NICE National Institute for Health and Care Excellence

**Slides for public observers**

# Pitolisant hydrochloride for treating excessive daytime sleepiness caused by obstructive sleep apnoea [ID1065]

# Chair's presentation

## 3rd Appraisal committee meeting

14 December 2021

# Pitolisant (Ozawave, Bioprojet UK)

| | |
|---|---|
| **Mechanism of action** | Orally active histamine H3-receptor antagonist/inverse agonist that enhances the activity of brain histaminergic neurones. It also modulates neurotransmitter systems, increasing acetylcholine, noradrenaline, and dopamine release in the brain. |
| **Marketing authorisation** (positive CHMP May 2021) | Indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnea (OSA) whose EDS has not been satisfactorily treated by, or who have not tolerated, OSA primary therapy such as continuous positive airway pressure (CPAP). |
| **Dosage and Administration** | Pitolisant should be used at the lowest effective dose, depending on an individual's response and tolerance, according to an up-titration scheme, without exceeding 18 mg/day:<br><br>Initial dose of 4.5 mg per day can be increased to 9 mg (two 4.5 mg tablets) per day in week 2.<br>The dose can be titrated up or down from week 3 (to one 18 mg tablet) or down to 4.5 mg per day. |
| **List price** | Wakix NHS indicative price £310 per 30 tablets, Ozawade list price Confidential<br>No commericial arrangement agreed by NHS England |

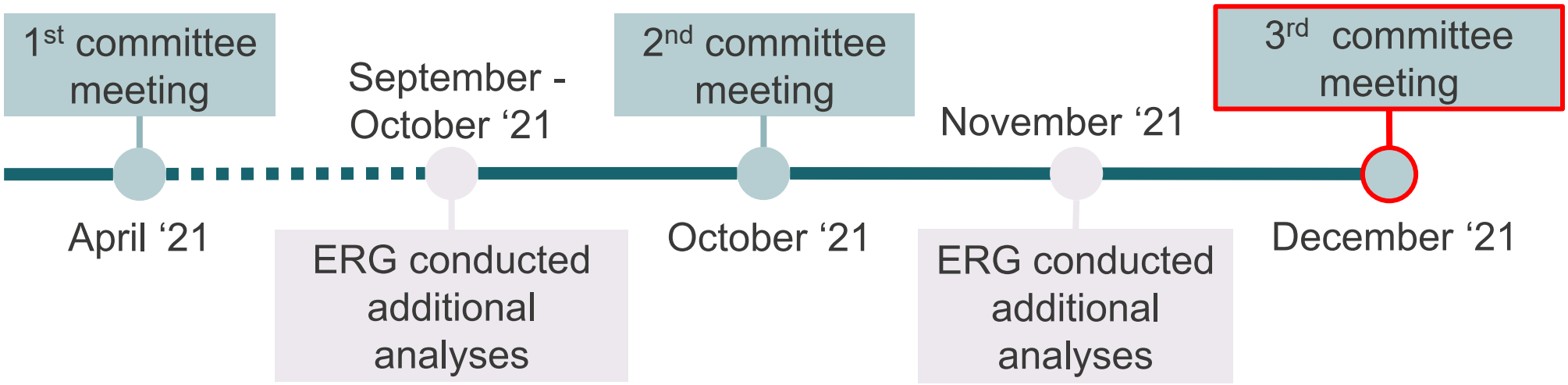


CHMP, Committee for Medicinal Products for Human Use; PAS, patient access scheme

# ACD current recommendations

Pitolisant hydrochloride is not recommended, within its marketing authorisation, to improve wakefulness and reduce excessive daytime sleepiness in adults with obstructive sleep apnoea whose sleepiness has not been satisfactorily treated by primary obstructive sleep apnoea therapy such as continuous positive airway pressure (CPAP), or who cannot tolerate it

# History




Using *ESS complete case* dataset:

Placebo effect

- 100% Hawthorne
- Regression to the mean
- True placebo effect
- 33% mix of each

Utility values

- ESS mapped using McDaid
- Trial EQ-5D
- 50% mix of each (average of utility values)

- Updated scenarios using *intention to treat ESS* dataset
- Applied health state utility values
- 50% mix of ESS mapped using McDaid and trial EQ-5D (average of coefficients)

NICE

ESS, Epworth Sleepiness Scale

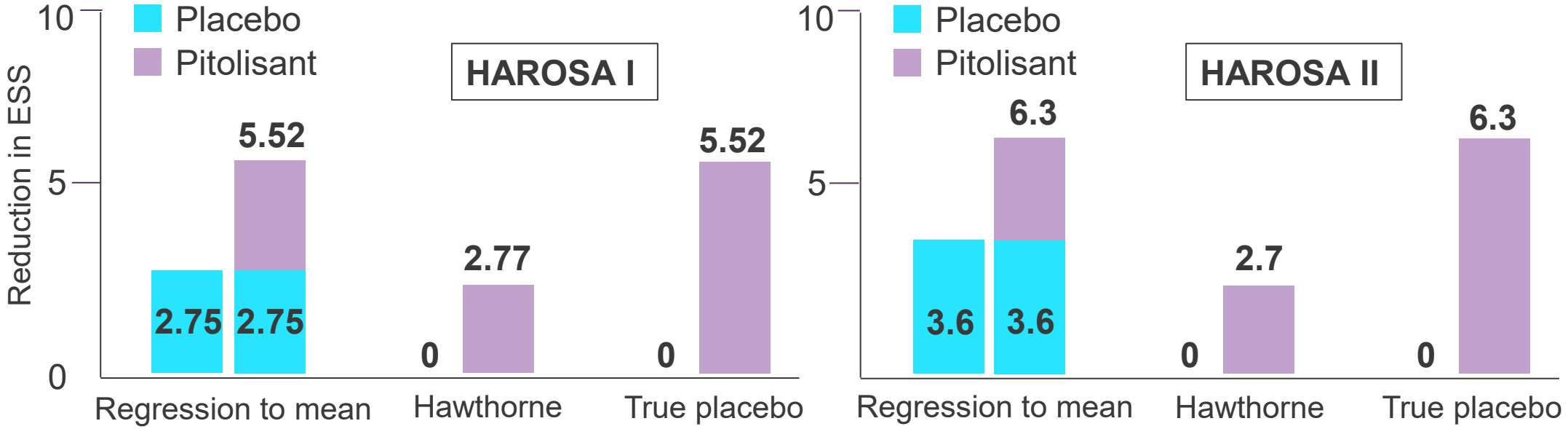
# Summary

| Issue | | Description |
|---|---|---|
| 1 | Placebo effect | • Hawthorne effect (*company base case*)<br>• Regression to the mean<br>• True placebo effect<br>• 33% mix of each<br>? Which adjustment for the placebo effect is most appropriate? |
| 2 | Utility values | • ESS mapped to EQ-5D using McDaid (*company base case*)<br>• EQ-5D values from HAROSA trials<br>• Average of ESS mapped and trial EQ-5D<br>➢ Average of utility values [method 1]<br>➢ Average of coefficients [method 2]<br>? Should utility values be based on trial EQ-5D, ESS mapped using McDaid, or an average of the 2? |

# Issue 1: Placebo effect (1/2)

## Issue background

- Epworth Sleepiness Scale (ESS) improved by week 12 in **placebo** in HAROSA trials
- Original model did not adjust for placebo effect, updated model adjusted for **Hawthorne**
- ID1499 solriamfetol explored Hawthorne effect, regression to the mean, and true placebo
- Committee concluded it was appropriate to explore adjustments




## Regression to the mean

- Tendency for extreme values to return to average
- Same response would be observed in routine practice without the placebo
- Do not adjust trial data

## Hawthorne effect

- Due to being observed in trial
- Assumes no response to placebo in routine practice
- Placebo response subtracted from pitolisant
- Adjustment called ‘centring’

## True placebo

- Placebo response would be seen irrespective of setting
- Response to active treatment / placebo will be same as in trial
- If placebo not administered, no response in routine practice

# Issue 1: Placebo effect (2/2)

**Company**

- Believe ERG suggested 50% Hawthorne, 50% true placebo most appropriate at ACM2
- Suggests that placebo effect and fluctuations in ESS make regression to mean inappropriate → suggest Hawthorne most appropriate approach

- Hawthorne effect (*company base case*)
- Regression to the mean
- True placebo effect
- 33% mix of each

? Which adjustment for the placebo effect is most appropriate?



EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale

*values assuming Hawthorne effect
**pooled HAROSA 1 & 2

# Issue 2: Utility values (1/3)

## Issue background

- EQ-5D showed no difference between pitolisant & placebo → company noted EQ-5D may not capture QoL benefits for people with OSA
- Company base case mapped ESS to EQ-5D using McDaid approach from TA139 CPAP
- At 2nd meeting, committee considered scenarios where utilities were from
  1. ESS mapped to EQ-5D using McDaid
  2. Trial EQ-5D
  3. Average of utility values from 1 & 2
- At 2nd meeting, committee interested in health state utility values & average of coefficients

## ERG

**Updates since 2nd meeting**

- Applied health state utilities
- Using ESS ITT dataset*

**Other comments**

- EQ-5D based on complete cases (not ITT)
- Differences in ESS change from baseline in company and ERG analyses – uncertain why

| HAROSA 1 (addon to CPAP) | ESS change from baseline | Mapped Utility | Treatment independent utility UK EQ-5D |
|---|---|---|---|
| Responder | -6.33 | 0.827 | [redacted] |
| Non-Responder | 2.20 | 0.745 | [redacted] |

| HAROSA 2 (CPAP non users) | ESS change from baseline | Mapped Utility | Treatment independent utility UK EQ-5D |
|---|---|---|---|
| Responder | -6.28 | 0.798 | [redacted] |
| Non-Responder | 1.99 | 0.718 | [redacted] |

*Missing values imputed using last observation carried forward

CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ITT, intention to treat; OSA, obstructive sleep apnoea

# Issue 2: Utility values (2/3)

## ERG

- Explored baseline utility with UK tariff (company French)
- Possible averages of mapped ESS and trial EQ-5D
  1. Methods 1: Average of the utility values from each method
  2. Methods 2: Average of the coefficients
- [redacted]

Baseline utility

| | French | UK | Average |
|---|---|---|---|
| HAROSA I | 0.766 | [redacted] | [redacted] |
| HAROSA II | 0.737 | [redacted] | [redacted] |

| HAROSA 1* | Mapped utility – French | Mapped Utility - UK | Treatment independent utility UK EQ-5D (CC) | Average slopes McDaid & observed | Average slopes McDaid & observed, pooled** |
|---|---|---|---|---|---|
| Responder | 0.827 | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-Responder | 0.745 | [redacted] | [redacted] | [redacted] | [redacted] |
| **HAROSA 2*** | Mapped utility - French | Mapped Utility - UK | Treatment independent utility UK EQ-5D (cc) | Average slopes McDaid & observed | Average slopes McDaid & observed, pooled** |
| Responder | 0.798 | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-Responder | 0.718 | [redacted] | [redacted] | [redacted] | [redacted] |

NICE

EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale

*values assuming Hawthorne effect
**pooled HAROSA 1 & 2

# Issue 2: Utility values (3/4)

## Company

- Similarity in EQ-5D from HAROSA and mapping data when estimating relationship between ESS and utility → validates mapping approach
- Intention to treat (ITT) rather than Complete Case (CC) → ICERs are higher → not unexpected because the number of responders in ITT are less than CC as not everyone completed the placebo-controlled study
- Believes NICE's Clinical experts at ACMs considered that other CPAP studies also showed no impact on EQ-5D, and that people with excessive daytime sleepiness impact QOL → improving EDS improves QOL
- Similar results in other studies for CPAP, modafinil and devices. AG for CPAP TA149, suggests SF-36/EQ-5D not designed to capture QOL in people with EDS
- All methods to estimate utility benefit show broadly similar results except using treatment independent utility UK EQ-5D using CC population. → Means EQ-5D does not capture QOL (see next slide)
- Mapping is most approach to estimating utilities



EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale

*values assuming Hawthorne effect
**pooled HAROSA 1 & 2

# Issue 2: Utility values (4/4)

| HAROSA 1* | Mapped utility – French | Mapped Utility - UK | Treatment independent utility UK EQ-5D (CC) | Average slopes McDaid & observed | Average slopes McDaid & observed, pooled** |
|---|---|---|---|---|---|
| Responder | 0.827 | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-Responder | 0.745 | [redacted] | [redacted] | [redacted] | [redacted] |
| Difference | **0.082** | [redacted] | [redacted] | [redacted] | [redacted] |

| HAROSA 2* | Mapped utility - French | Mapped Utility - UK | Treatment independent utility UK EQ-5D (CC) | Average slopes McDaid & observed | Average slopes McDaid & observed, pooled** |
|---|---|---|---|---|---|
| Responder | 0.798 | [redacted] | [redacted] | [redacted] | [redacted] |
| Non-Responder | 0.718 | [redacted] | [redacted] | [redacted] | [redacted] |
| Difference | **0.08** | [redacted] | [redacted] | [redacted] | [redacted] |

? **Should utility values be based on trial EQ-5D, ESS mapped using McDaid, or an average of the 2?**

values assuming Hawthorne effect; differences estimated by company
**pooled HAROSA 1 & 2

# Deterministic cost-effectiveness results

## *HAROSA 1 (add on to CPAP), pitolisant list price*

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| **Company base case – 100% Hawthorne[a]** | 10,912 | 0.34 | 32,430 |
| **100% Hawthorne** | | | |
| 1. Utility values from trial EQ-5D | 12,412 | [redacted] | [redacted] |
| 2. Utility values from ESS mapped to EQ-5D using McDaid | 12,412 | 0.25 | 50,154 |
| 3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1) | 12,412 | [redacted] | [redacted] |
| 4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2) | 12,412 | [redacted] | [redacted] |
| **Equal mix of 3 placebo models** | | | |
| 1. Utility values from trial EQ-5D | 14,240 | [redacted] | [redacted] |
| 2. Utility values from ESS mapped to EQ-5D using McDaid | 14,240 | 0.30 | 48,000 |
| 3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1) | 14,240 | [redacted] | [redacted] |
| 4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2) | 14,240 | [redacted] | [redacted] |

[a] Based on a complete case analysis, not ITT. N.b. ERG corrected ICER for company base case was 23,410 QALY gained

CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

# Deterministic cost-effectiveness results

## *HAROSA 2 (CPAP non-users), pitolisant list price*

| Scenario | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|
| **Company base case – 100% Hawthorne[a]** | 11,159 | 0.41 | 28,431 |
| **100% Hawthorne** | | | |
| 1. Utility values from trial EQ-5D | 13,178 | [redacted] | [redacted] |
| 2. Utility values from ESS mapped to EQ-5D using McDaid | 13,178 | 0.33 | 40,240 |
| 3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1) | 13,178 | [redacted] | [redacted] |
| 4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2) | 13,178 | [redacted] | [redacted] |
| **Equal mix of 3 placebo models** | | | |
| 1. Utility values from trial EQ-5D | 16,472 | [redacted] | [redacted] |
| 2. Utility values from ESS mapped to EQ-5D using McDaid | 16,472 | 0.48 | £34,557 |
| 3. Utility values 50% trial EQ-5D and McDaid mapping, average of values (method 1) | 16,472 | [redacted] | [redacted] |
| 4. Utility values 50% trial EQ-5D and McDaid mapping, average of coefficients (method 2) | 16,472 | [redacted] | [redacted] |

[a] Based on a complete case analysis, not ITT. N.b. ERG corrected ICER for company base case was 22,294 QALY gained

CPAP, continuous positive airway pressure; EQ-5D, EuroQol five-dimensions; ESS, Epworth Sleepiness Scale; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year