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Dear [redacted]

Re: Single Technology Appraisal – Ivabradine for the treatment of chronic heart failure

The Evidence Review Group (BMJ Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on 3rd April and updated submission received on 6 April by Servier. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost-effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to **all** questions in this letter to the Institute by **5pm, Tuesday 15 May**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] – Technical Lead ([redacted]@nice.org.uk). Any procedural questions should be addressed to [redacted] – Project Manager ([redacted]@nice.org.uk) in the first instance.

Yours sincerely

[redacted]

[redacted]
Associate Director Technology Appraisals - Committee C
National Institute for Health and Clinical Excellence

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Licensed population

A1: priority question
Please provide the information depicted in the following table for each of the subgroups listed below (i.e., 7 tables of information):

- subgroup of baseline resting heart rate ≥75 bpm (licensed population) achieving ***target*** β-blocker dose at baseline (n = 938; 22.6%);
- subgroup of baseline resting heart rate ≥75 bpm ***receiving β-blocker therapy at sub-target dose (i.e., optimal therapy)*** at baseline;
- subgroup of baseline resting heart rate ≥75 bpm ***not*** receiving a β-blocker at baseline;
- subgroup of baseline resting heart rate ≥75 bpm and aged ≥70 years;
- subgroup of baseline resting heart rate ≥75 bpm by subgroup of NYHA class, that is, separate tables for classes II, III, and IV.

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Hospitalisation for any cause				
Hospitalisation for cardiovascular reason				
Change in heart rate at last visit (change from baseline), bpm (SD)				
Additional outcome				
Cardiovascular death excluding death from heart failure				

n: number of people with the event
N: total number in the group

A2: priority question
For the licensed population, please complete the table below to provide absolute numbers for the outcomes listed in the subgroup of patients on ≥50% target dose β-blockade.

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Additional outcome				
Cardiovascular death excluding death from heart failure				

n: number of people with the event
N: total number in the group

A3: priority question
For the licensed population, please complete the table below to provide data for the outcomes listed based on maximally tolerated β-blocker dose; a similar analysis based on β-blocker category and in the full population of SHIfT is presented in Table 19 (pg 78) of the submission.

Outcome	**Ivabradine**		**Placebo**	
	n	N	n	N
No β-blocker				
Mean resting heart rate (SD) at baseline				
Primary outcome (composite): CV death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				

Additional outcome				
Cardiovascular death excluding death from heart failure				
<25%				
Mean resting heart rate (SD) at baseline				
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Additional outcome				
Cardiovascular death excluding death from heart failure				
25–<50%				
Mean resting heart rate (SD) at baseline				
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Additional outcome				
Cardiovascular death excluding death from heart failure				

50–<100%				
Mean resting heart rate (SD) at baseline				
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Additional outcome				
Cardiovascular death excluding death from heart failure				
≥100%				
Mean resting heart rate (SD) at baseline				
Primary outcome (composite): Cardiovascular death or hospitalisation for worsening heart failure				
Secondary outcomes				
Cardiovascular death				
Hospitalisation for worsening heart failure				
Death from any cause				
Death from heart failure				
Additional outcome				
Cardiovascular death excluding death from heart failure				

n: number of people with the event
N: total number in the group

A4

Please provide the median baseline heart rate (and range) for the licensed population in the ivabradine and placebo groups; data on the full population of SHIfT are presented in Table 6 (pg 48) of the submission.

A5
Please provide the standard deviation for the baseline sitting SBP and DBP, as well as the median (and range) baseline values for the licensed population in the ivabradine and placebo groups; data on the full population of SHIfT are presented in Table 6 (pg 48) of the submission.

A6
For the licensed population, please complete the table below to provide details for the patients who experienced symptomatic bradycardia as an adverse event.

Outcome	**Ivabradine**		**Placebo**	
	N		N	
Symptomatic bradycardia				
Mean heart rate (SD) of patients recorded at the visit immediately prior to bradycardia		bpm		bpm
Number of patients experiencing symptomatic bradycardia who required treatment in an intensive care unit (ICU)		n		n
For patients requiring ICU care, mean duration of stay (SD) in ICU		days		days

n: number of people with the event
N: total number in the group
bpm: mean heart rate in beats per minute
days: mean duration of stay in days

A7
For the licensed population, please complete the table below to provide details for the patients who experienced atrial fibrillation as an adverse event.

Outcome	**Ivabradine**		**Placebo**	
	N		N	
Atrial fibrillation				
Number of patients experiencing atrial fibrillation who required treatment in an ICU		n		n
For patients requiring ICU care, mean duration of stay (SD) in ICU		days		days

n: number of people with the event
N: total number in the group
Days: mean duration of stay in days

A8

For the subgroup of patients aged ≥70 years in the licensed population (resting heart rate ≥75 bpm), please complete the table below to provide details for and the number of patients experiencing atrial fibrillation as an adverse event.

Outcome	**Ivabradine**		**Placebo**	
	N		N	
Atrial fibrillation				
Number of patients experiencing atrial fibrillation		n		n
Number of patients experiencing atrial fibrillation who required treatment in an ICU		n		n
For patients requiring ICU care, mean duration of stay (SD) in ICU		days		days

n: number of people with the event
N: total number in the group

A9

Please provide follow-up data on the reduction in heart rate at various time points for the ivabradine and placebo on-treatment groups for the licensed population; follow-up data on the reduction in heart rate at various time points in the full SHIfT population are presented in the submission (Table 27, pg 99).

	Ivabradine		**Placebo**	
	N	HR lowering *vs* baseline (mean +/- SD) bpm	N	HR lowering *vs* baseline (mean +/- SD) bpm
Baseline				
D28				
M12				
M24				
M36				

A10

Please complete the table below to provide data on the number of patients in the ivabradine and placebo groups for the full and licensed population of SHIfT who were available for follow-up at the various time points indicated.

	Heart rate ≥70 bpm at baseline (N = 6,505)		**Heart rate ≥75 bpm at baseline (N = 4,150)**	
	Ivabradine N = 3,241	**Placebo N = 3,264**	**Ivabradine N = 2,052**	**Placebo N = 2,098**
Follow-up	n	n	n	n
After 6 months				
After 12 months				
After 18 months				
After 24 months				
After 36 months				

Section B: Clarification on cost-effectiveness data

B1: priority question
Please clarify which data from SHIfT (all patients or patients with baseline heart rate ≥75 bpm) were used to inform the regression model predicting NYHA progression within the model.

B2: priority question
Please provide the regression model for NYHA progression adjusted for patient baseline characteristics, in particular baseline heart rate.

B3: priority question
For consistency across all outcomes, please provide analyses using the heart rate covariate in the regression equation for NYHA distribution, as has been done for mortality, hospitalisation and quality of life.

B4: priority question
During extrapolation of NYHA classes, it has been assumed that 5% of patients will move from NYHA I to NYHA II and from NYHA II to NYHA III, and that there will be no change in the proportion of patients categorised as NYHA IV. Please describe the basis of this assumption.

B5
The Evidence Review Group's clinical advisor has emphasised that patients experiencing symptomatic bradycardia or atrial fibrillation may require treatment in an ICU. Please provide a scenario analysis in which additional costs for adverse events associated with bradycardia and atrial fibrillation are incorporated in the base case analysis.

B6
Please provide separate sensitivity analyses that use:

i. Overall mortality data (i.e., non-CV overall mortality) from SHIfT rather than UK population mortality data;
ii. Non-HF CV death calculated from a regression model (adjusted for patient baseline characteristics) based on non-HF CV mortality data from SHIfT.

B7
In the submission (pg 152), the manufacturer states that "...due to the inclusion of a weakly significant interaction term, the treatment covariate appears non-significant in the final regression equation". However, the treatment covariate in the full risk equation presented in Table 53 (pg 157) is associated with a p-value of 0.0270. Please clarify this potential discrepancy.

B8
The trial analysis is limited to 29 months, at which point 20% of the cohort is ***at risk***. Please clarify what is meant by "at risk".

B9
Please provide an updated base case analysis using the latest drug acquisition costs as reported in BNF 63 for all drugs used in the standard care arm.

Section C: Textual clarifications and additional points

C1
The manufacturer indicates that they "anticipate that ivabradine would be initiated by either a consultant cardiologist, a primary care GPwSI (GP with special interest) or other suitably qualified member of a multidisciplinary heart failure team" (pg 29), and goes on to highlight that an additional consultation may be needed to titrate the ivabradine dose. Please clarify whether post-titration of ivabradine dose patients can be safely discharged to continuous maintenance treatment by a non-specialist GP. Please provide an indication of how long after titration of ivabradine dose it will no longer be necessary for monitoring to be carried out by a specialist in the management of chronic heart failure.

C2
The number of patients in the full population of SHIfT who achieved target dose of β-blocker is reported to be 23% in Table 30 (pg 104), but 26.0% in Table 94 (pg 304). Please confirm the percentage of patients achieving target dose of β-blocker.

C3
In Table 6 (pg 48) in the submission, the lower value for the range of resting heart rates (presented with median resting heart) in both the ivabradine and placebo groups indicates that patients with resting heart rate <70 bpm were included in the trial. Please state how many patients in each group with a heart rate <70 bpm were enrolled in the trial and included in any analysis.

C4
Please confirm that the baseline characteristics presented below for smoking habits are correct (reproduced from Table 6, pg 48). In the ivabradine arm for the licensed population, the number of patients assessed represents 89.1% of the population.

	Heart rate ≥70 bpm at baseline (N = 6,505)		**Heart rate ≥75 bpm at baseline (N = 4,150)**	
	Ivabradine N = 3,241	Placebo N = 3,264	Ivabradine N = 2,052	Placebo N = 2,098
Smoking habits, n (%)				
Yes	541 (16.7)	577 (17.7)	381 (18.6)	402 (19.2)
Previous	1355 (41.8)	1364 (41.8)	410 (20.0)	857 (40.9)
Never	1345 (41.5)	1323 (40.5)	1039 (50.6)	839 (40.0)

C5
Throughout the clinical effectiveness section, analyses for the licensed population are based on 4,150 patients. However, in the cost effectiveness section, the text indicates that the licensed population includes 4,154 patients (e.g., section 6.2.1; pg 116 of the MS). Please clarify this potential discrepancy.

C6
Please provide the definitions for the terms “low dose”, “moderate dose” and “target dose” used in Table 30 of the submission (pg 104).

C7
In section 5.3.4 (pg 50 of the MS), there seems to be an incomplete sentence “Further details on therapy post-randomisation are provided in.” Please indicate where the additional details on post-randomisation therapy are provided.

C8
The tables presenting data for the regression models (Tables 37 [pg 131], 38 [pg 133], and 42 [pg 137]) contain duplicate descriptions for evaluated LVEF parameters (example provided below). Please clarify which, if any, of the descriptions is incorrect and provide corrected description(s).

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
LVEF >=26%<30% vs <26%yrs	0.8625	-0.1479	0.0929	0.111	-0.33	0.0342
LVEF >=30%<33% vs <26%yrs	0.7122	-0.3394	0.0893	0	-0.5145	-0.1644
LVEF >=26%<30% vs <26%yrs	0.5905	-0.5268	0.0921	0	-0.7073	-0.3462