NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA388; Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction

Original publication date:	27 April 2016
Review date	April 2018
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA388, see Appendix A.

1. Proposal

NICE technology appraisal 388 (TA388) should be incorporated into the on-going update of NICE clinical guideline 108 (chronic heart failure; CG108) and transferred to the static list.

2. Rationale

TA388 makes an optimised recommendation for sacubitril valsartan in people already receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) with NYHA class II-IV symptoms, and a left ventricular ejection fraction (LVEF) of 35% or less. Relevant trials identified since TA388 may address some of the uncertainties identified in the appraisal, but are unlikely to change the recommendation in the original guidance.

NICE is updating CG108 to produce a new guideline on chronic heart failure; this guidance is expected to be published in August 2018. The final scope for CG108 (published April 2016) includes updates to the guidelines on pharmacological therapies for managing chronic heart failure. Because TA388 is directly related to this guideline review question, it is proposed that the appraisal is incorporated into this guideline and transferred to the static list.

3. Summary of new evidence and implications for review

The key clinical evidence in the original appraisal came from 1 randomised controlled trial (PARADIGM-HF) and 1 network meta-analysis. Since the appraisal, 3 new trials have been identified which are relevant to the scope of TA388 (PARALLEL-HF, OUTSTEP-HF and LIFE study). However, these studies have not been completed and have not published results. PARALLEL-HF has the same study design as PARADIGM-HF but recruited Japanese patients; results are likely to be less generalisable than evidence from the original appraisal. OUTSTEP-HF and LIFE study may provide evidence addressing uncertainties identified in TA388, such as

better representation of people with NYHA IV symptoms, people with an LVEF of 35-40%, and people from Western Europe. However, these trials did not capture key outcomes relevant to the appraisal (such as mortality, cardiovascular mortality and hospitalisation for heart failure), and are hence unlikely to supersede PARADIGM-HF as the main source of evidence for an appraisal. New clinical evidence emerging from the trials is unlikely to lead to a change in the recommendations of the original guidance.

The cost and marketing authorisation of sacubitril valsartan have not changed since the original appraisal. The comparators drugs in this appraisal are inexpensive and widely available in generic forms; any changes in price would be unlikely to lead to a change in recommendations.

Overall, no relevant new evidence was identified that would change the existing recommendations in TA388.

Has there been any change to the price of the technology since the guidance was published?
The list/acquisition price for sacubitril valsartan has not changed (BNF [online]; accessed April 2018).
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no changes or proposed changes to the marketing authorisation that would affect the guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The original guidance compared sacubitril valsartan with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in people with chronic heart failure (NYHA class II-IV) with systolic dysfunction. All treatments were in combination with standard care (which includes treatment with a beta blocker and an aldosterone antagonist). The main sources of evidence for the appraisal came from 1 double-blind randomised controlled trial (PARADIGM-HF) and from 1 network meta-analysis. PARADIGM-HF compared sacubitril valsartan with enalapril (both given in combination with standard care) in people with NYHA class II-IV symptomatic heart failure with an LVEF of 35% or lower. The network meta-analysis compared sacubitril valsartan with ARBs, and also compared ARBs with ACE inhibitors. It was based on data from 28 randomised controlled trials. In the original guidance the committee identified the following uncertainties: 1. The lack of head-to-head evidence comparing sacubitril valsartan with ARBs, and the clinical heterogeneity in the trials underpinning the network meta-analysis

2. Absence of direct evidence of effectiveness in patients who had not received prior treatment with ACE inhibitors and ARBs

3. Weaker evidence of clinical effectiveness (and less potential for benefit) in people with an LVEF between 35% to 40%

4. Limited number of patients with NYHA class IV symptoms in the trial population

5. Differences between the dose of sacubitril valsartan administered in the trial and the dose normally tolerated in clinical practice

6. Weaker evidence of clinical effectiveness in the Western Europe subgroup, which was more representative of clinical practice in England than the total trial population

Sacubitril valsartan is indicated for the treatment of symptomatic chronic heart failure with reduced ejection fraction. Because of the uncertainties, the committee made an optimised recommendation, limited to people already receiving ACE inhibitors or ARBs with NYHA class II-IV symptoms, and an LVEF of 35% or less.

Since the original appraisal, 3 new relevant randomised controlled trials have been identified (PARALLEL-HF, OUTSTEP-HF and LIFE study). However, these studies have not been completed and have not published results.

PARALLEL-HF compares sacubitril valsartan to enalapril in Japanese patients with NYHA class II-IV stable chronic heart failure with an LVEF of ≤35%. Because the trial protocol and selection criteria were aligned to PARADIGM-HF but the trial population was Japanese patients, it is unlikely that PARALLEL-HF would provide results that are more relevant to UK clinical practice than PARADIGM-HF.

OUTSTEP-HF compares sacubitril valsartan to enalapril in patients with chronic symptomatic heart failure (NYHA ≥II) and an LVEF of ≤40%. Because OUTSTEP-HF was based in Europe and had several centres in the UK, results may be more generalisable to clinical practice in England than PARALLEL-HF. However, most of the outcomes captured in OUTSTEP-HF are not relevant to the appraisal (although symptoms of heart failure assessed by Patient's Global Assessment was included as a secondary outcome). Therefore, although OUTSTEP-HF includes patients with an LVEF of 35% to 40%, it is unlikely to substantially reduce uncertainty about this subgroup.

LIFE study compares sacubitril valsartan to valsartan alone in patients with symptomatic advanced heart failure (NYHA class IV) and an LVEF of ≤35%. A composite endpoint based on hospitalisation is included as a secondary

outcome. However, LIFE study did not capture any other relevant clinical efficacy outcomes. LIFE study may provide limited additional evidence about the clinical effectiveness of sacubitril valsartan in patients with NYHA class IV symptoms. It also provides head-to-head evidence on the effectiveness of sacubitril valsartan compared to an ARB. When published, evidence from OUTSTEP-HF and LIFE study may address areas of uncertainty identified in this appraisal. However, because these trials do not provide evidence on the key outcomes relevant to the appraisal (such as mortality, cardiovascular mortality and hospitalisation for heart failure), it is unlikely that they would supersede PARADIGM-HF as the main source of evidence in a review. Because these trials would only be used as supplementary evidence, they are unlikely to change the decision made in the original appraisal. Since the original guidance, there have not been any meta-analyses identified that provide additional evidence addressing areas of uncertainty identified in the appraisal. Overall, no relevant new evidence has been identified that would change the existing recommendations in TA388.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
The clinical guideline on chronic heart failure (CG108) is currently being updated. The scope of the update proposed to incorporate and contexualise recommendations for sacubitril valsartan in order to determine its place in the clinical pathway for this condition. The updated guideline is due to publish in September 2018.
Additional comments

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from April 2015 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

Comments raised during the consultation on TA388 highlighted that there are higher rates of angio-oedema in people of African family origin receiving ACE inhibitors, and that extra vigilance would be needed because of the low numbers of these patients included in PARADIGM-HF (5%). The committee concluded that there was no unfairness or unlawful discrimination and no need to alter its recommendations.

GE paper sign off: **Helen Knight, 28/06/2018**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of sacubitril valsartan within its marketing authorisation for treating heart failure (NYHA stage II-IV) with systolic dysfunction.

6. Current guidance

1.1 Sacubitril valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:

- with New York Heart Association (NYHA) class II to IV symptoms and
- with a left ventricular ejection fraction of 35% or less and
- who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).

1.2 Treatment with sacubitril valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE's guideline on *chronic heart failure in adults: management.*

1.3 This guidance is not intended to affect the position of patients whose treatment with sacubitril valsartan was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

7. Research recommendations from original guidance

None

8. Cost information from original guidance

- 24/26 mg (containing 24.3 mg sacubitril and 25.7 mg valsartan), 28 pack: £45.78
- 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 28 pack: £45.78
- 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 56 pack: £91.56
- 97/103 mg (containing 97.2 mg sacubitril and 102.8 mg valsartan), 56 pack: £91.56.

(excluding VAT; MIMS, April 2016)

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to publication of the results from OUTSTEP-HF and LIFE study.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	**Yes**

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Chronic heart failure in adults: management (2010) NICE guideline CG108

Ivabradine for treating chronic heart failure (2012) NICE technology appraisal guidance 267

Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (2014) NICE technology appraisal guidance 314

ENDURALIFE-powered CRT-D devices for treating heart failure (2017) NICE medical technologies guidance 33

Chronic heart failure in adults (2016) NICE quality standard QS9

Treating chronic heart failure due to left ventricular systolic dysfunction (2017) NICE pathway

In progress

Chronic heart failure in adults: diagnosis and management. NICE guideline. Publication expected August 2018

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
C3BS-CQR-1 (Celyad)	Phase 3 for the treatment of chronic heart failure after ischaemic cardiomyopathy	Yes
MyoCell stem cell therapy (US Stem Cell)	Phase 3 for congestive heart failure	No

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Indicated in adult patients for the treatment of symptomatic chronic	No change to previous indication. Sacubitril valsartan is currently in trials for heart failure with preserved

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
heart failure with reduced ejection fraction Price (excluding VAT; MIMS, April 2016): 24/26 mg (containing 24.3 mg sacubitril and 25.7 mg valsartan), 28 pack: £45.78 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 28 pack: £45.78 49/51 mg (containing 48.6 mg sacubitril and 51.4 mg valsartan), 56 pack: £91.56 97/103 mg (containing 97.2 mg sacubitril and 102.8 mg valsartan), 56 pack: £91.56	ejection fraction, and in paediatric heart failure.

4. Registered and unpublished trials

Trial name and registration number	Details
Study of Efficacy and Safety of LCZ696 in Japanese Patients With Chronic Heart Failure and Reduced Ejection Fraction. NCT02468232; CLCZ696B1301; PARALLEL-HF	Sacubitril valsartan vs. enalapril n = 225 Active, not recruiting Estimated completion date: November 2018
Randomized study using accelerometry to compare sacubitril/valsartan and enalapril in patients with heart failure NCT02900378; CLCZ696B3301; 2016-003085-32; OUTSTEP-HF	n = 600 Currently recruiting Estimated completion date: July 2018

Appendix C

Trial name and registration number	Details
EntrestoTM (LCZ696) In Advanced Heart Failure (LIFE Study) NCT02816736; Pro00071722; 5U01HL084904; HFN-LIFE	Sacubitril valsartan vs. valsartan n = 400 Currently recruiting Estimated completion date: March 2019

Appendix D – References

Study of Efficacy and Safety of LCZ696 in Japanese Patients with Chronic Heart Failure and Reduced Ejection Fraction (PARALLEL-HF). (2015). Retrieved from https://www.clinicaltrials.gov/ct2/ (Identification No. NCT02468232).

Randomized Study Using Accelerometry to Compare Sacubitril/Valsartan and Enalapril in Patients with Heart Failure (OUTSTEP-HF). (2016). Retrieved from https://www.clinicaltrials.gov/ct2/ (Identification No. NCT02900378).

EnestroTM (LCZ696) in Advanced Heart Failure (LIFE study) (HFN-LIFE). (2016). Retrieved from https://www.clinicaltrials.gov/ct2/ (Identification No. NCT02816736).