2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

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NDA number: —
Review number: 1 b(4)
Sequence number/date/type of submission: — , Sept. 28, 2007
Information to Sponsor: Yes ( ) No (X)
Sponsor and/or agent: Schwarz BioSciences, Inc.
Manufacturer for drug substance:

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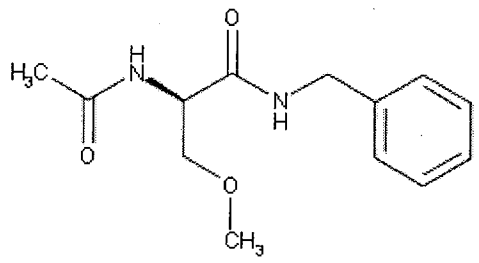
Reviewer name: BeLinda A, Hayes, Ph.D.
Division name: Anesthesia, Analgesia, and Rheumatology Products
HFD #: 170
Review completion date: May 8,, 2008

Drug:

Trade name: Vimpat™
Generic name: Lacosamide
Code name: SPM 927 (Schwarz BioSciences, Inc.), ADD 234937 (NIH/Anticonvulsant Drug Development program), Harkoseride (Harris FRC code)
Chemical name: (R)-2-Acetamide-N-benzyl-3-methoxypropionamide
CAS registry number: 175481-36-4
Molecular formula/molecular weight: $C_{13}H_{18}N_2O_3$/250.30
Structure:



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Relevant INDs/NDAs/DMFs:

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INDs	Status	Division	Indication	Stamp Date	Sponsor
57,939	Active	Neurology Products	Treatment of epilepsy	05/19/1999	Schwarz Biosciences
—	—	Anesthesia, Analgesia and Rheumatology Products	Treatment of neuropathic pain	—	Schwarz Biosciences
68407	Active	Neurology Products	Treatment of epilepsy	10/16/2003	Schwarz Biosciences
73,809	Hold	Neurology Products	Treatment of epilepsy	11/23/2005	Schwarz Biosciences

NDAs	Product	Status	Division	Indication	Stamp Date	Sponsor
22-253	Lacosamide Tablets	Pending	Division of Neurology Products	Adjunctive Therapy Treatment of Partial Onset Seizures in Patients with Epilepsy	09/28/2007	Schwarz Biosciences
22-254	Lacosamide Injection	Pending	Division of Neurology Products	Adjunctive Therapy Treatment of Partial Onset Seizures in Patients with Epilepsy	09/28/2007	Schwarz Biosciences
—	Lacosamide Tablets	—	Division of Anesthesia, Analgesia and Rheumatology Products	Management of Neuropathic Pain Associated with Diabetic Peripheral Neuropathy	—	Schwarz Biosciences

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DMFs №	Subject of DMF	Holder

Drug class: Anticonvulsant

Intended clinical population: Management of neuropathic pain associated with diabetic peripheral neuropathy

Clinical formulation: Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets. They are colored, oval, → tablets of different size and are compositionally proportional formulations. The tablets are debossed with "SP" on one side and the tablet strength ("50", "100", "150", "200", "250", "300") on the other side. The composition of the film-coated tablets is described in the table below. b(4)

Component	Function	Tablet Strength (mg)/Color					
		50/Pinkish	100/Dark Yellow	150/Salmon	200/Blue	250/	300
		Amount (mg)					
Lacosamide	Active Ingredient	50.0	100.0	150.0	200.0	250.0	300.0
Cellulose Microcrystalline							
Crospovidone							
Magnesium Stearate							
Hydroxy-propylcellulose							
Total (film-coated tablet)		126.00	252.00	378.00	504.00		

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Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

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Studies reviewed within this submission:

Report №	Study Title	Module/CTD Description
	Pharmacology	
№ N01-NS-4-2311	Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes.	
№ 1001020	Pharmacology Data Report	
[illegible]	[illegible]	b(4) 4.2.1.1/Primary Pharmacodynamics
№ NO1-NS-4-2311	The profile of anticonvulsant activity and minimal toxicity of ADD 234037 in mice and rat.	b(4)
№ A6	Report on in vitro carbonic anhydrase inhibition, change in heart rate and blood pressure in spontaneously hypertensive rats and saluresis/kaluresis in normal rats.	
	Safety Pharmacology	
№ 0200XH15.001	Neuropharmacological profile (NPP) in mice.	4.2.1.3/Safety Pharmacology
№ 6958-103	Neuronal vacuolization with SPM 927 in rats.	
№ 020316.TDA	Effect of SPM 927 on cloned hERG Channel expressed in mammalian cells.	
№ 20000377P	SPM927: Evaluation of effect on cardiac action potential in isolated canine purkinje fibers.	
№ A8	The effects of ADD 234037 on the transmembrane potentials of isolated canine ventricular myocytes.	
№ E-014-001	Electrophysiological examination of activity of SPM 927 on the SCN5A-sodium channel expressed in CHO cells.	
№ E-011119.TDA	Effect of SPM 927 on the human cardiac INa (hHNa) current expressed in mammalian cells.	
№ SB01D01	SPM 927: In vitro effect on INa and ICa recorded from human myocytes.	

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№ — 15066/01	Examination of SPM 927 on L-type Ca2+ inward current in isolated ventricular myocytes from guinea pig.	**4.2.1.3/Safety Pharmacology**
№ 0247DH15.001	Cardiovascular (Hemodynamic) evaluation of ADD 234037 in the open-chest anesthetized dog.	
№ 0247DH15.002	Cardiovascular (Hemodynamic) evaluation of ADD 234037 in dogs.	
№ 0247DH15.003	Cardiovascular Evaluation of ADD 234037 in a dog.	
№ 20000376P	Evaluation of haemodynamic effects and electrocardiogram following intravenous dosing in the anaesthetized dog.	
№ 0247XH15.004	Cardiovascular Evaluation of ADD 234037 in non-human primates.	
№ 20000378P	Behavioral Irwin Test and effect on body temperature following single oral administration on the rat.	
№ 20000380P	SPM 927: Evaluation of effect on intestinal transit in the rat following single oral administration.	
№ 20000381 P	SPM 927: Evaluation of interactions with neurotransmitters (Acetylcholine, histamine, serotonin) and barium chloride on isolated ileum of guinea pigs.	
№ 05.237/5	Evaluation of SPM 927 as a discriminative stimulus in a drug discrimination procedure in the rat.	
№ 05.637/4	Evaluation of SPM 927 for abuse potential using an i.v. self-administration paradigm in the rat.	
№ 05.122/6	Evaluation of SPM 927 in the conditioned place preference test in the rat.	
	Pharmacokinetics/Toxicokinetics	
№ 699/46	SPM 927: A study of absorption, distribution, metabolism and excretion following oral administration to the mouse.	**4.2.2.2/Absorption**
№ 18447/04	Single dose pharmacokinetics of SPM 927 in CD®-1 mice.	
№ 18772/05	14-Day toxicokinetics study by oral administration of SPM 927 in CD®-1 mice.	
№ 133418/00	Exposure of the mouse to SPM 927 after single intraperitoneal administration.	
№ 0699/023	[14C]-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat.	
№ 699/47	SPM 927: A study of absorption, and excretion following oral administration to the rat.	**4.2.2.3/Distribution**
№ F232	Bioavailability and excretion of [14C]ADD 234037 in male beagle dogs following single administration.	
№ 699/48	PM 927: A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog.	
№ — 15654/02	Pharmacokinetic study in male beagle dog after repeated (twice daily) oral administration of SPM 927.	
№ 0699/46	SPM 927: A study of absorption, distribution, metabolism and excretion following oral	

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