Safety of Deglusterol [CONFIDENTIAL]

C.4.1 13-Week Oral Toxicity Study in Rats

(b) (4)

(b) (4)

C.4.2 13-Week Oral Toxicity Study in Dogs

(b) (4)

(b) (4)

C.4.3 Bacterial Reverse Mutation Assay

(b) (4)

C.4.4 Chromosome Aberration Test

(b) (4)

C.4.5 Micronucleus Test Conducted in Mice

(b) (4)

(b) (4)

C.4.6 Additional Acute Studies with Safety-Related Endpoints

(b) (4)

(b) (4)

C.5 Clinical Studies [CONFIDENTIAL]

(b) (4)

C.6 Safety Narrative of Dietary Supplement [CONFIDENTIAL]

(b) (4)

(b) (4)

SECTION D – COMPLETE LIST OF REFERENCES

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