CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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QUESTIONS

Questions

fenoldopam

26 June 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiorenal Advisory Committee

Neurex proposes that their formulation of fenoldopam be approved for use as a parenteral antihypertensive agent. This formulation of fenoldopam has been administered to just over 1000 subjects in clinical trials. An oral formulation, administered to over 1400 subjects, was abandoned because of bioavailability problems.

Seven parenteral antihypertensive agents are already approved:

- Diazoxide (HYPERSTAT® I.V., Schering) is indicated "for short-term use in the emergency reduction of blood pressure in severe non-malignant and malignant hypertension in hospitalized adults, and in acute severe hypertension in hospitalized children, when prompt and urgent decrease of diastolic blood pressure is required. Treatment with orally effective antihypertensive agents should not be instituted until blood pressure is stable. The use of HYPERSTAT I.V. Injection for longer than 10 days is not recommended." Diazoxide is also available in oral dosage forms, but these are approved only for the treatment of hypoglycemia.

- Enalaprilat (VASOTEC® I.V. INJECTION, Merck) is indicated "for the treatment of hypertension when oral therapy is not practical." Enalapril, the pro-drug of enalaprilat, is available in oral dosage forms, which are approved for the treatment of hypertension and congestive heart failure.

- Hydralazine hydrochloride injection (SoloPak) is indicated "for severe essential hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure." Hydralazine is also available in oral dosage forms, which are approved for the treatment of hypertension.

- Labetalol (NORMODYNE®, Schering) is indicated "for control of blood pressure in severe hypertension." Labetalol is also available in oral dosage forms, which are approved for the treatment of hypertension.

- Nicardipine (CARDENE® I.V., Wyeth-Ayerst) is indicated "for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of blood pressure, patients should be transferred to oral medication as soon as their clinical condition permits." Nicardipine is also available in oral dosage forms, which are approved for the treatment of hypertension and angina.

- Nitroglycerin (NITRO-BID® IV, Hoechst Marion Roussel) is indicated "for treatment of perioperative hypertension . . . and for induction of intraoperative hypotension." Nitroglycerin is also available in several other dosage forms, but these are approved only as anti-anginals.

- Sodium nitroprusside (generic) is indicated "for the immediate reduction of blood pressure of patients in hypertensive crises. Concomitant longer-acting antihypertensive medication should be administered so that the duration of treatment with sodium nitroprusside can be minimized. Sodium nitroprusside is also indicated for producing controlled hypotension in order to reduce bleeding during surgery." Oral dosage forms are not available.

Excluding the specific claim for reduction of blood loss in surgery, the differences among the various approved indications are somewhat related to differences in trial design (*e.g.*, did the investigators make an effort to demonstrate that patients were suffering from a hypertensive "crisis"), but as much related to historical accident.

Some trials were limited to patients with marked elevations of blood pressure, with accompanying signs and symptoms that increased the attractiveness of prompt, easily titrated treatment. In other trials, the patients had only moderate levels of hypertension, but the patients were for some reason temporarily unable to take medicine by mouth, so a parenteral medication was needed.

In general (again excluding the claim related to blood loss during surgery), the accepted trials did not demonstrate that use of the test drugs caused irreversible deleterious changes to be averted. Instead, what was demonstrated in each case was simply that blood pressure was lowered. What was also demonstrated in each case was that instructions could be written, such that following the instructions allowed blood-pressure changes to be reasonably predicted and controlled.

1. Study 94–005 enrolled patients with mild to severe hypertension, excluding those with any signs of the ongoing end-organ damage that defines hypertensive crisis. These patients received placebo or fenoldopam, infused at rates of 0.04–0.8 µg/kg/min.

1(A). Did this study identify a minimal effective infusion rate for an antihypertensive response? If so, to what populations (mild hypertensives, moderate hypertensives, severe hypertensives) should this finding be expected to apply?

1(B). Did it identify a maximal infusion rate, above which the effect was unsafe or intolerable? If so, to what populations should this finding be expected to apply?

2. Study 94–006 enrolled patients with severe hypertension (diastolic pressure at least 120 mm Hg), many of whom had signs of ongoing end-organ damage. These patients received fenoldopam, infused at rates of 0.01–0.3 µg/kg/min.

2(A). Did this study identify a minimal effective infusion rate for an antihypertensive response? If so, to what populations should this finding be expected to apply?

2(B). Did it identify a maximal infusion rate, above which the effect was unsafe or intolerable? If so, to what populations should this finding be expected to apply?

3. Are there data that clarify the relationship (linear or otherwise) between the infusion rate of fenoldopam and its steady-state plasma concentration

3(A). in non-crisis hypertension? From what study or studies do the data come? What do the data show?

3(B). in hypertensive crisis? From what study or studies do the data come? What do the data show?

4. Are there data that clarify the relationship (linear or otherwise) between the infusion rate of fenoldopam and its steady-state antihypertensive effect

4(A). in non-crisis hypertension? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

4(B). in hypertensive crisis? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

5. Are there data that identify the time-to-pharmacokinetic-steady-state for various infusion rates of fenoldopam

5(A). in non-crisis hypertension? From what study or studies do the data come? What do the data show?

5(B). in hypertensive crisis? From what study or studies do the data come? What do the data show?

6. Are there data that identify the time-to-pharmacodynamic-steady-state (that is, the time to a steady-state antihypertensive effect) for various infusion rates of fenoldopam

6(A). in non-crisis hypertension? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

6(B). in hypertensive crisis? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

7. Are there data that characterize the time course of decline in plasma concentration of fenoldopam, after discontinuation of a fenoldopam infusion

7(A). in non-crisis hypertension? From what study or studies do the data come? What do the data show?

7(B). in hypertensive crisis? From what study or studies do the data come? What do the data show?

8. Are there data that characterize the time course of decline in antihypertensive effect of fenoldopam, after discontinuation of a fenoldopam infusion

8(A). in non-crisis hypertension? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

8(B). in hypertensive crisis? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

9. Fenoldopam can be metabolized by any of several hepatic pathways, and plasma clearance is not materially affected by cirrhosis or renal disease. These facts reduce the likelihood of drug-drug interactions, but are there data to describe (or rule out) organ-dysfunction-induced alterations in fenoldopam's antihypertensive effect

9(A). in non-crisis hypertension? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

9(B). in hypertensive crisis? Is this a meaningful goal? From what study or studies do the data come? What do the data show?

10. In Study B74, fenoldopam seemed to prolong the QT_c interval more than the sodium nitroprusside control. Perhaps relatedly, one patient with congestive heart failure in an early fenoldopam study developed ventricular fibrillation and died. Is fenoldopam's putative effect upon the QT_c interval of substantial concern?

11. Are there any other adverse effects that are of concern when fenoldopam is administered intravenously to patients with hypertension?

12. Should fenoldopam be approved for the treatment of hypertension when oral therapy is not practical? If so, how should the indicated population be identified in labeling? What should the labeling say about the transition from fenoldopam therapy to oral medication?

13. Should fenoldopam be approved for the treatment of "severe" hypertension, "malignant" hypertension, or "hypertensive crisis"? If so, how should the indicated population be identified in labeling?

Revised 6/13/97

QUESTIONS FOR THE
CARDIO-RENAL ADVISORY COMMITTEE
June 26, 1997

RE: Lovenox® (Enoxaparin Sodium) Injection
for the treatment of unstable angina or non Q wave MI

Rhone-Poulenc Rorer has requested approval of Lovenox ® (Enoxaparin Sodium) for "the treatment of unstable angina or non Q wave MI," as per the proposed labeling. The sponsor recommends that Enoxaparin be administered at a dose of 1.0 mg/kg sc q12h for 2 to 8 days, given concomitantly with aspirin. Support for the claimed indication is based on the results of a single, large, multicenter trial, Study RP54563q-303, the ESSENCE trial.

The primary composite endpoint of the ESSENCE trial was death, MI, or recurrent angina at 14 days. The prespecified alpha level was .048 to correct for a single interim analysis. A statistically significant benefit of the combination of enoxaparin and aspirin over heparin and aspirin in reducing the incidence of the primary composite endpoint of death, MI, and recurrent angina in patients with unstable angina and non Q wave MI was seen at 14 days (19.8% in the heparin group compared to 16.6% in the enoxaparin group, p=.019). Similar trends were seen in the individual endpoints of MI (4.5% in the heparin group compared to 3.2% in the enoxaparin group, p=.055), and recurrent angina (15.5% in the heparin group compared to 12.9% in the enoxaparin group, p=.031) at 14 days. The incidence of the composite endpoint of death, MI, or recurrent angina prompting revascularization, an endpoint used in some other studies that at least arguably included components of more nearly equal weight, was 14.5% in the heparin group compared to 11.1% in the enoxaparin group at 14 days (p=.004).

The Agency has considered the question of when it is appropriate to rely on results from a single controlled trial. Specifically, as discussed in the Draft Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, "reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, such that confirmation of the result in a second trial would be ethically difficult or impossible." Several characteristics of a single adequate and well-controlled study that could make a study adequate support for an effectiveness claim were identified in this Draft Guidance, and include:

A. The study is a large multicenter study in which 1) no single study site provided an unusually large fraction of the patients, and 2) no single investigator or site was disproportionately responsible for the effect seen.

B. There are multiple "studies" in a single study (e.g. strata).

C. There are multiple, independent endpoints involving different events (e.g. death, MI).

D. The finding is statistically very powerful.

In the present case the statistical significance of the effect of enoxaparin is not extreme, but the comparator is a treatment that may be active. This could be interpreted as suggesting that the difference between enoxaparin and placebo (which wasn't present) would be greater, and that in a sense, the "true" significance is greater than it seems.

With the above as background, we have the following questions:

1) Was the ESSENCE trial an adequate and well-controlled clinical trial that showed a significant clinical benefit of enoxaparin(added to aspirin), compared to heparin(added to aspirin), in the prevention of ischemic events associated with unstable angina and non Q wave MI?

2) Are there specific characteristics of the ESSENCE trial that would make this single study one that provided persuasive and adequate support for the proposed indication? Possible characteristics include:

   A. Enoxaparin was superior to heparin not only for the primary combined endpoint, but also for the separate recurrent MI and angina components?

   B. That the unspecified (but often used) endpoint of death, MI, and recurrent angina prompting revascularization at 14 days was very strongly significant?

   C. That the advantage of enoxaparin was still present at 30 days?

   D. That enoxaparin was superior in the ESSENCE trial to a probably active agent? Indicate how strong you think the evidence is that heparin is effective in unstable angina, and be specific about what you think the impact of this is on the inference to be drawn from the ESSENCE trial.

E. Information from other studies of the use of other LMWHs in the treatment of unstable angina, including the FRISC, FRIC, and Gurfinkel EP et al (JACC 1995 26 313) studies?

3) In light of your answers to question 2, do you believe that the ESSENCE trial provides substantial evidence of the effectiveness of enoxaparin for the proposed indication?

Additional Cardio-Renal Advisory Committee
Discussion Questions

In the ESSENCE study, the primary endpoint is a composite of three endpoints (death, MI, recurrent angina). A prespecified secondary endpoint is a composite of death and MI. Another post-hoc analysis demonstrated a significant reduction in an endpoint that is commonly employed in clinical trails, namely the composite of death, MI, and revascularization. Of these components and composites, which could be considered to meet the standard of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with potentially serious outcome.

A. Death
B. MI
C. Recurrent angina
D. Death plus non-fatal MI
E. Death plus non-fatal MI plus recurrent angina
F. Death plus non-fatal MI plus recurrent angina requiring revascularization

For which of these endpoints did the ESSENCE trial demonstrate superiority of enoxaparin over unfractionated heparin?