CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208944Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approve

NDA 208944
Review # 1

Drug Name/Dosage Form	Gocovri (amantadine) extended release capsules
Strength	68.5 mg, 137 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Adamas Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Haripada Sarker	ONDP/DNDAPI I/Branch I
Drug Product	Stephanie Emory	ONDP/DNDP I/Branch I
Process	Yaodong (Tony) Huang	OPF/DPA/Branch VIII
Microbiology	Yaodong (Tony) Huang	OPF/DPA/Branch VIII
Facility	Steven Fong	OPF/DIA/Branch I
Biopharmaceutics	Qi Zhang	ONDP/DB/Branch I
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP I/Branch I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD#: 0001	24-Oct-2016	All
SD#: 0002	18-Nov-2016	Drug Substance, Product, Process
SD#: 0005	23-Jan-2017	Drug Substance, Product
SD#: 0008	02-Feb-2017	Biopharmaceutics
SD#: 0012	31-Mar-2017	Facility
SD#: 0015	19-Apr-2017	Product, Process, Biopharmaceutics
SD#: 0016	11-Jul-2017	Biopharmaceutics

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	5/6/2016	Reviewed by G. Kumaran
	III			N/A [2]	N/A [2]	
	III			N/A [1]	N/A [1]	
	III			N/A [2]	N/A [2]	
	III			N/A [2]	N/A [2]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	IV			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [2]	N/A [2]	
	III			N/A [2]	N/A [2]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [2]	N/A [2]	
	III			N/A [2]	N/A [2]	
	III			N/A [1]	N/A [1]	
	III			N/A [2]	N/A [2]	

[1] Adequate information in application or no changes to information since previous reviews.

[2] Used during clinical development only.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78671	Clinical studies to support amantadine extended release capsule
NDA	16020, 16023, 17118, and 18101	Symmetrel Tablets and Syrup are cross-referenced under 505(b)(2)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 208944 for Gocovri (amantadine) extended release capsules. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Amantadine Hydrochloride was initially approved in 1966, as Symmetrel capsules, for prophylaxis and treatment of infections caused by influenza A virus strains. It was approved in 1973 for treatment of parkinsonism and drug-induced extrapyramidal reactions. In the current 505(b)(2) NDA, the applicant seeks approval of extended-release (ER) capsules for a more specific indication, i.e., treatment of levodopa induced dyskinesia in patients with Parkinson's disease.

Proposed Indication(s) including Intended Patient Population	Treatment of levodopa induced dyskinesia in patients with Parkinson's disease
Duration of Treatment	Chronic
Maximum Daily Dose	274 mg
Alternative Methods of Administration	Capsule contents may be sprinkled on soft food such as applesauce. The mixture should be consumed immediately after preparation.

B. Quality Assessment Overview

Drug Substance

Amantadine hydrochloride is a white or almost white crystalline powder. It is non hygroscopic, practically insoluble in ether, sparingly soluble in methylene chloride, soluble in chloroform, and freely soluble in water.

The bulk active ingredient (API) used to manufacture commercial product will be supplied by MOEHS Iberica S. L., Barcelona, Spain. Information regarding the characterization, manufacture, and control of the API is incorporated by cross-

reference to MOEHS Iberica's drug master file (DMF) [redacted] (b) (4) The DMF was most recently reviewed by G. Kumaran and deemed adequate. [Refer to review dated 5/6/2016.] The NDA itself includes the drug product manufacturer's acceptance specification. The bulk drug substance complies with USP and EP monograph requirements. Noncompendial analytical procedures are adequately described and validated.

Drug Product

The proposed products are extended-release capsules that contain amantadine hydrochloride equivalent to 68.5 mg or 137 mg amantadine base per capsule. The capsule fill consists of [redacted] (b) (4) The capsules contain conventional pharmaceutical excipients, i.e., microcrystalline cellulose, hypromellose, copovidone, talc, ethylcellulose, povidone, medium chain triglycerides, magnesium stearate, gelatin, and [redacted] (b) (4), all of which comply with compendial standards.

With the exception of capsule color and imprinting, the proposed commercial 137 mg capsule is the same formulation as used for the pivotal clinical study. The applicant submitted a biowaiver request for the 68.5 mg strength. The information provided regarding the BA/BE for the higher strength (137 mg), composition proportionality of the formulations for both proposed strengths, PK linearity in the proposed range, and dissolution profile comparison is appropriate and fully supports the approval of the BA/BE waiver request for the proposed lower strength (68.5 mg ER capsules). Therefore, the biowaiver is granted.

The information provided in the application supports the extended-release claim for the proposed amantadine ER capsules. However, based on in vitro dissolution studies, there is a potential for dose dumping if the product is taken with alcohol. The proposed labeling includes instructions in sections 2 and 17 that the product not be taken with alcohol. Inclusion of a stronger warning regarding potential CNS adverse events in section 7.5 of the labeling is therefore recommended.

The drug product manufacturing process involves [redacted] (b) (4)

The proposed regulatory specification for Gocovri extended-release capsules includes test parameters that are typical for an extended-release product. In general, the analytical procedures are straightforward and supported by adequate method validation studies. The proposed acceptance criteria for most test parameters are considered suitable. At the Agency's request, the applicant revised the acceptance criterion for (b) (4) from not more than (NMT) (b) (4)% to NMT (b) (4)% as the stability data indicate that (b) (4) in the finished product leads to faster dissolution. The applicant also agreed to add a 6-hour time point to the dissolution test procedure. Thus, the regulatory dissolution acceptance criteria are NMT (b) (4)% at 2 hours (b) (4)% at 6 hours, (b) (4)% at 8 hours, and NLT (b) (4)% of the labeled amount of amantadine dissolved at 12 hours [*USP apparatus II (Paddle) at 50 rpm; 500 or 900 mL of water at 37°C*].

Amantadine extended-release capsules are packaged in 60-count white, opaque HDPE bottles with induction sealed, (b) (4) closures and 7-count (b) (4))/aluminum push-through blister strips (physician samples). Based on stability data provided in the application, a 36-month shelf life for capsules packaged in bottles and a 24-month shelf for capsules packaged in blister strips are granted for product stored at controlled room temperature.

Methods Verification

Amantadine Hydrochloride is a well characterized small molecule that is subject to a USP monograph, and the analytical procedures for the finished product are straightforward. Thus, this is considered a low risk product from an analytical perspective, and methods verification studies were not requested.

Facilities

All facilities that will be involved in commercial manufacture and testing of Gocovri (amantadine) extended-release capsules are currently acceptable.

C. Special Product Quality Labeling Recommendations

Based on the potential for dose dumping, it is recommended that the following language be included in Section 7.5 of the product labeling: *"Concomitant use with alcohol should be avoided as it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension; and may result in dose-dumping based on in-vitro studies."*

D. Final Risk Assessment for Amantadine Extended Release Capsules

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	**L**	(b) (4)	Acceptable	
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	**L**		Acceptable	
Content uniformity	Low dose, particle size/shape, segregation, flow property	**L**		Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	**L**		Acceptable	
Bead size for sprinkles	Formulation, process parameters, scale/equipment	**L**		Acceptable	
Alcohol dose dumping	Formulation, solubility of rate controlling excipient and/or API	**H**		Acceptable	
Dissolution	Particle size, moisture, hardness, size, shape, film coat, formulation, process parameters	**M**		Acceptable	

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LABELING

R Regional Information

1.14 Labeling

Prescribing Information

1. "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	GOCOVRI® (amantadine)	Adequate
Dosage form, route of administration	extended release capsules, for oral use	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended release capsules: 68.5 mg and 137 mg	Adequate.

Reviewer's Overall Assessment: Adequate.

2. "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	GOCOVRI is available as capsules for oral administration.	Adequate.
Strengths: in metric system	Each capsule contains 68.5 mg or 137 mg of amantadine.	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The 68.5 mg capsule is a white opaque size #2 capsule, with black printing of 'ADAMAS' on front and '85' on back of the cap and three black bands printed on body of capsule. The 137 mg capsule is a light blue opaque size #0 capsule, with black printing of 'ADAMAS' on front and '170' on back of the cap and three black bands printed on body of capsule.	Adequate.

Reviewer's Overall Assessment: Adequate.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	GOCOVRI is an extended release formulation of amantadine hydrochloride.	Adequate
Dosage form and route of administration	GOCOVRI capsules are intended for oral use.	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each capsule contains 85 mg or 170 mg amantadine hydrochloride which is equivalent to 68.5 mg or 137 mg of amantadine free base, respectively.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Capsules also contain the following inactive ingredients: microcrystalline cellulose, [redacted] (b) (4), ethyl cellulose, povidone, copovidone, medium chain triglycerides, talc and magnesium stearate in a hard gelatin capsule.	Replace "[redacted] (b) (4)" with "hypromellose." Remove the space between "ethyl" and "cellulose." Change "medium chain" to "medium-chain" triglycerides. List in alphabetical order.
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Missing	Add pharmacological or therapeutic class
Chemical name, structural formula, molecular weight	Chemical name: tricyclo [3.3.1.1 3,7] decan-1-amine, hydrochloride or 1-adamantanamine hydrochloride Empirical formula: $C_{10}H_{17}N \bullet HCl$ Molecular weight: 187.71 (g/mol)	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Amantadine hydrochloride is a white crystalline powder and is non-hygroscopic, practically insoluble in ether, sparingly soluble in methylene chloride, soluble in chloroform and freely soluble in water, ethanol, and methanol.	Adequate.

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the changes noted above.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	GOCOVRI (amantadine HCl) extended release capsule is supplied as 68.5 mg and 137 mg capsules which is equivalent to 85 mg or 170 mg of amantadine hydrochloride, respectively...	Adequate
Available units (e.g., bottles of 100 tablets)	60 count bottles of 68.5 mg capsules (NDC# 70482-085-60) 60 count bottles of 137 mg capsules (NDC# 70482-170-60)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The 68.5 mg capsule is a white opaque size #2 capsule, with black printing of 'ADAMAS' on front and '85' on back of the cap and three black bands printed on body of capsule. The 137 mg capsule is a light blue opaque size #0 capsule, with black printing of 'ADAMAS' on front and '170' on back of the cap and three black bands printed on body of capsule.	Adequate (see "Available units" for NDC #)
Special handling (e.g., protect from light, do not freeze)	None stated.	Adequate
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	At the end of Section 16: Manufactured for: Adamas Pharma (b) (4) Emeryville, CA 94608 This information is also listed at the end of the "PATIENT INFORMATION" section.	Relocate to follow section 17

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the change noted above.

Patient Information

Item	Information Provided in NDA	Reviewer's Assessment
Storage conditions	Store GOCOVRI at room temperature between 68°F to 77°F.	Add temperature range in Celsius: "(20°C to 25°C)"
Active ingredient	amantadine hydrochloride	Adequate.
Inactive ingredients	microcrystalline cellulose, hydroxypropylmethyl cellulose, ethyl cellulose, povidone, copovidone, medium chain triglycerides, talc and magnesium stearate	Replace (b) (4) with "hypromellose." Remove the space between "ethyl" and "cellulose." Change "medium chain" to "medium-chain" triglycerides. List in alphabetical order. Add (b) (4) at the end of the list.

Reviewer's Overall Assessment: Adequate, pending the applicant's acceptance of the changes noted above.

Structured Product Labeling

[TRADENAME]
amantadine (b) (4) capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70482-085
Route of Administration	ORAL		

Structured Product Labeling - Continued

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
amantadine (b) (4) UNII: (b) (4) (amantadine - UNII:BF4C9Z1J53)	amantadine	(b) (4)

Inactive Ingredients

Ingredient Name	Strength
microcrystaline cellulose (UNII: OP1R32D61U)	24.29 mg
(b) (4)	(b) (4)
copovidone (UNII: D9C330MD8B)	5.66 mg
talc (UNII: 7SEV7J4R1U)	5.54 mg
hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	12.89 mg
ethylcellulose (7 MPA.S) (UNII: H3UP11403C)	31.06 mg
povidone K90 (UNII: RDH86HJV5Z)	4.20 mg
medium-chain triglycerides (UNII: C9H2L21V7U)	3.75 mg
magnesium stearate (UNII: 70097M6I30)	0.20 mg

Product Characteristics

Color	(b) (4)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	ADAMAS;85;Three;black;bands
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70482-085-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208944		

[TRADENAME]
amantadine (b) (4) capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:70482-170
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
amantadine (b) (4) UNII: (b) (4) (amantadine - UNII:BF4C9Z1J53)	amantadine	(b) (4)

Inactive Ingredients

Ingredient Name	Strength
microcrystaline cellulose (UNII: OP1R32D61U)	48.57 mg
povidone K90 (UNII: RDH86HJV5Z)	8.40 mg
medium-chain triglycerides (UNII: C9H2L21V7U)	7.50 mg
magnesium stearate (UNII: 70097M6I30)	0.39 mg
(b) (4)	(b) (4)
copovidone (UNII: D9C330MD8B)	11.32 mg
talc (UNII: 7SEV7J4R1U)	11.07 mg
hypromellose 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	(b) (4)
ethylcellulose (7 MPA.S) (UNII: H3UP11403C)	62.13 mg

Product Characteristics

Color	BLUE (BLACK)	Score	no score
Shape	CAPSULE	Size	22mm
Flavor		Imprint Code	ADAMAS (b) (4) hree;black;bands
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70482-170-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Structured Product Labeling - Continued

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208944		

Labeler - Adamas Pharmaceuticals, Inc. (192255110)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions (Somerset, NJ)		825745131	ANALYSIS(70482-085, 70482-170) , MANUFACTURE(70482-085, 70482-170)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions (Morrisville, NC)		014167995	ANALYSIS(70482-085, 70482-170)

Establishment

Name	Address	ID/FEI	Business Operations
Sharp Corporation, Allentown, PA		143696495	PACK(70482-085, 70482-170)

Establishment

Name	Address	ID/FEI	Business Operations
Sharp Corporation, Conshohocken, PA		002346625	PACK(70482-085, 70482-170)

Establishment

Name	Address	ID/FEI	Business Operations
Mooks Catalana SL		460021629	API Manufacture(70482-085, 70482-170)

Revised: 10/2016 Adamas Pharmaceuticals, Inc.

Reviewer's Assessment: Inadequate. The "basis of strength" must be revised to amantadine (free base) and the capsule strengths revised to reflect the quantities of amantadine free base (137 mg and 68.5 mg). The 68.5 mg capsule color must be revised from (b) (4) to white. The product name must be updated to the approved tradename GOCOVRI.

Labels - Overview

Draft labels are provided for the following 6 packaging configurations:

1. Bottle: 68.5 mg capsules (60-ct) (no outer carton)
2. Bottle: 137 mg capsules (60-ct) (no outer carton)
3. Blister (1-week sample): 68.5 mg capsules (7-ct)
4. Blister (1-week sample): 137 mg capsules (7-ct)
5. Blister (2-week combination sample): 68.5 mg capsules (7-ct) + 137 mg capsules (7-ct)
6. Blister (2-week 137 mg sample): 137 mg capsules (21-ct)

Immediate Container (Bottle) Labels

(b) (4)

Reviewer's Assessment: Inadequate. (b) (4) must be removed from the established name of the active ingredient, and the capsule strengths must be revised to express the quantity of amantadine free base (137 mg and 68.5 mg) instead of the (b) (4).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2-week 137 mg sample pack:

(b) (4)

[redacted]

Reviewer's Assessment: Inadequate. For all 3 blister pack configurations, "(b) (4)" must be removed from the established name of the active ingredient, and the capsule strengths must be revised to express the quantity of amantadine free base (137 mg and 68.5 mg) instead of the (b) (4)

List of Deficiencies:

Structured Product Labeling:

1. Revise "basis of strength" to "amantadine" (free base).
2. Revise capsule strengths to reflect amantadine free base quantities (137 mg and 68.5 mg).
3. Revise 68.5 mg capsule color from (b) (4) to white.
4. Update product name to the approved tradename GOCOVRI.
5. List the inactive ingredients in alphabetical order.

Labels (all):

6. Revise capsule strengths to reflect amantadine free base quantities (137 mg and 68.5 mg).
7. Remove (b) (4) from the established name of the active ingredient.

Stephanie Emory

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Date: 7/19/2017 08:10:46AM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/19/2017 08:49 00AM
GUID: 50816dbc000085595ca3284bbca465a8

BIOPHARMACEUTICS

NDA: 208944
Drug Product Name/Strength: Gocovri® (amantadine hydrochloride) Extended Release Capsules; 170 mg and 85 mg (as 137 mg and 68.5 mg base, respectively)
Route of Administration: Oral
Applicant Name: Adamas Pharmaceuticals, Inc.

Background: Adamas Pharmaceuticals, Inc. is seeking approval for Gocovri® (amantadine HCL) Extended Release Capsules; 170 mg and 85 mg, to be administered orally for the treatment of levodopa induced dyskinesia in patients with Parkinson's disease under the 505 (b)(2) path. The proposed drug product is a hard gelatin capsule filled with (b) (4) pellets containing the active ingredient, amantadine HCL. Amantadine HCL (b) (4) pellets are (b) (4)

This 505(b)(2) NDA relies in part on the FDA's findings of safety for Symmetrel® (NDAs 16-020, 16-023, 17-118, and 18-101, Endo Pharmaceuticals), an immediate-release (IR) form of amantadine HCL. It is noted that Symmetrel is no longer marketed in the US. The clinical package in support of this NDA for ADS-5102 includes the results of 3 efficacy studies, interim results of an open-label long-term safety study (currently ongoing), and 5 pharmacokinetics (PK) studies. The primary clinical support of this NDA for treatment of levodopa-induced dyskinesia in patients with Parkinson's disease is supported by two Phase 3 registration studies: ADS-AMT-PD301 and, ADS-AMT-PD304. Additionally, study ADS-PAR-AM201, a Phase 2/3 dose-finding study, provides supportive safety and efficacy findings.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the proposed dissolution method and acceptance criteria, **2)** the alcohol dose-dumping potential of the proposed drug product, **3)** the extended release claim for the proposed drug product, **4)** bridging throughout product development, and **5)** the Biowaiver request for the lower 85 mg strength of the proposed drug product.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution Method and Acceptance Criteria:*** The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 50 rpm; 500 or 900 mL of water at 37°C*] was fully validated and is considered acceptable. The proposed acceptance criteria of NMT (b) (4)% at 2 hours, (b) (4)% at 6 hours, (b) (4)% at 8 hours and NLT (b) (4)% of the labeled amount of amantadine HCL dissolved at 12 hours are table for release and on stability.

2) ***Alcohol Dose-Dumping Potential:*** The results from the in vitro alcohol dissolution showed that with increasing amounts of alcohol (25% ethanol and most noticeably at 30% and 40%), there is dose dumping. With 5% and 10% ethanol there is a small, no significant increase in the dissolution rate. However, the dissolution rate observed with 15% and 20% ethanol is unexpectedly lower than the dissolution rate of the control product with no ethanol. These results could be attributed to the

swelling of the [redacted] (b) (4) by 15% to 20% ethanol in acidic media, which may close the [redacted] (b) (4) thus reducing drug [redacted] (b) (4) in the dissolution medium. It is noted that the labeling of the proposed product includes in Sections 2 and 17, advise information that the proposed drug product should NOT be taken with alcohol. However, there is no clear labeling information regarding the potential risk or clinical consequence of concomitant use of alcohol. Therefore, the following statement was recommended to be added to Section 7.5 of the labeling: *"Concomitant use with alcohol should be avoided as it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension; and may result in dose-dumping based on in-vitro studies."*

3) ***Extended Release claim:*** The provided information fully support the extended release claim for the proposed amantadine HCL ER Capsules.

4) ***Bridging of Formulations:*** The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product, except for the color and imprinting on the capsule shells. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products was not needed.

5) ***Biowaiver Request:*** The provided information/data regarding the BA/BE for the highest 170 mg strength, composition proportionality of the formulations for all proposed strengths, PK linearity in the proposed range, and dissolution profile comparison/f2 values is appropriate and fully supports the approval of the BA/BE waiver request for the proposed lower strength (85 mg ER capsules) and therefore the biowaiver is granted.

RECOMMENDATION

From a Biopharmaceutics perspective, NDA 208944 for Gocovri® (Amantadine) Extended Release Capsules, 68.5 mg and 137 mg, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD **7/12/2017**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Angelica Dorantes, PhD **7/12/2017**
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

➢ LIST SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	10/24/2016	Original submission
0010 (11)	3/20/2016	Information Amendment
0014 (15)	4/19/2017	Quality/Response to information request
0015 (16)	7/11/2017	Quality/Response to information request

➢ DRUG PRODUCT

The proposed drug product, Gocovri® (amantadine HCL) Extended Release Capsules; 170 mg and 85 mg, is a hard gelatin capsule filled with (b) (4) pellets containing the active ingredient, amantadine HCL. Amantadine HCL (b) (4) pellets are (b) (4) pellets comprising an (b) (4)

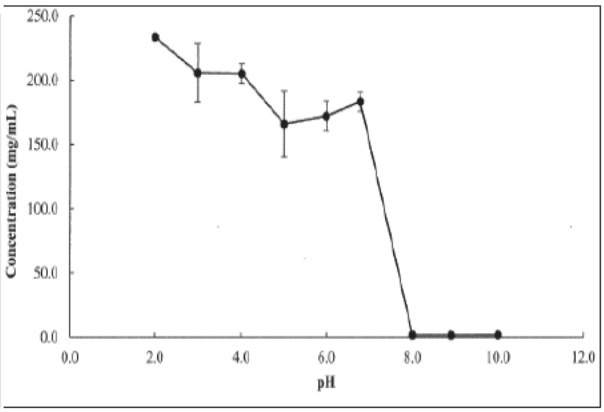
➢ *BCS DESIGNATION*

Amantadine HCL is reported in the literature as a BCS Class 3. However, a BCS designation request has not been submitted to FDA and therefore, this drug product was not been evaluated by the FDA's BCS committee ((V:\DIVISION\BIO\BCS\BCS Drug Lists: BCS Committee Reviewed Products; Last updated on 4/18/2017).

- ***Solubility:*** Amantadine HCL exhibits pH-dependent solubility. It is freely soluble (greater than 100 mg/ml) at pH 2.0 to 6.8 and slightly soluble (less than 10 mg/ml) at pH 8.0 to 10.0. The solubility of Amantadine HCL in various pH buffer solutions, as determined by the Applicant, is presented in **Figure 1.**

Figure 1: pH-Solubility Profile of Amantadine HCl

pH	Calculated Concentration (mg/mL)
2.0	> 230
3.0	205.8
4.0	205.2
5.0	165.9
6.0	172.2
6.8	183.5
8.0	1.955
8.9	1.736
10.0	2.073



- ***Permeability:*** Permeability information for amantadine HCL was not provided in the submission.
- ***Dissolution:*** Dissolution profile data were provided. Refer to the dissolution data below.

➢ *DISSOLUTION INFORMATION*

Proposed Dissolution Method and Acceptance Criteria: The dissolution method and dissolution acceptance criteria proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Acceptance Criteria
II (Paddle)	50	Degassed purified water	500 for the 85 mg strength 900 for the 170 mg strength /37	GC	2 hours: NMT (b) (4)% LC 6 hours: (b) (4)% LC 8 hours: (b) (4)% LC 12 hours: NLT (b) (4)% LC

Dissolution Method Development:

(b) (4)

(b) (4)

Discriminating Capability of the Dissolution Method:

- (b) (4) The proposed dissolution method was shown to be sensitive to the changes of the (b) (4) pellets. The (b) (4) pellets that produced under " (b) (4) conditions (Lot #15JM-481E) with a (b) (4) value of (b) (4)% had a markedly faster dissolution profile than those produced under " (b) (4) conditions (**Figure 3**). Based on the dissolution data, the Applicant established an (b) (4) as NMT (b) (4)% as requested by the Process reviewer, Yaodong Huang. It is also noted that upon the request from DP reviewer, Stephanie Emory, the Applicant (b) (4) the acceptance criterion for (b) (4) from NMT (b) (4)% to NMT (b) (4)% in the proposed release and stability drug product specifications, as the stability data indicate that the (b) (4) in the finished drug product leads to faster drug release.

Figure 3: Effect of (b) (4) Process Conditions on Dissolution Profile of (b) (4)% w/w (b) (4) (b) (4) Pellets

(b) (4)

- (b) (4): (b) (4) is considered to be a critical quality attribute (CQA) affecting dissolution of the amantadine HCL ER Capsules. The Applicant showed that the significant difference in release rate was observed between the lowest ((b) (4)% w/w) and the highest levels of (b) (4) ((b) (4)% w/w) (**Figure 4**). (b) (4) of (b) (4)% w/w to (b) (4)% w/w showed comparable dissolution profiles. (b) (4) of % and (b) (4)% w/w failed the proposed acceptance criteria at 8 h time point. Based on the dissolution profile data, an (b) (4)

(b) (4) of (b) (4)% w/w on (b) (4) pellets was chosen for the proposed amantadine HCL ER Capsules.

Figure 4: Dissolution Profiles of (b) (4) Pellets with Different Amounts of (b) (4)

(b) (4)

- ***Stability Samples:*** To determine the discriminating capability of the capsule dissolution method, the Applicant evaluated the dissolution of environmentally stressed capsules for the 170 mg strength capsules. The results (**Figure 5A**) show that the drug release is slightly faster for the samples stored in an open dish under 40°C/75%RH conditions for 19 days compared to that for samples stored in open dish under 23°C/60%RH, 23°C/90%RH or 60°C and an unstressed control sample. The dissolution of amantadine HCL ER Capsules stored for 6 months under accelerated conditions of 40°C/75%RH was faster from 4 to 8 hours when compared to the dissolution profile at T=0 (**Figure 5B**).

Figure 5A: Dissolution Profiles of ADS-5102 170 mg Lot l4JM-120 Stored for 7 Months under Different Open-Dish Stressed Conditions for 19 Days versus Unstressed Control Samples

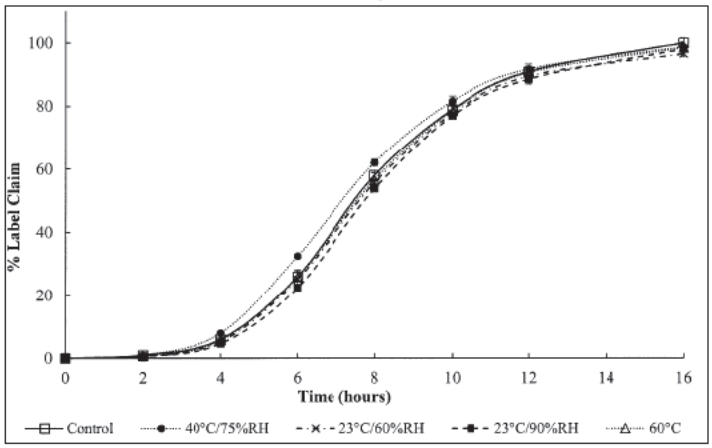
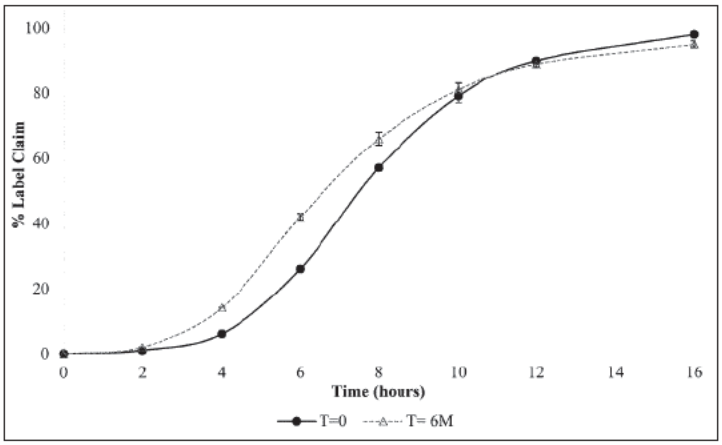


Figure 5B: Dissolution Profile of ADS-5102 170 mg, Lot 14JM-120 Stored for 6 Months Under Accelerated Conditions 40°C/75%RH Compared to T=0 (lot release)



Reviewer's Note: *The Reviewer did not consider the submitted data as depicted in* ***Figure*** *5 as evidence of discriminating power because the apparent profile differences were not significant (f_2<50) and all the tested stability samples passed the proposed dissolution acceptance criteria.*

Validation of Dissolution Method:

The GC method adapted from a previously validated dissolution method by HPLC for the dissolution portion and a previously validated Assay method by GC for the sample analysis portion at (b) (4) (b) (4), was used to quantify the drug in the dissolution samples at Catalent Pharma Solutions in Somerset, NJ for Adamas Pharmaceuticals, Inc.

The Applicant reported that, based on data for both 80 mg and 170 mg ER capsules at all sampling time points, the GC method passed the pre-specified acceptance criteria for validation of specificity, linearity, accuracy, instrument repeatability, intermediate precision, solubility stability, robustness with respect to HPLC (filter validation, mobile phase flow rate, composition, column temperature and detection wavelength) and robustness with respect to dissolution (dissolution RPM, media volume, temperature and deaeration of dissolution media).

Refer to the Drug Product Review, for the evaluation of the adequacy of the validation of the analytical method (including the GC method used for dissolution testing).

Reviewer's Assessment: ***ADEQUATE***

Overall, the proposed dissolution method is fully validated and is considered adequate for the quality control purposes based on the availability of sufficient sink condition, as well as, discriminating ability of the method towards critical manufacturing variables (e.g. [redacted]). It is noted that the proposed dissolution method is the same method as the FDA's Dissolution Method Database and the USP monograph for Amantadine HCL Tablets and Capsules.

Dissolution Acceptance Criteria:

The dissolution profile data (2, 4, 6, 8, 10, 12 and 16 hours) collected from all the clinical and registration batches at lot release are summarized in **Table 1**.

The originally proposed dissolution acceptance criteria by the Applicant for batch release and stability testing are as follows:

2 hours: NMT [redacted]% LC
8 hours: [redacted]% LC
12 hours: NLT [redacted]% LC

However, based on the provided dissolution data, an additional time point was needed for the initial phase of the dissolution profile. Therefore, on July 10, 1017, the following Biopharmaceutics Information Request Comment was conveyed to the Applicant:

> *"Based on the provided dissolution data, an additional 6-hour time point with a range of [redacted]% for the initial phase of the dissolution profile is needed. Therefore, we request that you add the 6-hour time point and implement the dissolution acceptance criteria of "NMT [redacted]% at 2 hours, [redacted]% at 6 hours, [redacted]% at 8 hours and NLT [redacted]% at 12 hours" at release and on stability for your propos covri ® (amantadine HCL) Extended Release Capsules product. Please provide a copy of the revised specifications table for your drug product with the updated acceptance criteria for the dissolution test and also update other sections of your submission as appropriate."*

On July 11, 2017, the Applicant responded (SDN-0016) to the above IR and agreed to the FDA's recommendation to include an additional 6-hour time point with a range of [redacted]% in the acceptance criteria of the dissolution test. The Applicant also provided the revised drug product specifications table with the updated acceptance criteria for the dissolution test.

Reviewer's Assessment: **ADEQUATE**

Based on the provided dissolution data, the proposed dissolution acceptance criteria of [redacted]% of drug released at 2 hours, [redacted]% at 6 hours, [redacted]% at 8 hours and [redacted]% at 12 hours are acceptable.

Table 1: Dissolution Data at Release for All the Clinical and Registration Batches

Lot Number	Strength	Mean Dissolution [Individual Values] (% Label Claim)					
		2 hours	4 hours	6 hours	8 hours	10 hours	12 hours
		Dissolution Limits:					(b) (4)
AMNH11-05	60 mg						
AMNH11-06	140 mg						
14JM-070	170 mg						
14JM-073	85 mg						
14JM-119	85 mg						
14JM-120	170 mg						
14JM-191	85 mg						
14JM-197	170 mg						
14JM-367	170 mg						
14JM-368	170 mg						
Mean		2	10	33	62	81	93
SD		0.767	3.70	5.79	3.93	7.63	2.59
Mean ± 3SD		0-4	0-21	16-50	50-74	58-104	85-101

LC = Label claim

- ***IN-VITRO ALCOHOL DOSE DUMPING***

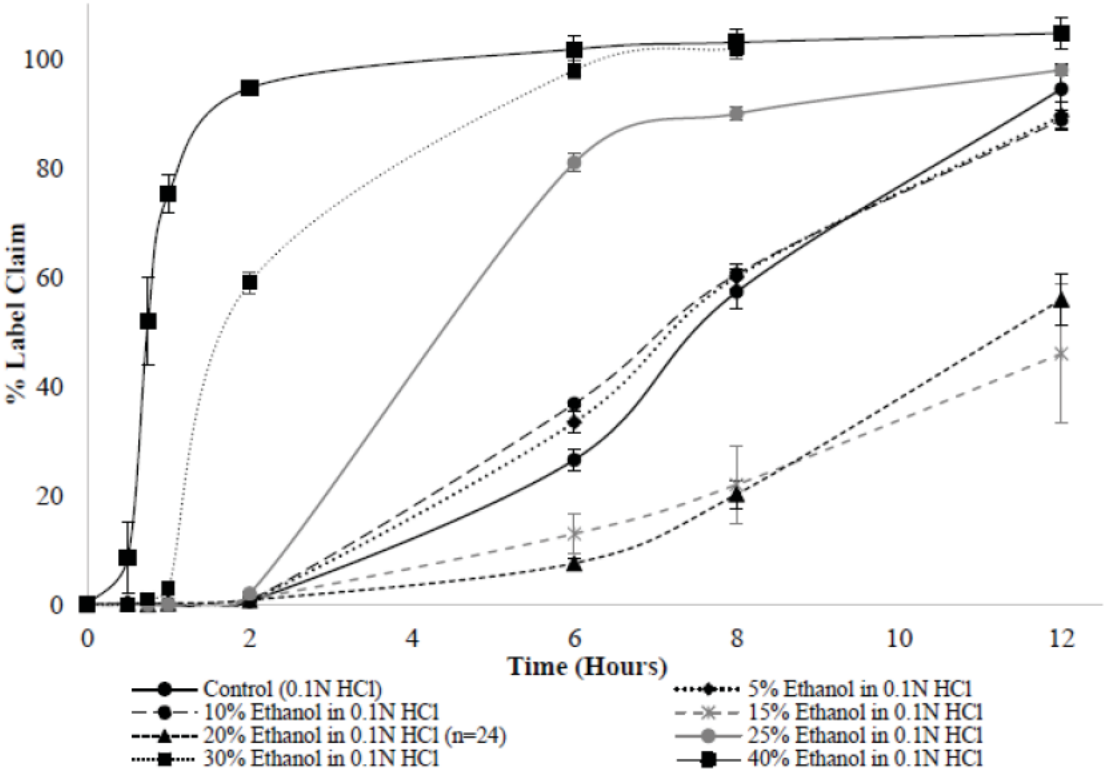
Three in-vitro alcohol dose-dumping studies were conducted using USP Apparatus II (paddle) at 50 rpm; 900 ml of 0.1 N HCL dissolution medium at 37°C. The studies designs are outlined below in **Table 2**. The results of the studies are summarized in **Figure 6**.

Table 2: Parameters for Dissolution Studies

Parameter	Experiment 1	Experiment 2	Experiment 3
Dissolution media	0%, 5%, 10%, 20% and 40% ethanol in 0.1N HCl	15%, 25% and 30% v/v ethanol in 0.1N HCl	20% and 40% v/v ethanol in water
Sampling times	0.5, 0.75, 1, 2, 6, 8, and 12 h	0.5, 0.75, 1, 2, 6, 8, and 12 h[a]	0.5, 0.75, 1, 2, 6, 8, and 12 h
Number of capsules	12	6	3
Capsule strength tested	170 mg (Lot 14JM-197) and 85 mg (Lot 14JM-191)	170 mg (Lot 14JM-197)	170 mg (Lot 14JM-197)

[a] 12 hour timepoint was not tested at 30% ethanol.

Figure 6: Dissolution Profiles of Amantadine HCL ER capsules, 170 mg Lot 14JM-197 From All the Various Ethanol Concentration Tested (0%, 5%, 10%, 15%, 20%, 25%, 30% and 40% v/v)



The results from the in vitro alcohol dissolution showed that with increasing amounts of alcohol (25% ethanol and most noticeably at 30 and 40%), there is dose dumping. With 5% and 10% ethanol there is a small, no significant increase in the dissolution rate. However, the dissolution rate observed with 15% and 20% ethanol is unexpectedly lower than the dissolution rate of the control product with no ethanol. These results may be attributed to the swelling of the (b) (4) by 15% to 20% ethanol in acidic media that may close the (b) (4) thus reducing drug wettability in the dissolution medium. Overall, the presence of increasing amount of ethanol at 25% and higher, dramatically increases the dissolution rate of the proposed drug product at early time points, whereas the presence of 15-20% ethanol significantly reduces the dissolution rates of the proposed drug product.

It is noted that the following language regarding alcohol intake was included in Sections 2 and 17 of the labeling of the proposed amantadine HCL ER Capsules product:

2. DOSAGE AND ADMINISTRATION

(b) (4)

17. PATIENT COUNSELING INFORMATION

(b) (4)

Reviewer's Assessment: ADEQUATE

The overall results of in-vitro alcohol study indicate that there is induced alcohol dose dumping with concentrations of alcohol ≥25%-40%. The proposed drug product labeling includes in Sections 2 and 17 the information that the proposed product should NOT be taken with alcohol. However, there is no clear labeling information regarding the potential risk or clinical consequence of concomitant use of alcohol. Therefore, the following language was recommended to be added to the labeling in Section 7.5: *"Concomitant use with alcohol should be avoided as it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness and orthostatic hypotension; and may result in dose-dumping based on in-vitro studies."*

- ***EXTENDED RELEASE CLAIM***

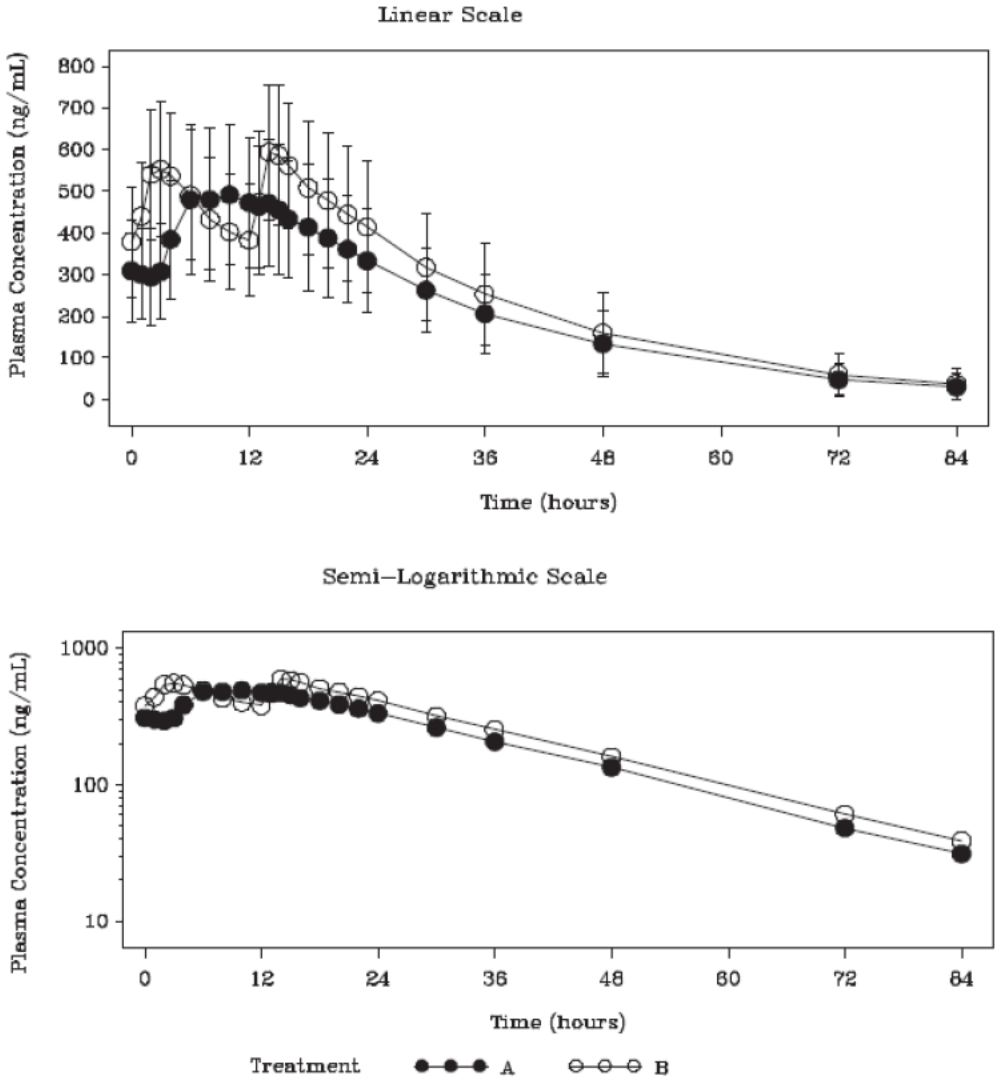
Extended-release products allow a two-fold or greater reduction in frequency of administration of a drug product in comparison with the frequency required by a conventional dosage form.

The 21 CFR 320.25 (f) requirements to support an extended release designation claim are as follow:

(I). The drug product meets the extended release claims made for it.
(II). The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.
(III). The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
(IV). The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

Amantadine HCL ER Capsules performance at steady-state is comparable (e.g., degree of fluctuation is lower) to Amantadine HCL IR product. The proposed amantadine HCL HCL ER capsules provide consistent PK performance between individual dosage units (based on information in the NDA). The pharmacokinetic comparison, as illustrated in **Figure 7**, indicates that amantadine HCL ER capsules exhibit characteristics of extended-release (noticeable the prolonged time to peak concentration or Tmax) in comparison with Amantadine HCL IR capsules. The data support the extended-release claim for the proposed drug product.

Figure 7: Mean (±SD) Plasma Concentrations of Amantadine HCL Versus Time – Steady-State – Steady-State Analysis Population



Abbreviations: BID, twice daily; ER, extended release; IR, immediate release; QD, once daily.

Note: Subject (b) (6) was excluded from the pharmacokinetic analysis populations due to vomiting on Day 1 of Period 1.

Study drug administered at 8PM (or 20:00 hours) for QD administration and 8PM and 8AM (20:00 hours and 08:00 hours) for BID administration.

Treatment A = ADS-5102 ER (170 mg, QD, single and multiple doses).

Treatment B = Amantadine IR (200 mg, QD, single dose and 100 mg, BID, multiple doses).

Reviewer's Assessment: ADEQUATE

The provided information fully supports the extended release claim for the proposed amantadine HCL ER Capsules.

➢ ***BRIDGING OF FORMULATIONS***

Different formulations of amantadine HCL ER capsules were studied at various stages of drug product development. Initial formulation development and manufacturing of the Phase 1 and Phase 2 clinical supplies were conducted at [redacted] (b) (4) After Phase 2/3 Dosing Finding Study was completed, the manufacturing of amantadine HCL ER capsules was scaled up and transferred from (b) (4) to Catalent Pharma Solutions (Catalent), Somerset, New Jersey, and a bioequivalence (BE) study (ADS-AMT-PK112) was conducted to bridge the 2 manufacturing sites. All subsequent Phase 3 clinical studies used amantadine HCL ER capsules manufactured at Catalent (studies ADS-AMT-PD301, ADS-AMT-PD302, ADS-AMT-PD304, and PK studies). Catalent is the proposed commercial manufacturing site for ADS-5102 capsules. The commercial formulation is the same as that used in Phase 3 clinical and registration stability studies, except for the color and imprinting on the capsule shells.

The Applicant stated that the phase 2/3 clinical batches manufactured at (b) (4) had a (b) (4)% w/w [redacted] (b) (4) and the phase 3 clinical batches at the commercial site Catalent, had an [redacted] (b) (4) of (b) (4)% w/w and both were bioequivalent (*Refer to the Clinical Pharmacology Review for the evaluation of the in vivo BE data supporting the bridging between the two manufacturing sites,* (b) (4) *and Catalent*). In vitro dissolution profiles of Lots AMNH11-05 and AMNH11-06 used in the Phase 2/3 study manufactured at (b) (4) and Lot 14JM-070 manufactured Catalent used in Phase 3 clinical study are presented in **Figure 8**, and are all within the specifications proposed for the commercial product.

Figure 8: Dissolution Profiles of ADS-5102 Lots AMNH11-05, AMNH11-06 used in Pivotal clinical studies and in the Bioequivalence study

Reviewer's Assessment: ADEQUATE

The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration-stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed.

- ***BIOWAIVER REQUEST***

It is noted that this submission did not include a biowaiver request for the proposed lower 85 mg strength. Therefore, on January 26, 1017, the following Biopharmaceutics Information Request Comment was conveyed to the Applicant:

> *"If you plan to market both strengths of the proposed Amantadine HCL product, you should submit a biowaiver request for the lower strength to the NDA. We request that you include supporting information with the request to fulfill the CFR requirements for a biowaiver".*

The Applicant's request for a waiver of the requirement to provide data from an in vivo BA/BE study for the proposed lower strength (85 mg) ER capsules is supported by the following data: **(1)** there is acceptable PK data for the proposed highest 170 mg strength, **(2)** the 85 mg and 170 mg ER capsules have the same dosage form; **(3)** the formulation of the 85 mg ER capsules is proportionally similar in composition to the formulation of the 170 mg ER capsules (**Table 3**); **(4)** the 85 mg and 170 mg ER capsules have the same manufacturing process; **(5)** the 85 mg and 170 mg capsules have comparable dissolution profiles (**Figure 9**); and **(6)** evidence of PK linearity over the proposed dose range.

Table 3: Composition of the Proposed Drug Product

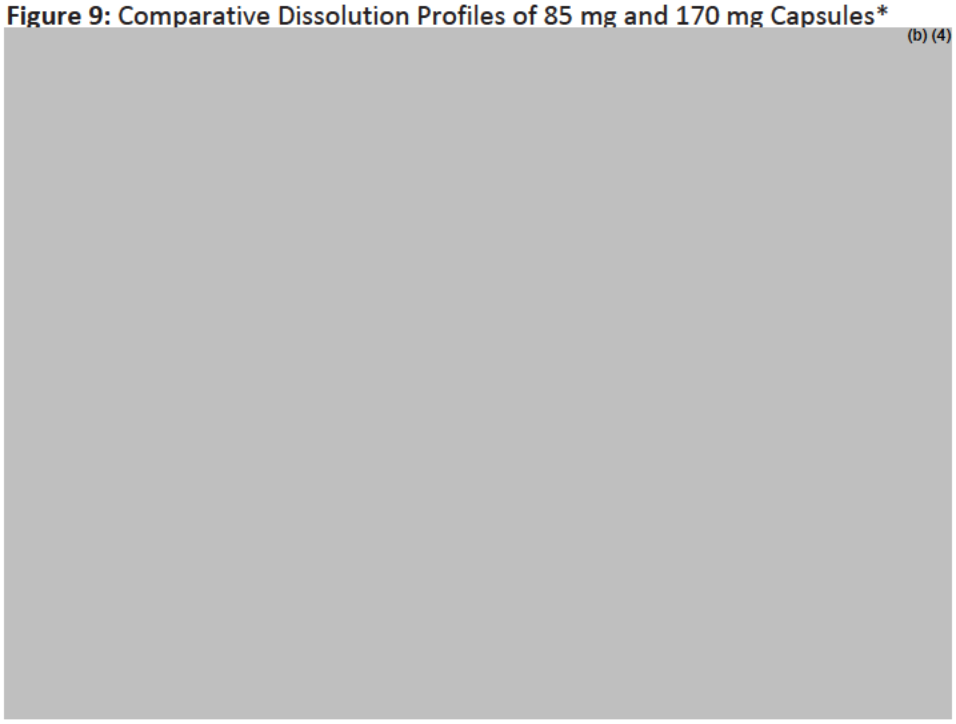
Components	Function	Quality Standard	% w/w in ER-coated pellets	Unit Dose Composition (mg/capsule)	
				85 mg capsule	170 mg capsule
Amantadine Hydrochloride *	Active	USP/Ph. Eur.	(b) (4)	85.00	170.00
Microcrystalline Cellulose (b) (4)	(b) (4)	NF/Ph. Eur.			(b) (4)
(b) (4)		USP/Ph. Eur.			
Copovidone		NF/Ph. Eur.			
Talc		NF/Ph. Eur.			
(b) (4) (Hypromellose 2910), 3 mPa·s		USP/Ph. Eur.			
Ethylcellulose, 7 mPa·s		NF/Ph. Eur.			
Povidone K-90		USP/Ph. Eur.			
Medium-Chain Triglycerides (b) (4)		NF/Ph. Eur.			
Magnesium Stearate		NF/Ph. Eur.			
(b) (4)		USP/Ph. Eur.			
		USP/Ph. Eur.			
Nominal target capsule fill weight (mg)			100%	195.25	390.49
Hard Gelatin Capsule (b) (4)			--	Size '2', white/white	Size '0',Light blue/Light blue

* Moehs DMF (b) (4)

(b) (4)

Figure 9: Comparative Dissolution Profiles of 85 mg and 170 mg Capsules*

(b) (4)



Reviewer's Assessment: ADEQUATE

The provided information/data regarding the BA/BE for the highest 170 mg strength, composition proportionality of the formulations for all proposed strengths, PK linearity in the proposed range, and dissolution profile comparison/*f2* values are appropriate and fully support the approval of the biowaiver request; therefore, the Applicant's request to waive the CFR requirement to conduct an in vivo bioavailability study for the proposed lower strength (85 mg ER capsules) is granted.

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 208944 for Gocovri® (Amantadine) Extended Release Capsules, 68.5 mg and 137 mg, is recommended for **APPROVAL.**

Qi Zhang

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Angelica Dorantes

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