Cardiovascular and Renal Drugs Advisory Committee Meeting
December 9, 2003

Committee Questions

The Cardio-Renal Advisory Committee is asked to opine on the next steps in the Ranexa development program. Ranexa (ranolazine) is under development for use as an anti-anginal agent. It is unclear which of its pharmacological properties contribute to clinical efficacy, but the Agency's review concluded that it is an effective antianginal drug.

The letter (October 30, 2003) communicating an "approvable" action listed the following deficiencies that are the subject of discussion today:
- Inadequate safety experience with the sustained-release formulation and doses in the range proposed for marketing, and
- Inadequate evidence of effectiveness in a setting commensurate with the risk associated with effects of ranolazine on ventricular repolarization.
- Inadequate information on dose-response and dosing interval.

1. ICH E1 recommends that drugs intended for chronic use have a safety database that includes at least 1500 individuals treated with relevant doses and 100 patients treated for at least one year. Greater exposure is recommended if there are specific concerns. The table below summarizes the available data for ranolazine.

Form	Dose	Duration				Patient -years
		Any	>30 d	>90 d	>365 d	
IV	Any	77	(Not available)			1
IR	Any	1299				430
	400 TID	518				—
SR	Any	1460	852	740	503	1285
	≥500 BID	1359	852	740	503	1283
	≥1000 BID	825	536	376	149	557

Evaluate the following as factors influencing the need for additional *safety* data:
1.1. Availability of other approved antianginals.
1.2. The nature of the efficacy demonstrated to date (i.e., symptomatic effects in general population).
1.3. Available safety data from short-term studies of the IV formulation.
1.4. Available safety data from short-term studies using the immediate release formulation.
1.5. Overall safety profile from the available data with the sustained release formulation.
1.6. Available data pertaining to cardiac repolarization:
   1.6.1. Pre-clinical data, including absence of after-depolarizations.

1.6.2. Relationship between plasma concentration and QT interval prolongation (e.g., steepness, 'plateau' of effect).

1.6.3. Drug-drug (ketoconazole, verapamil, diltiazem), and drug-disease (hepatic impairment) interactions, including effects not clearly mediated by metabolic inhibition, and combinations of these.

1.6.4. Lack of Torsade de Pointes in the clinical database.

1.6.5. Other cardiac adverse effects reported in the database.

2. Evaluate the following as factors influencing the need for additional *efficacy* data:

   2.1. Available data on effects of ranolazine on rate-pressure product or maximum oxygen utilization.

   2.2. Available controlled experience with the sustained release formulation in trials of duration greater than 1 week.

   2.3. Available information on the dose-response relationship for exercise tolerance.

   2.4. Effects of ranolazine on hemodynamic parameters (e.g., vital signs and rate-pressure product).

   2.5. The magnitude of the effect of ranolazine on exercise tolerance.

   2.6. Accumulated data on the use of ranolazine together with other antianginals.

   2.7. The effects of ranolazine on 'hard' clinical outcomes (e.g., death, MI).

3. What additional data, if any, are needed for ranolazine to obtain a claim for…

   3.1. …use in an unrestricted population with angina?

   3.2. …use restricted, because of a concern about effects on repolarization, to a 'resistant' population?

      3.2.1. If additional data are needed, what would constitute 'resistant'?

      - Patients who remain symptomatic despite treatment with maximally tolerated or labeled doses of *one* other antianginal.
      - Patients who remain symptomatic despite treatment with maximally tolerated or labeled doses of *more than one* other antianginal.
      - Patients with specific characteristics that would suggest they would not tolerate one or more classes of antianginal drug (e.g., patients with low blood pressure, low heart rate).

      3.2.2. Would further characterization of dose-response be necessary in the target population?

4. If further study of effectiveness is needed, …

   4.1. …what range of doses should be studied?

   4.2. …what duration of controlled exposure should be studied?

   4.3. …what considerations should be given to demographics?