Setmelanotide for treating obesity caused by LEPR or POMC deficiency [ID3764]

A Highly Specialised Technology Appraisal

Appendix #2

Summary of results of the cumulative ERG base case including patient access scheme, scenario analysis using the dosing schedule included in the updated European Public Assessment Report on the Summary of Product Characteristics and ERG assessment of reported response rates

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1. INTRODUCTION

The purpose of this separate appendix is threefold:

- To provide the ERG's preferred assumptions constituting the cumulative ERG base case, as presented in Appendix #1, with patient access scheme (PAS) discount for setmelanotide included.
- To present scenarios based on dosing as per the recently updated European Public Assessment Report (EPAR) of the Summary of Product Characteristics (SmPC) for setmelanotide.
- To formalise previous communication around the ERG's assessment of the time point of response rates presented in the company submission.

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2. METHODS

2.1. Additional model outputs – cumulative ERG base case with patient access scheme discount and dosing scenario analyses

Several additional tables have been generated by presenting the cumulative ERG base case with PAS discount for setmelanotide as well as scenario analyses resulting from the dosing schedule for setmelanotide as detailed in the recently updated EPAR for the SmPC. The additional tables are summarised in Table 1, the updated dosing protocol is shown in Table 2.

Table 1: Relevant tables included in appendix

Description	Location in appendix
Table 3: Summary of ERG's preferred assumptions and ICER (LEPR, Paediatric)	3.1.1
Table 4: Summary of ERG's preferred assumptions and ICER (LEPR, Adult)	3.1.1
Table 5: Summary of ERG's preferred assumptions and ICER (POMC, Paediatric)	3.1.1
Table 6: Summary of ERG's preferred assumptions and ICER (POMC, Adult)	3.1.1
Table 7: Scenarios with setmelanotide dosing based on SmPC	3.1.2

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; POMC, proopiomelanocortin; SmPC, Summary of Product Characteristics

Table 2: Dosing used in the scenario analyses

	Dose (mg)		
	Paediatric (6 to < 12 years)	**Adults and adolescents (≥ 12 years)**	**Source**
Starting dose			
Minimum possible	0.5	1.0	SmPC; Section 4.2
Maximum possible	1.0[a]	2.0[a]	
Dose after trial			
Minimum possible	2.0[a]	2.0	SmPC; Table 1 (Adult) and Table 2 (Paediatric)
Maximum possible	2.5[b]	3.0[c]	

Abbreviation: SmPC, Summary of Product Characteristics

[a] If dose is not well tolerated, patients may revert back to previous dose

[b] If clinical response is insufficient and 2 mg dose once daily is well tolerated

[c] If clinical response is insufficient and 2 and 2.5 mg dose once daily are well tolerated

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The ERG noted that in the SmPC children aged 6 to <12 years were considered paediatric, however, the company model considers children aged 6 to <18 years as the paediatric population. Therefore, for the paediatric population dose, the ERG made its selection based on the base age in the model. For example, if the base age used in the model was ≥ 12 years, then the dosing for adolescents and adults per SmPC was used; if the base age in the model was <12 years, then paediatric dosing was used. Furthermore, it is important to note that dosing in the SmPC was not stratified by subpopulation, therefore the scenario analysis could not be conducted separately for subpopulations with LEPR and POMC deficiency obesity.

2.2. ERG assessment of time point for response rates in the company submission

Based on a request from NICE the ERG formalised a response, previously captured via e-mail on 18 October 2021, relating to the time point of response rates captured in the company submission. This request relates to the company submission stating that percentage response rates used in the model derive from response at week 12, but that these response rates are the same as those reported at week 52. The NICE technical team noted that response rates at week 12 could not be obtained from the company submission or the clinical study reports, and requested the ERG's assessment on this matter. The response of the ERG to this request for clarification is detailed in Section 3.2.

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3. RESULTS

3.1. Additional model outputs

This section contains the results for the individual ERG preferred base case assumptions for paediatric and adult patients with leptin receptor (LEPR) and proopiomelanocortin (POMC) deficiency obesity, and dosing scenarios based on the updated EPAR, SmPC.

3.1.1. Results of ERG preferred base case assumptions

The results of the individual ERG preferred base case assumptions constituting the cumulative ERG base case, have been outlined for each of the subpopulations. The results for paediatric and adult patients with LEPR deficiency obesity (Table 3 and Table 4, respectively) and paediatric and adults patients with POMC deficiency obesity (Table 5 and Table 6, respectively) are shown below.

Table 3: Summary of ERG's preferred assumptions and ICER (LEPR, Paediatric)

Scenario	Incremental cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY; discounted)
Company's base case	[redacted]	[redacted]	[redacted]	£132,392
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	[redacted]	[redacted]	[redacted]	£133,528
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	£172,290
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	£186,782
Non-responder and BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	£184,443
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£298,476**

Abbreviations: BSC, best supportive care; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; QALY, quality-adjusted life years

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Table 4: Summary of ERG's preferred assumptions and ICER (LEPR, Adult)

Scenario	Incremental Cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY (discounted))
Company's base case	[redacted]	[redacted]	[redacted]	£145,738
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	[redacted]	[redacted]	[redacted]	£147,245
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	£203,012
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	£206,084
Non-responder and BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	£209,440
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£326,123**

Abbreviations: BSC, best supportive care; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; QALY, quality-adjusted life years

Table 5: Summary of ERG's preferred assumptions and ICER (POMC, Paediatric)

Scenario	Incremental Cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY (discounted))
Company's base case	[redacted]	[redacted]	[redacted]	£152,938
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	[redacted]	[redacted]	[redacted]	£154,265

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Scenario	Incremental Cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY (discounted))
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	£127,919
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	£133,300
Non-responder and BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	£131,054
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£218,390**

Abbreviations: BSC, best supportive care; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life years

Table 6: Summary of ERG's preferred assumptions and ICER (POMC, Adult)

Scenario	Incremental Cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY (discounted))
Company's base case	[redacted]	[redacted]	[redacted]	£146,381
ERG corrected company base case				
Hyperphagia related treatment effect applied at the end of the first cycle rather than at the start of the cycle	[redacted]	[redacted]	[redacted]	£147,713
ERG's preferred base case				
Setmelanotide dose based on average paediatric dose from clinical studies	[redacted]	[redacted]	[redacted]	£143,156
1% discontinuation throughout lifetime	[redacted]	[redacted]	[redacted]	£145,344
Non-responder and BSC life expectancy converted to equivalent HR multiplier	[redacted]	[redacted]	[redacted]	£150,498

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Scenario	Incremental Cost (discounted)	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER (cost/QALY (discounted))
3.5% discount rate for health outcomes	[redacted]	[redacted]	[redacted]	**£242,240**

Abbreviations: BSC, best supportive care; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; POMC, proopiomelanocortin; QALY, quality-adjusted life years

3.1.2. Results of setmelanotide SmPC dosing scenarios

Based on exploratory analysis undertaken by the ERG as per the minimum and maximum possible setmelanotide dosing according to the SmPC (described in Section 2.1), an increase of 9% to 65% in the ICER (compared to the ERG corrected company base case) was noted for the subpopulations; as given in Table 7 below.

It is important to note that this scenario does not use dosing stratified by subpopulation, as this information is not available in the SmPC. Hence, the same adult and paediatric dosing per SmPC has been used for both LEPR and POMC subpopulations.

Table 7: Scenarios with setmelanotide dosing based on the updated Summary of Product Characteristics

	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (Discounted)	ICER £/QALY (discounted)	% Change from ERG corrected company base case
LEPR, Paediatric					
ERG corrected company base-case	[redacted]	[redacted]	[redacted]	£133,528	-
Scenario: Minimum possible dose both at start and after trial based on SmPC	[redacted]			£145,560	9%

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	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (Discounted)	ICER £/QALY (discounted)	% Change from ERG corrected company base case
Scenario: Maximum possible dose both at start and after trial based on SmPC	[redacted]			£219,166	64%
LEPR, Adult					
ERG corrected company base-case	[redacted]	[redacted]	[redacted]	£147,245	-
Scenario: Minimum possible dose both at start and after trial based on SmPC	[redacted]			£160,115	9%
Scenario: Maximum possible dose both at start and after trial based on SmPC	[redacted]			£240,502	63%
POMC, Paediatric					
ERG corrected company base-case	[redacted]	[redacted]	[redacted]	£154,265	-
Scenario: Minimum possible dose both at start and after trial based on SmPC	[redacted]			£168,847	9%
Scenario: Maximum possible dose both at start and after trial based on SmPC	[redacted]			£254,537	65%
POMC, Adult					
ERG corrected company base-case	[redacted]	[redacted]	[redacted]	£147,713	-
Scenario: Minimum possible dose both at start and after trial based on SmPC	[redacted]			£161,523	9%

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	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (Discounted)	ICER £/QALY (discounted)	% Change from ERG corrected company base case
Scenario: Maximum possible dose both at start and after trial based on SmPC	[redacted]			£243,455	65%

Abbreviations: ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEPR, leptin receptor; POMC, proopiomelanocortin; QALY, quality-adjusted life years; SmPC, Summary of Product Characteristics

3.2. ERG assessment of time point for response rates in the company submission

The ERG noted that 12-week response rates have not been reported in the company submission, clinical study reports or published studies. The company stated that response rates were measured at 12 weeks (p.167 of the company submission) and that the 12-week response data were used in the economic model (p.177 of the company submission). The ERG concluded that response rates at 12 weeks may have been sustained up to 52 weeks, leading the company to use 12 weeks and 52 weeks interchangeably. However, as response rates at 12 weeks have not been explicitly provided, some uncertainty remains. The ERG suggested that further clarification from the company would be helpful.

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