CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208944Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 11, 2017

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 208-944 (ADS-5102 [amantadine hydrochloride] Extended Release capsules; Gocovri)

The sponsor (Adamas Pharmaceuticals) submitted NDA 208-944 (received on October 24, 2016), under section 505(b)(2), for amantadine HCl for treatment of levodopa-induced dyskinesia (LID) in patients with Parkinson's disease. Symmetrel is the reference listed drug (NDA 17-118; oral syrup; withdrawn FR Notice, effective date August 20, 2010) and is approved for "treatment of parkinsonism and drug-induced extrapyramidal reactions," as well as for non-neurological indications. The sponsor conducted clinical development under IND 78671.

A pre-NDA meeting was held (under IND 78671) on March 1, 2016 (Meeting Minutes, dated March 30, 2016). At that time, the sponsor stated that 28 nonclinical study reports (8 in vitro studies to assess amantadine's mechanism of action in LID; one in vivo study in an animal model of Parkinson's disease; 14 non-GLP pharmacokinetic studies; 5 in vitro drug transporter studies) and summaries of relevant data from the Symmetrel package insert, published literature, and the sponsor-conducted studies would be provided in the NDA. An NDA filing meeting was held on December 12, 2016. The application was determined to be suitable for filing. No nonclinical review issues were identified for the 74-day letter (Filing Communication – Filing Review Issues Identified, dated January 5, 2017).

The nonclinical studies and information provided by the sponsor have been reviewed by Dr. McKinney (Review of Pharmacology/Toxicology Data, NDA 208-944, July 26, 2017). Based on that review, Dr. McKinney has concluded that the NDA is approvable from a nonclinical standpoint.

The only nonclinical issues involve labeling, which was based on labeling for the RLD. In addition to the Symmetrel labeling, the sponsor provided a review of published

literature (#ADS-5102-LR-2016-005) relevant to Sections 8.1-8.3 of labeling and in vitro and in vivo assays to further characterize the pharmacological effects of amantadine.

Three published studies were submitted to support revisions to Section 8.1 (Kakinai H et al. Gendai No Rinsho [The Modern Clinic] 3(12):1-14, 1969; Lamar J et al Toxicol Appl Pharmacol (Abstract) 16(3):272, 1970; Yo I et al. Gendai No Rinsho [The Modern Clinic] 4(1):1-12, 1970).

According to the sponsor, the in vitro and in vivo pharmacology studies conducted on amantadine "…contribute to the overall mechanistic understanding of amantadine's…CNS…effects, and provide additional support for the use of amantadine for the treatment of LID." However, the sponsor also states that "Amantadine has multiple diverse pharmacological activities, and the exact mechanism underlying amantadine's anti-dyskinetic activity is not known." This is consistent with published literature, which suggests involvement of multiple neurotransmitter systems in levodopa-induced dyskinesia (e.g., Bezard E et al. Nat Rev Neurosci 2:577-588, 2001; Cenci MA et al CNS Neurol Disord 10:670-684, 2011; Fisone G, Bezard E. Int Rev Neurobiol 98:95-122, 2011; Iravani MM, Jenner P. J Neural Transm 118:1661-1690, 2011; Jenner P Transl Neurodegen 4:3, 2015). Amantadine is characterized as a weak noncompetitive (or uncompetitive) NMDA antagonist (K_i of 10-90 μM, including in assays conducted by the sponsor).

Recommendations:

Nonclinical studies of amantadine were not required to support clinical development or an NDA for amantadine for treatment of LID. Therefore, from a nonclinical standpoint, there is no objection to approval of the NDA.

Labeling recommendations have been communicated separately.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOIS M FREED
08/11/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208944
Supporting document/s:	1
Applicant's letter date:	OCT 24, 2016
CDER stamp date:	OCT 24, 2016
Product:	Amantadine ER (extended release)
Indication:	Drug-induced dyskinesia in Parkinson's disease
Applicant:	Adamas Pharmaceuticals, Inc.
Review Division:	Neurology Products
Reviewer:	LuAnn McKinney, DVM, DACVP
Supervisor Leader:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Anhtu Nguyen

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208944 are owned by Adamas Pharmaceuticals, Inc. or are data for which Adamas Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 208944 that Adamas Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 208944.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

This new drug application is for Gocovri®, an extended release (ER) formulation of amantadine and was submitted under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The intended indication is for Levodopa-induced dyskinesia (LID), a clinical manifestation in Parkinson's disease patients who have been on prolonged treatment with levodopa/carbidopa. The application relies on findings of safety for the reference listed drug (RLD) Symmetrel® (NDAs 16020, 16023, 17118, and 18101), an immediate-release (IR) formulation of amantadine HCl, and on published literature.

Symmetrel is no longer marketed, but amantadine HCl IR tablets and syrup are currently marketed as generic drugs in the US for prophylaxis and treatment of influenza A, for the treatment of Parkinson's disease/syndrome, and for drug induced extrapyramidal reactions.

1.2 Brief Discussion of Nonclinical Findings

A series of in vitro pharmacology studies of amantadine and several non-GLP pharmacokinetic studies were conducted in rat and mouse.

Amantadine is a weak NMDA receptor antagonist and had minimal effects on a broad array of receptors and enzymes, to include in vitro activity as a sigma-1 receptor agonist and a nicotinic acetylcholine receptor antagonist.

In a rat model of LID, by both single dose oral administration of the ER and continuous SC administration of the API by osmotic pump, amantadine significantly reduced the abnormal involuntary movements (AIM) in 6-OHDA-lesioned rats dosed with levodopa and benserazide. Amantadine had no effect on the counter-rotations characteristic of this model of Parkinson's disease.

In published embryofetal studies, amantadine caused embryolethality in rats and mice, and fetal malformations in rats at doses that were 1.8 times the recommended human dose (RHD) of 274 mg per day and adversely affected fertility at doses less than the RHD.

1.3 Recommendations

1.3.1 Approvability:

From a nonclinical perspective, with recommended labelling, this application is approvable.

1.3.2 Labeling

Labeling largely reflects that approved for the RLD; however, the following changes are recommended:

Comparisons to the recommended human dose should be based on the Gocovri® RHD of 274mg/day.

Section 8.1 should reflect the findings described in all three publications summarized in section 9 of this review.

Section 12.1 should reflect that there are adequate nonclinical data to support the claim that amantadine is a weak NMDA receptor antagonist.

2 Drug Information

2.1 Drug

Commercial name: Gocovri®

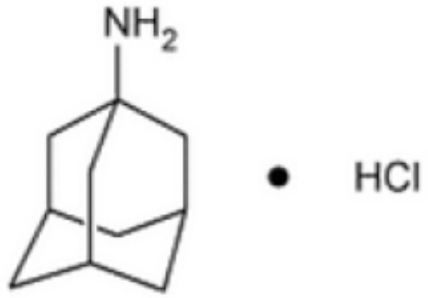
CAS Registry Number: 665-66-7

Generic Name: Amantadine hydrochloride

Chemical Name:
1-adamantanamine hydrochloride
Tricyclo [3. 3. 1. 1 $_{3,7}$] decan-1-amine, hydrochloride

Molecular Formula/mass: $C_{10}H_{17}N \cdot HCl$ / 187.7

Structure



Established Pharmacologic Class: Influenza A M2 protein inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 078671, submitted on AUG 03, 2007
Symmetrel® (NDA 018101)

2.3 Drug Formulation:

Amantadine ER will be formulated as 85 mg and 170 mg capsules, containing 68.5 mg or 137 mg, respectively, of amantadine, in (b) (4) pellets comprised of an (b) (4) (b) (4).
There are no novel excipients and impurities are within acceptable limits.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed dose of Gocovri® is 274 mg of amantadine administered as two 170 mg capsules (each containing 137 mg of amantadine) once daily at bedtime.

2.7 Regulatory Background

IND 078671 was submitted on AUG 03, 2007.
NDA 208944 was submitted on OCT 24, 2016.
No nonclinical studies were required to be submitted to either the IND or this NDA.

3 Studies Submitted

3.1 Studies Reviewed

The sponsor submitted in vitro pharmacology studies and several non-GLP pharmacokinetic and in vivo studies in rat and mouse that supported dose selection for efficacy studies in animal models of LID. The in vivo studies included subcutaneous administration of the amantadine API and oral administration of amantadine ER and API to both normal and 6-OHDA-lesioned rats.

3.3 Previous Reviews Referenced

None

4 Pharmacology

The sponsor submitted publications and a series of in vitro studies to elucidate the pharmacology of amantadine; however, while amantadine was demonstrated to have several pharmacologic activities, the mechanism of the in vivo effects on levodopa-induced dyskinesia is not known.

In a submitted CEREP binding panel, amantadine inhibited binding at the PCP site of the NMDA receptor by 42% at 10 µM and 83% at 100 µM. At 10 µM, amantadine inhibition of other receptors, to include dopamine transporter, did not exceed 26% and were not assessed further.

Sponsor's table:

APPENDIX 2. CONCENTRATION RESPONSE FOR BINDING AT THE PCP SITE OF GLUTAMATE RECEPTOR

Binding IC_{50}										
Reference	**7000502-2**									
Compound	**Amantadine HCl**									
Catalog Reference	**124**									
Assay	**Test Concentration (M)**	**% Inhibition of Control Specific Binding**	**1st / % of Control Specific Binding**	**2nd / % of Control Specific Binding**	**Mean / % of Control Specific Binding**	**SEM % Control**	**IC_{50} (M)**	**Ki**	**Reference Compound**	**IC_{50} Ref (M)**
PCP (antagonist radioligand)	1.00E-11	-9	94.7	123.2	108.9	14.3	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-10	11	81.6	97.2	89.4	7.8	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-09	-7	93.9	120.9	107.4	13.5	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-08	-7	94.1	119.9	107	12.9	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-07	6	82.9	104.9	93.9	11	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-06	1	95.2	102.5	98.8	3.6	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-05	34	59.7	72.8	66.3	6.5	2.00E-05	1.90E-05	MK 801	4.20E-09
PCP (antagonist radioligand)	1.00E-04	83	20	14.8	17.4	2.6	2.00E-05	1.90E-05	MK 801	4.20E-09

[^{3}H]TCP was used as the radioligand.

In two patch-clamp studies of rat coronal brain slices, amantadine blocked the delayed rectifying (DR) potassium current at all concentrations tested (10-1000 µM), blocked potassium leak currents at higher concentrations (100-1000 µM) and decreased the amplitude and increased the decay of the DR potassium current at the highest concentration (1000 µM). In embryo rat mixed cortical cell cultures, amantadine, in serial dilutions from 0.32-100 µM, gave protection at 1, 10, and 32 µM against the effects (cell death) of 5 hours of oxygen/glucose deprivation.

Amantadine did not significantly inhibit BCRP or P-gp: IC_{50} values were reported to be >750 µM, the highest concentration tested. There was minimal to no activity in in vitro assays of protection against 6-hydroxydopamine-induced or beta-amyloid-induced cortical cell death, of lipopolysaccharide-induced cytokine (TNF-α) release, or of neurite growth in rat cortical cell cultures.

There are reports in the published literature implicating amantadine as a sigma-1 agonist. Peeters et al. (Eur J Neurosci, 2004) reported that in vivo amantadine acts as a sigma-1 receptor agonist (Ki 5-8 µM) in the striatum, hippocampus, or cortex in mouse brain. Matsubayashi et al. (J Pharmacol Exp Ther, 1997) studied the effects of amantadine on nicotinic acetylcholine receptors and demonstrated that amantadine preferentially inhibited nicotinic currents in cultured hippocampal neurons.

In two in vivo efficacy studies, amantadine significantly reduced the abnormal involuntary movements (AIMs) in 6-OHDA-lesioned rats that had been dosed with levodopa and benserazide for 18 days. After a single PO dose (45 mg/kg amantadine ER+5 mg/kg or 50 mg/kg amantadine in capsules) 8 hours prior to L-dopa, the mean number of AIMs in the first 100-180 minutes after L-dopa in rats administered the ER combination was 64% lower than in rats administered the API alone and 42% lower than baseline AIMs in either group.

In a multi-dose study in 6-OHDA-lesioned rats that had been administered L-dopa for 5 weeks, 6 rats/group were implanted with osmotic (Alzet®) pumps that delivered 0, 22.5, 45, of 83 mg/kg/day of amantadine for 12 days. Mean plasma concentrations reached steady state after 1 day of infusion and remained steady; concentrations of amantadine in brain were greater than in plasma and correlated with dose. At the HD, the AIMs were reduced by 30% from baseline; however, amantadine administration did not affect the counter-rotational movements characteristic of this rat model of Parkinsonism.

5 PK/ADME

5.1 PK

After a single dose (50 mg/kg) in oral capsules in Sprague Dawley rats, the relative bioavailability of amantadine ER pellets was 72% (based on AUC) of that of an oral solution of the API. The Tmax was ~7 hours, the Cmax was 629 $\pm$ 333 ng/mL, and the mean AUC∞ was 10160 +/- 4759 h*ng/mL.

After a single dose of 50 mg/kg amantadine in oral capsules in Sprague Dawley rats, in various ratios of ER and API, the C_{max} did not differ widely among groups, but the T_{max} and the AUC of the API was significantly lower than the ER formulation. Amantadine was detectable at 24 hours after ER administration, but after API administration was below the LOQ at 12 hours.

5.2 ADME

No ADME studies were submitted to this NDA.

6 General Toxicology

No toxicity studies were required to be submitted to this NDA.

In the submitted animal efficacy study utilizing subcutaneous osmotic pumps, dose-related infusion site irritation was observed. The epidermis overlying the pumps was discolored and seroma formation and hardened tissues were noted at post mortem exam.

7 Genetic Toxicology

No genetic toxicology studies were required to be submitted to this NDA.

8 Carcinogenicity

Adequate carcinogenicity studies have not been conducted, and none were required to be submitted to this NDA.

9 Reproductive and Developmental Toxicology

No reproductive/developmental toxicology studies were submitted to this NDA. The Symmetrel labelling reflects publications of non-GLP studies by Vernier et al. (Toxicol Appl Pharmacology, 1969) and Lamar et al. (Abstracts: Annual Meeting, Soc of Tox, 1970). Vernier et al. (1969) reported that oral administration of amantadine to male and female rats at a dose of 32 mg/kg/day resulted in impaired fertility, but no fetal abnormalities were observed.

Lamar et al. (1970) reported that when amantadine was administered to Harlan Sprague Dawley rats at 0, 50 or 100 mg/kg/day 5 days prior to mating and through Gestation Day (GD) 6, decreased numbers of implants and increased absorptions were found at the HD. Lamar et al. further reported that oral administration of amantadine to pregnant Harlan SD rats from GD 7-14 resulted in marked fetal malformations at the MD and HD (50 and 100 mg/kg/day, respectively) of edema, malrotated hindlimbs, missing tail, stunting, brachygnathia, and ribs and sections of the lumbar and sacral spinal column were found to be absent at both dose levels. `

Table: Lamar et al.

Study	When dosed	Species	Mg/kg	Mg/m^2	Fold RHD*
Rat	GD 7-14	H-SD Rat AEL (HD) Malformations (**)	100	600	3.6
	GD 7-14	H-SD Rat LOAEL (MD) Malformations(**)	50	300	1.8
	GD 7-14	H-SD Rat NOEL (LD)	37	222	1.3
(**) Edema, malrotated hindlimbs, a missing tail, stunting, brachygnathia, absent ribs, absence of section(s) of the lumbar & sacral spine.					
*Recommended human dose: 274 mg/60 kg (4.6 mg/kg = 169 mg/m^2)					

In a publication submitted to this NDA (Kakinai et al. Mod Clin, 1970) of a non-GLP study of amantadine administered orally to pregnant ICR mice from gestation days (GD) 7-12, increased fetal loss and reduced fetal weights were found at the highest dose (40 mg/kg/day). An additional study in rat, conducted by the same laboratory, was also

submitted to this NDA, (Yo et al. Mod Clin, 1970). The authors reported that, in a non-GLP study of amantadine administered orally to pregnant Wistar rats from GD 9-14, increased fetal loss and reduced fetal weights were found at the highest dose of 120 mg/kg/day. In both the rat and mouse studies, when 5/15 females per group carried to term and the litters were observed through post-natal day 21, reduced litter sizes and birth weights were the reported differences from controls.

Table: Rat (Yo et al., 1970) and mouse (Kakinai et al., 1970) studies

Study	When dosed	Species	Mg/kg	Mg/m^2	Fold RHD*
Rat	GD 9-14	Wistar Rat AEL (HD) ↓fetal wt. ↑ fetal death	120	720	4.3
	GD 9-14	Wistar Rat NOEL (LD)	40	240	1.4
Mouse	GD 7-12	ICR Mouse AEL (HD) ↓ birth wt., ↑ fetal death	40	120	0.7
	GD 7-12	ICR Mouse NOAEL (LD)	10	30	0.18
*Recommended human dose: 274 mg/60 kg (4.6 mg/kg = 169 mg/m^2)					

11 Integrated Summary and Safety Evaluation

Gocovri® is an oral extended release encapsulated formulation of amantadine intended for treatment of Levodopa-induced dyskinesia (LID) in Parkinson's disease. The application relies largely on the findings of safety for the reference listed drug, Symmetrel®, an orally administered immediate release formulation of amantadine. No nonclinical studies were required; however, the sponsor submitted in vitro and in vivo pharmacology and pharmacokinetic studies to the NDA.

In vitro pharmacology studies were conducted to elucidate the mechanism of action of amantadine. These studies confirmed that amantadine is a weak NMDA receptor antagonist. Review of the published literature and of the submitted in vitro studies suggests that there may also be agonist activity at the sigma-1 receptor, antagonism at the nicotinic acetylcholine receptor; however, the mechanism of action in LID remains unclear.

PK studies were conducted to support efficacy studies in the rat 6-OHDA model of Parkinson's disease. The efficacy studies showed that continuous subcutaneous administration of amantadine, via an Alzet® pump, reduced the abnormal involuntary movements that are characteristic of the levodopa-induced dyskinesia in that model. There was no effect on the counter-rotational behaviors that characterize Parkinsonism in this model, and amantadine did not alter the efficacy of L-dopa.

Continuous administration via Alzet® pump caused local irritation at the infusion sites; however, the finding is not relevant to an orally administered drug and further studies are not warranted. Although carcinogenicity studies had not been conducted,

Symmetrel® has been approved for treatment of Parkinson's disease; therefore, a carcinogenicity study is not required for this application.

Developmental and reproductive toxicity studies have not been conducted according to current standards. According to published literature, amantadine has a negative effect on male and female fertility at a dose less than the recommended human dose (274 mg/day) and administration to pregnant rats and mice caused embryolethality and fetal malformations. On a body surface area basis, the dose associated with embryolethality and malformations in rats was 1.8-fold the recommended human dose of 274 mg per day and adverse effects on fertility were at a dose less than the RHD.

Aside from the published fertility and pregnancy findings for amantadine, there are no nonclinical findings that imply a risk to safety in the proposed patient population. From a nonclinical perspective, the application is approvable and no further studies are required.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUANN MCKINNEY
07/26/2017

LOIS M FREED
07/26/2017