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April 11, 2002

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IS LIMITED TO MATTERS AND PROCEEDINGS
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BY HAND-DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

4173 02 APR 11 P2

Re: Docket No. 01P-0495; Apotex Corp. Citizen Petition Regarding Ultram® (Tramadol)

Dear Sir or Madam:

The attached letter is submitted on behalf of Apotex Corp. (Apotex) in support of its October 24, 2001 citizen petition, which asked FDA to determine that a generic version of Ultram® tablets (tramadol) could be approved after omission of exclusivity-protected titration dosing labeling information. Specifically, the attached letter addresses whether the omission of the exclusivity-protected titration text from the labeling of generic tramadol presents safety concerns for patients. As discussed by Michael Byas-Smith, M.D., The Robert W. Woodruff Health Sciences Center, Emory University Hospital, there is no safety issue presented by the proposed generic labeling.

For this reason, FDA should promptly grant Apotex's requested relief. Thank you for your consideration of this letter.

Sincerely,

Susan P. Grymes
Counsel for Apotex Corp.

SPG.lws
Attachments

01P-0495

SUP 1



EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of Anesthesiology

March 25, 2002

Ms. Marcy Macdonald
Apotex Corp.
Suite 127
50 Lakeview Parkway.
Vernon Hills, IL 60061

Dear Ms. Macdonald:

You asked me for my views on whether the omission of the following text from the labeling of generic tramadol would present any safety concern for patients:

A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

I have reviewed the information set out in Schedule A to this letter, which includes reports describing the results of comparison of titration dose schedules, including Ruoff G.E., "Slowing the Initial Titration Rate of Tramadol Improves Tolerability" *Pharmacotherapy* 1999;19-88093 and Petrone D. et al, "Showing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double blind randomized trial" *J Clin Pharmacy and Ther* 199;24:115-123. Although the Petrone reference relates to the 16 day/25 mg titration dosing schedule, the Ruoff reference is instead an assessment of tramadol dosage titrated at 1, 4, or 10 days.

Summary of conclusions

In my view, no safety issues are presented by the proposed generic labeling. There is no evidence to suggest that the 25 mg/16 day titration dosing schedule results in a lower incidence of side effects, nor is there evidence that the titration dosing improves efficacy of the drug.

Discussion

The brand labeling refers to the 25 mg/16 day titration dosing schedule resulting in "fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule." I note that the approved labeling does not state that there is in fact a lower incidence of such side effects as dizziness, vertigo, nausea and vomiting as a result of using the 25 mg/16 day titration dosing schedule.

In general terms, it is standard and good practice to titrate to effect the dosing schedule of medications, particularly medications that have effects on the central nervous system and may cause significant side effects



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Ms. Marcy Macdonald
March 25, 2002
Page 2

such as dizziness, vertigo and upset stomach. To the extent that these symptoms can be relieved, it is wise and prudent practice to incorporate those maneuvers in one's prescribing practice to better serve our patients. In fact, titration of medications is the standard practice of care in both acute and chronic pain management with a variety of medications including opioid medications and drugs such as tramadol.

While recognizing the advantage of titrating medications, I have reviewed the results of the clinical trials described in the *Physicians Desk Reference*, the approved labeling, U.S. patent no. 6,339,105, as well as the Ruoff and Petrone et al references, and have found no evidence to indicate that the new recommended titration schedule for the drug tramadol will significantly reduce the incidence of dizziness, vertigo, nausea and vomiting in chronic pain patients or increase the efficacy of the drug.

The only information presented in the references relating to the 16 day/25 mg titration dosing schedule suggests that certain patients are less likely to discontinue the medication over a thirty-day period in comparison to the standard titration. In addition, the predicted effect of the 16 day/25 mg dosing is only applicable to an enriched population of patients who are prone to discontinue tramadol. Had this titration regimen been tested in the general population of chronic pain patients, it is unlikely to have been significantly different from the previously recommended dosing schedule.

"The study demonstrated that a slower initial titration rate of tramadol HCl lowered the rate of discontinuation due to nausea and/or vomiting in patients with chronic pain who were previously unable to tolerate it due to nausea and /or vomiting." (Petrone, at 120)

There is no evidence to suggest that the overall incidence of these side effects will be reduced in the population. In fact, the symptoms of nausea, vomiting, dizziness and vertigo are still present in 33% of patients ninety days after initiation of therapy long after the initial titration or initial dosing of the medication was started. The data presented in the *Physicians Desk Reference*, the approved labeling, U.S. patent no. 6,339,105, as well as the Ruoff and Petrone et al references concerning the incidence of these side effects has not changed with the new labeling recommendations. None of these references provides evidence to suggest that the overall incidence of these side effects is reduced. In addition, there is no indication that pain intensity was measured in the study, therefore no inferences concerning "improved efficacy" can be made.

While tolerability of the initiation of therapy may be improved with the titration recommendations in a sub-population of patients, there does not appear to be any evidence to suggest that the overall incidence of severe adverse events is reduced in the general population of chronic pain patients. I can only conclude, therefore, that the revised dosing schedule may improve patient compliance but certainly cannot be construed, based on the data presented, as a "patient safety" issue.

Sincerely,



Michael Byas-Smith, MD
Dictated by Dr. Byas-Smith; signed in his absence

MBS:gr

Schedule A: Material Reviewed

Ruoff G.E., "Slowing the Initial Titration Rate of Tramadol Improves Tolerability" *Pharmacotherapy* 1999;19-88093

Petrone D et al, "Showing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double blind randomized trial" *J Clin Pharmacy and Ther* 199;24:115-123

U.S. Patent No. 6,339,105 "Analgesic Regimen" to Kamin, M and Olson, W., assigned to Ortho-McNeil Pharmaceutical, Inc.

RW Johnson labeling for Ultram ® (Tramadol hydrochloride tablets), approved by FDA August 15, 2001

European labeling of Dominion Pharma Ltd. for Tramadol hydrochloride 50mg capsules

Citizen's Petition of Apotex Corp. to FDA dated October 24, 2001

Response to Apotex Citizen Petition of Johnson & Johnson dated January 22, 2002

Letter to M. Kamin, Ortho-McNeil Pharmaceutical Inc. from Russell K. Portenoy dated December 22, 2001

Letter from Apotex Corp. to FDA dated February 12, 2002

Letter from the Generic Pharmaceutical Association to FDA dated February 14, 2002

Physicians Desk Reference, 1999 and 2001

Proposed Apotex Tramadol label

August 31, 2001

**EMORY UNIVERSITY SCHOOL OF MEDICINE
STANDARD CURRICULUM VITAE**

Michael G. Byas-Smith, MD

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Anesthesiology Department
3rd Floor, B-Wing - Rm A304
Atlanta, GA 30322

E-mail Address: Michael_Byas-Smith@emoryhealthcare.org

Birth Date and Place: December 13, 1961; Union, South Carolina

Citizenship: USA

Academic Appointments:

Assistant Professor of Anesthesiology
Emory University School of Medicine
Department of Anesthesiology

Previous Academic/Professional Appointments:

Institute of Medicine (IOM), National Academy of Sciences, Committee Member 1996
Committee to Identify Strategies to Raise the Profile of Substance Abuse and
Alcoholism Research
University of Maryland School of Medicine
Department of Anesthesiology, Baltimore, Maryland
Clinical Instructor 1991-1993

Licensures/Boards: Georgia 1993
American Board of Anesthesiology, - 1992

Specialty Boards:

American Board of Anesthesiology September 1992
Subspecialty, Pain Management August 1994

Education:

Orangeburg Wilkinson High School, Orangeburg, South Carolina	1977-1979
Morehouse College, Atlanta, Georgia, B.S. Degree in Biology	1979-1983
University of Illinois School of Medicine, Chicago, Illinois, Medical Degree	1983-1987
Cook County Hospital, Chicago, Illinois, Internship, Transitional Program	1987-1988
Emory University School of Medicine, Atlanta, Georgia, Residency, Anesthesiology	1988-1991
National Institutes of Health, Bethesda, Maryland Clinical Associate (Pain Research Fellow)	1991-1993

Military or Government Service

Public Health Service, Lieutenant Commander National Institutes of Health, Bethesda, Maryland	1991-1993
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Editorships and Editorial Boards:

Dispelling the Myths About Addiction: Strategies to Increase Understanding and Strengthen Research. National Academy Press, Washington, DC	1996
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Manuscript reviewer:

Journal of Pain 1999-present
Pain, 1995-present
Clinical Journal of Pain, 1999-present
Anesthesia and Analgesia 1999-present

Honors and Awards:

Emory University School of Medicine, Atlanta, Georgia, Chief Resident
Anesthesiology 1990-1991

Raymond Zbick Award - Outstanding performance as a medical student in anesthesiology, University of Illinois School of Medicine, Department of Anesthesiology, 1987

Society Memberships:

American Society of Anesthesiologists
International Association for the Study of Pain
American Pain Society
Society of Neuroscience
American Medical Association
American Society of Regional Anesthesia
National Medical Association

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Georgia Society of Anesthesiologists

Research focus:

My primary research interest is understanding mechanisms of opioid tolerance, pain perception and analgesia. My projects are designed to determine the effects of pain and opioid analgesic medications on brain function and identify the long-term effects of opioid administration to patients.

Patents:

Method and Compositions for Controlling Oral and Pharyngeal Pain Using Capsaicinoids.
Ref: E269/82590. Patent issued 1998.

Grant Support:

Federally funded

Scientist Development Award (K20), NIDA, National Institutes of Health extramural award.

State funded

Advanced Technology Development Center/FRCP Grant. Title of Proposal: A developmental program for commercialization of a capsaicin formulation designed for treatment of painful diseases involving the oral, pharyngeal and gastrointestinal mucosa.

University funded

The Effects of Opioids on Driving Ability in Patients with Chronic Pain

Formal Teaching:

Clinical Instructor

Lecturer for pain management lectureship

Instructor in departmental journal club

University Committees

Advisory Board Member, General Clinical Research Center

Affirmative Action and Equal Opportunity Committee, Emory University Department of Anesthesiology

Lectureships, Seminar Invitations/Visiting Professorships:

Symposium, American Pain Society, Annual Scientific Meeting, Driving Under the Influence of Opioid Medications, November 2000

University of California, San Diego, California, Visiting Professor, Pharmacology of Pain Management, September 2000.

Free University of Amsterdam, Seminar on neuropharmacology, Visiting Professor, Molecular Mechanisms and Targets of Analgesic Drugs, April 2000

Georgia Society of Anesthesiologists, Semiannual Meeting, Mechanisms of Pain and Analgesia

40th Anniversary, Year end seminar, Emory University School of Medicine, Department of Anesthesiology. Meeting the Demand for Better Pain Control: Are we keeping pace? 1999.

University of Pennsylvania, Department of Anesthesiology, Visiting professor. Pain mechanisms and treatment, 1999.

Georgia Society of Anesthesiologists. Regional Anesthesia Workshop. Hilton Head South Carolina, 1998.

National Medical Association. Lecture Series on Pain Management. (Future of Pain Management for the Anesthesiologist), New Orleans, Louisiana, 1998.

American Academy of Pain Medicine. Management of Neuropathic Pain San Diego, California, March, 1998.

Stanford University, Department of Anesthesiology. Visiting professor. Measuring pain using Positron Emissions Tomography. Palo Alto, California, March, 1997.

University of Kentucky, School of Oral Surgery. Update on chronic pain management. Lexington, Kentucky, April, 1996.

American Society of Anesthesiologists, Regional Refresher Course. Workshop On Chronic Pain Management. Lectures: 1. Reflex Sympathetic dystrophy: Psychiatric or Neuropathic Pain Syndrome? 2. Historical and Current Diagnostic Techniques and Clinical Management of Reflex Sympathetic Dystrophy. Milwaukee, Wisconsin, August 1995.

Michigan Center For Pain Management and Rehabilitation. Update on chronic pain management. Dearborn, Michigan September, 1995.

Published research articles in refereed journals:

Byas-Smith M, Frolich M, Hoffman J, Votaw J: Cerebral Blood Flow During Propofol Induced Sedation and Anesthesia, *Molecular Imaging and Biology*, March/April 2002 4(2).

Byas-Smith M, Bennett G, Gracely R, Robinovic G, Max M, Dubner R: Tourniquet pain exacerbates hyperalgesia related pain induced by intradermal capsaicin injection. *Anesthesiology*, September 1999.

Iadarola MJ, Berman KF, Zeffiro TA, Byas-Smith MG, Gracely RH, Max MB, Zeffiro T, Bennett GJ: Neural activation during acute capsaicin-evoked pain and allodynia assessed with positron emission tomography. *Brain* 1998;121:931-47.

Byas-Smith MG, Max MB, Muir J, Kingman A: Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage "enriched" enrollment trial design, *Pain* 1995, 267-274.

Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH and Bennett GJ: Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain, *Pain*, 63 (1995) 55-64.

Max MB, Byas-Smith MG, Gracely RH and Bennett GJ: Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clinical Neuropharmacology*, 18(1995) 360-368.

Manuscripts submitted:

Byas-Smith M, Votaw J and Hoffman J: Cerebral Blood Flow Changes During Sensory Deprivation, under revision.

Byas-Smith M, Votaw J and Hoffman J: A regional and global blood flow study of intense thermal pain and innocuous cold stimulation using 3D PET scanning, under revision.

Byas-Smith M, Votaw J and Hoffman J: Fentanyl Decreases Regional and Global Cerebral Blood Flow (CBF) and Inhibit rCBF Changes Induced By Acute Pain, under revision.

Byas-Smith M, Hoffman J, Horowitz I and Votaw J: A Study of Hypnoanesthesia in a Single Patient Using FDG and EEG Monitoring, under revision.

Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Cerebral blood flow (CBF) during propofol sedation in humans, Submitted *Anesthesiology*.

Book Chapter:

Dispelling the myths about addiction: Strategies to increase understanding and strengthen research. National academy press. 1997.

Byas-Smith MG: Common Pain Syndromes Seen in Clinical Practice. In Guide to Pain Management, Springhouse Corporation, 1997.

Byas-Smith MG: Sympathetic Pain Syndromes: The Problem in Perspective. In: Tollison and Satterthwaite, editors: Sympathetic Pain Syndromes: Reflex Sympathetic Dystrophy and Causalgia, Philadelphia, 1996, Hanley & Belfus, Inc

Byas-Smith MG: Management of Acute Exacerbations of Chronic Pain Syndromes. In Sinatra, Hord, Ginsberg, Preble, editors: Acute Pain: Mechanisms and Management, St. Louis, 1992, Mosby Year Book.

Other publications:

Byas-Smith M, Votaw J and Hoffman J: Cerebral blood flow changes during somatosensory deprivation, Abstract, Society for Neuroscience, 1999.

Byas-Smith M, Votaw J and Hoffman J: Fentanyl Decreases Regional and Global Cerebral Blood Flow (CBF) and Inhibit rCBF Changes Induced By Acute Pain, Abstract, Society for Neuroscience, 1998.

Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Propofol attenuates pCO₂ mediated increase in cerebral blood flow (CBF) in normal volunteers. Abstract, Society for Neuroscience, 1996.

Byas-Smith MG, Votaw J, Alazraki N, Votaw D, Eshima D: A functional Imaging study of heat pain activation of the lower extremity using ? 3D? PET scan imaging techniques, Abstract, IASP 8th World Congress On Pain, August 1996.

Byas-Smith MG, Votaw JR, Hoffman JM, Votaw DB, Smith BO, and Eshima: Epidural lidocaine reduces global cerebral blood flow by 11%. Abstract, Society of Nuclear Medicine 43rd Annual Meeting, June, 1996.

Brose W, Pfeifer B, Hassenbusch S, Burchiel K, Byas-Smith M, Krames E, McGuire D, Tich N, and Luther R: Analgesia produced by SNX-111 in patients with morphine-resistant pain. Abstract, American Pain Society 15th Annual Scientific Meeting, November, 1996.

Byas-Smith MG, Umeakunne K, Wilson T, and Manatunga AK: Capsaicin relieves

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tonsillopharyngitis pain in patients with common cold symptoms. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith MG, Umeakunne K, Sebastianelli J, Bryant P and Manatunga AK: Capsaicin induced sensitization relieves pain when applied to painful conditions of the oral mucosa. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

McKenzie-Brown A, Byas-Smith MG, Sebastianelli J, Hord AH, and Manatunga AK: The effects of altered vascular dynamics on sympathetically maintained pain: a comparison of phentolamine, sodium nitroprusside and saline. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith M, Bennett G, Robinovic G, Gracely R, Max M, Dubner R: Exacerbation and rekindling of intradermal capsaicin-evoked pain correlates temporally with loss of cutaneous capillary blood flow. Abstract, American Pain Society 14th annual scientific meeting, November, 1995.

Byas-Smith MG, Max MB, Gracely RH, Bennett GJ: Intravenous ketamine and alfentanil in patients with chronic causalgic pain and allodynia, Abstract, IASP 7th World Congress On Pain, August 1993.

Iadarola MJ, Berman KF, Byas-Smith MG, Gracely RH, Max MB, Zeffiro T, Bennett GJ: Positron emission tomography (PET) studies of pain and allodynia in normals and patients with chronic neuropathic pain, Society for Neuroscience, August 1993.

Gracely RH, Barcellos SA, Saltzman SJ, Byas-Smith MG, Max MB, Bennett GJ: A-beta mechano-allodynia and cold hyperalgesia following large doses of intradermal capsaicin, Abstract, Society for Neuroscience, August 1993.

Staats PS, Yearwood TL, Charapata SG, Presley RW, Wallace MS, Byas-Smith MG, Fisher R, Pallares V, Bryce DA, Mangieri EA, Luther RR, Mayo M, McGuire D and the Ziconotide Malignant Pain Study Group. Intrathecal Ziconotide in the Treatment of Refractory Malignant Pain: A Controlled Clinical Trial. *New England Journal of Medicine*. 2001 pending.

Byas-Smith M, Votaw J, Goodman MM, Howell L and Wilcox K. Phenylephrine increases DAT binding potential in rhesus monkey during isoflurane anesthesia. Society of Neuroscience. Abstract 2001. San Diego CA

JR Votaw, M Byas-Smith, L Martarello, LL Howell, CD Kilts, K Wilcox, MM Goodman. Interaction of Isoflurane and Sevoflurane with the Dopamine Transporter. Society of Nuclear Medicine. Abstract 2001. Toronto, Canada

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Byas-Smith MG, Frolich M, Votaw JR, and Hoffman JM: Cerebral Blood Flow During Propofol Induced Sedation, Society of Anesthesiology. Abstract. 2001. New Orleans, LA