NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Clinical evidence review of [generic name] for treating [condition] in [adults/children]

NHS England unique reference number URN[XXX] / NICE ID[XXX]

Confidential – contains academic in confidence data [highlight confidential data in yellow and underline, delete if no confidential data]

First published: [Month year]

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Prepared by: NICE on behalf of NHS England Specialised Commissioning

About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Notes on using this template

Square brackets and [grey] highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey] highlighting with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the footer with appropriate text. (To change the footer, double click over the footer text. Double click back in the main body text when you have finished.)

This document has no minimum/maximum length but it should normally be around 50 to 70 pages.

Summary

[This evidence review considers x (include brand name and company name in brackets) for treating y. If necessary, briefly describe the condition]

[Give a summary of the evidence base and highlight any gaps in the evidence. This section should allow the reader to get a quick understanding of the clinical effectiveness evidence for the outcomes that matter to patients. Please include a lay description of what the outcome might mean to a patient. The paragraph options below can be deleted and amended as necessary]

[X studies were selected for inclusion in this review.]

[Evidence of the effect of technology x comes from one x-week double-blind, placebo-controlled randomised trial including xxx patients (reference) together with a long-term (up to x weeks) uncontrolled extension study (reference, in press). Patients in these studies had a confirmed diagnosis of [condition y]. Five additional studies with smaller sample sizes (x patients) also provide evidence.]

Effectiveness

[Evidence from the x-week regulatory trial (reference) suggests that [technology y] is associated with a greater reduction in [outcome] than placebo (x% and x% respectively). This outcome suggests that people who take [technology] as a treatment for [condition] can expect to have fewer [outcome of interest] than if they have no treatment for their condition [or similar lay wording]

[Add more for additional outcomes.]

Safety and tolerability

[Please ensure that the summary highlights the main safety concerns with the new technology and does not repeat the text from the main section below. Many drugs result in nausea, this should not be a focus for this section unless it is a key adverse event. Please check the scientific discussion to highlight any risks that the regulatory authority was particularly interested in. The evidence for any such adverse events should then be summarised here.]

Evidence gaps and limitations

[Include any evidence weaknesses. For example, the trials were short-term and there is no follow-up evidence available, yet the duration of treatment with the technology is likely to be longer than the period for which evidence exists. Or, when the new technology is expected to replace an existing treatment, yet there is no comparative evidence. If there are subgroups within the marketing authorisation that were not included in the trial, include this here.]

Table of contents

[Check page numbers]

Abbreviations

[Include a list of abbreviations and their definitions]

Term	Definition

Medical definitions

[Include a list of medical terms and their lay definitions]

Term	Definition

1 Introduction

Disease background

1.1 [Add text. Use 'numbered level 2 text' style.]

Focus of review

1.2 [Example first sentence: In line with the marketing authorisation, the focus of this review is on .....]

1.3 [Add text. Use 'numbered level 2 text' style.]

Epidemiology and needs assessment

1.4 [Add 1 to 3 paragraphs to summarise the epidemiology (in England ideally, second choice UK, third choice is wherever is most likely to reflect England). When hyperlinking, do this at the first mention in each section (under level 1 heading). Add a table at the end of this section if it is useful to help illustrate the calculations – see example given.]

1.5 [Add text. Use 'numbered level 2 text' style.]

Table [X] Patient numbers

Estimates	Data source	Number of people
Population in England in mid-2016	Office for National Statistics	55,268,100
8.8 to 10 in 100,000 with TSC	Previous NHS England clinical policies on SEGA and AML, and company submission	4,864 to 5,527
Epilepsy is in 84% of TSC patients	(Kingswood et al, TOSCA data, 2017) – from company submission	4,086 to 4,643
Refractory to treatment: 36% to 63%	(Kingswood et al, TOSCA data, 2017) – from company submission (Chu-Shore et al. 2010)	1,471 to 2,925
Abbreviations: TSC, [add definition]; SEGA, [add definition]; AML, acute myeloid leukaemia		

1.6 [Include any information, along with supporting references, about the disease burden, challenges using current treatments, and needs assessment. Please be aware that this section may need to be updated after the policy working group meeting, to maintain consistency with the

draft policy proposition. The evidence in this section will not necessarily be derived from the literature search that informed the clinical effectiveness review. Some additional searching may need to be done to find this supporting evidence – the policy working group members, company and existing policies and guidelines can be very helpful in providing references.]

Product overview

Mode of action

1.7 [Add text – ensure the language is suitable for a lay audience. Explain any terms that are not used in common everyday language.]

Regulatory status

1.8 [Add a short paragraph about the regulatory status of the medicine for the (expected) indication. Reference the source. Any reference to the summary of product characteristics (SPC) should be in sentence case that is, no capital letters. If data are commercial in confidence use publicly available information here.]

1.9 [Add text. Use 'numbered level 2 text' style.]

Dosing information

1.10 [Use publicly available sources where possible (usually the SPC).]

1.11 [Add text. Use 'numbered level 2 text' style.]

Treatment pathway and current practice

1.12 [Describe the treatment pathway – ideally in a diagram. Please do not copy the diagram from the company submission – if necessary, redraw it. Also describe what current practice is, ideally in 1 to 3 paragraphs.]

1.13 [Add text. Use 'numbered level 2 text' style.]

2 Evidence

Literature search

[Include wording similar to the following standard text:]

2.1 A literature search was done, which identified [insert number] references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and [insert number] full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and [insert number] studies were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

2.2 [Then add brief details about the evidence from the company submission. State whether this evidence included extra studies or just additional data on the same studies. In the case of the latter, make it clear which source was used as the primary data source – published paper or submitted data). If no studies were submitted state this for clarity.]

Overview of included studies

[Include wording similar to this example:]

2.3 [Two randomised controlled trials (RCTs) identified from the search (Borgohain et al. 2014a [study 016] and Borgohain et al. 2014b [study 018]) were included in this evidence summary. An additional 24-week RCT (the SETTLE study), which was considered by the European Medicines Agency during the regulatory process, was also included. This study was unpublished at the time of the search. A summary of the characteristics of the included studies is shown in table 2 (see evidence tables for full details).]

2.4 [Add text. Use 'numbered level 2 text' style.]

2.5 [Include a 'Summary of included studies' table, ordering the studies by hierarchy of evidence with the strongest evidence at the top. A completed

example is also shown. Check the table number in the heading if a table was inserted in a previous section.]

Table [X] Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Abbreviations:			

Example

Study	Population	Intervention and comparison	Primary outcome
Borgohain et al. 2014a (study 016) RCT	Mid to late Parkinson's disease (≥3 years) with motor fluctuations (n=669)	Safinamide 50 mg or 100 mg daily vs. placebo	Change in mean daily on time without troublesome dyskinesia
Borgohain et al. 2014b (study 018) RCT	Mid to late Parkinson's disease (≥3 years) with motor fluctuations (n=669[a])	Safinamide 50 mg or 100 mg daily vs. placebo	Change in mean DRS total score during on time
Schapira et al. 2016 (SETTLE study) RCT	Parkinson's disease (≥3 years) with motor fluctuations (n=549)	Safinamide 50 mg to 100 mg daily vs. placebo	Change in mean daily on time without troublesome dyskinesia
[a] Study 018 was an 18-month extension of study 016. 669 participants were randomised; 544 participants enrolled into study 018 Abbreviations: RCT, randomised controlled trial; DRS, [add definition]			

Key outcomes

2.6 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table X below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Effectiveness

2.7 [This is the main focus of the review. It should explain the clinical benefits the technology offers, based on the available evidence. It should help the

reader understand an outcome; the trial name for an outcome may not be sufficient so provide a lay explanation of what the outcome means, or how it was defined.]

[Add subheadings for each measure of effectiveness.]

[For each outcome discussed, briefly mention the grade of evidence and any important critical appraisal issues.]

2.8 [Add text. Use 'numbered level 2 text' style.]

Safety and tolerability

2.9 [Please note the grade of evidence table should be the main source of evidence. Do not discuss all outcomes in the text, just the most clinically important. Add subheadings if necessary, for example to separate results by similar outcomes.]

[For each outcome mention the grade of evidence and any important critical appraisal issues.]

2.10 [Add text. Use 'numbered level 2 text' style.]

Evidence gaps and limitations

2.11 [Use this section to note any gaps in the evidence base, such as lack of comparison to UK current practice, short-term outcomes. Provide more detail than provided in the summary section.]

2.12 [Add text. Use 'numbered level 2 text' style.]

Table [X] Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Overall survival	Study 1	7/10	Directly / indirectly applicable	A/B/C	From NHSE table notes: *Include following:* *1. Explanation/description of the outcome measure for example:* Overall response rate (ORR) is a combined metric for patients with any treatment response to bortezomib, whether partial or complete. The assessment is done using clinical criteria recommended by an international working group on non-Hodgkin's lymphoma (Cheson et al. 1999). *2. Results of the best study identified for the outcome measure* The longest study (Goy el al. 2009) with 155 patients and a median follow up of 26.4 months reported an ORR in 32% of patients who took part. *3. Description/impact of the magnitude of change of the health metric (where possible)* The result provides an estimate of the true value of the proportion of individuals who took the treatment and had a complete or partial response to it. The probability that the true value is contained within the range of 24% to 40% is 95%. 4. *Clinical benefit to the patient group and describe uncertainties of 1, 2 and 3 in relation to the quality of the evidence available* The results suggest that only a third of patients with unmanageable/deteriorating mantle cell lymphoma who have bortezomib have either complete or partial response. These results should be interpreted with caution because they are based on a single-arm study. This means that the study did not randomise patients or compare the treatment with any other standard treatment. Therefore other factors may be influencing the results and this study does not provide evidence that bortezomib is any better or worse than other treatments for this outcome.
	Study 2	5/10			
	Study 3	6/10			

3 Related NICE guidance and NHS England clinical policies

[Please clearly state if there are any related NICE guidelines, MIBs, evidence summaries, interventional procedures.]

[If listing multiple pieces of guidance or policy use a bulleted list with hyperlinks from the titles. For example:]

- [Type 2 diabetes: the management of type 2 diabetes (2009) NICE guideline 87.]

[There is no need to link to guidance for lots of different indications for the medicine. However, do include closely related indications – such as a slightly different age range, because these may be important to flag if you have little evidence.]

[If nothing is available:] NHS England and NICE have not issued any guidelines or policies on managing [indication] with [treatment].

[Also highlight any relevant NHS England policies and other guidelines if there are no NICE guidelines.]]

4 References

[Do not reference the BNF, SPCs, the EPAR, NICE guidance or CT.gov. These can all be linked to from the text. Reference studies and possibly other guidance. Examples of reference style are given below]

[Cetinkalp S, Karadeniz M, Erdogan M et al. (2009) The effects of rosiglitazone, metformin, and estradiol-cyproterone acetate on lean patients with polycystic ovary syndrome. Endocrinologist 19: 94–7]

[Cibula D, Fanta M, Vrbikova J et al. (2005) The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids in PCOS patients. Human Reproduction 20:180–4]

[Insert references here]

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

[Add in search strategy. Obtain from guidance information services (gIS).]

Appendix 2 Study selection

[Provide details of the inclusion criteria used – include only 1 table to cover all stages of study selection]

The search strategy presented in appendix 1 yielded [X] studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

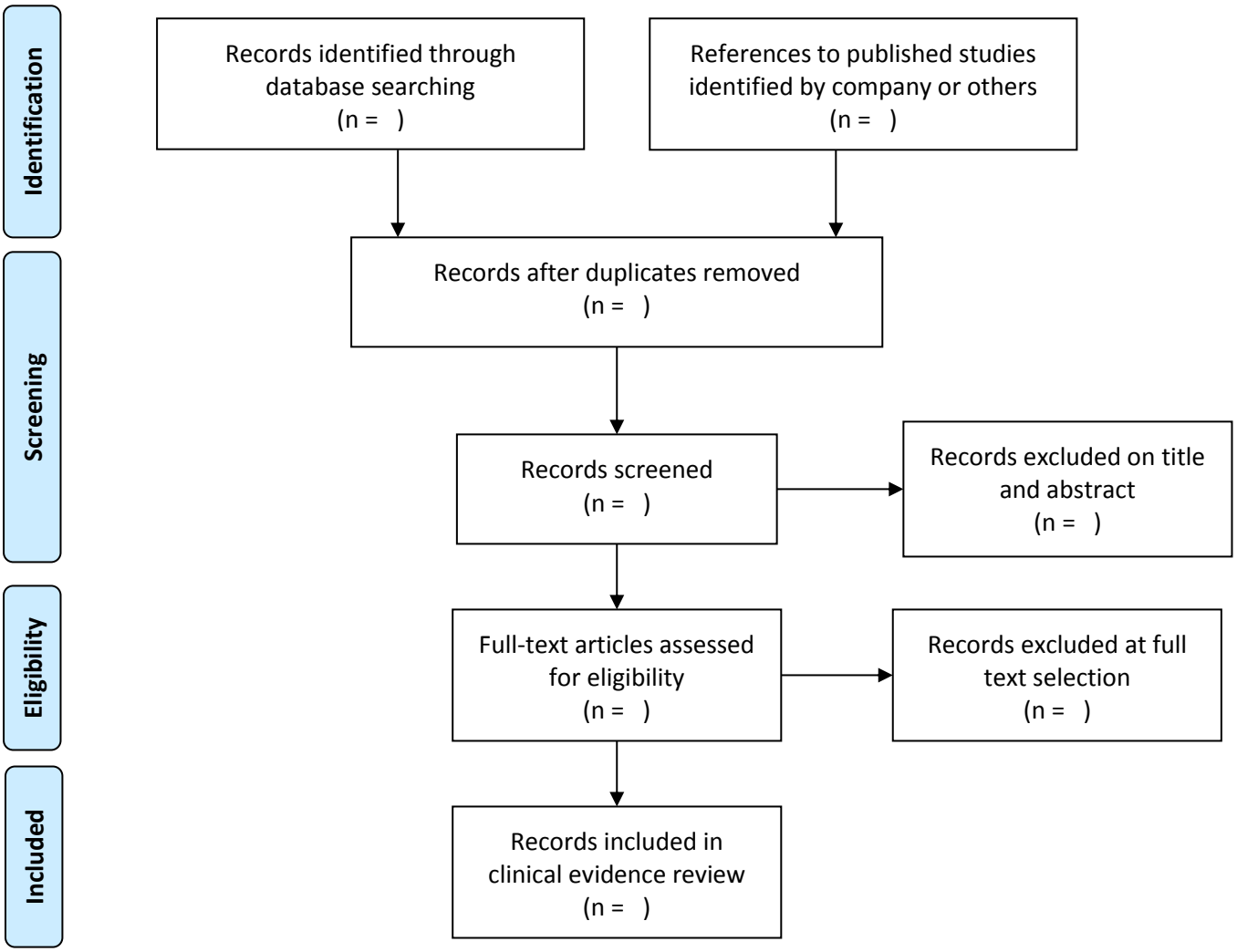
Sifting criteria	Inclusion	Exclusion
Population		Non-humans
Intervention		
Comparator		
Outcomes		
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies [Please add additional exclusion criteria if needed]

Table [X] Studies included at full text

[Provide a list of excluded studies table as shown below]

Study reference	Reason for exclusion

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

[Include tables similar to the following standard tables. The details of each study should be presented in lead author alphabetical order.]

[Adjust tables as necessary to fit the information.]

- [Add or remove rows but keep to portrait format]
- [Use table bullets style for listing outcomes, or other information that is better presented as a bulleted list. Add hyperlink to 'terms used in the guideline' section if the outcome is included there (see below).]
- [Add hyperlinks to unique identifier (from www.clinicaltrials.gov)]

[An example table title is shown below.]

Table [X] Borgohain et al. 2014a (Study 016)

Study reference	
Unique identifier	
Study type (and NSF-LTC study code)	(Put the code information here from the above table)
Aim of the study	
Study dates	
Setting	
Number of participants	
Population	
Inclusion criteria	
Exclusion criteria	
Intervention(s)	
Comparator(s)	
Length of follow-up	
Outcomes	Primary outcome: [bulleted list]
	Secondary outcomes: [bulleted list]
	Safety outcomes: [bulleted list]
Source of funding	

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	/2	[Use this field to briefly describe the study quality. Particularly use this field to make it clear why a study was downgraded.]
2. Is the research design appropriate for the aims and objectives of the research?	/2	
3. Are the methods clearly described?	/2	
4. Are the data adequate to support the authors' interpretations / conclusions?	/2	
5. Are the results generalisable?	/2	
Total	/10	
Applicability *	Directly / indirectly applicable	[Briefly describe the applicability]

* Note - Direct studies focus on people with the indication and characteristics of interest.
Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics.
We'll put this in our methods manual

[Continue format as above for each included study]

Appendix 4 Results tables

[Include tables similar to the following standard tables. The results of each study should be presented in lead author alphabetical order.]

- [Adjust tables as necessary to fit the information.]
- [Add or remove rows but keep to portrait format]
- [Use footnotes to explain any terms used in more detail and areas of clarification.]

[An example table title is shown below.]

Table [X] Borgohain et al. 2014a (Study 016)

	[Name of treatment]	**[Name of comparator]**
N		
[Name of primary outcome]		
[Name of secondary outcome 1]		
[Name of secondary outcome 2]		
[Name of secondary outcome 3]		
[Name of safety outcome 1]		
[Name of safety outcome 2]		
[Name of safety outcome 3]		

[Continue format as above for each included study]

Appendix 5 Grading of the evidence base

[NHS England has requested that NICE use the following system for grading the evidence:]

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.