CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218549Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

Integrated Quality Review

NDA 218549

Zunveyl (benzgalantamine) Delayed-Release Tablets

NDA Executive Summary

1. Application/Product Information

NDA Number	218549		
Applicant Name	Alpha Cognition, Inc.		
Drug Product Name	Zunveyl (benzgalantamine)		
Dosage Form	Tablet, delayed release		
Proposed Strength(s)	5 mg, 10 mg, 15 mg		
NDA Classification	Type 2, 3 - New Active Ingredient and New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	30 mg/day		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of mild to moderate dementia of the Alzheimer's type.		
Drug Product Description	5 mg: White, round, convex, DR tablet with printed B05 in grey 10 mg: Purple, round convex, DR tablet with printed B10 in grey 15 mg: Grey, round convex DR tablet with printed B15 in dark grey		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Katherine Duncan
	Drug Product/ Labeling	Grace Chiou	Martha Heimann/ Julia Pinto
	Manufacturing	Vicky He	Shu-Wei Yang
	Biopharmaceutics	Jia Leo	Ta-Chen Wu

Reference ID: 5412448

	Microbiology	N/A	N/A
	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA[1]

3. Action Letter Information

a. Expiration Dating:

For commercial product (HDPE bottles): 24 months stored at 20°C to 25°C.
For physician samples (blisters): 6 months stored at 20°C to 25°C.

b. Additional Comments for Action

To be communicated as PMC 4666-1:

Submission of the following PMC reports under a Prior Approval Supplement (PAS) to the NDA:

1. Investigation of root-cause of the high variability of the dissolution data for the proposed drug product.
2. A new dissolution method development report with new data evaluating the medium volume, adequate justification and evidence for using surfactant and its levels, and the discriminating ability of the proposed dissolution method.
3. Provide full in vitro dissolution profile data [including individual, mean (n=12) and %CV at each sampling time points] for all strengths of clinical and registration batches and the first six commercial batches using the revised dissolution method.
4. Propose a new set of dissolution acceptance criteria with appropriate time-point selection for the buffer stage, taking into consideration the results of method's discriminating ability.

Final report due date: 2/28/2025

[1] QPA: Product Quality Agreement, OPQ term for Post-marketing Commitment (PMC)

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL with QPAs of NDA 218549 for Zunveyl (benzgalantamine delayed release tablets) 5 mg, 10 mg, and 15 mg. The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product with respect to the drug substance, drug product composition, manufacture, and stability. However, the Biopharmaceutics team recommends that the dissolution method acceptance criteria proposed for release and stability testing be accepted on an interim basis only, with a post-marketing commitment (PMC) to develop and validate an optimized dissolution method. The applicant has agreed to the PMC and commits to complete the following by February 28, 2025:

- (b) (4)
- Provide full in-vitro dissolution profile data (including individual, mean [n=12] and %CV at each sampling time points) for all strengths of clinical and registration batches.
- Propose a new set of dissolution acceptance criteria with appropriate timepoint selection for the buffer stage, taking into consideration results of the revised method's discriminating ability.

Allowing the applicant to optimize the dissolution method under a PMC is reasonable given that the current method, while not optimal, does reflect the delayed-release characteristics of the product. Further, the dissolution method is primarily for quality control purposes. The requested post-marketing studies are intended to optimize test parameters for the current method, not to develop new method.

The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate with QPAs**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

Other than the PMC discussed Section 4.a, there are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
7/11/2024

Martha Heimann

Digitally signed by Martha Heimann
Date: 7/11/2024 05:37:06PM
GUID: 504f845f00000ed260627d268a8cdc9d
Comments: Revised to correct expiry information on page 2.

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	218549
Assessment Cycle Number	1
Drug Product Name	Benzgalantamine delayed release tablet

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0001**
Patient Information	N/A	**NA**
Instruction for Use (IFU)	N/A	**NA**
Container Labels	Adequate	**0001**
Carton Labeling	Adequate	**0010**

Brief Description of Outstanding Issues: Adequate pending revisions below. The main revisions are regarding the salt policy as the equivalency statements compare benzgalantamine salt to galantamine free base. Instead, the equivalency statements should be of benzgalantamine salt compared to benzgalantamine free base. The remaining outstanding items are alphabetization of inactive ingredients, range for storage conditions, and inclusion of physical property (i.e., pKa, solubility, etc.).

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Original Submission (eCTD 0001)	01/05/2024	Carton label
Labeling Amendment (eCTD 0010)	01/05/2024	Updated PI, container label

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	N/A
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	N/A
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Inadequate	See above. It should be revised to say "Tablets: 5 mg, 10 mg, 15 mg of benzgalantamine
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	N/A

Assessment: *Adequate*

Pending revision regarding salt policy to "Dosage and Administration"

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration,	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Inadequate	As this is a delayed-release drug product, language should be added to the PI to not crush or chew the tablets.
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Assessment: *Adequate*

In general, this section is adequate pending revision by Applicant to include language regarding to not chew or crush as this is a delayed-release tablet. ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg	Inadequate	(b) (4)

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
of drug-x hydrochloride). No equivalency statement.		(b) (4)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	

Assessment: *Adequate*

Pending the revision to the salt equivalency as noted above, this section is adequate.

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

1.2.3 Section 11 (DESCRIPTION)[14]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	Revise to include "delayed release tablet for oral use"
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency	Inadequate	Revise salt statement to equivalency in terms of benzgalantamine free base vs benzgalantamine gluconate.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		(b) (4) (b) (4) Thus, it should be revised to "…contains 5 mg, 10 mg, and 15 mg benzgalantamine equivalent to 7.49 mg, 14.98 mg, and 22.47 mg benzgalantamine gluconate, respectively." (b) (4) (b) (4).
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	Revise as structural formula should have number as subscript. Additionally, statement regarding (b) (4) Revise molecular weight statement as it is (b) (4) (b) (4) The statement should describe the molecular weight of benzgalantamine gluconate vs benzgalantamine.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Inadequate	Revise to include a physical property such as pH or pKa (only solubility in water is stated).
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

Pending Applicant revision to the comments above, this section is adequate.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) ***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Inadequate	Revise from (b) (4) to "debossed"

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Revise to :" Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex.*	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Avoid statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Inadequate	Add child resistant packaging statement since it is present on the carton and container labels.

Add

Assessment: *Adequate*

Adequate pending revisions above.

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Active ingredient made in Taiwan.

ZUNVEYL delayed-release tablets are manufactured for:

Alpha Cognition, Inc.

(b) (4)

[redacted]

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Inadequate	Remove "Active ingredient made in Taiwan."

Assessment: *Adequate*

Adequate pending revision above.

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

There was no medication guide provided. As such, each Item is adequate in lieu of this.

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

(b) (4)

[redacted]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Inadequate	Yes	Revise salt equivalency to be of benzgalantamine free base vs benzgalantamine gluconate (see comments regarding salt policy for PI above).
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	Yes	Revise to: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
For injectable drug products for parenteral administration, use appropriate package type	N/A	Yes	

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Inadequate	No	Inactive ingredients is not in alphabetical order on the carton box and is not present on the container closure. The lack of inactive ingredients on the container closure is adequate. However, if they are on the carton they should be alphabetized.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See	Adequate	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Yes	
And others if space is available.	N/A	Yes	

[31] USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

Adequate pending revisions above.
Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The PI and container closure system is adequate pending revisions above.

Primary Labeling Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Grace Chiou

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Date: 5/09/2024 12:13:47PM
GUID: 5c5df155002b1863abe42e6c00c2780f

Julia Pinto

Digitally signed by Julia Pinto
Date: 5/09/2024 02:45:49PM
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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-218549-ORIG-1
Assessment Cycle Number	01
Drug Product Name/ Strength	Benzgalantamine delayed-release tablet/ 5 mg, 10 mg, 15 mg
Route of Administration	Oral
Applicant Name	Alpha Cognition, Inc.
Therapeutic Classification/ OND Division	Neurologic Disorders /DN1
RLD/RS Number	NDA 021169 Razadyne® (galantamine hydrobromide) tablets and NDA 021615 Razadyne® ER (galantamine hydrobormide) extended-release capsules
Proposed Indication	Treatment of mild to moderate dementia of the Alzheimer's type
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant is seeking approval of benzgalantamine delayed-release tablet 5 mg, 10 mg, and 15 mg via 505(b)(2) pathway. The listed drugs are Janssen Pharmaceuticals, Inc.'s Razadyne® (galantamine hydrobromide) tablets (equivalent of 4 mg, 8 mg, and 12 mg free base, discontinued) under NDA 021169 and Razadyne® ER (galantamine hydrobromide) extended-release capsules (equivalent to 8 mg, 16 mg, and 24 mg free base, discontinued) under 021615. The proposed benzgalantamine delayed-release tablet is a prodrug (also referred to as GLN-1062 or ALPHA-1062). The active principle is galantamine. The proposed dosage strengths (5 mg, 10 mg, and 15 mg) contain the equivalent of (b) (4) (b) (4) respectively. The proposed dosing regimen is twice daily.

The key Biopharmaceutics review findings with respect to the proposed dissolution method and acceptance criteria, in vitro alcohol dose-dumping potential, and formulation bridging are summarized below.

Dissolution Method:

The originally proposed dissolution method was deemed unacceptable because of insufficient information. In response to the Agency's request, the Applicant submitted a new dissolution method development report with some additional tests performed with 12 units and new data for evaluation of the discriminating ability (**Appendix 1**).

Based on the re-submitted data/justification, the selection of apparatus, medium pH, and rotation speed is acceptable. (b) (4) (b) (4) (b) (4) Furthermore, the provided data supporting the discriminating ability of the proposed dissolution method are inadequate because the investigation of the method's discriminating ability was not properly performed. The deficiencies of the proposed dissolution method were conveyed to the Applicant in the post-market commitment (PMC) (**Appendix 2**).

Dissolution Acceptance Criteria:
The Applicant provided additional dissolution profile data for 10 mg clinical/registration batches using the proposed dissolution method, in addition to the data for 5 mg and 15 mg clinical/registration batches provided in the original submission. Given that the dissolution method is pending, the proposed dissolution acceptance criteria cannot be evaluated at this time. The proposed acceptance criterion of "no individual release > (b) (4)% in 120 min" for the acid stage is acceptable. (b) (4) (b) (4) the proposed dissolution acceptance criterion (Q = (b) (4)% in 60 min) for the buffer stage does not possess capability for serving as the quality control for batch release and stability testing. The deficiency of the proposed dissolution acceptance criteria was conveyed to the Applicant in the PMC (**Appendix 2**).

In Vitro Alcohol-Dose Dumping Potential:
The Applicant conducted in vitro alcohol dose-dumping study in the presence of 0%, 5%, 20%, and 40% (v/v) alcohol on the 5 mg and 15 mg strengths using the proposed dissolution test conditions. The presence of 20% alcohol resulted in greater drug releases at the buffer stage for both strengths, compared to the control (0%), suggesting the potential shift in PK curve, as well as the potential impact on drug exposure later in the dosing interval. With 40% alcohol, near complete drug release occurred at the acid sage by 2 hours, with implication for both safety and efficacy. Results showed the potential impact of 20% and 40% alcohol on the enteric coating and drug release mechanism of the proposed delayed-release drug product.

Formulation bridging:
The proposed commercial formulation and the formulation used in pivotal clinical studies are the same as the final formulation. No in vivo bridging study is needed.

RECOMMENDATION:
From a Biopharmaceutics perspective, NDA 218549 for benzgalantamine delayed-release tablet 5 mg, 10 mg, and 15 mg is recommended for approval. The proposed dissolution method and acceptance criteria for batch release and stability testing of Benzgalantamine from Benzgalantamine delayed-release tablet 5 mg, 10 mg, 15 mg are accepted on an interim basis. The Applicant agreed to the PMC On 6/27/2024 and will submit the final PMC report by 2/28/2025. Refer to Appendix 2 for the PMC # 4666-1.

The accepted interim dissolution method and acceptance criteria for batch release and stability testing of Benzgalantamine from Benzgalantamine delayed-release tablet 5 mg, 10 mg, 15 mg are as follows:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (basket)	50	Acid stage: 0.1N HCl Buffer stage: 0.05M Sodium Phosphate buffer pH 6.8 with 0.5% SDS	1000	Acid stage: No individual release > (b)(4)% in 120 min Buffer stage: Q = (b)(4)% in 60 min

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	9/27/2023
Sequence 0009 / Response to Biopharmaceutics Information Request	12/21/2023
Sequence 0013 / Response to Biopharmaceutics Information Request	3/29/2024
Sequence 0020/ Correspondence regarding post-marketing commitment (PMC)	6/27/2024

Highlight Key Issues from Last Cycle and Their Resolution:
None. This is the first review cycle.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):
The Applicant is requested to develop optimized dissolution method for the proposed delay-release drug product under PMC # 4666-1.

B.1 BCS DESIGNATION

Reference ID: 5412448

Assessment:
No BCS designation was requested. No permeability data for the drug substances were provided. Based on the provided aqueous solubility data and the highest single dose (15 mg), the drug substance, benzgalantamine, is highly soluble per BCS criteria and exhibits pH-dependent solubility.

Solubility:

Table 1. Aqueous solubility of benzgalantamine across pH 1.2 – 8.0[1]

Solvent	Solubility (mg/mL) [a)]			Descriptive Term [b)]
	B#71668AA001	B#71668AA002	B#71668AA003	
pH 1.2 buffer	515.55	452.78	445.09	Freely soluble
pH 4.5 buffer	95.16	90.39	96.64	Soluble
pH 6.8 buffer	0.40	0.37	0.39	Very slightly soluble
pH 7.4 buffer	0.35	0.34	0.34	Very slightly soluble
pH 8.0 buffer	0.084	0.086	0.081	Practically insoluble
H_2O (37℃)	924.93	921.13	936.17	Freely soluble
H_2O (25℃)	92.68	90.38	93.28	Soluble

Permeability:
No permeability data for the drug substances were provided.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Inadequate}***

1. Dissolution Method

(b) (4)

(b) (4) The originally proposed dissolution method (Table 2) is deemed unacceptable because 1) no numerical solubility data for the drug substance were provided, 2) the number of units (n = 1 – 3) were used in the dissolution tests to support the selection of dissolution parameters, and 3) the discriminating ability of the proposed dissolution method was not evaluated. The Applicant was requested to submit a new dissolution method development report in an Information Request (IR) dated 11/15/2023 (see Appendix 1). The Applicant submitted new solubility data only on 12/21/2023. On 3/29/2024, the Applicant submitted a new dissolution method development report with additional tests performed with 12 units and new data for evaluation of the discriminating ability.

Based on the provided data/justification, the selection of apparatus, medium pH, and rotation speed is acceptable. The selection of medium volume is unacceptable and the data supporting the selection of (b) (4) are inadequate. The provided

[1] \\CDSESUB1\EVSPROD\nda218549\0009\m3\32-body-data\32s-drug-sub\galantaminebenzoategluconate-scinopharmtaiwanltd\32s3-charac\gln1062-solu-ard2455so01.pdf

Reference ID: 5412448

(b) (4)

The provided data supporting the discriminating ability of the proposed dissolution method are considered inadequate in that the investigation of the method's discriminating ability was not properly performed, thus the claim and provided data in support of method's discriminating ability are not convincing. (b) (4)

(b) (4)

The deficiency of the proposed dissolution method is conveyed to the Applicant in the post-market commitment (PMC; see Appendix 2).

Table 2. Proposed dissolution method (TP81834)

Apparatus	I (Baskets)
Dissolution Media	Acid Stage: 0.1 N HCl Buffer Stage: 0.05 M Sodium Phosphate Buffer pH 6.8 with 0.5% SDS
Sample Volume	1000 mL
Temperature	(b) (4)
Pull Volume	
Pull Times	Acid Stage: 120 Minutes Buffer Stage: (b) (4) 60 Minutes and (b) (4)
Rotations Per Minute	50
Filter	(b) (4)

1) Dissolution method development

(b) (4)

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(b) (4)

2) Discriminating power of the dissolution method

The original submission did not include evaluation of the discriminating ability of the proposed dissolution method. The Applicant was requested to provide a new dissolution development report with evaluation of the discriminating ability in the IR dated 11/15/2023. In response submitted on 3/29/2024, the Applicant evaluated the discriminating ability of the proposed dissolution method (b) (4)

(b) (4)

(b) (4) Based on the results (**Figures 5 - 10** and **Tables 26 - 28**), the Applicant concluded that the proposed dissolution method is discriminating. However, this Reviewer disagreed because the changes of the tested variables are considerably greater than the Agency's typically recommended ± 10-20% to the target values or ranges, specifically, (b) (4)

(b) (4)

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(b) (4)

2. Dissolution Data and Acceptance Criterion

Table 29. Proposed dissolution acceptance criteria

Acid stage	No individual release > (b) (4)% in 120 min
Buffer stage	Q = (b) (4)% in 60 min

The Applicant provided dissolution profile data for 5 mg and 15 mg clinical/registration batches only in the original submission, using the proposed dissolution method (**Tables 30 – 35**).[4] In response to Biopharmaceutics IR dated 11/15/2023 (see Appendix 1), the Applicant provided additional dissolution profile data for 10 mg clinical/registration batches using the proposed dissolution method (**Tables 36 – 39**).[5]

[4] \\CDSESUB1\EVSPROD\nda218549\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\rpt142945\rpt142945-r00-in-vitro-dissolution.pdf

[5] \\CDSESUB1\EVSPROD\nda218549\0009\m1\us\111-info-amend\1-11-4-multi-info-amend-21dec2023.pdf

As the dissolution method is pending, the proposed dissolution acceptance criteria cannot be evaluated at this time. (b) (4)

(b) (4)

(b) (4) Therefore, the proposed dissolution acceptance criterion (Q = (b) (4)% in 60 min) for the buffer stage, doesn't adequately serve the quality control purpose. The deficiency of the proposed dissolution acceptance criteria is conveyed to the Applicant in the PMC.

(b) (4)

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B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol-Induced Dose Dumping*

Assessment:

The Applicant conducted in vitro alcohol dose-dumping studies in the presence of 0%, 5%, 20%, and 40% (v/v) alcohol on the 5 mg and 15 mg strengths using the proposed dissolution conditions.[6,7] Based on the provided data, for both 5 mg and 15 mg strengths with 20% alcohol, greater drug releases were observed at the buffer stage (**Tables 40 and 41; Figures 11 and 12**). With 40% alcohol, drug is nearly completely released at the acid sage by 2 hours (**Tables 42 and 43**), with implication for both safety and efficacy.

The proposed drug product is a delayed release tablet, which is designed to completely release the contents after passing through the acidic gastric environment. Results showed the potential impact of 20% and 40% alcohol on the enteric coating and drug release mechanism of the proposed delayed-release drug product. Early drug release in the presence of alcohol concentrations at 20% and higher could potentially lead to shifting of PK curve to the earlier timepoints, shortened Tmax, and potential safety concern early and loss of disease control late in the dosing interval.

Figure 11. 5 mg - Results for buffer stage with varying amounts of alcohol

Figure 12 15 mg - Results for buffer stage with varying amounts of alcohol

[6] \\CDSESUB1\EVSPROD\nda218549\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\rpt143665\rpt143665-01-alcohol-dose-dumping.pdf

[7] \\CDSESUB1\EVSPROD\nda218549\0001\m2\27-clin-sum\271-sum-biopharm-studies.pdf

Reference ID: 5412448

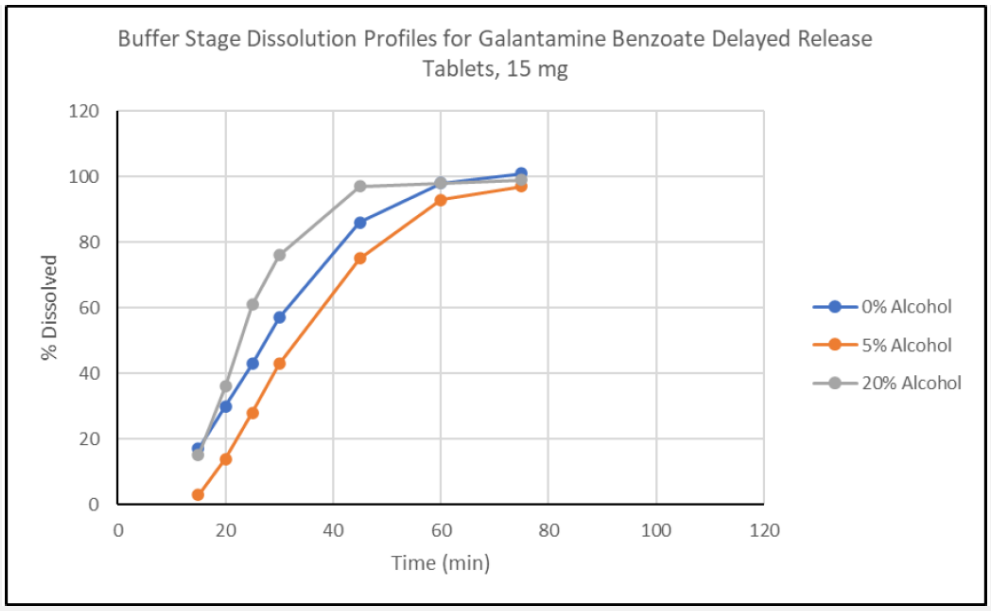

Table 40. 5 mg - Results for acid stage with 20% alcohol

Vessel	% Dissolved			
	30 Minutes	60 Minutes	90 Minutes	120 Minutes
1	ND	ND	ND	ND
2	ND	ND	ND	ND
3	ND	ND	ND	ND
4	ND	ND	ND	ND
5	ND	ND	ND	ND
6	ND	ND	ND	ND
7	ND	ND	ND	ND
8	ND	ND	ND	ND
9	ND	ND	ND	ND
10	ND	ND	ND	ND
11	ND	ND	4	13
12	ND	ND	ND	ND
Mean	–	–	–	–
% RSD	–	–	–	–

Table 41. 15 mg - Results for acid stage with 20% alcohol

Reference ID: 5412448

Vessel	% Dissolved			
	30 Minutes	60 Minutes	90 Minutes	120 Minutes
1	ND	ND	ND	ND
2	ND	ND	ND	ND
3	ND	ND	ND	1
4	ND	ND	ND	ND
5	ND	ND	ND	ND
6	ND	ND	ND	ND
7	ND	ND	1	3
8	ND	ND	ND	ND
9	ND	1	2	4
10	ND	1	1	5
11	ND	ND	ND	ND
12	ND	ND	ND	ND
Mean	–	–	–	–
% RSD	–	–	–	–

Table 42. 5 mg – Results for acid stage with 40% alcohol

Vessel	% Dissolved			
	30 Minutes	60 Minutes	90 Minutes	120 Minutes
1	1	87	102	102
2	ND	63	89	91
3	ND	67	97	96
4	ND	26	93	96
5	3	81	96	97
6	ND	60	103	104
Mean	1	64	97	98
% RSD	167.5	33.3	5.4	5.0

Table 43. 15 mg - Results for acid stage with 40% alcohol

Vessel	% Dissolved			
	30 Minutes	60 Minutes	90 Minutes	120 Minutes
1	1	6	41	93
2	2	27	79	101
3	1	27	91	97
4	1	3	28	91
5	ND	5	50	99
6	1	15	70	94
Mean	1	14	60	96
% RSD	81.7	79.0	40.4	3.9

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

According to the Applicant, the formulation of the proposed drug product has not changed throughout the development. The final formulation (**Table 44**) is the

Reference ID: 5412448

proposed commercial formulation. All clinical studies were completed using the same formulation. No in vitro or in vivo bridging is needed.

Table 44. Composition of benzgalantamine tablet

Ingredients	% w/w	5 mg	10 mg	15 mg	Functionality	Quality Standards
		mg per tablet	mg per tablet	mg per tablet		
Galantamine benzoate gluconate (equivalent to free form)[1]	(b) (4)	7.49 (5)	14.98 (10)	22.47 (15)	Active	In-house
Mannitol	(b) (4)				(b) (4)	NF
Colloidal Silicon Dioxide	(b) (4)					NF
Sodium Stearyl Fumarate						NF
Magnesium Stearate						NF
						(b) (4)
Total Theoretical Enteric Coted Tablet weight		68.2	135.1	199.8	NA	NA

[1] 1 mg galantamine benzoate free form = 1.501 mg galantamine benzoate gluconate salt

(b) (4) (b) (4)

NF: National Formulary (US); USP: United States Pharmacopeia

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Ta-Chen Wu

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Jia Leo

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/s/

MARTHA R HEIMANN
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