FDA CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum to the File

NDA 10-997 Darvon (propoxyphene hydrochloride) Capsules
NDA 16-862 Darvon-N (propoxyphene napsylate and acetaminophen) Tablets
NDA 17-122 Darvocet-N 50 and Darvocet-N 100 (propoxyphene napsylate and acetaminophen) Tablets

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DATE: November 18, 2010

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SUBJECT: Recommendation on a Regulatory Decision for Propoxyphene-containing Products

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1. Executive Summary

The Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) recommend that propoxyphene products be removed from the U.S. market.

Propoxyphene is an opioid medication, initially approved by FDA in 1957. Since 1976 this agent, either as a single ingredient or in combination with acetaminophen, has been marketed in the U.S., under Schedule IV of the Controlled Substances Act, for the treatment of mild to moderate pain. Since 1978, two Citizen Petitions [1] have been submitted to FDA seeking rescheduling of propoxyphene from Schedule IV to Schedule II, or removal of propoxyphene products from the market. Until now, based on all evidence available to the agency, FDA concluded that the benefits of propoxyphene for pain relief at recommended doses outweighed the safety risk when used as directed in the approved labeling.

In recent years, postmarket data have been suggestive, but inconclusive, about the risk for propoxyphene-related cardiac toxicity when this agent is used at therapeutic doses. To address these concerns, in 2009, under authority granted by FDAAA, FDA required the sponsor (Xanodyne Pharmaceuticals, Inc.) to conduct a Thorough QT (TQT) Study to formally evaluate the adverse effects of propoxyphene on cardiac electrophysiology.

FDA has now reviewed the results of the sponsor's preliminary pharmacokinetic study, conducted to determine appropriate dosing for the TQT study, and concluded that the data demonstrate a clear, dose-related effect on cardiac electrophysiology. The results of the new TQT study in conjunction with the postmarket signals, including expanded epidemiological analyses, provide evidence that propoxyphene can have an adverse cardiotoxic effect at therapeutic doses.

It follows then that an individual patient may be at increased risk of cardiotoxicity even if she or he follows the directions for use in the approved labeling. Furthermore, an individual patient's risk for cardiotoxicity on propoxyphene may change as a result of even a small change to the patient's metabolic status, concomitant drug use, or renal function. Although the other commonly prescribed analgesic drug products for use in chronic mild-to-moderate pain have toxicities that are also potentially lethal (e.g. respiratory failure and addiction with opioids), the risk of these toxicities occurring can be mitigated with proper use, appropriate risk management strategies, and monitoring. However, it is not possible to monitor for, or mitigate, the risk of a fatal cardiac arrhythmia that may occur within the recommended dosing range for propoxyphene.

As a result, we conclude that the weight of evidence has shifted and the overall balance of risk and benefit can no longer be considered favorable. It is the conclusion of OND and OSE that propoxyphene-containing products should be withdrawn from the market.

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[1] Following the decision in July 2009 to deny the most recent Citizen Petition, which requested that propoxyphene be withdrawn, the petitioners submitted a request that FDA reconsider its decision. See Docket No. FDA-2006-P-0270 (formerly FDA Docket No.2006P-0090).

2. Regulatory History

There are currently six single-entity propoxyphene products and 22 propoxyphene and acetaminophen combination products marketed in the U.S.[2] The first propoxyphene-containing products were approved in 1957 based on a demonstration of safety. In 1969, a Drug Efficacy Study Implementation (DESI) review of propoxyphene and its aspirin-containing combination drugs published in the *Federal Register* found that combination products containing 65 mg of propoxyphene HCl were effective analgesics for mild to moderate pain.[3] In 1971, Darvon-N Tablets (NDA 16-862), Darvon-N oral suspension (NDA 16-861), Darvon-N/aspirin tablets (NDA 16-863), and Darvon-N/aspirin capsules (NDA 16-829) were approved based on bioequivalence to Darvon. In 1972, Darvocet-N (propoxyphene/acetaminophen 32.5/325 mg) was approved based on efficacy trials and a bioequivalence trial. The approved indication was for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

FDA Advisory Committee Meetings and Citizen Petitions

The safety of propoxyphene has been considered in several settings over time. In 1974, and again in 1976, advisory committee meetings were convened to discuss the scheduling of propoxyphene products. Following the 1976 meeting, propoxyphene was added to Schedule IV of the Controlled Substance Act. In 1978, a Citizen Petition requested the removal of propoxyphene from the U.S. market or an upscheduling of these products to Schedule II. This request was denied by FDA. In 1979, an advisory committee meeting was convened to assess the safety and efficacy of propoxyphene. The committee concluded that propoxyphene should remain on the market and should remain under Schedule IV.

In 2006, a Citizen Petition was filed requesting the removal of propoxyphene-containing products from the U.S. market due to safety concerns. The petitioner asserted that the products have a high level of cardiotoxicity, are associated with a substantial number of deaths (both accidental and intentional), are over-prescribed in the elderly, have addiction-causing properties and potential for abuse, and are relatively ineffective as pain medications. Another advisory committee was held on January 30, 2009, to discuss the overall safety of propoxyphene containing products.

To respond to the Citizen Petition and to prepare for the 2009 advisory committee meeting, FDA conducted a full review of the efficacy and safety data from the NDAs, the literature, and postmarket safety databases.

The January 30, 2009, advisory committee meeting was a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. At this meeting, presentations were made by Dr. Sidney Wolfe on behalf of the petitioner, the NDA sponsor (Xanodyne) and speakers from FDA.

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[2] Propoxyphene is contained in approved drugs products in either the napsylate or hydrochloride form. Levopropoxyphene is approved in NDA 12-928 for use as a cough suppressant.

[3] *Federal Register* April 8, 1969, and amended on Dec 13, 1972.

FDA's review of the available information about the efficacy of propoxyphene found that although there are data that demonstrate propoxyphene has analgesic effects in the labeled dosing range, the efficacy of propoxyphene is limited. Efficacy evidence from the NAS-NRC's report for the DESI review primarily relied upon two published review articles.[4,5,6,7] These reviews found that propoxyphene is a mild oral analgesic in doses of 65 mg or greater, but is of questionable efficacy in doses lower than 65 mg. Efficacy studies submitted in support of NDA 17-122, propoxyphene napsylate 50 mg and acetaminophen 325 mg, demonstrated superiority of the combination over acetaminophen and propoxyphene alone in only one of seven studies. In addition, in 2006, the Veterans Health Affairs (VHA) published a review of the efficacy and safety of propoxyphene-containing products.[8] Based on review of the literature and meta-analyses, the authors concluded that propoxyphene alone was shown to have a weak analgesic effect for moderate-to-severe post-operative pain. They also found that the combination of propoxyphene and acetaminophen was more effective than propoxyphene alone and was found to be similar in efficacy to codeine 60 mg with acetaminophen 650 mg or tramadol 100 mg based on indirect comparisons. Overall, the VHA authors concluded that continued prescribing of propoxyphene was warranted and that for patients with mild-to-moderate acute pain who do not have certain characteristics associated with intentional or unintentional overdose, short-term therapy with the combination product probably provides adequate analgesia with an acceptable safety profile.

FDA's review of all previous NDA reviews found propoxyphene to be well tolerated and did not reveal unacceptable safety concerns when used according to the approved product label instructions. Safety studies in the NDA were conducted according to then-current standards (single-dose), although these were not as rigorous as current standards to evaluate the safety of a new product. In its review of the literature conducted in 2006, the VHA likewise concluded that standard therapeutic doses of propoxyphene are generally well tolerated and seem to be associated with few serious adverse events and that there was a lack of convincing evidence suggesting that single or multiple doses of propoxyphene alone or in combination with acetaminophen were associated with a higher frequency of nonserious adverse events than codeine-acetaminophen combinations.[9]

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[4] Beaver WT: Mild analgesics. A review of their clinical pharmacology. II. *Am J Med Sci* 251(5):576-599 concl, 1966.

[5] Lasagna L: The clinical evaluation of morphine and its substitutes as analgesics. *Pharmacol Rev* 16:47-83, 1964.

[6] Moore RA, Collins SL, Edwards, J, Derry, S and McQuay HJ: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev* (3):CD001440, 2008.

[7] Collins SL, Edwards JE, Moore RA and McQuay HJ: Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review. *Eur J Clin Pharmacol* 54(2):107-112, 1998.

[8] VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Review of the Efficacy and Safety of Propoxyphene, March 2006.

[9] Id.

Nonclinical studies have shown propoxyphene and norpropoxyphene effects at the hERG (human Ether a-go-go Related Gene) encoded K^+ channel.[10] Relatively low concentrations (5 μmol/L) of these drugs facilitated potassium ion currents, while higher concentrations blocked ion currents (IC_{50} ~40 μmol/L), although at levels well beyond the therapeutic range. The relevance of these concentration-dependent effects in Xenopus oocytes to the impact that therapeutic propoxyphene and norpropoxyphene blood levels may have on hERG currents in human cardiac cells was not elucidated. The same study demonstrated an increase in sodium permeability. Whether this alteration in sodium permeability is confined to the oocyte preparation or can be extrapolated to mammalian cardiac cells was unclear.

At the 2009 advisory committee meeting, FDA staff shared postmarket data that have been suggestive, but inconclusive, about the risk for propoxyphene-related cardiac toxicity when used at therapeutic doses. No cases of torsades de pointes (TdP) causally associated with propoxyphene have been reported despite extensive use for many years. In an analysis of serious adverse events reported to the Adverse Event Reporting System (AERS) covering the period from marketing to February 2, 2005 (approximately 33 years), there were 91 U.S. deaths associated with Darvocet, the most commonly dispensed formulation of propoxyphene.[11] Most of the reports identified opioid drug overdoses in individuals with profiles of drug dependency, in which there was co-ingestion of multiple medications, or in those attempting suicide. An updated review conducted by OSE in 2008 produced qualitatively similar findings.

In both the original and updated reviews, a dominant causal role for propoxyphene-containing products could not be established based on the presence of underlying medical conditions or multiple co suspect medications. OSE also reviewed the medical literature for evidence of an association between propoxyphene-containing products and cardiotoxicity in humans. This review focused on the published literature and concluded that there was not enough evidence to support an association between the therapeutic use of propoxyphene and cardiac-related deaths. In contrast, the review identified published cases of new onset cardiac failure, bradycardia, asystole, heart block, widening of the QRS complex and/or cardiac arrhythmias associated with propoxyphene overdose.[12] Although OSE found strong evidence for the presence of life-threatening or lethal outcomes associated with the cardiotoxic effects of propoxyphene overdosing, it has been difficult to find direct evidence of similar events in patients exposed to therapeutic doses of this product. This observation was and remains difficult to interpret, since it is possible that such serious adverse events in elderly individuals or other patients with underlying medical conditions may incorrectly have been attributed to causes other than

[10] Ulens C, Daenens P, Tytgat J: Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. *Cardiovasc Res* 44:568-578, 1999.
[11] OSE Review: Review of serious adverse serious adverse events reported in association with propoxyphene and Darvocet 7-25-2005. Bonnel, Renan. Dormitzer, Catherine. Ahmad, Syed Rizwanuddin.
[12] OSE Review: Serious Adverse Events: Propoxyphene and Darvocet. 12-15-2008. Lee, Joann. Kuyateh, Fatmatta. Mehta, Hina.

propoxyphene. In settings in which careful monitoring is absent, these events could be ascribed by health care providers to natural causes.

After discussing the information presented, the advisory committee was asked to comment on three questions and vote on a fourth question. The three discussion questions were as follows:

> (1) whether there is evidence that propoxyphene contributes to the efficacy of propoxyphene and acetaminophen combination products;
>
> (2) (a) whether there is evidence that propoxyphene is cardiotoxic in the therapeutic range, (b) whether additional data are needed to adequately assess the potential for cardiac effects, and if so, what data; and
>
> (3) what are the potential risks associated with alternative products that may replace propoxyphene should it be removed from the market.

A majority of the committee members agreed that there was evidence of propoxyphene's efficacy, but that it was marginal. The committee also found that, based on the available nonclinical and postmarket data, there was no evidence of cardiac toxicity within the therapeutic range. The committee members were mixed in their opinions about the risks of the alternative products relative to propoxyphene, with some stating there would be little problem with withdrawing propoxyphene from the market while others noted that the risks of the alternative therapies would be problematic for some patients.

The fourth question asked committee members to vote on whether the balance of risk and benefit supported continued marketing of propoxyphene-containing products for the management of mild-to-moderate pain. The committee voted by a narrow margin (14 to 12) against continued marketing of propoxyphene products. Those who voted for propoxyphene to remain on the market advised requiring improved labeling, particularly with warnings about use in elderly patients and about use with concomitant opioids or alcohol. Finally, there was general agreement that additional information about the cardiac effects of propoxyphene would be relevant in further weighing the risk and benefit.

3. FDA Deliberations and Actions Following the Advisory Committee Meeting

Following the advisory committee meeting, FDA reviewed the comments and recommendations of committee members. The toxicities of the possible analgesic alternatives to propoxyphene were also considered further. The analgesic alternatives include acetaminophen alone, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol-containing products, codeine/acetaminophen combination products, hydrocodone/acetaminophen combination products and single-entity and combination Schedule II opioids (hydromorphone, morphine, oxycodone, oxymorphone, tapentadol). Although cardiotoxicity is not a known feature of most analgesics when used

therapeutically, each of these products has other known side effects that can be serious, even leading to death, as listed in Table 1.

Table 1 Analgesic Alternatives to Propoxyphene

Alternative Drug	Key Adverse Events
Acetaminophen	Hepatotoxicity, serious allergic reactions
Aspirin	GI bleeding, tinnitus, hypersensitivity/asthma
NSAIDs	GI bleeding, serious cardiovascular events renal injury, liver injury, serious skin reactions
Tramadol	Respiratory depression, seizures, nausea, vomiting, serotonin syndrome
Codeine in combination with acetaminophen	Respiratory depression, constipation, sedation, nausea, vomiting, hepatotoxicity, serious skin reactions
Hydrocodone in combination with acetaminophen	Respiratory depression, nausea, vomiting, constipation, sedation, addiction, hepatotoxicity, serious skin reactions
Schedule II opioids	Respiratory depression, central nervous system (CNS) depression sedation, nausea, vomiting, constipation, addiction

Aspirin and NSAIDs have a substantial risk for GI bleeding. The NSAIDs also have risks of serious cardiovascular thrombotic events, renal injury, liver injury, and serious skin reactions. The risk of GI bleeding in the elderly associated with the use of nonselective and COX-2 selective NSAIDs is great enough that in April 2009, the American Geriatrics Society published a new pain management guideline stating that nonselective and COX-2 selective NSAIDs should generally not be prescribed for elderly patients.[13]

The VA's 2006 review of safety and efficacy of propoxyphene-containing products[14] evaluated the number of opioid-related adverse drug experiences (ADEs) voluntarily reported in 2004 and 2005 to the VAMedWatch system as part of the FDA MedWatch Program. The rates of ADEs in the VAMedWatch are expressed in terms of the number of unique patients prescribed any products containing the respective opioids. The results are shown in Table 2, taken from the VHA review. The authors note that, since the opioids shown are not new drugs, the ADEs are likely to be serious adverse events (SAEs).

[13] American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons, http://www.americangeriatrics.org/education/pharm_management.shtml (providing, among other things, "nonselective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals.")

[14] VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. Review of the Efficacy and Safety of Propoxyphene, March 2006.

Table 2 Number and Rate of Opioid-Related Adverse Drug Experiences Reported to VAMedWatch.

Drug as Reported	ADE count 2004	ADE count 2005	Total uniques FY04	Total uniques FY05	ADE count / unique (x 1000) 2004	ADE count / unique (x 1000) 2005
Fentanyl	113	94	25,243	24,829	4.5	3.8
Morphine	247	270	64,717	71,380	3.8	3.8
Methadone	82	63	27,100†	32,981†	3.0	1.9
Oxycodone/Acetaminophen	74	95	179,999	177,096	0.4	0.5
Oxycodone	103	76	235,852	238,095	0.4	0.3
Tramadol	37	49	164,636	209,504	0.2	0.2
Hydrocodone/Acetaminophen‡	74	89	356,154	418,927	0.2	0.2
Propoxyphene/Acetaminophen	33	13	102,214	99,499	0.3	0.1
Codeine	37	18	204,536	199,380	0.2	0.1
Propoxyphene	4	8	126,105	120,111	0.0	0.1

† Rx Uniques may not include methadone dispensed from OAT clinics
‡ Includes one ADE in 2004 for hydrocodone/carbinoxamine/pseudoephedrine

Note: "Total Uniques" is the total number of unique patients prescribed the drug product

Based on the VHA experience, the reported rate of ADEs associated with the use of propoxyphene was no worse than the reported rate associated with the nine comparators. The authors concluded that the data did not suggest a greater safety problem with propoxyphene than with other opioids in use in veterans.[15]

Foreign Regulatory Action

On June 25, 2009, the European Medicines Agency (EMA) recommended that member states gradually withdraw propoxyphene products from their markets.[16] The EMA's recommendation was based largely on two factors: First, EMA's concern about the number of intentional (suicides) and accidental fatal overdoses occurring in EMA countries with dextropropoxyphene-containing drugs; and second, EMA's conclusion that the available data do not provide evidence that propoxyphene products are more effective than other painkillers.

Response to the 2006 Citizen Petition

In July 2009, FDA issued a letter denying the 2006 Citizen Petition.[17] Taking into consideration the discussion from the advisory committee, the available data supporting

[15] The authors of the VHA review acknowledge the limitations of the data used for this analysis. The MedWatch program was intended to identify unexpected problems with a drug, and not to register all adverse events related to drug products. It is estimated that only about 1% of all SAEs are reported to the FDA. The number of ADEs reported to MedWatch are probably underestimated because of under-reporting by health professionals, and are subject to reporting bias.

[16] EMA: European Medicines Agency, Opinion of the Committee for Medicinal Products for Human Use Pursuant to Article 31 of Directive 2001/83/EC, discussed at http://www.mhra.gov.uk/NewsCentre/CON049300. The EMA action followed an earlier regulatory phase-out of propoxyphene products in the United Kingdom. See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1004254.

[17] Docket No. FDA-2006-P-0270, Letter from Janet Woodcock, MD to Sidney M. Wolfe, M.D., Dan Surman, Ulf Jonasson, DrPH, and Birgitta Jonasson, PhD, July 7, 2009 .

the decision by the EMA, available literature about the safety and efficacy of propoxyphene, data from NDAs and U.S. postmarket data, and the safety of the analgesic alternatives, FDA determined that notwithstanding the limited efficacy of propoxyphene drug products, risk factors associated with the use of propoxyphene products could have confounded the interpretation of the observed safety findings and thus did not support withdrawal of these products from the market at that time. FDA did agree that, at very high doses, there was evidence of cardiac effects that do not appear to respond to an opioid antagonist, like naloxone. However, there were inadequate data to conclude that propoxyphene was cardiotoxic when used as directed, including in the elderly. The reasoning is detailed in FDA's response to the Citizen Petition.

In the petition denial letter, FDA also stated that, even though the evidence then available did not warrant removal of propoxyphene from the market, other measures short of withdrawal were necessary pursuant to our drug safety authority under the Food and Drug Administration Amendments Act of 2007 (FDAAA), codified as sections 505(o)4, 505-1(a), 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. First, product sponsors were required to revise product labeling with increased warnings alerting prescribers about the risk of death due to the use of concomitant CNS depressants and overdose, and important drug-drug interactions that could result in increased levels of propoxyphene and norpropoxyphene. [18] Additionally, sponsors were required to develop a Medication Guide (MedGuide)[19] as part of a Risk Evaluation and Mitigation Strategy (REMS) to alert patients to important information necessary for safe use.

Finally, although there was not clear evidence of cardiotoxicity in the labeled dosing range, to address concerns about the epidemiologic data, FDA required the sponsor of the NDA product, Xanodyne, to conduct a Thorough QT (TQT) study to formally evaluate the effects of propoxyphene on cardiac electrophysiology. Such studies were not required at the time of approval of the currently marketed propoxyphene products, but they are now an established element of the drug screening and review process. QT prolongation and other electrocardiographic abnormalities are recognized as important signals of increased cardiac risk by FDA and medical experts, and FDA has frequently relied on the results of such studies, both before and after marketing, to support regulatory actions, including actions to refuse or withdraw approval of NDAs.[20] FDA believed that if the TQT study demonstrated conduction abnormalities, this would fill the existing gap in our knowledge by providing a link between the postmarket data and clinically relevant dosing and could lead to additional regulatory action.

In the response to the petition, FDA further stated that

> FDA's surveillance of propoxyphene products does not end with the actions we are taking today. . . . We will keep closely attuned to the

[18] See example Darvon®, NDA 10-997 Boxed Warning, Warnings, Drug Interactions and other Safety labeling changes to prescribing information for propoxyphene containing products

[19] See example Darvon®, NDA 10-997 Medication Guide for propoxyphene containing products

[20] FDA's past use of QT data to support regulatory decisions is discussed in the report of the Interdisciplinary Review Team for QT Studies, attached as Appendix.

> safety information provided to us about propoxyphene products, including the development and results of the clinical trial that we are requiring. Should we later discover that additional measures are necessary to ensure the safe and effective use of propoxyphene, we have the authority to take that action, and we will.

Petition for Reconsideration and Additional Safety Reviews

In August 2009, the petitioners filed a Petition for Reconsideration requesting that FDA reconsider the decision not to withdraw the propoxyphene products.[21] As part of addressing the Reconsideration Petition, a further analysis of emergency department and postmortem data from several sources was conducted by OSE. The data indicated that, when the only drug detected on postmortem examination was propoxyphene, blood concentrations ranged from within the therapeutic range to well above the therapeutic range.[22,23]

In a further analysis by OSE of the Medical Examiners (ME) data collected via the Drug Abuse Warning Network (DAWN), the number of deaths per 100,000 prescriptions was often higher for propoxyphene than tramadol or hydrocodone, but there was a great deal of regional variability, and there were no associated data about patient selection or concomitant medications that would indicate whether bias was present.[24] In January 2010, OSE reviewers concluded that data from the Florida Department of Law Enforcement ME Reports and from DAWN Emergency Department (ED) and ME data all indicate, when adjusted for prescription volume, an excess frequency of death and ED visits associated with propoxyphene, compared to tramadol and hydrocodone.[25] Over a five-year period (2003-2007), the Florida data showed the number of drug-related deaths adjusted for drug use was approximately 16 deaths per 100,000 prescriptions for propoxyphene, 10 deaths per 100,000 prescriptions for tramadol and 8 for deaths per 100,000 prescriptions for hydrocodone. The number of deaths per 100,000 prescriptions in the DAWN data was consistently higher for propoxyphene than the comparator drugs through four years (2004-2007) of data.[26] The OSE reviewers concluded that these data provided adequate evidence to withdraw propoxyphene from the market. This recommendation, along with other data, were presented to, and discussed by, the Drug Safety Board in January 2010 (see below).

In January 2010, cardiotoxicity from nonclinical studies was further reviewed by the pharmacology/toxicology team in the Division of Anesthesia, Analgesia and

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[21] Docket no FDA-2006-P0270/PRC, filed August 6, 2009. 2010.

[22] Hudson P, Barringer M and McBay AJ. Fatal poisoning with propoxyphene: report from 100 consecutive cases *South Med* J 1977, 70(8):938-42.

[23] Finkel BS, et. al., Propoxyphene in postmortem toxicology 1976-1978, *J Forensic Sci* 1981 26(4):739-57.

[24] SDI: Vector One® National, Extracted 11/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network.

[25] Memorandum from Gerald Dal Pan to John Jenkins dated November 18, 2010, Updated Epidemiological Review of Propoxyphene Safety.

[26] OSE Review: Review of Propoxyphene/Combination Products Safety Issues and Dawn Data Analysis. 2-27-09. Kuyateh, Fatmatta. Mosholder, Andrew. Dormitzer, Catherine.

Rheumatology Products (DAARP) and the Division of Cardiovascular and Renal Products (DCRP). [27,28] In its consult review dated January 21, 2010, DCRP concurred with the DAARP evaluation, which concluded that, based on available nonclinical data, clinically relevant levels of propoxyphene and norpropoxyphene have the potential to exert a negative inotropic effect on the myocardium.

On January 21, 2010, the FDA Drug Safety Oversight Board met and discussed whether and how the risk–benefit assessment for propoxyphene could be affected by additional safety data from the Drug Abuse Warning Network-Medical Examiner (DAWN-ME) and the Florida Department of Law Enforcement (FDLE). OSE reviewers presented their conclusion that the data provided adequate evidence to withdraw propoxyphene from the market. The regulatory history of propoxyphene products was reviewed, including the information about the efficacy and safety of propoxyphene products, nonclinical toxicology safety issues associated with propoxyphene and propoxyphene's receptor activity and cardiotoxicity in relationship to other opiates. An overview of propoxyphene pharmacokinetics, including the effect of food, hepatic and renal impairment, and age on its metabolism was presented. Drug use trends for propoxyphene in the U.S. were reviewed. The Board then discussed the strengths and weaknesses in using summary safety data from a large database when making regulatory decisions and what standards FDA should use to make regulatory decisions using summary safety data.

The Board was not in consensus about whether the DAWN-ME and FDLE data changed the risk–benefit assessment. Some Board members expressed the belief that the data simply represented confirmation of propoxyphene's toxicity among patients likely to be abusing and therefore overdosing on the product. Among Board members who felt the data did affect the risk–benefit assessment, it was unclear as to the weight to give the medical examiner data. The Board noted that, although propoxyphene might have unique toxicities, withdrawal from the market would have a negative public health impact. According to the data presented, there were 20 million propoxyphene prescriptions in 2008 in the U.S. The Board feared that many patients would switch to alternate therapies for pain relief (e.g. NSAIDs, hydrocodone), which might result in exposure to other drug risks.

The Board recommended that the CDER divisions consider how to lessen the risk of propoxyphene use, if possible, in the population of patients who abuse the drug, pursue having the sponsor perform a QT study to better define any cardiac risk from use in various patient populations and continue to monitor the safety of propoxyphene and revisit the topic as needed. The Board further advised that the risk–benefit profile of the

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[27] Pharmacology/Toxicology Review: Division of Anesthesia, Analgesia, and Rheumatology Products Synopsis of Cardiac Inotropic Effects of Propoxyphene and Its Major Metabolite Norpropoxyphene, and the Possibility of Similar Effects by Alternative Opiate Analgesics if Propoxyphene was Discontinued. 1-25-2010. Leshin, L.Steven, Wasserman, Adam.

[28] Pharmacology/Toxicology Review: Division of Cardiovascular and Renal Products Consult to Evaluate Non-clinical Cardiac Safety Data for Propoxyphene. 1-21-2010 Koerner, John

product should be reassessed if the results of the required TQT study demonstrated cardiac toxicity.

In view of the Board's recommendations, management of OSE and OND determined that the available data did not provide sufficient evidence to conclude that propoxyphene, at recommended doses, was responsible for the observed excess mortality. Further review was undertaken, as described below.

In an attempt to further consider the weight of evidence of all available safety data, an April 19, 2010, OSE review of the scientific and regulatory considerations concerning propoxyphene discussed the toxicology of propoxyphene with respect to effects on cardiac inotropy and conduction.[29] With increasing levels, propoxyphene and norpropoxyphene have been found to cause changes in three distinct cardiac functions. These are:

- inhibition of Purkinje fiber contractility and cardiac muscle inotropy;
- inhibition of inward sodium current similar to Class IC anti-arrhythmics; and
- perturbation of hERG currents (either facilitation or inhibition, depending on drug concentrations).

In the clinical arena, a sufficient deterioration of any of these functions, if caused by propoxyphene and norpropoxyphene alone or through a dynamic interaction of these drugs with other patient risk factors, could lead to a substantial reduction in cardiac performance or life-threatening arrhythmias. There has been a concern that, with therapeutic dosing, some individuals who are elderly or have renal insufficiency may be vulnerable to propoxyphene-induced cardiotoxicity, because of a reduction in clearance of the parent compound and its longer-half-life metabolite, norpropoxyphene. In the presence of rising blood and tissue concentrations of these compounds, certain underlying medical conditions might be associated with an increased risk for propoxyphene-induced serious adverse events. These include heart failure, coronary disease, ion concentration abnormalities, concomitantly administered arrhythmogenic drugs, or dysregulated ion channel functions.

The April OSE review also discussed postmortem toxicologic studies of propoxyphene overdose deaths. The reviewer noted that the postmortem blood levels of propoxyphene are highly variable; in a small percentage of fatal cases in which postmortem propoxyphene blood levels were measured, the levels appear to be close or even overlapping with upper bound measurements of propoxyphene measured in multiple dose PK studies in 'outlier' elderly normal test volunteers.

[29] OSE review: Scientific Issues and Regulatory Considerations concerning Propoxyphene. 4-19-2010. Avigan, Mark.

In the April OSE review, three regulatory options were considered:

1. Defer a decision concerning the U.S. marketing of propoxyphene, pending completion of new epidemiological studies, although these studies alone may not provide results that would be a primary driver of regulatory decision-making. The planned studies (Tennessee Medicaid/Medicaid/Medicare/Other HMOs) have multiple challenges in reliably identifying and characterizing propoxyphene-associated life-threatening cardiac events and/or deaths.

2. Defer a decision, pending characterization of propoxyphene's cardiotoxic profile with the sponsor's FDAAA-required TQT study. A set of in vitro and preclinical studies comparing propoxyphene's cardiotoxic profile to other opioids (which also have never been evaluated for possible QT prolonging effects) could also be performed if a conclusion from the ECG study is uncertain. It was predicted that these studies, in particular the ongoing FDAAA-required TQT study, would be performed relatively expeditiously.

3. Initiate a phased withdrawal of propoxyphene from marketing in the U.S., without waiting for the completion and review of new studies, based on the following:

    - Findings of DAWN and U.S. ME data suggesting that lethality is higher with propoxyphene than some other opioids, when controlling for prescription availability
    - Possible effect that overall suicides and accidental deaths from opioids in the U.S. would be reduced
    - Worrisome potential of propoxyphene's cardiac toxicity
    - Modest or low analgesic effectiveness of propoxyphene
    - Availability of other opioids and non-opioids to control pain

At the time of the April OSE review, the TQT study protocol had been submitted and was under review. A decision was made by OND and OSE senior management to defer a decision about the possible withdrawal of propoxyphene from the market until additional information from the required TQT study was available.

4. Latest Data

The sponsor submitted a preliminary report on August 26, 2010, of the ECG and pharmacokinetic data following dosing with the 600 mg total daily dose of propoxyphene napsylate and a preliminary report from the 900 mg dosing cohort on October 10, 2010.

The Multiple Ascending Dose (MAD) study was a randomized, double-blind, placebo-controlled sequential multiple-ascending dose study of propoxyphene napsylate for 11 days. The first cohort of volunteer study subjects was dosed with a total daily dose of 600 mg (the present maximal labeled daily dose), and the second cohort was dosed with a total daily dose of 900 mg. Subjects were monitored with telemetry and intermittent ECG recordings, comparable to the monitoring that would occur during a TQT study.

The results of the first two dosing cohorts were reviewed by the QT-Interdisciplinary Review Team (QT-IRT.) [30] As indicated in the review, significant QTc interval prolongations were observed with the 600 mg and 900 mg dose levels. For example, with the 600 mg daily dose, at steady state on treatment day 11, the largest mean change of QTcF (ΔΔQTcF)[31] was 29.8 msec, which occurred 7 hours after the last dose; with the 900 mg dose the largest mean change was 38.2 msec, which occurred 2 hours after the last dose. The testing of higher doses was planned, but following the results from the 900 mg daily dose the sponsor was informed by DAAP to stop any further dosing and the protocol was placed on clinical hold. FDA's regulations 314.42(b)(1)(i) authorize the agency to stop a trial when preliminary results indicate an "unnecessary and significant risk of illness or injury to human subjects."

As described in the QT-IRT review, an exposure-response analysis demonstrated a significant linear relationship between norpropoxyphene concentration and ΔΔQTcF. As discussed in the E14 guidance, hERG channel blockers with mean QT/QTc interval prolongation greater than 20 msec have a substantially increased likelihood of being proarrhythmic.[32] Exposures in elderly patients and those with renal impairment could exceed those observed at the 900-mg dose in this study and result in even greater QT prolongation.

Additional effects noted were dose-dependent prolongation of PR and QRS intervals, indicating significant sodium channel blockade. The executive summary from the QT-IRT review can be found in the appendix.

5. Current Recommendations

The decision to deny the 2006 Citizen Petition requesting removal of propoxyphene-containing products from the market was based on a review of existing efficacy and safety data, including reviews of clinical and nonclinical studies and analyses of postmarket data. Although the postmarket data were suggestive of a risk for death associated with propoxyphene that was greater than for other analgesics, there was insufficient information available to understand possible factors related to patient population and prescribing decisions that could account for those differences. The nonclinical data were also suggestive of possible cardiac toxicity, but the data were incomplete and did not clearly associate risk with the human therapeutic range despite decades of use.

As detailed above, the analgesic benefits and potential safety risks of propoxyphene products have long appeared to be very closely balanced. However, the results of the

[30] Interdisciplinary Review Team for QT Studies Consultation: Multiple Ascending Dose (MAD) Study Review , September 23,2010.

[31] ΔΔQTcF is the change in QTcF from baseline after subtracting change for placebo. QTcF is the QT interval corrected for heart rate using the Fridericia method.

[32] Although the ICH E14 guidelines were created for use with antiarrythmic drugs, FDA has relied on QT prolongation and other electrocardiographic effects to support regulatory action for other types of drugs (See Appendix).

MAD study, required under FDAAA, have added substantially to the knowledge of the effects of propoxyphene and norpropoxyphene on human cardiac electrophysiology. The findings of prolongation of the PR interval and the QT interval and widening of the QRS complex, in a dose-related manner, were present at doses within the therapeutic dosing range. This provides a previously missing link between suggestive, but not persuasive or conclusive, evidence from earlier reviews. OSE's January 2010 epidemiological review also strengthened prior suggestive, but not conclusive, evidence.

With this new information, it is important to consider that the risk of toxicity for the individual patient on propoxyphene can change as a result of even a small change to the patient's metabolic status, concomitant drug use, or renal function. Although the other commonly prescribed analgesic drug products for use in chronic pain have toxicities that are also potentially lethal (e.g. respiratory failure and addiction with opioids). Nevertheless, the risk of these toxicities occurring can be mitigated with proper use, appropriate risk management strategies, and monitoring. However, it is not possible to monitor for, or mitigate, the risk of a fatal cardiac arrhythmia that may occur within the recommended dosing range for propoxyphene.

As a result, the weight of evidence has shifted and the overall balance of risk and benefit can no longer be considered favorable. It is the conclusion of the Office of New Drugs and the Office of Surveillance and Epidemiology that propoxyphene-containing drug products should be withdrawn from the market.

Appendix

Interdisciplinary Review Team for QT Studies Consultation:

Multiple Ascending Dose (MAD) Study Review- Executive Summary

IND	70462
Brand Name	Darvon, Darvon-N, Darvocet-N-50/100
Generic Name	Propoxyphene
Sponsor	Xanodyne Pharmaceuticals, Inc
Indication	Relief of mild to moderate pain when pain is present alone or when accompanied by fever
Dosage Form	Oral tablets
Drug Class	Opioid analgesic
Therapeutic Dosing Regimen	100 mg q4h Maximum dose is 6 tablets per day
Duration of Therapeutic Use	Acute or chronic
Maximum Tolerated Dose	Not known
Submission Number and Date	SDN 039/040, September 3, 2010
Clinical Division	DAAP/HFD 170

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A significant QTc interval prolongation was observed at two dose levels (i.e., 600 mg and 900 mg) of propoxyphene.

In this randomized, double-blind, placebo-controlled, sequential multiple-ascending dose, parallel study, 18 healthy subjects were randomized to receive propoxyphene 600 mg and 900 mg for 11 days. The results are summarized in Table 1.

Table 1: The Point Estimates and 90% Confidence Interval Corresponding to the Largest Mean ΔΔQTcF Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)

Treatment	Outcome	Time (hour)	Mean and 90% CI (ms)
Dose Level 1: 600 mg	ΔΔQTcF	7	29.8 (11.7, 47.9)
Dose Level 1R: 600 mg	ΔΔQTcF	2	18.8 (-0.2, 37.9)
Dose Level 2: 900 mg	ΔΔQTcF	2	38.2 (19.0, 57.4)

Exposure-response analysis demonstrated a significant linear relationship between norpropoxyphene concentration and ΔΔQTcF. The ΔΔQTcF for 600 mg was 16.8 ms

with an upper 90% CI of 21.8 ms. It is recognized in the E14 Guidelines that hERG channel blockers with mean QT/QTc interval prolongation > 20 ms have a substantially increased likelihood of being proarrhythmic. Several examples are presented in 1.2.1.

The maximum concentrations of propoxyphene and norpropoxyphene following 900-mg dose at steady state were 2.6- and 1.5-fold higher than those observed following 600-mg/day dose at steady state (399 ng/mL for propoxyphene and 1290 ng/mL for norpropoxyphene). At the 900-mg dose, model predicted ΔΔQTcF was 27.9 ms (90% CI: 20.3; 35.4). The norpropoxyphene exposures achieved with the 900-mg dose in normal young volunteers is similar to those observed in elderly patients taking 300 mg. In Flanagan *et al.* (Br. J. Clin. Pharm. 1989), mean steady state norpropoxyphene C_{max} in 12 patients age 70-79 years (creatinine clearance 45-95 mL/min) administered 300 mg was 1100 ng/mL. Based on our exposure response analysis, the model predicted ΔΔQTcF at 1100 ng/mL is 22.9 ms (90% CI: 16.5; 29.4).

The exposure from the 900-mg dose is not sufficient to address the high exposure scenario, that is, patients with severe renal impairment. Based on the linear pharmacokinetics of the metabolite, patients with severe renal impairment (e.g. creatinine clearance of 20 mL/min) administered 600 mg are expected to have a steady-state C_{max} of 3397 ng/mL. This is 2.6-fold higher than the C_{max} at 900 mg and will result in greater QT prolongation.

In addition, dose-dependent prolongation of PR and QRS intervals was also observed in the trial. The results are summarized in Table 2.

Table 2: The Point Estimates and 90% Confidence Interval Corresponding to the largest ΔΔPR, and ΔΔQRS Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)

Treatment	Outcome	Time (hour)	Mean and 90% CI (ms)
Dose Level 1: 600 mg	ΔΔPR	4	28.3(4.3, 52.3)
Dose Level 1R: 600 mg	ΔΔPR	2	17.7 (-4.2, 39.6)
Dose Level 2: 900 mg	ΔΔPR	2	25.1 (4.4, 45.7)
Dose Level 1: 600 mg	ΔΔQRS	7	15.4 (5.7, 25.0)
Dose Level 1R: 600 mg	ΔΔQRS	2	7.2 (-1.0, 15.3)
Dose Level 2: 900 mg	ΔΔQRS	2	17.9 (8.9, 27.0)

1.2 QT-IRT EXPERIENCE REGARDING PREVIOUS REGULATORY ACTION WITH SOME QT_C, PR AND QRS PROLONGERS WITH SIMILAR EFFECT SIZE.

The QT-IRT was asked to provide a summary of some regulatory actions for known QTc prolongers with similar effect size. It is to be noted that anti-arrhythmic drugs associated with Torsade de Pointes (TdP) e.g. sotalol at a dose of 160 to 640 mg/day shows a dose-related mean increase of QTc of 10-40 ms (sotalol PI). Similarly dofetilide (TIKOSYN)

at a therapeutic dose increased QTc by 15 ms to 87 ms (dofetilide PI). This summary will focus on regulatory actions of some non-antiarrhythmic drugs that were known QT or PR prolongers, for which the QT-IRT was consulted. We would like to emphasize that regulatory actions are a balance of efficacy vs. risk assessments which we defer to the review division.

1.2.1 QT-prolongers

Sertindole (NDA 20644) is an atypical antipsychotic agent, the original NDA for which was submitted in September 1995. An "Approvable" Action Letter was issued on June 16, 1997, with the greatest issues of concern being (1) a dose dependent QTc prolongation in phase II/III studies (with effect size over 20 ms with the therapeutic dose), and (2) a seemingly disproportionate incidence of sudden and unexpected deaths (SUDS) among schizophrenics treated with sertindole as compared to those treated with other recently developed anti-psychotic drugs.

The sponsor withdrew the NDA in January 1998 and resubmitted the NDA in 2008 after conducting a randomized, active-controlled, open-label, prospective use study (SCoP Study; n=9858) comparing the safety of sertindole and risperidone. The sponsor reported that sertindole and risperidone had comparable all-cause mortality. Based on this study, the sponsor proposed that although sertindole has the potential to prolong the QT interval, this does not appear to translate into an increased safety risk. Although all cause mortality was comparable, the estimated hazard ratio (sertindole versus risperidone) of documented sudden death (including cases with cardiac origin probable), adjusting for age and sex, was 5.0 (95% CI: 1.4 to 17.5), showing a statistically significant (p=0.01) higher risk of sudden death in the sertindole group than in the risperidone group. Specifically, 8/13 cases were young females with no pre-existing cardiac conditions. These findings were presented at an advisory committee who concurred that the concern over a potential proarrhythmic effect of sertindole raised by the substantial QT-prolonging effect was well-founded. (refer to NDA 20-644, (b) (4) , for further details).

ANZEMET (dolasetron mesylate, NDA 20623) is approved since 1997 for the following indications as an IV and oral formulations:
1) the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin (CINV);
2) the prevention and treatment of postoperative nausea and vomiting (PONV).
In April 2006, the sponsor (Sanofi-Aventis) submitted to the FDA supplemental labeling changes to contraindicate Anzemet (dolasetron) use in pediatrics. Their action was prompted following the UK Medicines and Healthcare Products Regulatory Agency's (MHRA) initial drug application review and decision to contraindicate Anzemet (dolasetron) in children and adolescents due to cardiovascular safety concerns (January 2006) observed in pediatric trials. The Agency's review of the submitted pediatric cases from the pediatric trials found the information inconclusive and the sponsor was asked to conduct a TQT study. The sponsor submitted the TQT study, QT-IRT's findings were discussed in a regulatory briefing held in July 16, 2010.

In the TQT (refer to QT-IRT review under NDA 20623 & 20624, March 12, 2010), dolasetron prolonged the QT PR and QRS intervals in a dose and concentration-dependent fashion. The effect size (upper bound of 2-sided 90% CI) on QTc for the 100 mg therapeutic dose and 300 mg IV supra-therapeutic dose was over16 and 38 ms. Based on concentration-QTc modeling, it was determined that mean effect sizes in adult and pediatric cancer patients could be over 20 ms and DGP has withdrawn the CINV indication for the IV formulation and the contraindications and warning and precautions section of the PI has been updated to describe the ECG effects and populations at risk. With the oral formulation, the upper bounds of the derived QTc intervals based on the established concentration-QT relationship were below 20 ms for elderly patients and patients with compromised renal function. Additional language in the warning and precautions section was added for these special patient populations.

Chloroquine and hydroxychloroquine (PLAQUENIL) are indicated for the treatment of malaria. Hydroxychloroquine is also indicated for the treatment of discoid and systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) on a long-term basis at a dose of 400mg to 600 mg/day. (b) (4)

INVIRASE [Saquinavir (SQV)1000 mg/ritonavir (RTV)100 mg, NDA 21785 & NDA 20628] is an inhibitor of human immunodeficiency virus (HIV- 1) viral protease. Ritonavir (NORVIR, RTV), a protease inhibitor (PI) with antiviral activity against HIV-1 and HIV-2, is a potent inhibitor of CYP3A4 and P-glycoprotein (P-gp). Low dose RTV is administered in combination with SQV (and other antiretroviral agents) to increase SQV exposure due to CYP-3A4 inhibition. In a TQT study, significant QT prolongation (largest upper bound of 90% CI over 20 ms) with the therapeutic dose was noted on Day 3. Due to auto induction of metabolism higher exposures are expected around this time compared to steady-state. In a previous TQT study, the QT effect (upper bound of 90% CI) for ritonavir 400 mg was 5.2 ms (7.5ms). Our estimated QT effect for ritonavir 100 mg based on concentration-QT analysis is 1~2 ms, indicating that the QT effect size observed in this study is likely due to SQV alone. Dose dependent PR prolongation was also noted which will be discussed in the next section. There was only one report of TdP which was confounded due to co-morbidities and concomitant medications. However, the division indicated that utilization of this protease inhibitor in the U.S. is very low. DAVP is updating the PI with a contraindication and warning & precaution statement related to ECG effects. A drug safety letter was sent to health providers to communicate major changes in the label.

Some marketed oncology products that are known QTc prolongers with mean effect size over 20 ms include arsenic trioxide, for acute pro-myelocytic leukemia, nilotinib for imatinib resistant and newly diagnosed CML, sunitib for advanced renal cell cancer or GIST tumors and toremifene for advanced breast cancer in post-menopausal women (NDA 20-497) or prevention of bone fractures in men with prostate cancer on androgen deprivation therapy (NDA 22-477). Arsenic trioxide and sunitinib have been associated with documented cases of TdP. There were sudden deaths in the nilotinib clinical development program Arsenic trioxide and nilotinib have a boxed warning statement in the PI. A boxed warning has also been recommended for toremifene based on effect size (26 ms) with therapeutic dose even in the absence of events in the clinical trial or post-marketing (b) (4). Sunitinib only has a warning and precautions statement about QT prolongation effects.

1.2.1.1 QT-IRT reviews for opiate agonists

Other than propoxyphene, the QT-IRT has been consulted regarding opiate agonists on limited occasions:

- We have reviewed a TQT study for transdermal buprenorphine (NDA 21-306). The maximum mean ΔΔQTcF exceeded the 10 ms threshold at the supra-therapeutic dose which was sufficient to cover the increased exposure for patients with severe renal impairment. Review of AEs in the clinical program did not suggest significant arrhythmogenic potential at the doses studied. Higher exposures can be expected with oral buprenorphine and we have no information regarding the same.
- (b) (4)
- We have not received consults or reviewed information regarding QT or ECG effects of morphine sulfate, tramadol, codeine, hydrocodone or oxycodone.

1.2.2 PR prolongation

- We have noted dose dependent PR prolongation of similar effect size to propoxyphene in the following TQT studies for the following products:
    - Lopinavir (LPV NDA 21906) is an antiviral protease inhibitor co-formulated with ritonavir (RTV) to boost exposure due to CYP-3A4 inhibition. In the TQT study LPV 400mg/RTV 100 mg BID (KALETRA) and RTV 400 mg bid (NORVIR, NDA 20945) and had a maximum mean effect size on the PR interval greater than 20 ms. There have been reports of second and third degree heart block post-marketing. Both these drugs have a warning and precaution statement in the PI related to PR interval effects and patients at risk.

- SQV 1000 mg/RTV 100 mg (discussed earlier) also had a maximum mean effect size on the PR interval over 28 ms with reports of second and third-degree AV block post-marketing. DAVP has proposed a labeling update with a contraindication statement for patients with/high risk for complete heart block without implanted pacemakers, and a warning and precautions statement related to PR effects.
- Dolasetron (discussed in section 1.2.1) had an effect size of 10 ms on the PR interval with the therapeutic dose and 33 ms with the supra-therapeutic dose. A warning and precautions statement is being included in the updated PI regarding PR effects.

- In the literature PR prolongation is reported to be associated with increased risk of atrial fibrillation, pacemaker implantation and all cause mortality[33]

1.2.3 QRS prolongation

We have had very limited experience with regulatory action related to QRS prolongation. All the drugs discussed in section 1.2.2 had dose dependent QRS prolongation but the mean effect size was less than 4 ms with the therapeutic dose. With dolasetron the 300 mg IV dose had a mean effect size of 13 ms. QRS prolongation effects were included in the PI update.

With the local anesthetic type Class Ic anti-arrhythmic (flecainide) the mean effect size reported in the PI is 25% change from baseline (approximately 20- to 25- ms change from baseline), but mean effect size as low as 8 ms have been reported in the literature[34] Flecainide at therapeutic dose increases mortality in post- MI patients[35]

[33] Long-term outcomes in individuals with prolonged PR interval or First-Degree Atrioventricular block: *JAMA.* 2009;301(24):2571-2577

[34] Oral flecainide acetate for the treatment of ventricular arrhythmias; *N Engl J Med.*1981; 305:473-7)

35 Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction The Cardiac Arrhythmia Suppression Trial (CAST) Investigators N Engl J Med 1989; 321:406-412, August 10, 1989

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/s/

SHARON H HERTZ
11/18/2010

MARK I AVIGAN
11/18/2010

CURTIS J ROSEBRAUGH
11/18/2010

GERALD J DALPAN
11/18/2010
This memo represents my response to Dr. Avigan's memorandum of 19 April 2010.

JOHN K JENKINS
11/19/2010
I concur that the benefits of propoxyphene no longer outweigh its risks and that a REMS is not appropriate to manage the risk. Therefore, market withdrawal is appropriate.