



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
Tel (301) 594-5365, FAX (301) 594-5494

### Divisional Memorandum

**DATE:** 10.28.03

**FROM:** Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**SUBJECT:** NDA 21-526

**NAME OF DRUG:** Ranolazine

**SPONSOR:** CV Therapeutics

#### DOCUMENTS USED FOR MEMO:

1. NDA submissions to 21-526, including letter to Robert Temple dated 10.20.03
2. Medical/Statistical Efficacy Review, by Shari Targum, M.D. and Valeria Friedlin, Ph.D., dated 8.28.03.
3. Medical Safety Review, by Maryann Gordon, M.D., dated 7.31.03.
4. Supervisory Medical Officer Review, by Norman Stockbridge, M.D., Ph.D., dated 9.29.03
5. Reports of bioequivalence study audits, by Nilufer M. Tampal, Ph.D., dated 8.5.03 and C.T. Viswanathan, Ph.D., dated 4.1.03.
6. Clinical study inspection report, by Robert Shibuya, dated 8.21.03.
7. Pharmacology/Toxicology Review by Elizabeth Hausner, Ph.D., dated 9.2.03.
8. Clinical Pharmaceutics and Biopharmaceutics review, by Nhi Nguyen, Ph.D., Atul Bhattaram, Ph.D., and Peter Hinderling, Ph.D., dated 8.18.03.
9. Chemistry Reviews, by N. Chidambaram, Ph.D., dated 9.16.03 and 10.10.03.
10. Carcinogenicity report to the Carcinogenicity Assessment Committee (CAC), by Elizabeth Hausner, Ph.D., dated 1.31.02.
11. Executive CAC meeting summary, by Joseph Contrera, Ph.D. (for the Exec CAC), dated 1.29.02.
12. Memoranda on non-clinical electrophysiological and proarrhythmic effects of ranolazine, by John Koerner, Ph.D., dated 9.4.03, and 10.23.03.
13. Debarment Certification, dated 12.19.02.

#### CONCLUSIONS

This memorandum constitutes the Divisional memorandum recommendation that an approvable action be taken for the NDA named above for ranolazine in the treatment of angina. As summarized below, ranolazine SR, while efficacious as an antianginal in an undifferentiated population of patients, including patients receiving sub-maximal treatment with other antianginals, has sufficient safety concerns to warrant additional studies prior to approval. The safety concerns are two-fold:

- 1) Delayed cardiac repolarization, manifest by prolongation of the QT interval. For reasons discussed below, the available data are not reassuring as to ranolazine's arrhythmic potential.
- 2) Potential testicular toxicity, manifest as impaired fertility in rats. As discussed below, the data are inadequate to determine finally whether or not ranolazine has this effect. While no clinical signs of

toxicity were reported, this is not surprising, and additional animal data are needed to characterize the effect of ranolazine on the testicle.

Regarding the consequences of the effects of ranolazine on cardiac repolarization, the most straightforward way to alleviate these concerns is to provide compelling data supporting novel therapeutic efficacy of ranolazine (*e.g.*, demonstrating efficacy in a resistant population). The sponsor has argued that they have identified such populations in post-hoc analyses of their database, and sufficiently demonstrated efficacy of ranolazine in that setting. As discussed below, neither the reviewers nor I am not at all convinced. Alternatively, the sponsor can argue that these issues do not represent safety concerns. Again, the attempts to convince the Division that the effects of ranolazine on QT are not concerning. The arguments, including those based on non-clinical work by Dr. Antzelovitch, are discussed extensively in the reviews (in particular, see Dr. Koerner's review). Overall, they are not compelling. In the end, for a drug like ranolazine, the available efficacy data are modest at best, and are simply insufficient to bear any significant safety concerns.

The drug has other issues to be resolved. They do not rise to the same level as the safety concerns identified above:

- 1) There is evidence suggesting a decreased/absent effect of ranolazine in women, an effect not related to differences in pharmacokinetics of the parent compound. This needs to be addressed in future studies or the drug should be clearly labeled to reflect this potential lack of efficacy (as the label will necessarily reflect the absence of data on non-White populations).
- 2) The dissolution testing for release needs to be adjusted per the recommendations of the Clinical Pharmacology team review.

#### **BACKGROUND AND OVERVIEW**

This submission includes over 200 clinical studies along with numerous non-clinical studies, stretching back to the early 70s. Much of the clinical data are of minimal use as regards efficacy of the current sustained-release formulation, and much of the animal work was done using a lower standard of quality than is now in place.

#### **CHEMISTRY**

The Chemistry Reviewer, Dr. Chidambaram, identified no deficiencies in the NDA submission for either the drug substance or product. Ranolazine has one chiral center, but is synthesized as a racemate (see his Review #1 for details). The drug product is an extended release product, achieved by placing the ranolazine in a pH-dependent polymer (dissolves at pH >5). The reviewer also identified no deficiencies in any of the associated Drug Master Files (page 7 of review #2). The categorical exclusion for the environmental assessment was submitted and found acceptable.

As regards shelf life, the reviewer recommends the addition of a retest date of 18 months for the drug substance and an expiration date of 18 months for the drug product, based on the stability data provided.

#### Good Lab Practices Site Reviews

The clinical and analytical portions of study CVT 301-15 (a bioequivalence study) were inspected. While a number of deficiencies were identified, none appear critical to the interpretation of the study.

#### **PRE-CLINICAL PHARMACOLOGY TOXICOLOGY**

The multitude of non-clinical studies have been reviewed primary by Elizabeth Hausner, Ph.D., along with some additional review of the 'QT' studies of ion channel activities by John Koerner, Ph.D.

#### Pharmacology: Receptor/Channel Effects

Ranolazine and its metabolites interact *in vitro* with a number of receptors and channels, including several relevant for cardiac function:

- Adrenergic receptors (especially alpha 1A, 1B and 2A)
- Serotonin receptor (5-HT1A)
- Calcium channels (both dihydropyridine and benzothiazepine types)
- Potassium channels and other channels affecting cardiac repolarization. John Koerner commented on the system used to assess this (in particular the HERG expressed in oocytes), and its deficiencies, such that the standard discussion of IC<sub>50</sub> values is not relevant here (see his first memo, page 2). Suffice to say that inhibition of IKr was easily demonstrated at micromolar

concentrations. Several of the metabolites also inhibit IKr, but the studies were done only at a single concentration. The effects of ranolazine on other relevant channels (*e.g.*, IKs, I<sub>Na</sub>) have been the source of significant discussion by Dr. Koerner (his second memo deals with this issue heavily). I take from his memos that the results are less clear than the sponsor asserts, and as a result less reassuring than they wish. As regards action potential duration, the sponsor looked at the effects of ranolazine in a number of repolarization and arrhythmia models (see Dr. Koerner's and Dr. Hausner's reviews for a discussion of their adequacy). Of particular interest, ranolazine prolongs the action potential duration in the M-cell region under conditions of hypokalemia. This is of some concern, as failure to prolong the APD in this region has been proposed as a putative marker for a drug that prolongs the QT 'safely'. The negative findings from the *in vivo* dog studies are of limited use for a variety of methodological reasons (see Dr. Koerner's first memo, pages 5-7).

- Miscellaneous other receptor binding: There is also evidence of binding to the opioid receptors (with 30% inhibitory concentrations of around 100 micromolar), although the significance of this binding is not known.

#### Pharmacology: Mechanism of Action

Simply put, any discussion of the mechanism of action is speculative, as was pointed out by several reviewers. First, as suggested from the receptor binding data above, ranolazine has a variety of effects on more standard vascular targets for an antianginal (*e.g.*, calcium channels) that could easily be linked to antianginal efficacy. There are other, more speculative, effects that the sponsor has chosen to emphasize when describing the effects of ranolazine. First, ranolazine does stimulate an increase in free fatty acid (FFA) and glucose uptake by the myocardium in disease models (*e.g.*, see CFT303.035-P in dogs with CHF, page 17 of Dr. Hausner's review). It also appears to decrease lactate efflux from ischemic myocardium and to protect against ischemia-reperfusion injury in a number of models, although no positive controls were included in the studies to provide a comparator for the relevance of the observed effects). Ranolazine inhibits fatty acid metabolism in several cardiac injury models (see pages 33-40 of Dr. Hausner's review for details).

#### Metabolism and Excretion

The metabolism of ranolazine is complex, and species-specific. The primary Clinical Pharmacology reviewer, Dr. Nguyen concluded that the primary route of elimination was via CYP 3A4, with a smaller fraction metabolized by CYP 2D6 (see her page 13). It is also a substrate/inhibitor of P-glycoprotein, explaining the interaction with digoxin and 'statins'.

The primary route of excretion for ranolazine is non-renal, with around 3% of an IV dose recovered unchanged in the urine and around 75% of radioactivity recovered in the feces.

#### Protein Binding

In a single study using human blood from 3 volunteers, 60-64% of radioactivity was bound to human plasma. Albumin binding was reported as 30% of the radioactivity. There is no evidence that the drug sequesters in RBCs (see Dr. Hausner's review, page 108).

#### General Toxicology

Many of the toxicology studies had a number of methodological flaws discussed by the reviewer, in part because they were conducted >10 years ago at a time when standardization of these studies was less.

Toxicities seen following short-term high doses included sedation, convulsions and ataxia. It is interesting that acute mortality (within minutes of drug administration) occurred in both rodent and non-rodent studies (for instance, see Dr. Hausner's review page 118). This mortality was associated with convulsions.

Toxicities following chronic administration included convulsions in the high-dose animals, vomiting, ataxia, subdued behavior and ophthalmic changes (pupils dilated, pupils non-responsive to light, conjunctival congestion), with no toxicities in the 3-month toxicity study at 5 mg/kg dose in dogs. Histopathological findings have not been presented in clear fashion by the sponsor, despite efforts by Dr. Hausner to obtain clarification, and apparently not

collected from all animals, although the sponsor asserts there were no compound-related lesions seen in the high-dose animals.

In the one-year toxicology studies the findings included the ataxia and subdued behavior seen in the shorter studies (seen at  $\geq 50$  mg/kg dose for rats). There were slight decreases in hemoglobin and slight increases in reticulocytes counts and LDH, consistent with a hemolytic process seen in the high-dose groups (200 mg/kg/day in rats).

#### Special Toxicology (Cardiac, Adrenal)

##### *Cardiac: Toxicology and ECG Interval Effects of Ranolazine*

No effect on heart rate was seen in a 3-month study in dogs with doses up to 60 mg/kg/day (see Dr. Hausner's review page 128). Other ECG parameters are discussed above and by Dr. Koerner and Hausner in their reviews. No clear signal of concern regarding changes in the QT interval can be found in the standard cardiac evaluations of the animals, but methodological flaws prevent this from being reassuring. No arrhythmias were captured during the standard toxicology studies.

##### *Cardiac: Channel Effects of Ranolazine*

Dr. Koerner's reviews are thorough-going and critical with regard to the assertion by the sponsor that they have demonstrated that ranolazine is a 'safe' QT prolonger (see the letter to Dr. Temple dated 10.20.03). To summarize: the sponsor asserts that the effects of ranolazine on QT are 'fundamentally different from that of drugs known to cause torsade de pointes, and similar to that of drugs known to increase the QTc without causing torsades de pointes.' They believe the drug has different effects on the 'M-cells' of the myocardium, effects that predict a lack of arrhythmic potential. The M-cell data is derived from work done by Dr. Antzelevitch with his 'wedge-prep'. In this preparation, an increase in the transmural dispersion of repolarization is the critical parameter to be examined (dispersion is associated with an increased arrhythmic potential in the model). John has made a strong case, I believe, that even if we accept this argument (it has not been validated either prospectively or by looking at a large battery of compounds carefully) ranolazine still causes dispersion under conditions of hypokalemia. The sponsor has also made a case for effects of ranolazine at multiple channels, including some that would presumably decrease the arrhythmic potential (*e.g.*, late sodium current). John is also critical of this assertion, based on the way the studies in question were conducted, and the reader is referred to his memoranda for detail.

##### *Other Organ-Specific Toxicities of Ranolazine*

One organ-specific effect of note is an increase in adrenal weight and vacuolization. While small changes in serum sodium were reported sporadically in the toxicology studies, no evidence of metabolic effects of this increased weight was seen in the animal studies. A special study (see Dr. Hausner's review page 168) suggests an effect of ranolazine to reduce adrenal hormone production in animals; the clinical consequences of this are unknown.

A second 'organ-specific' effect of ranolazine comes from the observation that ranolazine binds to melanin, potentially leading to accumulation in the retina and in the skin. Again, the clinical consequences of this binding are unknown, although no gross ocular lesions were noted in the animal toxicity studies.

#### Genetic Toxicology, Carcinogenicity, Reproductive Toxicity

As reviewed, ranolazine is neither mutagenic nor genotoxic. The *in vivo* mouse micronuclease assay did not meet the standards for testing today, and the reviewed concluded the results were 'equivocal', based on this failing.

With regard to carcinogenicity, the CAC reviewed the two carcinogenicity studies (rat and mouse) and concluded that 'there were no noteworthy findings'.

With regard to reproductive toxicology, Dr. Hausner has expressed concerns regarding the effects of ranolazine on male fertility from the rat studies (begins on page 187 of her review). Her concerns have also been addressed by Dr. DeFelic in his secondary review. The following is an attempt to summarize:

- 1) Male reproductive toxicity—there appears to be an effect of high doses to decrease male fertility, as measured by decreased percentage of successful matings in one study. In the rat fertility study, three males in the high-dose group were identified as having atrophic testes, thus contributing to the overall decreased fertility in that group. This may be related to a direct testicular effect or it may be a chance event that these males were all apparently in the high-dose group; here the data are not clear. As

summarized by Dr. DeFelice, no evidence of histopathological effects was reported in the long-term rat and dog toxicity studies, but whether ‘no change’ was positively asserted, or simply nothing reported needs confirmed. Dr. Hausner has tried to clarify this without success with the sponsor. In his review, he believes a conservative estimate for the observed testicular toxicity seen in rats was at a dose that is 2X the clinical dose, not a reassuring multiple (but higher than the 0.03X multiple proposed by Dr. Hausner). In the end, I don’t think we know enough about this to make a final conclusion. What is needed, as a start, is an evaluation of the long-term toxicity studies in rats and dogs.

- 2) Female reproductive toxicity—no evidence for that was seen by either reviewer.
- 3) Teratogenicity/ Developmental toxicity—Regarding teratogenicity, there was a nominal increase in the incidence of osseous malformations in rats exposed to ranolazine, but Dr. DeFelice did not view this as evidence for a teratogenic effect; rather, he felt it to be a commonly-observed finding in the population, irrespective of drug exposure. He otherwise saw no evidence for teratogenic effects in the data. Regarding development toxicities, there was some delay in development for rats exposed to ranolazine, although they ‘caught up’ by the end of the finals assessment. There was also a small decrease in rat newborn survival (around 100 to around 95% survival). Dr. DeFelice did not view the small decreases as a signal of concern. I do not see this as an approvability issue.

In the end, we don’t have enough information to interpret the impaired fertility seen in the high-dose rats. In particular, absent histological data from the long-term toxicity studies, we don’t know if the testicular effects were drug-induced or ‘spontaneous’. A resolution of this deficiency will require, at a minimum, re-reading of the relevant tissue slices from the chronic tox studies conducted in rats and dogs. If this is not possible, additional studies are warranted. Should an animal toxicity be identified it will be important to characterize the clinical consequences of this animal toxicity.

#### **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS**

The clinical pharmacology of ranolazine has been reviewed by a number of the Clinical Pharmacologists, including Dr. Peter Hinderling, Dr. B. Nhi Nguyen, Dr. Atul Bhattaram, and Dr. Joga Gobburu. Their combined review is a rich source of information; my summary should serve mainly to send the reader to that document. In addition, the modeling conducted by the group provides important additional information on the interactions of ranolazine with relevant demographics, drugs and disease states with regard to QT interval prolongation (begins on page 372 of the review). Some salient points from their reviews:

- 1) Ranolazine is well-absorbed, and there is no food effect.
- 2) The PK of ranolazine is not linear and not dose-proportional, but the increases in C<sub>max</sub> and AUC are not large (17 and 34% respectively). The terminal half-life is between 6 and 9 hours for the SR formulation.
- 3) While ranolazine is a racemate, the kinetics of the two forms are similar.
- 4) Ranolazine has a wide intersubject variability with regard to PK (CV 38-76%).
- 5) Ranolazine is metabolized via CYP 3A4 and 2D6, along with sulfatases and glucuronidases. The anticipated drug-drug interactions have been studied and confirmed (summarized on page 14 of the Clin Pharm review). It is a substrate/inhibitor of the P-glycoprotein transporter. It appears to be an inhibitor of 2D6, but at the concentrations likely to be achieved is not an inhibitor of 3A4 (see Clin Pharm review, page 102-3). The anticipated effects on QT interval related to concentration of ranolazine were seen for inhibitors of CYP 3A4; less is known for poor metabolizers related to 2D6.
- 6) The pharmacokinetics of ranolazine change with either hepatic or renal impairment, with increases in both C<sub>max</sub> and AUC in both populations increasing with increased severity of disease. The anticipated consequences of increased concentrations on QT were seen with renal impairment. There was an unanticipated (by me, anyway) interaction with liver impairment such that a given concentration caused a larger than anticipated prolongation of QT (see below).
- 7) There is a demonstrated relationship between ranolazine concentration and effect on exercise, and the Agency derived a PK-PD model for effect on exercise (not done by the sponsor). The Clinical Pharmacologists concluded the relationship was non-linear relationship, and the reviewers postulated that minor active metabolites might account for this observation. The non-linear nature of the relationship appears to have little consequence as to dosing. The model did not predict a plateau with regard to efficacy at higher concentrations. The reviewers also noted that gender was a significant cofactor in the model, reflecting the decreased effect of ranolazine in women (see Clinical section below). Their model also predicts an optimal 8-hour interdosing interval (see page 29 of the review for summary).

### Biopharmaceutics

Bioequivalence of the to-be-marketed formulation and the clinical formulation were demonstrated. A biowaiver for lower strengths was approved given the dose-proportionality and comparable dissolution testing of the 375 and 500 mg SR strengths. The Divisions has recommendations about the appropriate dissolution testing to be done for release (see review page 7 of the Clin Pharm review); these should be transmitted to the sponsor.

## **MEDICAL/STATISTICAL REVIEW**

### Clinical Audits

Two sites were chosen for auditing because they were high enrollers in a pivotal trial. No issues were found on either inspection of substance, and the data, per Dr. Shibuya, 'appear acceptable.' No follow-up actions were recommended.

### **Efficacy**

The reader is referred to the primary reviews for source material. Dr. Targum has correctly focused her attentions on the two trials conducted with the SR formulation of ranolazine (studies CVT 3031 and 3033). Both trials found a significant, if not overwhelming, effect on exercise tolerance testing (ETT) (see Dr. Targum's review, tables 5 and 6). Supportive analyses confirming the antianginal effect of ranolazine were effect seen on time to 1mm ST-segment depression (both studies), the use of nitrates (reduced with ranolazine in the one studied where it was measured, CVT 3033) and a reduction in the number of anginal episodes (from around 3.3 episodes to something around 2.2 episodes in study 3033). The trough effect was noticeably smaller than the peak effect (for instance, see table 6 from Dr. Targum's review). Some salient points from her review:

- 1) While antianginal efficacy was demonstrated adequately in two trials, the dose-response curve for efficacy is quite obscure, with little overall difference demonstrated for doses between 750 and 1500 BID. In study 3033, the doses of 750 and 1000 mg BID were not distinguishable from each other (her table, page 28). In study 3031, doses of 1000 and 1500 BID were not distinguishable from each other (her table, page 44).
- 2) As regards the interdosing interval, one trial clearly demonstrated antianginal efficacy at trough for the drug given BID. On this basis, the reviewer suggested the most appropriate dosing schedule remains to be determined. This was based primarily on her conclusion that there was a significant 'by period' interaction in the CVT 3031 trial, which was cross-over in design. When only the first period was examined, the trough results were no longer significant (see her discussion starting on page 44 of her review). The sponsor contests this, but the pharmacokinetics suggest that a more frequent dosing regimen could improve the overall efficacy. The clinical evidence is less clear-cut (Dr. Stockbridge concluded that a BID regimen was defensible, given the >50% retention of antianginal efficacy at trough, see his review, page 4).
- 3) There was evidence for persistence of antianginal efficacy, and no evidence for rebound angina through 12 weeks (see trial CVT 3033, which included a withdrawal period of 48 hours followed by an ETT). There is the suggestion in the one trial of significant length (3033) of reduced efficacy at weeks 6 and 12, compared with 2 weeks (her table 6, page 28).
- 4) Ranolazine has very small effects on blood pressure and heart rate (see table 17-18, and pages 37-38 in Dr. Targum's review).
- 5) Ranolazine appears to work on a background of other approved antianginals at less than maximal doses. Dr. Targum was not convinced that the sponsor had identified a population on maximally-tolerated or labeled doses of antianginals, or that they had demonstrated efficacy in such a population or populations (see her discussion beginning on page 16 of her review).
- 6) Like the Clinical Pharmacologists, she concluded that females benefited significantly less from ranolazine than men. This is seen vividly in the data from CVT 3033 (table 15).

### Sub-Group Analyses of Efficacy

Dr. Targum and Stockbridge have written of the difficulties in sub-set analyses in this database, derived first and foremost from the marginal nature of the demonstration of efficacy; any splitting of the overall population will leave you with small sub-groups and uncertain power to see anything by noise. For some subsets (non-White) there are simply too few individuals to even try to look (a thing not to be lost in any future labeling). For other subsets, women and patients with CHF, there is some evidence for reduced efficacy that bears a bit more examination. Dr.

Targum has summarized the primary findings from the 3033 study by gender and presence of CHF on page 31 of her review (table 11). The decrease in change in exercise tolerance is especially striking for women, and to a lesser degree for CHF. The Clinical Pharmacology reviewer, Dr. Hinderling, agreed that there was evidence of decreased efficacy in women, an effect not attributed to differences in kinetics (see his comments, page 38 of the Clin Pharm review). The sponsor should be asked to describe this effect more fully, or be prepared to label the drug as less efficacious (for a given dose/concentration) in women. The population with CHF seems less clear, and I would remain silent on it given the uncertainty of subset analyses.

## Safety

### Overall Safety

Dr. Gordon has reviewed the overall safety database, and no alarming signals for rare (*e.g.*, liver injury) or unanticipated adverse effects of ranolazine emerge. A number of constitutional adverse events seem demonstrably higher in the ranolazine group (*e.g.*, see her table on page 17 from the controlled angina trials—dizziness, constipation, nausea, asthenia). The majority of these are monitorable (which provides some reassurance) and they also appear dose-related (which might limit dose-exposure in some patients—reassuring?). The overall size of the safety database is small for angina, although the data from the immediate release experience helps some for lower doses than would be used here. It's worth noting that only one of the angina trials exposed subjects to a given dose of drug for more than a week.

### Effects on QT/QTc

The clinical effects of ranolazine on the QT have been summarized by several other reviewers, most concisely by Dr. Stockbridge. Dr. Bhattaram has also performed elegant modeling of the available data (begins on page 375 of the Clinical Pharmacology review). Some salient points to make:

1) That ranolazine prolongs the QT interval is accepted by all parties. At 1500 mg BID (less than 2X upper dose proposed by the sponsor of 1000 mg BID), the prolongation is around 12 msec in the overall population. At this dose, 7.5% of the individuals had QT >500 msec<sup>1</sup>. Keeping the dose below 1000 mg BID would limit the QTc prolongation to somewhat less than 10 msec, but large inter-subject variability in pharmacokinetics and drug metabolism will still have individuals with larger effects (suggested by the percentage of outliers).

2) That ranolazine has a more dramatic effect on the QT interval in patients with hepatic impairment is accepted by all parties (see table below). Of interest, the modeling conducted by the sponsor suggests the relationship between concentration and effect on QT is non-linear (Clin Pharm review, page 405), although no rationale for this difference from the findings in patients without hepatic impairment is forwarded (although Dr. Stockbridge questions whether a non-linear relationship might not be appropriate for all populations).

QTc Prolongation Following Ranolazine<sup>2</sup>

	Change in QT
Population excluding hepatic impaired	2.56 msec per 1000 ng/ml ranolazine <sup>1</sup>
Hepatic impairment population	7.10 msec per 1000 ng/ml ranolazine <sup>1</sup>

1. Serum concentration. For reference, the typical doses of ranolazine achieve concentrations <10,000 ng/ml.

2. From Clin Pharm review, page 382.

This observed difference in the concentration-effect relationship for QT prolongation is as dramatic as any I am aware of (we have little data in this regard, however).

3) Inhibitors of CYP3A4 increase blood levels by around 2-fold, with their associated expected effect on QTc interval.

4) Other ECG markers of uncertain concern include an increase in the frequency of 'notched' T-waves. At very high levels of ranolazine (10,000 ng/ml) their frequency was 75% (see Dr. Gordon's review, page 37).

5) Clinical signs of arrhythmias have apparently not been systematically summarized in other reviews.

a) Deaths: in a total exposure of 2682 patients there were 29 deaths on ranolazine through 10.15.01, of which 13 were described by the reviewer as 'sudden' (no definition available to me, Dr. Gordon's table page 18). This fraction (45%), with all its uncertainties, is somewhat higher than other drugs that have been approved and do not appear to cause torsade de pointes (TdP) (range 0-20%, n=3) and in the range for surveyed drugs that cause TdP (30-55%, n=4). However, of the four deaths in patients exposed to placebo (all short duration exposure), two were defined as 'sudden'. I believe we have too few deaths to draw any meaningful reassurance and too little information about most of them to draw any meaningful concerns from such analyses.

b) Clinical Adverse Events: there were no cases of TdP reported by the sponsor. Discontinuations due to dizziness occurred more frequently in patients taking ranolazine (1.0% vs. 0.1% in placebo, see Dr. Gordon's table 25R). Palpitations and dizziness were also reported as adverse events more frequently in the ranolazine group in the integrated safety population (2.4% vs 1.0% and 13.2% vs.

<sup>1</sup> See Dr. Gordon's review, page 55, table 39R. The sponsor disputes this figure based on the selection of a single lead rather than any lead.

2.9% respectively, Dr. Gordon's page 16, table 12). Syncope was reported only in patients on the two highest doses of ranolazine (see her table page 18).

In the end, this is not a reassuring database. Despite the small numbers, the clinical events clearly raise some concern, especially for a drug that does not decrease heart rate or blood pressure appreciably (removing other, usual reasons for these events). While there could be other reasons for each and every one of these clinical observations, these findings, coupled with the presence of sub-populations like the hepatically-impaired where ranolazine has much larger effects on the QT, leads me to conclude that this is a safety concern that needs to be addressed with a larger safety database (size undetermined) or offset by substantive evidence of meaningful efficacy (discussed below).

#### SUMMARY

That ranolazine is effective as an antianginal in an undifferentiated population with angina is not an issue, although the efficacy data for trough dosing using a BID regimen are not overwhelming and it is unclear precisely what doses of ranolazine to recommend for use (certainly no rationale for recommending anything above 1000 mg BID, maybe even 750 mg BID). The efficacy data also rest on a single trial lasting more than one week of exposure, a small database, particularly given the uncertainty about how to dose ranolazine and the suggestion of reduced efficacy in women. Study 3033 did look at a variety of parameters linked to antianginal efficacy, and all tell a similar story of modest efficacy in the population studied. These effects on the symptoms of angina are, however, insufficient to offset the identified safety concerns (which include potential testicular toxicity and demonstrated QT prolongation). The available data, both non-clinical and clinical, do not provide comfort as to the proarrhythmic risk of this compound. On the contrary, given the absence of significant hemodynamic effects, the observed increases in the incidence of dizziness and palpitations give one pause, even if these adverse events are typically very difficult to interpret.

Given the symptomatic nature of the efficacy claim, and the availability of other antianginals that lack these issues, additional data are needed to offset or alleviate the identified safety concerns. As for the potential testicular toxicity, additional evaluation of currently available data may well suffice to resolve the issue. As for the QT effects, the most direct way forward would be to demonstrate a benefit for ranolazine not shared by other agents (*e.g.*, efficacy in prospectively-define resistant populations, benefits on more durable clinical endpoints). The collection of such data would provide an additional trial to collect more information on the dosing of ranolazine, and additional safety exposure as well. Given the availability of other therapies, there is no attraction to considering these studies as Phase IV commitments.