SMC2862

zuranolone hard capsule (Zurzuvae®)

Biogen

16 January 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

zuranolone (Zurzuvae®) is not recommended for use within NHSScotland.

Indication under review: treatment of moderate or severe postnatal depression (PND) in adults following childbirth.

In a double-blind, phase III study, zuranolone, compared with placebo, improved depression measured by 17-item Hamilton Rating Scale for Depression (HAMD-17) in adults with severe PND.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Zuranolone is a neuroactive steroid that modulates the gamma-aminobutyric acid-A (GABA-A) receptor and enhances GABA activity, which is inhibitory. This may regulate an imbalance of inhibitory and excitatory signalling in the brain that can be associated with PND. Zuranolone capsules are swallowed whole, 50 mg once daily, in the evening with fat-containing food, for 14 days; treatment beyond this has not been evaluated. The dose may be reduced to 40 mg, if 50 mg is not tolerated.[1]

1.2. Disease background

Postnatal depression can affect about 10% to 15% of pregnancies.[2] Patients can experience symptoms of a major depressive episode including low mood, loss of interest or pleasure, reduced energy and fatigue, changes in sleep and/or psychomotor function, difficulty concentrating, feelings of worthlessness, inappropriate guilt, or hopelessness and recurrent thoughts of death or suicide. In moderate PND several symptoms are present to a marked degree, with considerable but not complete functional impairment. In severe PND many of the characteristic symptoms are present to a marked degree, and / or several are present to an intense degree, with complete or near-complete functional impairment. Suicide is a leading cause of death in the postnatal period.[3] Early mother-infant relationships are the foundation for development of an infant's early emotional regulation and adaptive functioning; impaired attachment can predispose a child to future mental health problems.[2] Also, PND may be associated with infant malnutrition.[4] Episodes of PND last 3 to 6 months on average, but may last for months or years, depending on severity and nature of symptoms.[3]

1.3. Treatment pathway and relevant comparators

The Perinatal Mental Health Network Scotland has developed care pathways to guide treatment of people with perinatal mental health problems. Those who require specialist assessment and intervention for severe or complex problems are referred to the Community Perinatal Mental Health Teams (CPMHTs).[5] The Scottish Intercollegiate Guidelines Network (SIGN) national clinical guideline 169: perinatal mental health conditions, recommends psychological intervention and antidepressants for management of moderate and severe depression in the perinatal period, with selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacological treatment. It notes that sertraline has good tolerability and is excreted in breastmilk in low levels.[2]

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Zuranolone has received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the SKYLARK study and is detailed in Table 2.1.[4, 6, 7]

Table 2.1. Overview of relevant study.[4]

Criteria	SKYLARK
Study design	Double-blind, phase III study
Eligible patients	Women, age 18 to 45 years, with postnatal depression, defined as major depressive episode on DSM-5 with onset in third trimester or ≤4 weeks postpartum, who had HAMD-17 score ≥26 and were ≤12 months postpartum. Patients were not allowed to breastfeed during the study and for 7 days after the last dose of study drug.
Treatments	Patients were randomised to zuranolone 50 mg orally once daily in the evening with fat-containing food for 14 days or placebo. Those who could not tolerate 50 mg dose, could receive zuranolone 40 mg for the rest of the treatment period. Antidepressant use was permitted, if patients were on a stable dosage for ≥30 days and remained on it until day 45 assessments.
Randomisation	Equal randomisation, stratified by use of antidepressant therapy (current/stable versus not treated/withdrawn ≥30 days or >5 half-lives).
Primary outcome	The primary outcome was change from baseline to day 15 in HAMD-17 total score.
Secondary outcomes	Key secondary outcomes controlled for multiplicity in the order: change from baseline in HAMD-17 total score at day 3, day 28 and day 35, and in CGI-S at day 15. Other secondary outcomes were: MADRS, HAM-A, CGI-I, EPDS and PHQ-9.
Statistical analysis	The primary analysis was in the full analysis set, which comprised all randomised patients who had ≥1 dose of study medication plus baseline and ≥1 post-baseline score. Key secondary outcomes were tested in the hierarchy detailed above, if the primary outcome was significant. Other secondary outcomes were descriptive.

Abbreviations: CGI-I = clinical global impression – improvement; CGI-S = clinical global impression – severity scale; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EPDS = Edinburgh Postnatal Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LSM = least square mean; MADRS = Montgomery-Asberg Depression Rating Scale; PHQ-9 = 9-item Patient Health Questionnaire.

The primary outcome, change from baseline to day 15 in 17-item Hamilton rating scale for depression (HAMD-17) total score, was significantly improved with zuranolone compared with placebo, as were the key secondary outcomes controlled for multiplicity: change from baseline in HAMD-17 score at day 3, day 28 and day 35, and in clinical global impression – severity scale (CGI-S) at day 15. There appeared to be improvements with zuranolone in other secondary measures of depression and anxiety. Results are detailed in Table 2.2.[4]

Table 2.2: Primary and secondary results of SKYLARK study.[4, 6]

	Zuranolone 50 mg	Placebo	Difference or odds ratio[A] (95% CI), p-value
	N=98	N=97	
Primary outcome			
LSM change HAMD-17 at day 15	-15.6	-11.6	-4.0 (-6.3 to -1.7), p<0.001
Key secondary outcomes			
LSM change HAMD-17 at day 3	-9.5	-6.1	-3.4 (-5.4 to -1.4), p<0.001
LSM change HAMD-17 at day 28	-16.3	-13.4	-2.9 (-5.4 to -0.5), p=0.020
LSM change HAMD-17 at day 45	-17.9	-14.4	-3.5 (-6.0 to -1.0), p=0.007
LSM change CGI-S at day 15	-2.2	-1.6	-0.6 (-0.9 to -0.2), p=0.005
Other selected secondary outcomes – physician assessed			
LSM change HAM-A at day 15	-12.8	-10.6	-2.2 (-4.2 to -0.3)
LSM change MADRS at day 15	-19.7	-14.6	-5.1 (-8.4 to -1.7)
HAMD-17 response[B] at day 15	57%	39%	2.0 (1.1 to 3.7)
HAMD-17 response[B] at day 45	62%	54%	1.5 (0.84 to 2.8)

HAMD-17 remission[C] at day 15	27%	17%	1.8 (0.9 to 3.6)
CGI-I response[D] at day 15	67%	47%	2.2 (1.2 to 4.1)
CGI-I response[D] at day 45	74%	66%	CIC
Other selected secondary outcomes – patient assessed			
LSM change EPDS at day 15	-10.3	-8.4	-2.0 (-3.8 to -0.1)
LSM change EPDS at day 45	-12.2	-9.8	-2.4 (-4.5 to -0.3)
LSM change PHQ9 at day 15	-10.5	-8.6	-1.9 (-3.7 to 0.0)
LSM change PHQ9 at day 45	-11.7	-9.8	-1.9 (-4.0 to 0.1)

Abbreviations: A = difference for change from baseline, odds ratio of responder analysis; B = response defined as at least 50% reduction in HAMD-17 score; C = remission defined as HAMD-17 score of seven or lower; D = CGI-I response defined as very much or much improved; E = response defined as at least 50% reduction in MADRS score; CGI-I = clinical global impression – improvement; CGI-S = clinical global impression – severity scale; CI = confidence interval; CIC = confidential information; EPDS = Edinburgh Postnatal Depression Scale; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LSM change = least square mean change from baseline; MADRS = Montgomery-Asberg Depression Rating Scale; NR = not reported; PHQ-9 = 9-item Patient Health Questionnaire.

Zuranolone was associated with a quick response, with median time to first HAMD-17 response of 9 days, compared with 43 days in the placebo group and median time to first HAMD-17 remission of 30 versus 50 days in the respective groups. Details of relapse and loss of HAMD-17 response or remission between day 15 and day 45 are detailed in Table 2.3.[4]

*Other data were also assessed but remain confidential.**

Table 2.3: Relapse and loss of response in SKYLARK.[4]

	Zuranolone	**Placebo**
Relapse at day 45 in patients with HAMD-17 response at day 15	5.7% (3/53)	5.7% (2/35)
Loss of HAMD-17 response at day 45 in patients with HAMD-17 response at day 15 and non-missing HAMD-17 score at day 45	19% (9/47)	12% (4/33)
Loss of HAMD-17 remission at day 45 in patients with HAMD-17 remission at day 15 and non-missing HAMD-17 score at day 45	14% (3/22)	27% (4/15)

HAMD-17 response defined as ≥50% reduction from baseline in HAMD-17 total score. HAMD-17 remission defined as a HAMD-17 total score ≤7. HAMD-17 relapse defined as at least 2 consecutive HAMD-17 total score ≥20 after Day 15 HAMD-17 evaluation including the last value.

2.2. Health-related quality of life outcomes

General health-related quality of life outcomes, such as short-form 36 (SF-36) were not available for SKYLARK but are available for the supportive study, ROBIN, suggesting benefits in some scales.[8]

2.3. Supportive studies

A double-blind phase III supportive study, ROBIN, had similar inclusion criteria (although patients were ≤6 months postpartum) and the same primary outcome as SKYLARK. It assessed an unlicensed dose and formulation of zuranolone 30 mg capsule, with higher relative bioavailability, estimated to correspond to about 40 mg of the licensed formulation. The primary outcome, change in HAMD-17 from baseline to day 15 was significantly improved with zuranolone compared with placebo and there appeared to be benefits of similar magnitude to SKYLARK for secondary measures of depression and anxiety. Results are detailed in Table 2.4.[4, 7, 9, 10]

Table 2.4: Primary and secondary results of ROBIN study.[4, 9, 10]

	Zuranolone 30 mg	Placebo	Difference or odds ratio[A] (95% CI), p-value
Full analysis set	**N=76**	**N=74**	
Primary outcome			
LSM change HAMD-17 at day 15	-17.8	-13.6	-4.2 (-6.9 to -1.5), p=0.003
Secondary outcomes			
LSM change HAMD-17 at day 3	-12.5	-9.8	-2.7 (-5.1 to -0.3)
LSM change HAMD-17 at day 45	-19.2	-15.1	-4.1 (-6.7 to -1.4)
HAMD-17 response[B] at day 15	72%	48%	2.63 (1.34 to 5.16)
HAMD-17 remission[C] at day 15	45%	23%	2.53 (1.24 to 5.17)
LSM change MADRS score at day 15	-22.1	-17.6	-4.6 (-8.3 to -0.8)
LSM change HAM-A at day 15	-16.6	-12.7	-3.9 (-6.7 to -1.1)
CGI-I response[D] at day 15	72%	52%	2.2 (1.1 to 4.3)

Abbreviations: A = difference for change from baseline, odds ratio of responder analysis; B = response defined as at least 50% reduction in HAMD-17 score; C = remission defined as HAMD-17 score of seven or lower; D = CGI-I response defined as very much or much improved; E = response defined as at least 50% reduction in MADRS score; CGI-I = clinical global impression – improvement; CGI-S = clinical global impression – severity scale; CI = confidence interval; HAMD-17 = 17-item Hamilton Rating Scale for Depression; LSM change = least square mean change from baseline; MADRS = Montgomery-Asberg Depression Rating Scale.

3. Summary of Safety Evidence

The European regulator concluded that the licensed dose of zuranolone in PND was generally well tolerated, with most adverse events mild or moderate in severity. Common adverse events included somnolence, dizziness and sedation but an increase in falls has not been observed. The patient information leaflet warns that zuranolone may impair ability to drive and cause sleepiness, slow thinking, trouble remembering, confusion, and dizziness during the day, which may interfere with daily activities. Dose reduction can mitigate adverse events. Although zuranolone is present in low levels in breast milk, there is insufficient data to recommend its use during breast feeding and it must not be given during pregnancy.[1, 4]

In the SKYLARK study, within the zuranolone and placebo groups, adverse events were reported by 66% (65/98) and 53% (52/98) of patients, respectively, with few patients having adverse events that were severe (3.1% and 1%), serious (2.0% and 0) or led to treatment discontinuation (4.1% and 2.0%). However, a larger proportion of patients in the zuranolone group, compared with placebo, had adverse events that led to dose reduction: 16% versus 1.0%.[6]

In the SKYLARK study, within the zuranolone and placebo groups, common adverse events included somnolence (26% and 5.1%), sedation (11% and 1.0%), dizziness (13% and 10%), headache (9.2% and 13%), diarrhoea (6.1% and 2.0%), nausea (5.1% and 6.1%), urinary tract infection (5.1% and 4.1%), and COVID-19 (5.1% and 0).[6]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the double-blind, phase III, SKYLARK study, the licensed dose of zuranolone (50mg) compared with placebo, significantly improved depression, with differences over placebo of about 3 to 4 points for HAMD-17 from day 3 to 45 (which are around estimates of the minimum important difference of 3 to 5 points). It was associated with benefits in other measures of depression and anxiety. This was supported by similar benefits with a different formulation and dose of zuranolone in the ROBIN study. These were considered clinically relevant by the European regulatory authority and it was noted that zuranolone produced a quick response.[4]
- Zuranolone is the first medicine in its pharmacological class to be licensed for treatment of PND.

4.2. Key uncertainties

- Improvements from baseline in the placebo group were substantial and often greater than the benefit of zuranolone over placebo. As patients were followed up for a month after the 14-day course of treatment, there is a lack of data on maintenance of effect and long-term outcomes, such as relapse rates.[4]
- The comparator in the SKYLARK was placebo. This may not reflect Scottish practice. The 2023 SIGN guideline notes that SSRIs are recommended as the first-line pharmacological therapy for PND in the perinatal period. It notes that sertraline has good tolerability and is excreted in breast milk in low levels.[2] This was confirmed by clinical experts working in NHS Scotland, with one also noting the use of benzodiazepines, which also enhance activity at GABA-A receptor. There was no indirect comparison of a strategy including zuranolone versus current standard of care, including treatment with antidepressants, such as SSRIs, and/or with psychological therapies.
- Zuranolone can be used in combination with antidepressant medicines. However, there is limited evidence in this group, with only 16% (30/183) and 19% (28/147) of patients in the SKYLARK and ROBIN taking concomitant antidepressant medicines. In SKYLARK, subgroup analyses of the primary outcome in these patients did not favour zuranolone, with a least square mean (LSM) difference of 0.8 (95% confidence interval [CI]: -5 to 6.7) but, in those not taking concomitant antidepressants, the LSM difference of -5.0 (95% CI: -7.5 to -2.5) was consistent with the primary analysis.[4] The size of the concomitant antidepressant subgroup is too small to support definitive conclusions but raises a concern about potential lack of effect.
- As allopregnanolone is expected to increase during pregnancy with a peak concentration during the third trimester, efficacy of zuranolone is expected especially during this period.[4] In SKYLARK, patients could commence treatment with zuranolone (or placebo) up to 12 months postpartum (if the symptoms of PND had commenced in the third trimester or within 4 weeks postpartum).[4] Within the subgroups who had a duration of current PND episode <4 months (<122 days), 4 to 6 months (122 to 182 days), and ≥6 months (≥183

days), LSM difference (95% CI) between zuranolone and placebo for the primary outcome was -5.3 (-9.3 to -1.3), -3.9 (-7.8 to 0) and -2.8 (-6.9 to 1.3), respectively. Within the groups who had onset of depression within postpartum period or in the third trimester the corresponding figures were -4.6 (-7.3 to -1.8) and -2.7 (-7.0 to 1.6), respectively.[4] It is not possible to draw conclusions from these subgroup analyses.

- Zuranolone is licensed for use in moderate to severe PND. SKYLARK recruited patients with HAMD-17 score ≥26, which is indicative of severe depression. Two thirds of patients had baseline HAMD-17 total score of ≥28 and in this subgroup the primary outcome LSM difference (95% CI) between zuranolone and placebo was -4.9 (95% CI: -7.9 to -1.9, compared with -2.3 (95% CI: -5.8 to 1.2) in those with baseline HAMD-17 <28.[4] However, these subgroup analyses cannot support definitive conclusions. The study did not include patients at significant risk of suicide and there are no data in this group or indirect comparison with alternative treatments in this group, which may include electroconvulsive therapy (ECT).
- The majority of patients recruited to the SKYLARK and ROBIN studies lived in the United States of America: 97% (191/196) and 100%.[4, 9] It is not known whether there are differences in perinatal support compared with NHS Scotland.
- In SKYLARK, 21%, 30% and 49% of patients had a body mass index (BMI) that was normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2) respectively; and in ROBIN the corresponding figures were 21%, 27% and 50%. In the 2023 Scottish Health Survey, 32% of adults in Scotland had an obese BMI ≥30 kg/m^2, which is lower than the study populations. Subgroup analyses of the primary outcome indicated a LSM difference (95% CI) between zuranolone and placebo of -2.2 (-7.3 to 2.9), -5.3 (-10.1 to -0.6), and -3.9 (-7.1 to -0.6) in the respective groups.[4, 9, 12] Subgroup analyses of the primary outcome indicated a possibly reduced effect, LSM difference (95% CI) between zuranolone and placebo, in 91 (50%) patients taking progestogen-only contraceptives, -1.6 (-4.9 to 1.7).[4] These subgroup analyses do not support definitive conclusions.

*Other data were also assessed but remain confidential.**

4.3. Innovative Licensing and Access Pathway (ILAP)

The submitting company advised that zuranolone has an Innovation Passport but there are no ongoing studies that are expected to provide additional data. Therefore, zuranolone is not suitable for interim acceptance.

4.4. Clinical expert input

Clinical experts consulted by SMC advise that zuranolone in the treatment of PND may be a therapeutic advance due to its novel approach, fast action and short duration of treatment. However, there was no clear consensus on how or where it would be used in practice.

4.5. Service implications

As there was no clear consensus on how it would be used in practice and in which setting (specialist versus primary care) it would be given, service implications are uncertain.

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company conducted an economic analysis, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	29 years to align with the long-term follow-up period available in the ALSPAC[13] dataset to capture extended impacts of postnatal depression (PND) on health and costs.
Population	Adult women diagnosed with postnatal depression (PND) consistent with the SKYLARK[11] study population (mean age 30.5 years, baseline EPDS 21.1, 5 months post-birth).
Comparators	The comparator was established clinical management (ECM) compared to zuranolone plus ECM. In the company base case 15.30% of patients are assumed to be taking ADTs (including fluoxetine and sertraline) as part of ECM.
Model description	Patient-level simulation tracking individual trajectories in EPDS scores, utilities, and costs. Short-term data from SKYLARK were linked to long-term projections from the ALSPAC cohort. The short-term EPDS trajectory was estimated using the SKYLARK mixed model for repeat measures (MMRM), which included fixed effects for baseline EPDS, time, antidepressant (ADT) use at baseline, age group (>24 years), treatment arm, an "on-treatment" indicator (Days 1–14), and a time × on-treatment interaction, with a patient-level random intercept. From Month 3 onward, long-term EPDS changes were modelled using the ALSPAC MMRM, which estimates the incremental change in EPDS between periods using coefficients for time and time² only, applied as ΔEPDS rather than absolute predictions to remove random-effect dependence between the short- and long-term components. The first 6 cycles (informed by short-term data) covered the first 3-months and had variable cycle lengths. Subsequent cycles (informed by long-term projections) had a length of 3-months. A discount rate of 3.5% was applied to costs and outcomes.
Clinical data	Short-term effectiveness was estimated using data from SKYLARK; long-term trajectories were estimated using data from ALSPAC. Adverse events were sourced from SKYLARK and mortality was according to ONS life tables.[14]
Extrapolation	Short-term EPDS projections from SKYLARK extended from 45 days to 3 months. Between Day 45 and 3 months (corresponding to 8 months postpartum), the company did not apply the full MMRM equation. Instead, EPDS was projected forward from the Day-45 value using only the estimated SKYLARK time coefficient multiplied by the change in time to Month 3, effectively assuming a linear time-based trend while holding all other predictors constant. These short-term EPDS changes were then fed into a long-term projection model, using data from ALSPAC. In this phase, the model took the EPDS score at Month 3 as a starting value and then applies a change equation in which the incremental change in EPDS between time points depends only on time and time-squared coefficients from the ALSPAC MMRM. This structure generated long-term EPDS trajectories over the 29-year horizon in both arms.

Quality of life	Utilities were mapped from the ROBIN[15] study which collected SF-36 data to the SF-6D using UK tariffs and EPDS bands were converted to utilities. AE disutilities were applied from UK-based literature.
Costs and resource use	Healthcare resource use (HRU) data were sourced from Petrou et al. (2002)[16] for the first 18-months postpartum and Byford et al. (2011)[17] thereafter. Unit costs were from NHS Reference Costs (2023/24)[18] and PSSRU (2023),[19] inflated to 2024 price levels. Included components were for treatment acquisition, AE management, and health/social care utilisation.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price.

Abbreviations: ADT = antidepressant therapy; AE = adverse event; ALSPAC = Avon Longitudinal Study of Parents and Children; CUA = cost–utility analysis; ECM = Established Clinical Management; EPDS = Edinburgh Postnatal Depression Scale; HRQoL = health-related quality of life; HRU = healthcare resource use; MMRM = mixed model for repeated measures; NHS = National Health Service; ONS = Office for National Statistics; PAS = Patient Access Scheme; PND = postnatal depression; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year; SF-6D = Short-Form Six-Dimension; SF-36 = Short-Form 36-Item Health Survey.

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

6.3. Sensitivity analyses

A description of key scenario analyses are presented in Table 6.2.

Table 6.3 Scenario analysis results zuranolone

	Parameter	**Base case**	**Scenario**
1	Mortality	No additional mortality for patients with PND i.e., general population mortality applied for all patients	Additional mortality is applied for patients who have PND
2	ADT use at baseline	The short-term EPDS model from SKYLARK forces the inclusion of ADT use at baseline	The short-term EPDS model with no forced ADT at baseline is applied, and the costs associated with ADT are removed
3	HRU inputs	HRU resource use is sourced from Petrou et al. (2002)	The data from Petrou et al. (2002) has been augmented with feedback from clinicians to reflect current clinical practice
4	PND remission threshold (EPDS)	An EPDS of <13 indicates PND remission	The remission threshold is changed so that an EPDS of <10 indicates PND remission
5	Model time horizon	29 years to align with the long-term data from ALSPAC	Lifetime time horizon of 60. The EPDS score at year 29 is carried forward for the duration of the time horizon.
6	Dose reductions	Additional pack of zuranolone is applied to 3% of patients who require a dose reduction	No dose reduction applied
7	EPDS scores	No EPDS adjustment is made for the	EPDS is decreased to 12.99 over 24-months for patients who have not

		model time horizon	achieved remission after 10-years (both arms)
8			EPDS is decreased to 12.99 over 24-months for patients who have not achieved remission after 5-years (both arms)
9			EPDS is decreased to 12.99 over 24-months for patients who have not achieved remission after 2-years (both arms)
10	ADT use at baseline	15.3% of patients have concomitant ADT and ADT is included as a covariate in the MMRM	100% of patients on ADT with ADT
11	EPDS utility	SF-6D mapped from ROBIN	EPDS utility values mapped from ROBIN PHQ-9 to EQ-5D
12	Time horizon	29 years	2 years
13			5 years
14			10 years
15	ADT use at baseline + updated MMRM formula	15.3% of patients have concomitant ADT and original MMRM formula used derived from SKYLARK	15.3% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)
16			50% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)
17			70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)
18			15.3% concomitant ADT (revised MMRM using SKYLARK only)
19			50% concomitant ADT (revised MMRM using SKYLARK only)
20			70% concomitant ADT (revised MMRM using SKYLARK only)
21	Day 45 to 3 months modelling assumption	SKYLARK MMRM	LOCF
22	ADT use at baseline + updated MMRM formula + GAD/MDD subgroup analysis	15.3% of patients have concomitant ADT, original MMRM formula used derived from SKYLARK and MDD/GAD subgroup not separated using MMRM	70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN) and 13.8% MDD/GAD
23			70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN) and 100% MDD/GAD

24	Time horizon + ADT use at baseline + updated MMRM formula	29 year time horizon, 15.3% of patients have concomitant ADT and original MMRM formula used derived from SKYLARK	2-year time horizon 70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)
25			5-year time horizon 70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)
26			10-year time horizon 70% concomitant ADT (revised MMRM using pooled SKYLARK+ROBIN)

Abbreviations: ADT = antidepressant therapy; ALSPAC = Avon Longitudinal Study of Parents and Children; EPDS = Edinburgh Postnatal Depression Scale; EQ-5D = EuroQol 5-Dimension; GAD, generalised anxiety disorder; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; LOCF, Last Observation Carried Forward; MMD, major depressive disorder; MMRM = mixed model for repeated measures; PHQ-9 = Patient Health Questionnaire-9; PND = postnatal depression; QALY = quality-adjusted life year; SF-6D = Short-Form Six-Dimension; SF-36 = Short-Form 36-Item Health Survey.

6.4. Key strengths

- The patient-level simulation model structure was reasonable as it captured heterogeneity and individual response trajectories.

6.5. Key uncertainties

- Optimistic durability of benefit was the most significant uncertainty as the model assumed a persistent between-arm Edinburgh Postnatal Depression Scale (EPDS) difference carried across 29 years without waning or planned retreatment, beyond the 45-day evidence window. This likely inflated lifetime quality adjusted life years (QALYs) and biased the incremental cost effectiveness ratio (ICER) downward, though the real-world persistence of treatment benefit beyond the short-term was uncertain. A key driver of this persistence was the structure of the ALSPAC long-term model, which predicted very small natural changes in EPDS over time (based only on time and time^2), meaning the initial treatment difference from SKYLARK is mechanically maintained over the entire time horizon. Adjusting the time horizon to 2, 5 and 10 years (Scenarios 12, 13 and 14, respectively) demonstrated the impact this long-term benefit had as a key driver of cost-effectiveness.
- The method used to project EPDS from Day 45 to Month 3 was uncertain and likely over-optimistic. The company extended the SKYLARK MMRM time coefficient, estimated only from the 45-day trial window, beyond the observed data, assuming the same rate of symptom change continues for another 45 days after treatment ends. There was no evidence supporting this continuation, and it likely overstated improvement in both arms. A more conservative approach was the Last Observation Carried Forward (LOCF) method to avoid imposing unvalidated short-term gains before entering the ALSPAC long-term model. A scenario analysis which used the LOCF method showed a small upward impact on the ICER (Scenario 21).
- Petrou (2002)[16] and Byford (2011)[17] may not reflect contemporary perinatal pathways or Scottish service intensity. If current care is more intensive (and costly), base costs may be understated and affect incremental cost offsets and the ICER. A scenario that augmented the base case sources for healthcare resource use costs with clinical expert input was minimally impactful on the ICER (Scenario 3).

- Modelling ECM with 15% antidepressant therapy under-represented Scottish practice where antidepressant use is higher amongst people with PND.[2] The company conducted scenario analysis to attempt to address this. However, as Scenario 10 did not include an interaction term it cannot be tested whether concurrent antidepressant therapy narrowed the incremental effect of zuranolone. The company provided scenarios 15 to 20 in response to SMC request to separate effect of intervention and ADT. These used separate MMRMs for ADT and non-ADT populations on either pooled SKYLARK and ROBIN data or SKYLARK data alone. There was a concern around the face validity of scenarios 15 to 20 as they suggested better outcomes amongst patients with concomitant ADT with zuranolone, whereas in the respective pre-planned subgroup analysis the primary analysis results did not favour zuranolone.
- PND is known to be highly impactful not only on the mother, but the child and wider family. Despite this, these effects were not explored. Inclusion of these effects may have had a large downward effect on the incremental cost-effectiveness ratio.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept zuranolone for use in NHSScotland.

8. Guidelines and Protocols

In December 2023, the Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline, 'SIGN 169: perinatal mental health conditions.'[2]

9. Additional Information

9.1. Product availability date

27 August 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
Zuranolone	**50 mg orally once daily for 14 days**	**£13,065**

Costs from Monthly Index of Medical Specialities (MIMS) on 4 November 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

References

1. Biogen Idec. Zuranolone hard capsule (Zurzuvae®) hard capsule Summary of Product Characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 29 September 2025.
2. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 169: perinatal mental health conditions, December 2023.
3. British Medical Journal. BMJ Best practice: postnatal depression, last updated 12 January 2024. www.bestpractice.bmj.com.
4. European Medicines Agency (EMA). European public assessment report for zuranolone (Zurzuvae®), EMEA/H/C/006488/0000, 24 July 2025. www.ema.europa.eu.
5. NHS National Service Scotland. Perinatal Mental Health Network Scotland (PMHNS) Scottish Perinatal Mental Health Care Pathways. www.nn.nhs.scot/pmhn.
6. Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the treatment of postpartum depression. Am J Psychiatry 2023; 180: 668-75.
7. US Food and Drug Administration (FDA). Integrated review for zuranolone (Zurzuvae®), 217369Origs000. www.fda.gov.
8. Deligiannidis KM, Citrome L, Huang MY, et al. Effect of zuranolone on concurrent anxiety and insomnia symptoms in women with postpartum depression. J Clin Psychiatry 2023; 84(1): 22m14475.
9. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psychiatry 2021; 78(9): 951-9.
10. Clinicaltrials.gov: Entry for NCT02978326.
11. Sage Therapeutics. Clinical study report for 217-PPD-301 (SKYLARK), 22 August 2022.
12. Scottish Government. The Scottish Health Survey 2023. www.gov.scot.
13. Netsi E, Pearson RM, Murray L, et al. Association of persistent and severe postnatal depression with child outcomes. JAMA Psychiatry 2018; 75: 247-53.
14. Office of National Statistics (ONS). National life tables: UK. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
15. Sage Therapeutics. Clinical study report for 217-PPD-201 (ROBIN), 19 September 2019.
16. Petrou S, Cooper P, Murray L, Davidson LL. Economic costs of post-natal depression in a high-risk British cohort. Br J Psychiatry 2002; 181: 505-12.
17. Byford S, Barrett B, Despiegel N, Wade A. Impact of treatment success on health service use and cost in depression: longitudinal database analysis. Pharmacoeconomics 2011; 29: 157-70.
18. NHS England. 2023/24 National Cost Collection Data Publication (2024), 2024. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.
19. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care programme (2022 – 2027), 2023.
20. Office for National Statisticsn (ONS). Consumer price inflation time series. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/datasets/consumerpriceindices.

This assessment is based on data submitted by the applicant company up to and including 12 December 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.