Trends-in-Medicine

December 2003
By Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Cardiovascular and Renal Drugs Advisory Committee Meetingon CV Therapeutics' Ranexa (ranolazine)

December 9, 2003
Gaithersburg, MD

The FDA's Cardio-Renal advisory panel agreed with the FDA that CV Therapeutics' Ranexa is approvable but not until another trial is completed, and then probably only with a restricted label for use in patients who cannot take other anti-anginal medications or whose angina is not controlled with maximum tolerated doses of available drugs. The panel was less concerned with QT prolongation than the FDA, but more concerned about syncope. This means Ranexa is unlikely to be approved for at least 12-24 months. In addition, the company still must address FDA concerns about testicular toxicity.

Ranexa would be the first novel therapy for angina in 25 years. CV Therapeutics was seeking FDA approval specifically for:

- Treatment of chronic angina in patients with severe coronary artery disease.
- A usual starting dose of 500 mg BID with upward titration to 750 mg and 1,000 mg BID as needed.
- Tablet dosages of 375 mg and 500 mg.

In October 2003, the FDA issued an "approvable" letter for Ranexa. However, the FDA did not feel the benefits outweighed the risk. The agency raised several issues and warned the company that it had to comply with each and every point that was raised. The wording was interesting:

> *Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options…If you do not follow one of these options, we will consider your lack of response a request to withdraw the application…Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.*

After the approvable letter, CV Therapeutics still sought – and was granted – an advisory panel meeting. A company official said the goal was to convince the panel that the drug should be approved, so the company can go back and discuss that possibility with the FDA and perhaps get the bar to approval lowered.

The advisory committee chairman summarized the panel's conclusions, and the members concurred with his summary: "What we collectively said is that, with some exceptions, we would not be happy with approval of this drug for unrestricted use based on the current dataset…Wider experience, perhaps with some longer duration, some associated use with other anti-anginal drugs (so we can understand potential problems), and some more experience to help us understand

the magnitude of the syncope issue would be appropriate before an unrestricted approval. (Ranolazine) could be approved for a restricted label only with the appropriate studies in the population (as we defined them)." In an interview after the meeting, the chairman said: "No matter what, ranolazine will need more data (another trial) for approval…The company did a great job, and it came close, but the efficacy data had holes in it that we felt were important…The risk:benefit ratio was not adequate; it was not broad enough for our comfort. That's why we need more data. The company will need another trial, and it can't be done as a Phase IV."

The chairman suggested that the new trial should be somewhere between the size of the 648-patient CARISA (Combination Assessment of Ranolazine in Stable Angina) and the 191-patient MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) trials, and he said that a length of 12 weeks would be sufficient. He commented, "There has never been an anginal drug that lost its effect after three months." Dr. Douglas Throckmorton, Director of the FDA's Division of Cardio-Renal Drug Products, added, "One week is not sufficient in this population – ***ever***…I am not sure yet how long a trial will be needed. I heard a mixed message from the committee (on this)."

Dr. Throckmorton was asked if there is enough data for a study in patients resistant to other anti-anginal drugs without more dose-ranging drug-drug interaction work. He said, "I need to think about that…There are no new safety signals…At this point, I'm comfortable that a study is the way to get information on drug-drug interaction…It is possible they (the sponsor) could need other trials first if they don't have the underpinning."

What would a resistance study, if there is one, look like? Dr. Throckmorton said, "We haven't settled yet on what it will look like. Dr. Temple (Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs) does have a concern on the number of patients, and the committee has a concern with nitrate use…I can't imagine that a resistance trial wouldn't have an efficacy outcome… There are safety concerns that can't be determined without more patients, and showing a benefit in a resistant population is one way to bounder (overcome) that risk."

In particular, the panel chairman cited these issues overhanging ranolazine:

1. The data was not generalizable to the general population.
2. CARISA was considered adequate but not MARISA.
3. There is a lingering low level of safety concern – with syncope more than QTc prolongation. He said, "QT remains a concern, but the level was markedly reduced by the company's presentation…The people presenting the QT data were very credible, and I trust their judgment."
4. There was a lack of data on combination therapy.

CV Therapeutics officials were pleased with the panel meeting. One commented, "There were a lot of positives. I think the discussion was very productive. We appreciated the comments on the quality for the presentation. One of the central issues was QTc, and we are very pleased how well that data was received by the committee. In general, we're pleased with the meeting. The next step is to talk with the agency… While individual members felt no additional data is necessary, a majority of the committee did suggest additional data would be useful prior to approval, and their request for data were wide-ranging, so it is important to discuss that with the agency."

THE FDA PERSPECTIVE

In its Action Letter to CV Therapeutics, the FDA indicated Ranexa is "approvable," but the agency specified approval is contingent on the company adequately addressing three "deficiencies:"

1. **Potential testicular toxicity.** The FDA said this requires more animal data.
2. **QT prolongation.** The FDA said this could be met through a randomized, prospective trial in a restricted population or by a survival study.
3. **Longer-term safety data.** At the panel meeting, FDA officials indicated that existing trials had too few patients given the drug long enough for approval of a symptomatic treatment. The standard is 1,500 patients treated with relevant doses and 100 patients treated for at least one year. FDA officials pointed out that too few patients were treated more than one week with ranolazine, and there was a suggestion that the FDA may require additional data for at least 12 weeks and perhaps six or even 12 months.

The FDA laid out its position to the committee through extensive briefing documents but did not make and oral presentation to the panel. The key FDA concerns expressed to the panel were:

1. Marginal efficacy

The FDA wrote: "Based on our reviews of the submitted materials, *there is evidence that ranolazine is an effective anti-anginal drug* in an undifferentiated population of patients, including patients receiving sub-maximal treatment with other anti-anginals."

However, the FDA is not convinced that the efficacy profile has been adequately identified. In another document, the FDA's Dr. Throckmorton wrote, "*The available data are not reassuring* as to ranolazine's arrhythmic potential…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…*Neither the reviewers nor I am at all convinced."*

2. Decreased/absent effect in women

The FDA wrote, "The available data suggest a smaller effect of ranolazine in women with angina. (This is) 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).

3. Safety

The FDA is concerned about several safety issues, primarily:

a. Delayed cardiac repolarization (QT prolongation). The FDA wrote, "The attempts to convince the Division that the effects of ranolazine on QT are not concerning…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…We are not convinced by the available data that the effects of ranolazine on the QT interval would not lead to increased risk of arrhythmias at doses and in populations where it is likely to be used."

The FDA wants additional safety studies on QT or trials that show a benefit that offsets the QT concerns. The FDA wrote, "This additional benefit could include showing efficacy in populations not adequately treated with maximally-tolerated or labeled doses of more than one class of approved anti-anginals. Such data should be obtained from randomized, prospectively-designed trials, exploring a broad range of doses of ranolazine, to be conducted following discussions with the Agency. Demonstration of a benefit on fixed clinical endpoints, such as myocardial infarction or death, also would obviously overcome concerns about effects on the QT interval."

b. Potential testicular toxicity (impaired fertility in rats). This was in the briefing documents the panel members received, but it was not discussed by the panel. No clinical signs of toxicity were reported, but the FDA felt there is a need for additional animal data to characterize the effect of ranolazine on the testicle. The FDA wrote, "An effect on the QT interval was seen in all patient populations studied, particularly at higher blood concentrations of ranolazine, and (the sponsor has) neither provided sufficient rationale for discounting this as a potential clinical concern nor devised dosing strategies that would avoid significant QT prolongation in some patients. In particular, in certain populations (*e.g.*, patients with hepatic impairment and those taking inhibitors of CYP3A4 or the Pglycoprotein transporter), larger effects of ranolazine on the QT interval were seen or can be expected…There needs to be a clear reason to approve a therapy with what appears to be an additional, possibly life-threatening risk."

The FDA is asking for more studies to investigate this possible problem. The agency wrote, **"**Additional animal data are needed, beginning with a more thorough review of the available histologic materials from the chronic animal toxicity studies. Depending on the outcome of that review, additional animal studies may be needed. Should a toxic effect of ranolazine on the testes be confirmed, the clinical consequences of this toxicity will need to be understood."

c. Adequate safety exposure data. Dr. Temple commented, "I have to tell the committee we haven't seen anything like that before (angina trials this short)…Trials are usually longer." He explained that there is one 12-week trial, but most of the other exposures are only one week, commenting, "That is very unusual." He added, "We thought your safety database was on the low side…We think six to 12 months is standard and not a problem...but (this) is on the light side…There are about 800 patients exposed for at least a month, which is about half what we usually expect...If you did something really important, you could shave that...If it is something (a drug) you already have, then you are more interested in a reasonably-sized safety database." The FDA also wrote, "The present database has information on fewer than 1,000 patients given relevant doses of ranolazine for at least one month, an exposure well below what is typically expected for a chronic treatment for a symptomatic claim."

4. Unclear mechanism of action

The FDA is not convinced that the mechanism of action of ranolazine is understood. The FDA wrote: "Simply put, any discussion of the mechanism of action is speculative, as was pointed out by several reviewers."

5. Lack of clear dose response information

The FDA said the data from the ranolazine trials do not provide sufficient information on the relationship between dose and therapeutic effect to provide labeling instructions for its use. The FDA wrote, "Our analyses suggest a relationship of ranolazine concentrations in plasma to clinical effects. However, the great inter-subject variability in these plasma levels and the small number of studies exploring the dose range of ranolazine in patients with angina make it difficult to adequately describe in labeling how ranolazine should be dosed."

After the panel meeting, Dr. Throckmorton discussed the panel meeting and issues relating to ranolazine. Among the questions he answered were:

What is the agency's approach to QTc prolongation going forward?

"The agency position is that the non-clinical data relating to QT prolongation are not dispositive…Nothing here will change the agency approach, but this is interesting data, and we are always open to change."

Are you clear on the mechanism?
"No."

Why wasn't the testicular toxicity addressed sooner in broader animal studies?
Toxicity wasn't a committee issue…and it may not have come up at the end of Phase II meeting (with the sponsor)."

What will the panel recommendations mean for ranolazine?
"Dr. Temple will make the final call."

What is the next step?
"The sponsor responds to the approvable letter, and we will meet with them to discuss how to craft how they want to respond."

THE COMPANY PERSPECTIVE

CV Therapeutics officials indicated they hoped the panel would find the benefits of ranolazine outweigh the risk. The company brought a number of big name cardiologists to the meeting as consultants and advisers, including:

- Dr. Eugene Braunwald of Harvard/Brigham & Women's Hospital, who discussed the unmet need for a new anti-angina drug. He estimated that 8.6 million Americans have angina with >13 million episodes of angina a week in the U.S. He also commented that a significant percentage of patients have relative intolerance to full doses of beta blockers, CCBs and nitrates. He concluded, "Ranolazine would open a new chapter in the treatment of angina."
- Dr. Jeremy Ruskin, an electrophysiologist from Harvard/Mass General.
- Dr. John Camm, an electrophysiologist from London who reviewed the case narratives – but not the ECGs -- for the syncope cases.
- Dr. Charles Antzelevitch, a professor of pharmacology and Executive Director of Research at the Masonic Medical Research Laboratory in Utica, New York.

Ranolazine

Benefit	Risk
Anti-angina efficacy	Adverse events
Minimal hemodynamic effect	Theoretical risk of Torsade de Pointes (TdP) due to prolongation of QTc
Well-tolerated	---

Company officials noted:

- The effect **is** less in women, but an official said that this is seen in other agents as well, and it could mean that exercise testing is not as fine a tool in assessing women rather than a problem with ranolazine.
- Most angina patients are already on multiple medications. An official said, "Market research shows ~5%-10% of angina patients are taking three drugs, and the majority in every study we've seen take more than one – 55%-60% are taking two or three drugs."
- The 1,000 mg dose of ranolazine is more effective than the 500 mg dose. An official insisted there is a difference in response between those two doses.

Overall Safety

A CV Therapeutics official pointed out that:

- Adverse events are generally mild to moderate.
- There is no serious organ toxicity.
- Discontinuations were infrequent.
- A large preponderance of patients elected to continue therapy when given the choice.
- There are drug/drug interactions, but he claimed "they are well characterized."
- There is a concentration-dependent effect on QTc.

Ranolazine Mortality Data

Death	Placebo	Ranolazine
Sudden death, death due to ventricular fibrillation/ tachycardia or cardiac arrest	2 patients	21 patients
Cardiac arrest	3 patients	45 patients
All cause mortality	3 patients	53 patients

Ranolazine Adverse Events

Measurement	MARISA (n=191)				CARISA (n=648)		
	Placebo	Ranolazine			Placebo	Ranolazine	
		500 mg	1000 mg	1500 mg		750 mg	1000 mg
Adverse Events	14.5%	15.5%	20.5%	33.5%	25.4%	31.2%	32.7%
Dizziness	0.6%	1.1%	5.0%	11.8%	1.9%	3.6^%	6.9%

QTc Prolongation

Speakers for CV Therapeutics defended ranolazine with respect to QTc prolongation. They pointed out that:

- The company and the FDA agree that ranolazine is associated with a small increase (2 ms-3 ms) in QTc at normal doses and up to 20 ms at conditions of maximal inhibition of CYP3A4.
- Ranolazine is different from all drugs that cause TdP in that it:
  - Does not increase dispersion of ventricular repolarization.
  - Is not associated with early after depolarizations (EADs).
  - Actually reverses these effects when they are caused by other drugs.
  - Has no potential to cause TdP, and there have been no cases of TdP in the clinical development program, which covers 1,700 patient years of exposure.
- QT is not an issue because of:
  - Comprehensive preclinical assessments.
  - There is careful measurement of QT effect in appropriate studies.
  - No correlation between the magnitude of QT and the potential for TdP.
  - A lack of actual cases of TdP or events that could be interpreted as complications of QT prolongation.
- Dr. Camm, who looked at the data on the syncope patients, commented, "Looking at the dossier as a whole, QT, TdP, etc…just doesn't emerge at all (as a problem)."

Ranolazine and Syncope

Concomitant Drug Use	% of Syncope Patients n=37
Nitrates	81%
Long-acting nitrates	35%
ACEI	49%
CCB	5%
Diltiazem	32%
Beta blockers	43%
Alpha blockers	14%
Diuretics	38%

Risk management proposals

- Dose titration
- Labeling
- Physician and patient education
- Post-marketing studies

THE PANEL PERSPECTIVE

Panel members were prepared for this meeting, and they had a lot of questions for the company. In particular, the issues the members – like the FDA -- wanted to know more about included:

Mechanism of action. One concern of panel members was whether the benefit came through lowering blood pressure.

Drug-Drug interactions. Panel members wanted to know if the effect could have been confounded by the concomitant use of diltiazem and atenolol, and they waned to know about CYP2D6 activity, but they were particularly interested in any interaction with nitrates, which the company said it hadn't studied. A panel member commented, "What about patients where the nitrates were pushed, etc., and the patients still have angina? It would be persuasive to me to see data in these patients…Why were nitrates ignored? They are commonly used anti-angina and don't appear here…We need to tell people in the label how to mix these drugs...Most of my patients with medically significant refractory angina will be on nitrates, and there is nothing in your database to say what to do with those patients." A company official responded, "We do have the open label usage where patients went on to use ranolazine with nitrates, and we see no problem giving it with nitrates."

A panel member said, "You have preclinical data that tends to be reassuring, but the QT data tends to make us worry…so we want to know more about giving this drug with other agents…I want to try to understand what happens if you give ranolazine to patients on an anti-arrhythmic agent." A company official responded, "Our proposed labeling is to caution against use of another QT prolonging agent with ranolazine."

However, the panel did not find answer sufficient. A panel member said, "My concern is that when this drug gets into the community, despite the label, people tend to give drugs together."

Efficacy. A panel member commented, "We are trying to balance risk:benefit, so I want to probe on efficacy, even though I think the (efficacy) data you presented are reasonably compelling." The chairman said, "I don't think we need more efficacy data."

The populations studied. The low rate (~30%) of revascularization (PCI or CABG) among the trial patients. A company official responded, "I think it is concludable the drug works whether or not the patient has been revascularized." The panel chairman dismissed this concern.

- Lack of non-Caucasians (<5%) in the trials.
- The sudden cardiac deaths.
- The meaning of the syncope and dizziness signals.

- Any impact on cognitive function. A company official said this was not assessed, but he said he doesn't think the drug gets into the CNS until it reaches higher concentrations.
- The narrow therapeutic index of the drug.
- Dosing in patients with chronic kidney disease or hepatic disease.

QT prolongation. Members seemed to agree that the QT prolongation with ranolazine is about 8 ms. The panel definitely was impressed with both the company's preclinical data and the company's experts. Several members commented that they came to the meeting concerned about QTc prolongation and left relatively reassured. One commented, "I was very persuaded by the clinical data that this agent is electrophysiologically safe."

QT Prolongation with Ranolazine

Measurement	Placebo	50 mg	750 mg	1000 mg	1500 mg
Number of patients	422	647	694	609	162
≥60 ms from baseline	0.7%	1.1%	0.9%	2.3%	3.7%
>500 ms	0.2%	0.3%	0.3%	0.7%	0.66%

One thing most members agreed on: **a new, large QTc trial is not warranted and would not be useful.** A member said, We simply don't know if this drug will produce TdP in man based…and we won't know by adding another 1,000 patients…I was pretty impressed by the preclinical data…I recognize it isn't definitive, and we will need several years of testing, but it sure made me feel a lot better about the degree of QT…but I'm not sure I want to bet my patient's life on the preclinical data…I think this drug will ultimately be approved, and we will have to be vigilant…We will not see (a problem) before the drug is released…**There is no amount of exposure data you could reasonably ask the sponsor to produce that would reassure me that 8 ms prolongation is safe.**"

Syncope. This replaced QT prolongation as the key concern of panel members. One panel member said, "I'm not concerned about syncope in young people, but in the elderly it is a concern…The prognosis in elderly patients with syncope is very different; they may break bones, etc."

FDA Questions for the Panel

The questions for this panel were lengthy, but, since there were no votes, they were discussed in a less structured manner than is the custom at many advisory committee meetings. Following are selected questions, discussion points and responses.

Q: If we had two pivotal trials clearly demonstrative of efficacy rather than one with no dose response and one that does – if you had more compelling information on efficacy about dose response, about sub-populations, and the activity of this drug -- would that lower the bar on safety?

Yes, but the consensus of the panel was that more studies in various patient populations are needed.

Comment on drug-drug interactions.

Most panel members had concerns with this issue, but there were a variety of concerns, from anti-anginal agents to statins.

Mechanism of action.

Panel members didn't understand the mechanism of action of ranolazine, but neither did the FDA or even the company.

Available controlled trials with SR form in trials of duration greater than 1 week.

A panel member said, "I doubt there is anyone who doesn't think this is comparable in efficacy to the other (three) anti-angina agents (diltiazem, atenolol and nitrates). The question is whether we have enough information for labeling to know exactly how to dose it." Another panel member said, "I still find syncope con-cerning…The company has a wonderful database, the drug is well-tolerated, and it will be used, but no data on nitrates is a potential concern."

Is the available information on dose response sufficient?

Yes. The panel generally agreed the 1500 mg dose is too high, and they supported the idea of a 375 mg tablet, even though there is no data on that dosage. A panel member said, "The dose is very variable by individual…Even the 375 mg dose is likely to be efficacious in some people."

The effect of hemodynamic parameters.

A panel member said, "I would check for hypotension before prescribing this." A company official added, "There is little change in blood pressure until 1000 mg, and then in healthy volunteers you see an 8-10 mm change."

The magnitude of the effect on exercise tolerance.

The chairman said, "No one thinks that's a show stopper."

Concomitant therapy with other anti-anginals.

Panel members definitely wanted to know how ranolazine works in patients taking one or more anti-anginal agents – and in patients at maximum dose of those agents.

What additional data is needed for use in an unrestricted population with angina?

A new trial. Panel members agreed a new trial is required before use in an unrestricted population. Most panel members also wanted another trial for approval in a restricted angina population. The panel chairman concluded that the consensus was that a new trial – sized somewhere between the 684 patients in CARISA and the 191 patients in MARISA – will be needed for *any* approval of ranolazine.

Among individual panel members comments were:

- "This is the crux of it all…It depends on how much you worry about QTc…To use it in an unrestricted setting, you need good evidence it doesn't cause TdP, and you won't have that until it is out a long time."
- "We have long term data on other anticoagulants…So, I would be concerned about unrestricted use (of ranolazine)…(For) patients fail other agents, I want more data on patients who are taking more maximum doses of other anti-anginals."
- "I personally would be very comfortable with a modest label restriction -- perhaps patients who remain symptomatic despite treatment on one or more anti-anginal drugs."
- "I've been persuaded this is a safe, effective agent…But we can't gloss over the precious little testing in blacks. I would vote for unrestricted use."
- (Consumer representative) "I am for approval, but we need more information on representative populations by gender, race, etc."
- (Chairman) "I agree that we haven't seen a representative sample to give unrestricted approval…For that, we need some data – not from a well-controlled trial, but from experience in 50 patients on both – on concomitant administration of nitrates and on this drug. I think we need to study it in women and important subpopulations…and I would like more information on dose response...so I think additional data is necessary for approval in an unrestricted population…and along the way we would get more data on TdP and QT, but that isn't a show stopper for approval. If the company doesn't want to do the additional study for unrestricted approval – and wants to go restricted label route -- then I don't think we have data to provide an approval or to write a label for such patients….Who should be studied (for a restricted label)? I think it would be reasonable to study patients with angina on the maximum tolerated dose of ≥1 anti-anginal drug…and in that study I would allow patients to be included who would be inappropriate for or who can't take other agents."
- "I would vote to restrict the population and require another trial that includes a sample that represents the population who will be using the drug – the elderly, different races, women, people on other anti-anginals. The sample used (in CARISA and MARISA) does not represent the American population...But the available data is sufficient for approval in a resistant population."
- "I am quite persuaded by the efficacy and safety...I would like the CARISA population to be the approved population…The concept of defining a resistant population and labeling that population is one of these situations where the devil really is in the details…It would be very difficult…And if you took that protocol to an angina clinic, the investigators would say they had thousands of (eligible) patients, but they wouldn't be able to recruit anyone…I am troubled by the notion of saying we should restrict the drug to a population that has not been studied. I don't believe that is necessary."
- "I'm convinced of the effectiveness of the drug…and I think the safety is reasonable, particularly at the lower dose…so I would label this for a resistant group, similar to the CARISA study – patients who remain symptomatic despite treatment with the maximum tolerated or labeled dose of one or another anti-anginal and patients who don't tolerate one or more classes. To give it to patients who remain symptomatic despite treatment with the maximum tolerated dose of more than one needs more study…It is approvable right now for restricted use…The company needs more patients, over a longer time with better background therapy if they want an unrestricted claim."
- **An FDA official said, "One way out of the box is to start out with a resistant population claim and then follow that in the future with an expanded claim."** ♦