CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 01/27/98

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SLIDES (HANDOUT)

Evaluation of Long-term Treatment with Cyclic AMP-Dependent Positive Inotropic Agents

Introduction

All positive inotropic agents approved for intravenous use for the short-term treatment of patients with acutely decompensated heart failure act by increasing myocardial levels of cyclic AMP. Three types of cyclic AMP dependent agents have been developed: (1) adrenergic receptor agonists (such as dobutamine and dopamine); (2) phosphodiesterase inhibitors (such as amrinone and milrinone); and (3) multiple action agents with phosphodiesterase inhibitory effects (several drugs under development). All intravenous drugs were approved for use based on their ability to produce hemodynamic improvement for short periods of time; none had data supporting long-term use at the time of their introduction for clinical use.

With the advent of new infusion systems and short stay infusion clinics, it is now possible to administer intravenous agents (continuously or intermittently) to patients with heart failure for weeks, months or even years — periods not anticipated at the time of initial approval of these agents. Furthermore, such use has now been actively promoted by at least one company who markets an intravenously administered positive inotropic drug. As a result, there is now increasing long-term use of intravenous positive inotropic agents for the treatment of chronic heart failure.

Objectives

The intent of this review is to summarize the data available from clinical trials on the efficacy and safety of long-term positive inotropic therapy for heart failure. Several trials have suggested that continuous or intermittent treatment with positive inotropic drugs for periods up to one month can produce symptomatic improvement. The question is: Is such therapy effective and safe when administered for longer periods?

To address this question, all controlled clinical trials using a positive inotropic drug (oral or intravenous) were reviewed. Trials were included in this summary if the trial fulfilled the following criteria:

- The trial evaluated a drug with positive inotropic properties that were dependent (in part or in whole) on cyclic AMP. This criterion was used because all positive inotropic agents approved for intravenous use act by such a mechanism. The trials included (1) adrenergic receptor agonists (such as dobutamine, xamoterol and ibopamine); (2) phosphodiesterase inhibitors (such as milrinone and enoximone); and (3) multiple action agents with phosphodiesterase inhibitory effects (such as pimobendan, vesnarinone and flosequinan).

- The trial was double-blind and placebo-controlled with a parallel-group design. Trials were excluded if they were crossover in design or allowed crossovers after the initial treatment assignments (the only exception was a trial with dobutamine, since this was the only long-term study of intermittent inotropic therapy). Trials were also excluded if they used a withdrawal design.

- The trial was of sufficient duration (at least 3 months) to allow an adequate evaluation of efficacy and safety. This criterion was chosen so that the data would resemble that generally available to the Committee for the evaluation of drugs for long-term use.

• The results of the trial were published in English in either preliminary or final form. Trials submitted to the FDA (as a part of an NDA) but not published were not included; a brief survey suggested that most of these showed no evidence of efficacy. Trials published only in sponsored journal supplements were also not included.

Twenty-four trials fulfilling these criteria are summarized below. Reprints for each study are provided in the Appendix. No attempt has been made to validate the results of these studies, and in many cases, the results were questioned by the FDA or its Advisory Committee. No attempt has been made to correct P values for the multiplicity of endpoints, treatments or interim analyses. A treatment effect is noted if the difference between placebo and active therapy was nominally significant ($P < 0.05$) at the end of the treatment period (except where noted otherwise).

Summary of Individual Trials

Dobutamine (1 trial)

#1. Reference: Circulation 1986; 74 (suppl II): II-38 (Dies)
Drug: Dobutamine
Number of patients: 60 (1:1 randomization)
Treatment assignments: placebo; dobutamine (8.1 μg/kg/min for 48 hr per week)
NYHA class: III-IV
Background medications: digoxin, diuretics ± vasodilators
Duration of double-blind therapy: 24 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration; no change in symptom scores
Safety results: deaths (5 on placebo, 13 on dobutamine) [P= 0.147]
Comments: study terminated by sponsor because of mortality concerns

Ibopamine (3 trials)

#2. Reference: J Am Coll Cardiol 1993; 22: 1564-73 (van Veldhuisen)
Drugs: Ibopamine and digoxin
Number of patients: 161 (1:1:1 randomization)
Treatment assignments: placebo; ibopamine (300 mg/day); digoxin (0.25 mg/day)
NYHA class: class II-III
Background medications: diuretics (no ACE inhibitors)
Duration of double-blind therapy: 6 months
Primary endpoint: exercise duration
Efficacy results: no effect of ibopamine on exercise, symptoms or NYHA class
Safety results: deaths (3 on placebo, 2 on digoxin, 1 on ibopamine) [P= NS]

#3. Reference: J Cardiac Failure 1996; 2: 185-92 (Szabo)
Drug: Ibopamine
Number of patients: 59 (1:1 randomization)
Treatment assignments: placebo; ibopamine (300 mg/day)
NYHA class: class III-IV
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: no effect on exercise duration
Safety results: no deaths reported

#4. Reference: Lancet 1997; 349: 971-7 (Hampton et al./PRIME II)
Drug: Ibopamine
Number of patients: 1906 (1:1 randomization)
Treatment assignments: placebo; ibopamine (300 mg/day)
NYHA class: class III-IV
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: up to > 18 months
Primary endpoint: all-cause mortality
Efficacy results: no effect on symptoms or NYHA class
Safety results: deaths (193 on placebo, 232 on ibopamine) ↑ risk by 26% [P= .017]
risk particularly ↑ in class IV; also ↑ hospitalizations and ↑ dropouts with ibopamine
Comments: study terminated by ethical committee because of mortality concerns

Xamoterol (3 trials)

#5. Reference: Lancet 1988; 1: 489-93 (German-Austrian study)
Drugs: Xamoterol and digoxin
Number of patients: 433 (1:1:1 randomization)
Treatment assignments: placebo; xamoterol (400 mg/day); digoxin (0.125 mg/day)
NYHA class: I-III
Background medications: diuretics (no ACE inhibitors or vasodilators)
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration and ↓ symptoms
Safety results: no deaths reported

#6. Reference: Eur Heart J 1989; 10: 1003-10 (Waller)
Drug: Xamoterol
Number of patients: 240 (1:2 randomization)
Treatment assignments: placebo; xamoterol (400 mg/day)
NYHA class: I-III
Background medications: diuretics ± nitrates (no ACE inhibitors)
Duration of double-blind therapy: 3 months
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration and ↓ symptoms
Safety results: no deaths reported

#7. Reference: Lancet 1990; 336: 1-6 (Severe Heart Failure Trial)
Drug: Xamoterol
Number of patients: 516 (1:2 randomization)
Treatment assignments: placebo; xamoterol (400 mg/day)
NYHA class: III-IV
Background medications: digoxin + diuretics + ACE inhibitor
Duration of double-blind therapy: 13 weeks
Primary endpoint: exercise duration
Efficacy results: ↓ symptoms but no effect on exercise duration
Safety results: deaths (6 on placebo, 32 on xamoterol) [P= .02]
↑ dropouts with xamoterol (particularly for cardiovascular reasons)
Comments: study terminated by ethical committee because of mortality concerns

Milrinone (2 trials)

#8. Reference: N Engl J Med 1989; 320: 677-83 (DiBianco)
Drugs: Milrinone, digoxin and the combination
Number of patients: 230 (1:1:1:1 randomization)
Treatment assignments: placebo; milrinone (40 mg/day); digoxin (0.125-0.50 mg/day) and the combination
NYHA class: primarily II-III
Background medications: digoxin + diuretics ± vasodilators (no ACE inhibitors)
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration with milrinone when substituted for digoxin, but no ↑ exercise duration with milrinone when added to digoxin
Safety results: deaths (6 not on milrinone, 15 on milrinone) [P= .064]
↑ dropouts with milrinone (particularly for cardiovascular reasons)

#9. Reference: N Engl J Med 1991; 325: 1468-75 (Packer/PROMISE)
Drug: Milrinone
Number of patients: 1088 (1:1 randomization)
Treatment assignments: placebo; milrinone (40 mg/day)
NYHA class: III-IV
Background medications: digoxin + diuretics + ACE inhibitor
Duration of double-blind therapy: up to 20 weeks
Primary endpoint: all-cause mortality
Efficacy results: no effect on symptoms, NYHA class or QOL scores
Safety results: deaths (127 on placebo, 268 on milrinone) ↑ risk by 28% [P= .03]
risk ↑ by 53% in class IV; also ↑ hospitalizations and ↑ dropouts with milrinone
Comments: study terminated by ethical committee because of mortality concerns

Enoximone (3 trials)

#10. Reference: Circulation 1990; 82: 774-80 (Uretsky)
Drug: Enoximone
Number of patients: 102 (1:1 randomization)
Treatment assignments: placebo; enoximone (150-450 mg/day)
NYHA class: primarily II-III
Background medications: digoxin + diuretics (no vasodilators or ACE inhibitors)
Duration of double-blind therapy: 16 weeks
Primary endpoint: exercise duration
Efficacy results: no effect on exercise duration, symptoms or NYHA class
Safety results: deaths (3 not on placebo, 10 on enoximone) [P < .05]
↑ dropouts with enoximone (particularly for cardiovascular reasons)

#11. Reference: Am Heart J 1991; 121: 1471-9 (Narahara)
Drug: Enoximone
Number of patients: 164 (1:1:1 randomization)
Treatment assignments: placebo; enoximone (150 mg/day); enoximone (300 mg/day)
NYHA class: II-III
Background medications: digoxin + diuretics (no ACE inhibitors)
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: no effect on exercise duration or symptoms
Safety results: deaths (3 on placebo, 4 on low dose and 4 on high dose enoximone)
↑ dropouts with high dose enoximone (particularly for adverse reactions)

#12. Reference: Br Heart J 1994; 72: 226-30 (Cowley)
Drug: Enoximone
Number of patients: 151 (1:1 randomization)
Treatment assignments: placebo; enoximone (300 mg/day)
NYHA class: III-IV
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: up to > 18 months
Primary endpoint: all-cause mortality
Efficacy results: ↑ QOL scores (at isolated visits early in treatment) but no effect at most timepoints; also, no effect on NYHA class
Safety results: deaths (18 on placebo, 27 on enoximone) [$P < .05$]
↑ risk of hospitalizations and ↑ risk of dropouts with enoximone
Comments: study terminated by ethical committee because of mortality concerns

Pimobendan (3 trials)

#13. Reference: Circulation 1992; 85: 942-9 (Kubo)
Drug: Pimobendan
Number of patients: 198 (1:1:1:1 randomization)
Treatment assignments: placebo; pimobendan (2.5 mg/day); pimobendan (5.0 mg/day); pimobendan (10 mg/day)
NYHA class: primarily III
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: no effect on any measure with 2.5 mg/day; ↑ exercise duration with 5 and 10 mg/day; ↑ QOL scores with 5 mg/day but not 10 mg/day; ↓ hospitalization with pimobendan (all doses combined vs placebo)
Safety results: deaths (3 on placebo, 0 on 2.5 mg; 3 on 5 mg; and 5 on 10 mg/day)

#14. Reference: Heart & Vessels 1994; 9: 113-20 (Sasayama)
Drugs: Pimobendan
Number of patients: 21 (1:1:1 randomization)
Treatment assignments: placebo; pimobendan (2.5-5.0 mg/day)
NYHA class: II-III
Background medications: diuretics ± digoxin ± ACE inhibitors
Duration of double-blind therapy: up to 30 weeks
Primary endpoint: not specified
Efficacy results: ↓ risk of worsening heart failure (5 on placebo; 0 on pimobendan)
↑ specific activity scale (similar to NYHA class), but no ↑ in exercise tolerance
Safety results: no deaths reported

#15. Reference: Heart 1996; 76: 223-31 (Lubsen/PICO)
Drugs: Pimobendan
Number of patients: 317 (1:1:1 randomization)
Treatment assignments: placebo; pimobendan (2.5 mg/day); pimobendan (5.0 mg/day)
NYHA class: II-III
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: ≥ 24 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise time with 2.5 and 5 mg/day; no effect on QOL or NYHA class
Safety results: deaths (11 on placebo, 20 on 2.5 mg/day, and 16 on 5 mg/day)
deaths + hospitalizations (27 on placebo, 40 on 2.5 mg/day, and 33 on 5 mg/day)
effect of 2.5 mg/day = $P \approx 0.10$ for deaths and $P < 0.05$ for deaths + hospitalizations

Vesnarinone (4 trials)

#16. Reference: Cardiovasc Drugs Ther 1990; 4: 419-25 (OPC-8212 Group)
Drug: Vesnarinone
Number of patients: 83 (1:1 randomization)
Treatment assignments: placebo; vesnarinone (60-120 mg/day)
NYHA class: primarily II-III
Background medications: digoxin + diuretics + vasodilators
Duration of double-blind therapy: 12 weeks
Primary endpoint: not specified
Efficacy results: no effect on NYHA class; ↑ QOL on one scale but not another; ↑ global assessment; and ↓ risk of heart failure with vesnarinone
Safety results: deaths (2 on placebo, 0 on vesnarinone)

#17. Reference: Am J Cardiol 1991; 68: 1203-10 (Feldman)
Drug: Vesnarinone
Number of patients: 76 (1:1 randomization)
Treatment assignments: placebo; vesnarinone (60 mg/day)
NYHA class: II-IV
Background medications: diuretics + ACE inhibitors ± digoxin
Duration of double-blind therapy: ≥ 12 weeks
Primary endpoint: death + worsening heart failure requiring IV inotropes
Efficacy results: ↓ risk of primary endpoint (9 on placebo, 1 on vesnarinone), P=0.007
no effect on exercise duration or QOL (unless data are imputed)
Safety results: deaths (6 on placebo, 1 on vesnarinone) [P < 0.05]

#18. Reference: N Engl J Med 1993; 329: 149-55 (Feldman)
Drug: Vesnarinone
Number of patients: 253 (1:1:1 randomization)
Treatment assignments: placebo; vesnarinone (60 mg/day); vesnarinone (120 mg/day)
NYHA class: II-IV
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: 6 months
Primary endpoint: death + worsening heart failure requiring IV inotropes
Efficacy results: ↓ risk of primary endpoint (50 on placebo, 26 on vesnarinone), P=0.003
no effect on exercise duration, NYHA class or QOL (unless data are imputed)
Safety results: deaths (6 on placebo, 16 on vesnarinone 120 mg/day) [P = 0.01]; deaths (33 on placebo, 13 on vesnarinone 60 mg/day) [P = 0.002]
Comments: 120 mg arm stopped by ethical committee because of mortality concerns

#19. Reference: J Am Coll Cardiol 1997; 29: 64A (Feldman/Cohn/VEST)
Drug: Vesnarinone
Number of patients: 3833 (1:1:1 randomization)
Treatment assignments: placebo; vesnarinone (30 mg/day); vesnarinone (60 mg/day)
NYHA class: III-IV
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: up to 18 months
Primary endpoint: all-cause mortality
Efficacy results: no effect on NYHA class or hospitalizations; abstract states no effect on QOL scores, but presentation showed ↑ QOL scores at 16 weeks (but not later)
Safety results: deaths (239 on placebo, 266 on 30 mg/day; and 289 on 60 mg/day); 23% ↑ risk with 60 mg (P < 0.02); 12% ↑ risk with 30 mg (P =0.20)

Flosequinan (5 trials)

#20. Reference: J Am Cardiol Coll 1993; 22: 65-72 (Packer/REFLECT I)
Drug: Flosequinan
Number of patients: 193 (1:1 randomization)
Treatment assignments: placebo; flosequinan (100 mg/day)
NYHA class: II-III
Background medications: digoxin + diuretics (no vasodilators or ACE inhibitors)
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration and ↓ symptoms, but no change in NYHA class
Safety results: deaths (2 on placebo, 7 on vesnarinone) [P=NS]

#21. Reference: Circulation 1991; 84 (suppl II): II-311 (Pitt/REFLECT II)
Drug: Flosequinan
Number of patients: 311 (1:1:1 randomization)
Treatment assignments: placebo; flosequinan (100 mg/day); flosequinan (150 mg/day)
NYHA class: primarily II-III
Background medications: digoxin + diuretics (no vasodilators or ACE inhibitors)
Duration of double-blind therapy: 12 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration with 100 mg/.day but not 150 mg/day; improved NYHA class with 150 mg/day but not with 100 mg/day
Safety results: deaths (2 on placebo, 5 on 100 mg/day, and 6 on 150 mg/day) [P=NS]

#22. Reference: Int J Cardiol 1993; 38: 167-75 (Cowley)
Drug: Flosequinan
Number of patients: 135 (1:1 randomization)
Treatment assignments: placebo; flosequinan (125 mg/day)
NYHA class: primarily II
Background medications: diuretics ± digoxin (no vasodilators or ACE inhibitors)
Duration of double-blind therapy: 16 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ NYHA class but no effect on exercise or QOL
Safety results: deaths (1 on placebo, 1 on flosequinan) [P=NS]

#23. Reference: Circulation 1993; 88: 493-501 (Massie/FACET)
Drug: Flosequinan
Number of patients: 322 (1:1:1 randomization)
Treatment assignments: placebo; flosequinan (100 mg/day); flosequinan (150 mg/day)
NYHA class: II-III
Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: 16 weeks
Primary endpoint: exercise duration
Efficacy results: ↑ exercise duration and ↑ QOL with 100 mg/.day but not 150 mg/day; no effect on global assessment, NYHA class or hospitalizations
Safety results: deaths (6 on placebo, 8 on 100 mg/day, and 5 on 150 mg/day) [P=NS]

#24. Reference: Circulation 1993; 88 (suppl I): I-301 (Packer/PROFILE)
dated cited below updated by author since publication of abstract
Drug. Flosequinan
Number of patients: 2345 (1:1 randomization)
Treatment assignments: placebo; flosequinan (100 mg/day)
NYHA class: III-IV

Background medications: digoxin + diuretics + ACE inhibitors
Duration of double-blind therapy: up to 22 months
Primary endpoint: all-cause mortality
Efficacy results: ↓ symptoms and ↓ hospitalizations at 1 month but not later
Safety results: deaths (181 on placebo, 245 on flosequinan) 41% ↑ risk [P = .0004]
35% ↑ risk in class III (P = 0.007) and 72% ↑ risk in class IV (P = 0.008)
↑ risk of hospitalizations and dropouts in flosequinan group

Summary of Trials

Efficacy

It is difficult to draw conclusions from the existing database about the effect of long-term treatment with positive inotropic agents on the symptoms and clinical status of patients with heart failure.

- Although many studies reported a favorable effect of treatment on at least one measure of clinical status, this measure was commonly not the primary prespecified measure of efficacy and was not supported by changes in other clinical endpoints measured in the same study.

- In many cases, claims of efficacy are difficult to interpret since the investigators excluded and imputed data; failed to account for the effect of dropouts; and did not attempt to correct for the multiplicity of endpoints and comparisons.

- The trials that reported a favorable effect of treatment on symptoms and clinical status were nearly always carried out in patients with mild-to-moderate symptoms. However, such patients do not represent the target population being proposed as ideal candidates for intermittent or continuous positive inotropic therapy.

- If only trials in patients with class III-IV heart failure are considered, there is no evidence of a favorable effect of treatment on symptoms or clinical status. In nearly all cases, treatment failed to have any favorable effect on the three measures of efficacy most commonly evaluated in class III-IV patients (NYHA class, symptoms and hospitalizations). Only two studies showed an improvement in symptoms or quality-of-life (after 2-4 weeks), but neither effect was sustained during long-term therapy.

- In all studies carried out in class III-IV patients, treatment with a positive inotropic agent was associated with either no effect or a significant *increase* in the frequency of hospitalization. This finding is of interest, since studies that failed to utilize a placebo control have reported a dramatic *decrease* in the risk of hospitalization with the use of intermittent intravenous positive inotropic therapy.

- Even if symptoms and quality-of-life had been significantly improved by active treatment, it would be difficult to determine how much symptom improvement would be needed to offset an increase in the risk of death.

Safety

The existing database raises important concerns about the safety of long-term treatment with positive inotropic agents in patients with heart failure.

- There is consistent evidence that all positive inotropic agents evaluated in this summary increase the risk of death in patients with chronic heart failure. For all 8 drugs, at least one trial demonstrated a significant increase in the mortality rate in patients assigned to active therapy. In most cases, this adverse effect was observed in a study that was specifically designed to evaluate the effect of treatment on mortality. In 6 of 8 cases, the trial was stopped early by an ethical committee or by the sponsor because of concerns about an increased risk of death. In all 8 cases, concerns about mortality led the sponsor to terminate development of the drug for long-term use.

- Evidence that active therapy is associated with an increase in mortality is available for every cyclic AMP dependent positive inotropic agent, regardless of its mechanism of action. The most consistent evidence is derived from trials of pure phosphodiesterase inhibitors: of the 5 studies performed with these drugs, 4 reported an increase in mortality that was statistically significant or nearly so.

- An increase in mortality risk with active therapy is evident even though the dropout rate (for adverse reactions or nonfatal cardiovascular events) was usually higher in patients assigned to active therapy. This higher dropout rate would have been expected to decrease the study's ability to find an increased risk of death, when data are analyzed according to the intention-to-treat principle.

- An increase in mortality risk was not readily apparent early in the development of each drug. Early trials reported very few deaths and did not have the power to discern an adverse effect on survival. In one case, an early study (with 46 deaths) reported a statistically significant *reduction* in mortality, whereas a subsequent trial (with 594 deaths) using same dose of the same drug observed a significant *increase* in the risk of death.

- Given the difficulties inherent in the classification of death, no conclusions can be reached regarding the mechanism(s) by which long-term positive inotropic therapy might increase mortality. Various studies have reported an increase in pump failure deaths or sudden deaths, or both.

- Few conclusions can be reached about the relation of dose to the risk of death, since many studies evaluated only a single dose. However, in the case of ibopamine, pimobendan, flosequinan and vesnarinone, the dose associated with an increased risk of death was 50-75% lower than the highest dose evaluated in a randomized trial during the drug's development (these trials may have lasted < 12 weeks and thus were not included in this summary). In trials that evaluated more than one dose, all doses were associated with an increased risk of death (hazard ratio > 1.0), and the risk at smaller doses was not different than the risk associated with larger doses. In one case (vesnarinone), two distinct doses (which differed by a factor of 2) were independently associated with a significantly increased risk of death. When a trial reported symptomatic improvement, this was always observed at a dose that was subsequently associated with a significant mortality risk.

- All subgroups of patients appeared to have an increased risk of death, but patients with class IV heart failure appeared to be at particularly enhanced risk as a result of treatment with a positive inotropic drug. This finding is of interest, since physicians are most likely to utilize intermittent intravenous positive inotropic therapy in class IV patients.

Summary and Recommendations

Positive inotropic agents have not been shown to be effective or safe in the treatment of heart failure during long-term use, whether given continuously or intermittently or whether given orally or intravenously. Instead, long-term treatment has been associated with a consistent increase in the risk of hospitalization and death. Patients with class IV symptoms may be at particular risk of serious adverse cardiovascular reactions. Data supporting an effect of treatment on symptoms and clinical status are inconsistent and are particularly lacking in patients with class IV symptoms. As a result, in patients with advanced or end-stage heart failure, there is no evidence that any assessment of risk to benefit would favor the long-term use of these drugs.

Given the increasing use of intermittent intravenous positive inotropic therapy by physicians and the promotion of such use by the pharmaceutical industry, it would seem appropriate to include the information summarized in the previous paragraph in labelling. This would be appropriate for drugs presently approved for use as well as those approved in the future, unless the sponsor presented data demonstrating the long-term efficacy and/or safety of the drug in class III-IV patients.