Division of Cardio-Renal Drug Products
Medical Officer Review
Addendum #1

NDA 20-920
Name of Drug: Natrecor® (nesiritide)

Date of Review May 10, 2001

This addendum attempts to address the following issues:

1) A fuller description of the hypotensive episodes in study # 703.329
2) To ascertain whether there is a relationship of between hypotension and alterations of renal function (as defined as an increase in creatinine values of 0.5 mg/dL relative to baseline measurements). Since there were more hypotensive events among those treated with the higher doses of Natrecor, the analysis was limited to the outcomes of study 703.329.
3) To ascertain whether the hypotension associated with Natrecor treatment was unaccompanied by a reflex tachycardia in Study 703.329.

The information included in this addendum was submitted on 20 April 2001.

1) Description of the hypotensive episodes.

Table Addendum-1 includes information with respect to the onset and duration of both symptomatic and asymptomatic episodes of hypotension.

Table Addendum-1. Description of All Hypotensive events study 703.329

	Dobutamine (n=83)	Natrecor (ug/kg/min)		P-value
		0.015 (n=84)	0.03 (n=79)	
Number with at least one episode (symptomatic) Number of episodes	2 (2%) 2	14 (17%) 16	19 (24%) 19	0.000 Fisher
Onset of hypotension (symptomatic)				
< 1 hour	0	1 (1%)	0	0.6
1- 3 hours	1 (2%)	0	3 (4%)	
> 3 hours- 6 hours	0	3 (4%)	4 (5%)	
>6- 24 hours	1 (2%)	12 (14%)	12 (15%)	
Duration of hypotension (symptomatic)				
< 30 minutes	1 (1%)	2 (2%)	2 (3%)	0.7
31-< 60 minutes	0	3 (4%)	2 (3%)	
61-120 minutes	0	4 (5%)	5 (6%)	
121-180 minutes	0	2 (2%)	2 (3%)	
3 hours –7 hours	0	3 (4%)	2 (3%)	
> 7 hours	1 (1%)	2 (2%)	6 (8%)	
Number with at least one episode (asymptomatic) Number of episodes	4 (5%) 4	9 (11%) 11	17 (22%) 17	0.000 Fisher
Onset of hypotension (asymptomatic)				
< 1 hour	1 (1%)	1 (1%)	1 (6%)	0.5
1- 3 hours	1 (1%)	0	2 (3 %)	
> 3 hours- 6 hours	0	2 (2%)	2 (3%)	
>6- 24 hours	2 (2%)	8 (10%)	12 (15%)	
Duration of hypotension (asymptomatic				

< 30 minutes	1 (1%)	5 (6 %)	1 (1%)	0.08
31-< 60 minutes	0	1 (1%)	3 (4%)	
61-120 minutes	0	0	1 (1%)	
121-180 minutes	0	2 (2%)	2 (3%)	
3hours –7 hours	0	1 (1%)	2 (3 %)	
> 7 hours	1 (1%)	2 (2%)	7 (9%)	

The total number of hypotensive episodes was greater on Natrecor than while on dobutamine and the number of subjects with these events among those treated with Natrecor appear to be dose related. Approximately 50% of the episodes (both symptomatic and asymptomatic) among those treated with Natrecor lasted > 2 hours. The onset of such events were generally scattered throughout the infusion regimen (the > 6 – 24 hour span is substantially longer than the other time intervals).

2) There was no obvious relationship between hypotension and creatinine changes. The sponsor submitted the ID numbers of those who had hypotension. This reviewer compared this listing with those subjects whose creatinine increased by more than 0.5 mg/dL. Overall, there were 13 and 15 subject in the 0.015 and 0.03 who had increases in creatinine of > 0.5 mg/dl. There were 23 and 35 patients with hypotension (either symptomatic or asymptomatic). There were 4 (5%) and 8 (10%) subjects who had hypotension (either symptomatic or asymptomatic) and also had increases in creatinine of > 0.5 mg/dL in the Natrecor 0.015 and 0.03 ug/kg/min infusions, respectively. The fraction of subjects in the overall population who had increases in creatinine of > 0/05 was not enriched among those with hypotensive episodes.

Table Addendum-2. Relationship between hypotension and creatinine increases of > 0.5 mg/dL.

	Natrecor dose (ug/kg/min)	
	0.015	0.03
Total enrolled (A)	84	79
Total with hypotension (B) (B/A x 100%)	23 (27%)	35 (44%)
Total with increased Creatinine (C) (C/A x 100%)	13 (15%)	15 (19%)
Total with both hypotension and increase in creatinine (D)	4	8
Increased Creatinine among those with hypotension (D) (D/B x 100%)	4/23 (18%)	8/35 (23%)

With respect to the magnitude of change in creatinine among those with either symptomatic or asymptomatic events, these are shown below. There was a marked increase in creatinine among those with symptomatic hypotension at day 2 especially for the 0.015 ug/kg/min dose, but the results seem to re-approach baseline at day 14. It is, therefore, difficult to attribute chronic changes in renal function among those treated with Natrecor to hypotensive episodes. The mechanism by which changes in renal function occur among those treated with Natrecor is still obscure.

Table Addendum –3 Time effect of the creatinine among those with hypotension

		Natrecor Dose					
		0.015 ug/kg/min			0.03 ug/kg/min		
		Baseline	Change day 2	Change day 14	Baseline	Change day 2	Change day 14
All Patients	N (missing)	84 (0)	79 (5)	74 (10)	78 (1)	74 (5)	64 (15)
	Value	1.6 ± 0.8	0.1 ± 0.4	0.1 ± 0.4	1.5 ± 0.9	**0.1 ± 0.3***	0.1 + 0.6
Symptomatic Hypotension	N (missing)	14 (0)	14 (0)	12(2)	19 (0)	18(1)	17(2)
	Value	1.4 ± 0.5	0.5 ± 0.5	-0.1 +0.2	1.3 + 0.4	0.2 +0.3	0 +0.4
Asymptomatic Hypotension	N (missing)	9 (0)	9 (0)	7 (2)	16 (0)	15 (1)	12 (4)
	Value	2.0 ± 1.1	0.0 ± 0.3	0.1 + 0.9	1.6 + 0.5	0.1 + 0.3	0.0 + 0.39

3) Lastly, It appears that the hypotensive episodes were not associated with tachycardia. This conclusion is subject to some caveats. First heart rates at the time of hypotension were not always available. Often blood pressure data was recorded at the time of the event, but no corresponding heart rate data was available any where near these events (i.e. within 15 minutes of hypotension). Second, there is no adequate control group for comparison. The appropriate heart rate response for a given degree of hypotension cannot accurately be assessed. The available control data is dobutamine, which on its own increase heart rate is less than optimum comparator.

Table addendum-4 lists the maximum percentage decrease in heart rate for those Natrecor-treated subjects with symptomatic and asymptomatic hypotension and those who were not hypotensive (the data was supplied by the sponsor). The table lists also the baseline heart rate and the heart rate response at the time of maximum BP drop.

Among those <u>not</u> categorized as having hypotensive episodes, the maximum SBP drop was 15- 17 % of their baseline values (the baseline value was approximately 120 mm Hg). The heart rate change for those not hypotensive were –3.9 to + 1.5 BPM for the two Natrecor groups.

Among those with <u>symptomatic</u> hypotension there was a 30 and 38% drop in SBP for the 0.015 and 0.03 ug/kg/min, respectively (the baseline SBP was between 108-110 mm Hg). The corresponding heart rate changes were modest +2.7 BPM and + 8.5 BPM, for the low and high dose group, respectively.

With respect to <u>asymptomatic</u> hypotensive patients the drop of blood pressure was equivalent 23-30% (the baseline blood pressure was approximately 110 mm Hg). The heart rate response was decreased for the low dose group (-5 BPM) and minimal increased for the high dose group (0.7 BPM).

Table Addendum-3 Hypotension and heart rate increases all values are Mean + SD

		Natrecor dose					
		0.015 (ug/kg/min)			0.03 (ug/kg/min)		
		Maximum SBP Drop %	Baseline Heart Rate (BPM)	Change in Heart rate at Max BP Drop (BPM)	Maximum SBP Drop (%)	Baseline Heart Rate (BPM)	Change in Heart rate at Max BP drop (BPM)
No Hypotension	N (missing)	60 (1)	60 (1)	60 (1)	44 (0)	44 (0)	44 (0)
	Value	17 ± 9	84 ± 16	-3.9 ± 8	15 ± 9.0	83 ± 15	1.5 ± 10
Symptomatic	N (missing)	14 (0)	14 (0)	12 (2)	19 (0)	19 (0)	14 (5)
	Value	30 ± 12	82 ± 13	2.7 ± 10	38 ± 10	84 ± 11	8.5 ± 10
Asymptomatic	N (missing)	9 (0)	9 (0)	9 (0)	16 (0)	16 (0)	15 (1)
	Value	33 ± 7	83 ± 13	-5 ± 17	23 ± 11	82± 20	0.7 ±10

Some of the more extreme heart rate changes are shown in the table below. There were several subjects whose BP dipped but had minimal tachycardia or even a profound bradycardia.

Table Addendum –5: Some extremes in heart rate changes associated with hypotension.

Pt ID	Dose	Baseline SBP	SBP at Event (change)	Symptomatic or Asymptomatic	Time of Event	Baseline HR	HR at time of Event (change)
502-213	DOB	157	72 (-85)	Asymptomatic	17:15	79	72 (-7)
352-202	NAT 0.015	111	77 (-34)	Symptomatic	18:00	75	66 (-9)
367-201	NAT 0.015	98	80 (-18)	Symptomatic	4:20	72	60 (-12)
369-201	NAT 0.015	110	70 (-40)	Asymptomatic	16:05	76	73 (-3)
369-218	NAT 0.015	100	76 (-24)	Asymptomatic	0:48	88	72 (-16)
538-203	NAT 0.015	135	74 (-61)	Symptomatic	13:11	54	50 (-4)
560-201	NAT 0.015	105	76 (-29)	Symptomatic	6:38	95	45 (-50)
560-205	NAT 0.015	122	85 (-37)	Asymptomatic	14:40	95	69 (-26)
624-205	NAT 0.015	125	78 (-47)	Asymptomatic	12:20	105	65 (-40)
627-705	NAT 0.015	124	80 (-44)	Asymptomatic	16:05	73	72 (-1)
357-202	NAT 0.030	131	108 (-23)	Symptomatic	11:05	77	71 (-6)
370-203	NAT 0.030	104	78 (-26)	Asymptomatic	8:17	76	71 (-5)
387-201	NAT 0.030	150	110 (-40)	Asymptomatic	8:10	84	72 (-12)
539-210	NAT 0.030	155	78 (-77)	Symptomatic	6:00	86	90 (+4)
554-215	NAT 0.030	117	78 (-39)	Asymptomatic	8:00	104	98 (-6)
560-210	NAT 0.030	128	80 (-48)	Symptomatic	8:58	97	96 (-1)

Although there is not an adequate control, some of those treated with Natrecor had profound drops in blood pressure but had unusually low heart rate response, the mechanism is unclear.

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/s/

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