Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 21, 2010

From: John Koerner, Ph.D.
Senior Pharmacologist
Division of Cardiovascular and Renal Products /CDER

Through: Albert Defelice, Ph.D.
Pharmacology/Toxicology Team Leader
Division of Cardiovascular and Renal Products /CDER

Stephen Grant, M.D.
Deputy Director
Division of Cardiovascular and Renal Products /CDER

Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Ayanna Augustus
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products /CDER

Subject: DCRP consult to evaluate nonclinical cardiac safety data for propoxyphene.

Applications: NDA 10997, NDA 16862 and NDA 17122

This memo responds to your consult requesting us to review the nonclinical cardiac safety data of propoxyphene and its metabolite norpropoxyphene. In particular, you asked the following specific questions.

1) Do you concur with the DAARP nonclinical evaluation that based on nonclinical data available, propoxyphene and norpropoxyphene, at levels likely to be attained with therapeutic use, have the potential to exert a negative inotropic effect on the myocardium? Do you believe this possibility is significantly enhanced in the setting of abuse/overdose?

2) The Division has consulted the QT-IRT on the design of a Thorough QT study as well as obtain recommendations on other studies to be conducted. A nonclinical recommendation contained in this consult includes the following:

"…we suggest that the sponsor evaluates functional effects on cardiac ion channels. Ion channel currents to be evaluated in whole cell voltage clamp studies include sodium, L-type calcium and potassium (hERG) channel currents. The sponsor should also characterize ECG effects of propoxyphene in animals at both therapeutically relevant and supratherapeutic

doses, and monitor plasma exposures of parent and metabolite in this study to allow comparisons to human exposures. Finally, the sponsor should evaluate cardiac contractility effects of parent and metabolite in vitro and in vivo."

Do you have any further recommendations on nonclinical evaluations that would be useful and appropriate for elucidating the cardiovascular risk of propoxyphene use under conditions of therapeutic use or overdose?

DCRP received the following material:

- Presentation by L. Steven Leshin, DVM, PhD. to Joint Meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees, on January 30, 2009.
- Draft Review by L. Steven Leshin, DVM, PhD.: Inotropic Effects of Propoxyphene and Norpropoxyphene (metabolite) Compared to Opiates
- Several literature references cited in this review.

Review and Evaluation

Question 1.
We concur with the DAARP nonclinical evaluation that based on nonclinical data available, propoxyphene and norpropoxyphene, at levels likely to be attained with therapeutic use, have the potential to exert a negative inotropic effect on the myocardium.

Therapeutic plasma drug levels
Plasma drug levels (Cmax) in healthy young and elderly human subjects given a therapeutic dose (65 mg, tid) for 7 days are shown below.[1]

Subjects	Propoxyphene (μM)	Norpropoxyphene (μM)
Young (21-28 yrs)	0.34	2.1
Elderly (70-79 yrs)	0.71	3.4

Nonclinical data
In vitro

1) Propoxyphene and norpropoxyphene depressed contractile force and reduced sinus rate in isolated guinea pig atria with similar potencies: estimated EC50s of ~30 μM; effects starting at 3 μM. [2]
2) Propoxyphene and norpropoxyphene depressed Vmax (maximal rate of rise of the cardiac action potential) in canine Purkinje fibers, consistent with blockade of sodium current. Norpropoxyphene was 2 times more potent than propoxyphene, with EC50s of ~30 μM and ~60 μM for norpropoxyphene and propoxyphene, respectively (ED50s estimated from manuscript figure).[1] Drugs that inhibit cardiac sodium current decrease cardiac contractility.
3) Propoxyphene (60 μM) inhibited the rapid sodium current (whole cell voltage clamp in isolated rabbit atrial myocytes) in a rate dependent manner. Recovery from inhibition was slow ($\tau_{recovery}$ 20.8 ± 3.9 s) in contrast to lidocaine ($\tau_{recovery}$ 0.4-0.6 s), indicating that propoxyphene behaves as a class IC type local anesthetic. [3] Potency was not evaluated in this study.

In vivo

1) Intravenous infusion of propoxyphene to conscious dogs increased PR interval, QRS duration, and lowered heart rate at plasma drug levels ranging from 1.3 to 10.5 μM. [1]

[1] Flanagan etal. Br J Clinical Pharmacol. 28: 463-469, 1989
[2] Holland and Steinberg. Toxicology and Applied Pharmacology 47: 123-133, 1979.
[3] Whitcomb, etal. J. Clinical Invest. 84: 1629-1636, 1989.

2) Intravenous infusion of propoxyphene and norpropoxyphene to anesthetized dogs increased AH and HV intervals in a concentration related way, at concentrations ≥2-5 μM. Second degree AV block occurred at plasma concentrations of 14±0.2 μM (propoxyphene) and 16±3 μM (norpropoxyphene).[1]
3) Intravenous infusion of propoxyphene and norpropoxyphene to conscious rabbits increased QRS and PQ intervals at plasma concentrations ranging from 5 to 10μM. [4]
4) Intravenous infusion of propoxyphene to anesthetized pigs produced circulatory collapse (defined by the authors as a systolic blood pressure < 60 mm Hg and a cardiac output of 2 l/min/M2) at plasma propoxyphene concentrations of 28-45 μM. The plasma norpropoxyphene concentration at this time was ~4 μM. Propoxyphene infusion decreased cardiac output, cardiac contractility (LV dp/dt max), blood pressure, heart rate prior to circulatory collapse. [5]

Clinical overdose data

Evaluation of blood propoxyphene levels in overdose situations was provided in a postmortem evaluation of 1859 cases that occurred between 1976-1978. Blood concentrations ranged from 0.1 to > 20 μg/ml (0.29 to >59 μM). The most commonly seen blood concentrations ranged from 0.29 to 3μM. This accounted for about 22% of cases in which only propoxyphene was involved. 44 percent of cases occurred in the range of 0.29 to 5.9 μM. Norpropoxyphene levels were not reported. [6]

Clinical presentation of 222 patients presenting to the hospital following propoxyphene overdose included 3 major types of toxicity: acute respiratory depression, convulsions and cardiovascular toxicity. It was reported that acute respiratory failure predominated in patients younger than 30 years of age, whereas cardiac effects predominated in elderly patients. Cardiac effects listed included wide QRS, bradycardia, cardiac failure and asystole, effects consistent with findings in animals. Among patients with asystole about half were resuscitated and were discharged without further issues. The remaining half did not survive.[7] Convulsions, wide QRS waves and asystole are consistent with sodium channel blockade.

Propoxyphene is similar to Class IC antiarrhythmic agents, based on its ability to inhibit sodium channels with a long recovery time constant from inhibition. The CAST trial demonstrated that Class IC type antiarrhythmics increase mortality in patients who have had previous myocardial infarction.[8] Therefore propoxyphene may increase mortality in patients with ischemic heart disease.

Relationship of animal to human findings

Findings in isolated tissues and in animals demonstrate the potential of propoxyphene and norpropoxyphene to induce cardiac depression, cardiac conduction disturbances and proarrhythmia. Drug levels needed for these effects are similar to those seen in clinical cases of overdose, and within an order of magnitude of levels seen in healthy (especially elderly) subjects given a therapeutic dose. While it's clear that propoxyphene and norpropoxyphene can inhibit sodium current, ECG findings suggest effects on additional channels/currents. For example PR and PQ changes suggest effects on the L-type calcium current, which also would explain AV and SA nodal conduction disturbances and blood pressure changes seen in nonclinical studies. If so, propoxyphene is likely to interact pharmacodynamically with other drugs that affect these parameters to yield cardiovascular side effects due to drug-drug interactions.

[4] Lund-Jacobsen. Acta Pharmacol. et toxicol 42: 171-178, 1978.
[5] Sorensen etal. Acta Anaesthesiol Scand. 29: 130-136, 1985
[6] Finkle, etal. J Forensic Sciences. 26: 739-757, 1981
[7] Sloth Madsen etal. Acta Anaesthesiol Scand. 28: 661-665, 1984
[8] The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med. 321: 406-412, 1989

Question 2.
We continue to recommend that the sponsor evaluate functional effects of propoxyphene on cardiac ion channels. Additionally, we believe an evaluation of the effect of the metabolite norpropoxyphene on cardiac ion channels should also be performed.

Lastly, based on propoxyphene's effects on cardiac sodium current, it may have the potential to increase mortality in patients with ischemic heart disease. The sponsor may be able to address this potential with clinical data on cardiac conduction and contractility, and nonclinical data in an animal model of sudden cardiac death with an appropriate positive control to assess assay sensitivity. Alternatively, this could be handled in the labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-10997	ORIG-1	XANODYNE PHARMACEUTICS INC	DARVON (PROPOXYPHENE HYDROCHLROIDE) CAPS

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

/s/

JOHN E KOERNER
01/21/2010

ALBERT F DEFELICE
01/21/2010

STEPHEN M GRANT
01/21/2010

NORMAN L STOCKBRIDGE
01/21/2010