National Institute for Health and Care Excellence

Health Technology Evaluation

Zuranolone for treating postnatal depression [ID6431]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Biogen	This is appropriate.	Thank you for your comment. No action required.
	NHS England	Agree	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	The Single Technology Appraisal route is certainly the most appropriate pathway.	Thank you for your comment. No action required.
Wording	Biogen	While the marketing authorisation for zuranolone is yet to be granted, the application to Medicines and Healthcare products Regulatory Agency (MHRA) states the draft label language as “Zurzuvae is indicated for the treatment of postnatal depression (PND) in adults.”	Thank you for your comment. The title and scope have been updated to reflect the revised wording.

Section	Stakeholder	Comments [sic]	Action
		Biogen request the draft remit to read “To appraise the clinical and cost effectiveness of zuranolone within its marketing authorisation for treating adults with PND.”	
	NHS England	yes	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	Yes, current wording is appropriate.	Thank you for your comment. No action required.
Timing issues	Biogen	There is an urgent need for a licensed treatment for women with PND in the UK. An estimated 11-16% of mothers in the UK are affected by PND [1, 2], with no treatments with a marketing authorisation for this indication. Current treatment options are limited to best supportive care (BSC), i.e., psychological interventions with or without off-label antidepressant treatments such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors (SNRIs). If approved, zuranolone will be the first and only treatment with a marketing authorisation for the treatment of PND. Due to its unique mechanism of action, zuranolone has the potential to be the first treatment to target the disruption of perinatal adaptive signalling, which has been shown to play a role in the pathophysiology of PND (subject to regulatory approval). A timely decision following market authorisation and licensing of zuranolone will ensure that patients in this vulnerable period should not face any unnecessary delays in access to appropriate treatment.	Thank you for your comment. This topic has been scheduled into the work programme.
	NHS England	I do don’t consider this as an urgent issue and should be considered following the outcome of the MHRA licencing review	Thank you for your comment. This topic has been scheduled

Section	Stakeholder	Comments [sic]	Action
			into the work programme.
	College of Mental Health Pharmacy	There currently exists no licensed treatments for post-natal depression specifically; all current treatment are licensed for depression in general. This should be considered a priority to assess given the relatively common nature of PND, potential severity of the condition and lack of existing licensed treatments.	Thank you for your comment. This topic has been scheduled into the work programme.
Additional comments on the draft remit	Biogen	No additional comments.	Thank you.
	NHS England	-	Thank you.
	College of Mental Health Pharmacy	It is worth noting that the NICE guidance being used to identify comparators (CG192) has remained relatively unchanged since its publishing in 2014 (only minor wording updates to Valproate). It is worth noting that there have been publications not including in the original NICE guidance or produced since publishing that may impact on the comparisons eg evidence showing that guided self-help not only improves women's health-related quality of life, but leads to a small reduction in health care costs, and is cost-effective An exploratory parallel-group randomised controlled trial of antenatal Guided Self-Help (plus usual care) versus usual care alone for pregnant women with depression: DAWN trial - ScienceDirect	Thank you for your comment. Guided self-help has been added to the comparator list as an example psychological therapy.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen	Biogen notes that the current scope does not capture the difference between PND and major depressive disorder (MDD), and the description omits that some women with no prior mental health issues and a robust support network may still suffer from PND.	Thank you for your comment. Please note that the background section is intended as a

Section	Consultee/ Commentator	Comments [sic]	Action
		Biogen requests that the scope includes a clear definition of PND and a short description of the pathophysiology mechanism leading to PND, emphasizing that it is distinct from other forms of depression and can affect any peripartum woman.[3-5] Biogen requests that this is important to highlight to further educate the public about PND, in order to directly address the stigma associated with PND that causes some women with the disease to avoid seeking treatment.[6] Please consider the following points: • PND is generally defined as a major depressive episode with onset during pregnancy or in the first 4 weeks to 12 months following delivery.[7, 8] • Although several factors may increase the likelihood of developing PND, it is important to stress that any woman, irrespective of the history of mental health problems and/or situational factors can experience symptoms of PND.[3] • Although PND is a form of depression, there are distinct mechanisms and characteristics associated with PND that make PND a distinct disease. While the exact causes are not fully understood, the available research suggests that PND and depression involve complex interactions of genetic, metabolic, endocrine, environmental, and neurobiological factors.[5] • In PND specifically, the rapid changes in neuroactive steroids during pregnancy and after childbirth, particularly involving allopregnanolone and GABAA receptors, may contribute to the vulnerability to depressive symptoms in some women.[4] Biogen would request the following points to be considered to ensure the background information relating to BSC, and therefore comparators relevant to the scope (see comparator section below), is accurate: • There are currently no approved treatments indicated for the treatment of PND in the UK.	brief overview of the condition and should not be considered a comprehensive description. The background has been updated to note: • that PND can develop in the absence of risk factors. • that there are no treatments specifically licensed for PND. • that anxiety is a key symptom. • that PND can increase the risk of poor outcomes for the child. • that a study found increasing PND prevalence in the UK.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Zuranolone has been accepted into the Innovative Licensing and Access Pathway (ILAP) programme based on the MHRA's evaluation on the level of unmet need in the PND patient population. • Antidepressants such as a tricyclic antidepressants, SSRIs, and SNRIs do not have marketing authorization to treat PND and are used off-label. Furthermore, these treatment options are associated with several limitations: o Multiple safety concerns including withdrawal effects, sexual difficulties, weight gain, emotional numbness, dry mouth, agitation, and drowsiness.[9-11] This is a particularly important consideration among women who choose to breastfeed. o Currently available first-line antidepressants are slow responding, with a time to treatment response of 6 to 8 weeks and a time to first effect of 3 to 4 weeks. This response time may not be sufficient given the urgency to treat and resolve PND symptoms as soon as they occur, in order to reduce the risk of future relapse and minimise the associated emotional burden of PND.[12, 13] • Currently available treatments do not specifically target the underlying pathophysiology of PND, as most have been adapted from the treatment of MDD outside of the peripartum period. Current evidence of antidepressant treatment for postpartum depression is limited by the small number of randomized clinical trials, underpowered samples and lack of long-term follow-up.[14] Please note that the NICE scope excludes some key symptoms (notably anxiety), and while the condition often improves within a few months, it can have profound short- and long-term effects on the mother, the child and the family as a whole, and this is exacerbated if left untreated. Biogen would like the scope to capture the impact of PND on children and families, in order to	

Section	Consultee/ Commentator	Comments [sic]	Action
		accurately reflect the overall humanistic and economic impact of PND, and the benefits of early diagnosis and treatment, considering the following: • Anxiety is one of the most common symptoms among patients with PND, with prevalence estimates as high as 70% of patients.[15, 16] In women with PND, anxiety symptoms have been associated with more severe depression, longer time to treatment response, and a greater risk of self-harm ideation.[16] • PND increases the risk of poor mother-child bonding by five-fold and can result in worse outcomes of the child, including: delayed cognitive development due to maternal insensitivity, substantial negative effect on language development, higher degree of emotional disorders, lower social engagement at 9 months of age, and an increase in behavioural problems at 2 years of age.[17] • PND also puts additional strain on relationships with partners and has been associated with decreased marital satisfaction and higher separation and divorce.[18, 19] Partners of women experiencing PND also face higher rates of stress, anxiety, and paternal depression compared to partners of women without PND.[15, 20] Families of women experiencing PND are associated with a higher level of disruption to parenting behaviours and relationship separation compared to other households.[15] • The negative long-term impact of PND on mothers, children, partners, and families, leads to substantial economic impact.[21, 22] Perinatal mental illnesses (also including anxiety and psychosis) carry a long-term cost to society of an estimated £8.1 billion for each one-year cohort of births in the UK.[22] Approximately 72% of the costs relate to the child; the cost impact of PND on children is estimated to be £51,462 per birth, which can be attributed to factors such as emotional problems, special educational needs, and leaving school without qualifications.[22]	

Section	Consultee/ Commentator	Comments [sic]	Action
		• The early diagnosis and treatment of PND can substantially improve outcomes, reduce the risk of future relapse and minimise the associated emotional and financial burden of PND.[13] Please update the scope to include the following points to ensure that the prevalence of PND is accurately reflected: • Based on the data collected between 2000 and 2013, the number of women affected by PND in the UK is estimated at approximately 11% [1]; however more recent publication focusing on England suggest an increasing trend in prevalence of PND, with estimates reaching up to 16% in 2018 (up from 10.3% in 2014).[2] • Additionally, these numbers may not reflect the full scale of the problem, as it is widely recognised that many women never receive a formal diagnosis of PND. It is estimated that less than 50% of cases are identified in routine clinical assessment.[23] Some studies suggest that only 15% of mothers receive a diagnosis of PND.[24] Please note the following points and ensure the description of the technology is accurate: • Zuranolone has been studied in two placebo-controlled clinical trials, which compared safety and efficacy of zuranolone in combination with BSC* versus placebo in combination with BSC. • Zuranolone is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator.[25] • Zuranolone will be taken orally once daily in the evening for 14 days.[25] * Biogen would like to clarify that the terminology BSC in this context refers to “usual care” or “established clinical management” which was permitted in both arms of the trial. This consists of psychological therapies, and antidepressant treatments.	

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	yes	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	• Wording mentions that "about 30% of women may continue to experience symptoms after the first year." Then later says "PND affects over 10% of women within a year after childbirth." – the second figure of 10% is generally accepted. • It would be worth including in this section the risks – firstly the risks to both mum and baby as highlighted in the MBRRACE (suicide in the perinatal period being a leading cause of maternal death). Whilst not all due to PND, a proportion will be. Secondly, the potential impact on baby of PND and their ongoing attachment issues. The potential impact on baby is a key issue with perinatal mental health conditions that needs to be clearly included throughout the scoping document. • The Maternal Mental Health Alliance produce some sound economic models of the costs of Perinatal Mental Health: https://maternalmentalhealthalliance.org/about-maternal-mental-health/counting-costs/ • The original report from 2014 finding lost term annual costs of £8.1 billion, mostly related to costs associated with the child in later life : Costs of perinatal mental health problems - Centre for Mental Health	Thank you for your comment. The 30% figure refers to the proportion of women with PND that continue to experience symptoms after the first year. The scope has been updated to include a description of the potential for negative outcomes for the child.
Population	Biogen	The intended population for zuranolone is adults with PND, which is aligned with the marketing authorisation application submitted to MHRA, which states the draft label language as "Zurzuvae is indicated for the treatment of postnatal depression (PND) in adults."	Thank you for your comment. The title and remit have been updated to reflect the indication.
	NHS England	Yes assuming the use of this product in people under 18years of age is excluded/out of scope.	Thank you for your comment. The draft licence is for adults only.

Section	Consultee/ Commentator	Comments [sic]	Action
	College of Mental Health Pharmacy	It is worth noting that the NICE depression guidelines (NG222) wording around depression now uses the terms 'more severe' and 'less severe' depression. The use of the term 'severe' in this context is in line with the traditional grading of severity and CG192 still refers to this in mild/moderate/severe depression. It is worth noting that the diagnosis of post-natal depression is not clearly defined. The NICE CKS guidelines reference back to the depression section for diagnosis. DSM requires onset within 4 weeks of childbirth for a diagnosis of postpartum depression. Potentially a clearer definition of severe post-natal depression might be needed to avoid confusion regarding the above – this could be clarified elsewhere but potential timeframes for diagnosis, number of symptoms, use of rating scale may help ensure consistency.	Thank you for your comment. The title and remit have been updated to reflect the indication and no longer refer to 'severe' PND.
Subgroups	Biogen	Not applicable / No subgroups to consider.	Thank you for your comment. No action required.
	NHS England	I note that the US label for this drug indicates "Black or African American participants had a 14% higher CL/F compared to participants of other races (Asian, White, or other)." I assume that the MHRA or other regulatory body will assess the need for dose adjustments (or not) in people from black or Asian races. I suspect that this treatment may be associated with dependence or misuse – I do not know if this treatment will be classed as a controlled drug, schedule 2,3,4 or 5?.	Thank you for your comment. Both of these issues are within the remit of the MHRA.

Section	Consultee/ Commentator	Comments [sic]	Action
		If schedule 2 (?unlikely) It will be important to ensure that appropriate safeguards are in place to ensure that any regulatory controls for the prescribing/dispensing of this drug do not unduly restrict equal access to this drug if it proves to be a clinical and cost effective treatment.	
	College of Mental Health Pharmacy	Presumably those where there is a biological cause – ie ruling out those with existing long-term histories of depression.	Thank you for your comment. The committee will assess the evidence on subgroups if available.
Comparators	Biogen	Biogen requests that NICE rephrase the "Comparators" to state: BSC without zuranolone, which may include: • Psychological therapies (e.g., CBT) • Antidepressant treatments: o Tricyclic antidepressant o SSRIs o SNRIs • High-intensity psychological intervention combined with antidepressant treatments. Please note the following points to ensure that the most accurate comparators are used in the evaluation: • No current treatment with a marketing authorisation for PND. • Biogen consider the terms "Established clinical management" and "BSC" to be the same and all refer to the "usual care" received by patients. • Tricyclic antidepressants, SSRIs, and SNRIs do not have marketing authorisation for treatment of PND and are all being used as off-label treatment options in a small number of patients. Where used, Biogen considers antidepressant treatment with or without psychological therapies are all part of "BSC" (usual care).	Thank you for your comment. The committee will determine the most relevant comparators. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	yes	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	These treatment options differ from those in the NICE depression in adults (NG222) guidelines for 'more severe' depression. In practice, the use of TCAs is less common and the potential for other antidepressants outside of SSRIs, SNRIs or TCA would be considered eg Mirtazapine. NG222 includes the potential for other antidepressant options following a shared decision making conversation. 'More severe' depression treatments in NG222 include augmentation with additional antidepressants, antipsychotics and potentially ECT – this may all be appropriate treatment for PND if severe enough. See notes above regard other potential psychological options not included. It is worth noting that the comparators selected are from the NICE recommended for 'moderate or severe depression in pregnancy or the postnatal period' – it is likely that treatments would differ between the severity of moderate and severe which may underplay the intervention. For example, CBT along may appropriate for moderate depression but less so in severe. Similarly, interventions during pregnancy are included alongside those post-natally, which may differ in appropriateness – likely given that the intervention is only proposed post-natally. Considering the above, potentially moderate and severe should be separated out, as well as antenatal and postnatal depression.	Thank you for your comment. The comparator list has been updated to include atypical antidepressants and to note the possibility of augmentation. The committee will determine which are the relevant comparators.
Outcomes	Biogen	Biogen consider the outcomes appropriate to capture the key health-related benefits of zuranolone.	Thank you for your comment. No action required.
	NHS England	Yes, but usure if these will capture the soft outcomes such a maternal bonding and impact on perinatal resourcing.	Thank you for your comment. The committee will consider all evidence presented to it, including any on

Section	Consultee/ Commentator	Comments [sic]	Action
			child outcomes. However, note the company's response to a consultation question (below): • 'While Biogen will endeavour to incorporate the impact on the child and partners within the economic model, many of these aspects i.e., longer term outcomes for a child (when they became an adult) and the full impact on partners cannot be fully captured within the QALY calculation.'
	College of Mental Health Pharmacy	No outcomes seemed to be related to that of the baby. It may be hard to define but there is a clear body of evidence showing the impact of maternal mental health conditions and the potential impact of child development and longer term costs. Taking this into account will potentially show clearer benefits to the intervention. Additionally, impact of mother and baby bonding/relationship would be good to include/recognise.	Thank you for your comment. The committee will consider all evidence presented to it, including any on child outcomes. However, note the company's response to a consultation question (below):

Section	Consultee/ Commentator	Comments [sic]	Action
			• 'While Biogen will endeavour to incorporate the impact on the child and partners within the economic model, many of these aspects i.e., longer term outcomes for a child (when they became an adult) and the full impact on partners cannot be fully captured within the QALY calculation.'
Equality	Biogen	None presently.	Thank you for your comment. No action required.
	NHS England	I am not aware of anything within the scope that could exclude achieving equity	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	None identified	Thank you for your comment. No action required.
Other considerations	Biogen	Biogen have no additional items for consideration.	Thank you for your comment. No action required.
	NHS England	The US label for this drug states a single course of 14 days treatment. However there is no reference to whether or not this drug can be…or indeed should be used, for example following "partial response" , or "relapse". My understanding is that there may be up to 30% of women with post natal	Thank you for your comment. The committee will consider repeated use of

Section	Consultee/ Commentator	Comments [sic]	Action
		depression whose symptoms persist beyond one year… therefore the timeline for benefit of this drug should be assessed beyond one year.	zuranolone, and whether a stopping rule is required.
	College of Mental Health Pharmacy	None	Thank you.
Questions for consultation	Biogen	"Would zuranolone be a candidate for managed access?" Comment/response: Biogen are open to discussing options to ensure the timely access to zuranolone for adults with PND. "Do you consider that the use of zuranolone can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits." Comment/response: There is evidence that PND can have an effect on the mother-child relationship and the burden faced by partners: • PND increases the risk of poor mother-child bonding by five-fold and can result in worse outcomes for the child, including delayed cognitive development, lower social engagement at 9-months of age, increase in behavioural problems at 2 years of age.[17] • PND also puts additional strain on relationships with partners and has been associated with decreased marital satisfaction and higher separation and divorce. [18, 19] Partners of women experiencing PND also face higher rates of stress, anxiety, and paternal depression compared to partners of women without PND.[15, 20] While Biogen will endeavour to incorporate the impact on the child and partners within the economic model, many of these aspects i.e., longer term	Thank you for your comment. No action required. Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		outcomes for a child (when they became an adult) and the full impact on partners cannot be fully captured within the QALY calculation.	
	NHS England	Where do you consider zuranolone will fit into the existing care pathway for postnatal depression? Please select from the following, will zuranolone be: A. Prescribed in primary care with routine follow-up in primary care – No unlikely B. Prescribed in secondary care with routine follow-up in primary care - Possible C. Prescribed in secondary care with routine follow-up in secondary care Likely D. Other (please give details) For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Would zuranolone be a candidate for managed access? - Possible but would need advice from NHS Specialised commissioning on this	Thank you for your comment. No action required.
	College of Mental Health Pharmacy	None	Thank you for your comment.
Additional comments on the draft scope	Biogen	The draft scope refers to 'Related NICE Technology Appraisals' and Biogen does not consider the stated related technology appraisals for MDD (esketamine and vortioxetine) are appropriate for consideration within the context of a PND appraisal, considering that pathophysiology of PND and MDD are distinctly different.	Thank you for your comment. References to the MDD appraisals have been removed from the section.