National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nalmefene for reducing alcohol consumption in people with alcohol dependence

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 "For Comparison 3, the ERG ventured that delayed nalmefene is probably a more cost-effective approach than immediate nalmefene for all patients. The rationale for this statement was that with low-intensity PI data from the pivotal trials indicate that approximately 20% of patients had low-risk drinking levels or were abstinent at month 3, a value that would be expected to be higher if the PI used were that recommended in NICE CG115"	The manufacturer would propose deleting this section on the basis that it is appears speculative.	The ERG has not presented any evidence to demonstrate that "delayed" nalmefene is likely to be more cost-effective than "immediate" use of nalmefene. If one takes into account the public health, resource and capacity-saving benefits of early intervention for alcohol dependence, the converse is likely to be true when considering nalmefene for patients in the licensed indication. Moreover, the expectation expressed is not consistent with CG115, which concluded that there was no real difference in efficacy between different types of PI of varying intensity, even when	Not a factual error. The ERG has made it clear that this is its opinion, and provided a rationale for its conclusion. We expect that the manufacturer would present an alternative view directly to the Appraisal Committee who will form their own conclusions

		the intensity varied in duration between 6 hours, 40 minutes and some 12 hours.	

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18 "3) That currently pharmacological intervention would be considered for use in patients with mild alcohol dependence only in those who had not responded to PI or those who have specifically requested a pharmacological intervention (Section 7.16.5 of NICE CG115). The ERG acknowledges that NICE CG115 was written before nalmefene was licensed, but notes that it is a plausible strategy that nalmefene, in those who have not requested a pharmacological intervention, be reserved for those who have not adequately responded to PI. A clinical advisor to the ERG stated that a possible reason as to why PI is recommended first-line in CG115 is that the techniques recommended can change a person's approach to their addiction problem and hence their behavior. PI can teach coping skills which can be called on in the future to help maintain abstinence whereas pharmacological interventions do not change	We would propose amending the paragraph to: (i) Clarify that the CG115 recommendations for pharmacological intervention in mild dependence were based on 'limited evidence', which is the reason why those treatments were positioned after PI when PI alone had not been effective. (ii) Clarify that pharmacological interventions can change behaviour (iii) Clarify that there are no data available allowing a precise assessment of nalmefene as a second line treatment for patients failing psychosocial intervention (P116 of ERG report) given this is a key factor when considering whether this strategy is plausible.	CG115 states "Due to limited literature in this [harmful & mild dependent] population, a meta-analysis of RCTs could not be conducted. […] The Guideline Development Group (GDG) considered that given the limited evidence to support the use of naltrexone to reduce drinking in non-dependence or mild dependence that it should only be used where psychological interventions alone have not been effective. It should be prescribed in conjunction with a psychological intervention." It is also important to note that pharmacological intervention is not given alone, but in conjunction with some form of psychological intervention or PI. The nalmefene SPC requires that continuous psychosocial support is provided alongside nalmefene. In addition, nalmefene is only licensed for patients who continue to drink at high or very high drinking risk levels (DRL) two weeks after an assessment has taken place,	Not a factual error, however text has been amended for clarity. (i)The manufacturer is speculating that the reason for the positioning of pharmacological intervention is simply because there is limited evidence rather than because of a preference for PI as a therapeutic strategy or cost implications. (ii)The text has been amended to clarify that the view of the clinical advisor is that pharmacological interventions would not change behaviour once the intervention is discontinued. The ERG accepts that pharmacological interventions can affect behaviour whilst they are being taken. (iii) The ERG believes that the comments regarding the dearth of data for comparison 3 are stated prominently enough on pages 116, 117 and 118 to not warrant further comment on p18

behaviour.”		where the intervention of brief advice may have been given. It is not obvious why a treatment regimen of nalmefene + PI would not have the potential to change behavior, if PI alone has that potential. Moreover, there is considerable evidence to suggest that pharmacological therapy can also change behaviour. For example, the evidence base for behaviour change with methadone is substantial, with NNTs of only 2-6 for reducing crime, injecting behaviour, street drug use and death. Secondly, NICE TA114 (2007) cites a number of RCTs demonstrating the effectiveness of methadone/buprenorphine in changing drug-taking behaviour in opioid dependence. It is also important to note that CG115 pre-dates the licensing of nalmefene by more than two years and is due for an update. While the manufacturer understands that CG115 is the current basis of reference from an evidential standpoint and a clear indicator of what good clinical practice should look like, we would question whether it is appropriate to position nalmefene, which has a recognised evidence base, within the context of the pre-existing pathway, when the	

		pathway for this particular patient population was based on 'limited evidence' for the pharmacological interventions available at the time and may now have been, at least in part, superseded.	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 30 Finally, the statement of the decision problem proposes that the standard comparators to consider include PI alone or naltrexone in conjunction with PI. Whilst the former comparator was considered in the nalmefene systematic review, it is not clear whether the latter was considered (see Table 2) due to a possible typographical error in Table B2 of the MS (p63). However, the ERG believes that the MS has appropriately considered naltrexone in conjunction with PI as a comparator in the nalmefene systematic review.	The systematic review considered the comparator 'naltrexone in conjunction with PI'. Please refer to Table B23, page 108 of the MS.	Clarification of text.	Not a factual error. The clarification, if required, can be made to the Appraisal Committee.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 34 Country (sites) and population information for the SENSE study is	As these data are now in the public domain, we would propose to remove the turquoise CiC highlighting from this	These data are no longer confidential.	Amendment made

highlighted as commercial in Confidence (CiC) date in Table 4 (Characteristics of included studies).	text, in accordance with the revised MS submitted by the manufacturer on 4th April 2014.		

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 38 "The people included had an average daily alcohol consumption level conferring low risk or higher or ≤ 14 abstinent days in the 4 weeks preceding the screening visit."	As these data are now in the public domain, we would propose to remove the turquoise CiC highlighting from this text, in accordance with the revised MS submitted by the manufacturer on 4th April 2014.	These data are no longer confidential.	Amendment made

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42 Nevertheless, the primary published papers and the MS suggest (p298-301) that no clinically relevant differences in baseline demographic or clinical characteristics were observed across the treatment groups between the ESENSE1 and ESENSE2 trials (total population and licensed population). In the SENSE study, notable differences were only observed between treatment groups of the licensed population	We would propose correcting this statement to read: "…or clinical characteristics were observed across the treatment groups within the ESENSE1 and ESENSE2 trials (total population and licensed population)."	Clarification of text.	We are happy with the original wording which also includes comparison between RCTs rather than just comparator / intervention.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 45 "For some of these outcomes the manufacturer undertook pooled analyses based on individual patient data (measures which included responder analysis, SF-36, EQ-5D and the Drinker Inventory of Consequences total score), whereas for other outcomes data were reported for each individual study. The rationale for the different approaches was not provided."	The manufacturer would propose amending this to read: "Where pooling of data was pre-specified, the manufacturer undertook pooled analyses based on individual patient data (measures which included responder analysis, SF-36, EQ-5D and the Drinker Inventory of Consequences total score). Where pooling was not undertaken, outcomes data were reported for each individual study."	The nalmefene studies were powered for the primary outcomes. The pooling of data for health economic outcomes and the responder analysis (secondary outcomes) was, therefore, done to increase the power. As described in the MS, a number of pooled analyses were pre-specified and these have been reported, wherever possible.	For clarity, the following amendment has been made: "Where pooling of data was pre-specified, the manufacturer undertook pooled analyses based on individual patient data (measures which included responder analysis, SF-36, EQ-5D and the Drinker Inventory of Consequences total score). Where pooling was not undertaken, outcomes data were reported for each individual study. A detailed rationale for the different approaches was not provided in the MS"

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 53 There are some errors in the numbers reported in Table 13 (Treatment-emergent adverse events with an incidence of ≥ 5% in either treatment group: Total population (Data derived from p130 of the MS and clarification	Contrary to the Table 13 presented in the ERG report, for ESENSE1, adverse event figures for decreased appetite, diarrhoea, accidental overdose and fall were not reported. In ESENSE2, the adverse event figures for diarrhoea were 8 (2.3%) in the nalmefene +PI group (n=341) and 17	The amendment is justified to correct errors in the data reported in Table 13.	Factual errors corrected

response to question B19).	(5.0%) in the Placebo + Pi group (n=337). A corrected version of Table 13 is presented below.		

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 62 "The manufacturer conducted a systematic review to identify clinical trials investigating the use of PI in alcohol dependence that were most similar to BRENDA (the PI used in the nalmefene studies). The review updated an existing review of psychosocial comparators that was undertaken to inform NICE CG115,3 within the context of the manufacturer's systematic review. "	The systematic review to identify clinical trials investigating psychosocial interventions was designed to cover or include all of the PI examples listed in the final scope for nalmefene, as well as those PI regimes recommended by NICE CG 115 (namely, cognitive behavioural therapies, behavioural therapies, or social network and environment-based therapies); in addition, to the psychosocial interventions listed in NICE CG115 that were most similar to BRENDA.	This is not an accurate summation of the systematic review.	For clarity, the following amendment has been made: "In the absence of direct head-to-head studies comparing BRENDA with PI (as defined in NICE CG115),[3] the manufacturer investigated whether a network meta-analysis or indirect comparison could be undertaken. As a result, the manufacturer conducted a systematic review to identify clinical trials investigating the use of PI (as listed in the final scope issued by NICE, for nalmefene, in addition to interventions listed in NICE CG115[3] that were most similar to BRENDA) in alcohol dependence."

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 70 "The manufacturer assumed that BRENDA would be performed by GPs on 75% of occasions with the remaining 25% performed at a specialist level. The clinical advisors to the ERG disagreed with this assumption stating that the proportion undertaken in specialist care would be much higher were best practice followed; NICE CG115 states that 'all interventions for people who misuse alcohol should be delivered by appropriately trained and competent staff."	We would propose adding a sentence to this paragraph to clarify that the generalist/tier 2 setting is an appropriate setting for treating patients with mild alcohol dependence.	The SPC/licence requires only that nalmefene be prescribed in conjunction with continuous psychosocial support, which the manufacturer maintains equates to PI of a low intensity similar to BRENDA, and which is not at the level of intensity recommended in CG115. A PI *at this lower level of intensity* is capable of being provided in primary or secondary care, and within the context of a usual medical consultation, in the same way that a clinician might manage any other patient with a long-term medical condition, such as diabetes or hypertension. The regulatory authorities accepted that nalmefene treatment, in conjunction with continuous psychosocial support, could be prescribed by GPs in primary care. The manufacturer readily acknowledges that many, if not all, of the types of PI recommended in NICE CG115 will require the expertise and input of a clinical psychologist or other specialist. However, specialist care is not needed to deliver BRENDA-level interventions. GPs and nurses	Not a factual error.

		already offer brief advice to patients with alcohol-related problems; they are sufficiently-trained, and have the skills base and competence to deliver BRENDA-level interventions in primary care such as extended brief interventions or motivational interviewing. This is also supported in CG115 where it states that extended brief interventions would be an appropriate level of psychological intervention for treating mild dependence in a generalist tier 2 setting (Raistrick 2006, P85 CG115 full).	

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 73 No costs or HRQoL reduction is explicitly associated with adverse events with the manufacturer assuming that costs are negligible and disutility is captured by the EQ-5D estimates in the modified ITT population. However, since both the nalmefene plus PI and PI alone treatments use the same utility values per drinking state it is incorrect that the nalmefene specific adverse events would be appropriately captured, which will be favourable to	Clarification: Both the nalmefene plus PI and PI alone treatments use the same utility values per drinking state for years 2 to 5 of the model. For year one (main treatment period) of the base case, the mean QALY difference between the two treatment strategies was estimated using the area between the curves of pooled adjusted mean utility scores for nalmefene and placebo patients from the trials, at every three months from baseline to		Factual error corrected. A comment was inserted that imputation was not used for missing utility data. A sensitivity analysis has also been conducted to assess the sensitivity of the results to changes in the utility assigned to patients in the two arms. This did not form part of the ERG base case. A change was also made on page

nalmefene.	one year (adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point). This method of applying utilities has the advantage of being able to capture the disutility of adverse events relating to nalmefene.		95 to incorporate this point

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92 The manufacturer states that in 'the pivotal clinical trials, the observed case analysis showed that patients took medication an average of 127 days per annum. With a cost per patient based on nalmefene costing £3.03 per tablet, the average cost of nalmefene would be £385 per year. According to the primary statistical mixed model repeated measures analysis, patients took medication on an average of 56% of days (204 days),' which the ERG has calculated would be a cost of £620 per year for nalmefene.	Clarification: During the nalmefene clinical trials, when the 3 nalmefene trials are pooled together (ESENSE 1, ESENSE 2 and SENSE), nalmefene intake was on 56% of days while patients were active in the trial. This estimate was calculated by dividing the number of days of drug intake per individual patient by the number of days the patient was in the trial (until drop-out or end of study); then an average was calculated for all patients. When drug intake was integrated in the nalmefene cost-effectiveness analysis, this figure was used in order that the cost effectiveness modelling used a methodology where patient drop-out was specifically considered with modeling features accounting for discontinuation. In an economic assessment where drop-outs are not modeled as a specific feature, a way to consider		The text has been amended for clarity

	discontinuation for calculating nalmefene drug cost is by adjusting the drug intake. This is performed by dividing the number of days of nalmefene intake during the nalmefene clinical trials by the full study period (per individual patient and then averaged for all patients – the 3 trials pooled together). This resulted in a nalmefene drug intake for 35% of days over one year (127 days over 365 days). This approach is believed to appropriately calculate the nalmefene drug cost with consideration for all of the components related to the performance of the medicine, including patient discontinuation.		

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 93 However, there appear to be a number of discrepancies between the values reported by the manufacturer and the values reported in the University of Sheffield report. The reasons for the discrepancies are unknown but it is noted that most of the manufacturer's values were unfavourable to nalmefene. The uninflated University of Sheffield values have been detailed in Table 28. These costs are stated to be 'Total cost per person-specific hospitalisation' and thus ongoing	Clarification: Based on Appendix 5 (Morbidity cost to the NHS), Table A5.1 (Morbidity cost data) of the University of Sheffield report, we have divided the 'Total cost per person-specific' by the 'Multiplier', having interpreted that the 'multiplier' was the average number of hospital admission per year per patient.		Factual error corrected The original advice provided by a member of the Sheffield Alcohol Research Group has been retracted. The current advice is that the manufacturer's approach is appropriate. Text both added and deleted at the bottom of p93 and column removed from Table 28. Comments relating to this being an unfavourable assumption to nalmefene have also been removed throughout the

costs, for example for patients who have had a stroke, are not considered. This omission is likely to be unfavourable to nalmefene.			document.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 95 "The area under the curve was estimated at every three months from baseline to one year (adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point). The manufacturer states in response to clarification question C5 that "this method of applying utilities from a clinical trial was informed by NICE CG115 and has the advantage of being able to capture the disutility of adverse events relating to nalmefene."	We would propose amending this section to read as follows: "The area under the curve was estimated at every three months from baseline to one year (adjusted for the baseline utility, and assuming a linear transition between the mean utilities at each time point). The manufacturer states in response to clarification question C5 that "this method of applying utilities from a clinical trial was informed by NICE CG100 and has the advantage of being able to capture the disutility of adverse events relating to nalmefene."	This method of applying utilities from a clinical trial was informed by NICE CG100, not CG115.	Factual error corrected

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 97 "Utility data derived from the STREAM RCT"	We would propose amending this sentence to read: "Utility data derived from the STREAM study"	STREAM (STudy of REal-life mAnageMent of alcohol dependence) is not a Randomised Controlled Trial. A short summary of STREAM study. It is a non-interventional, prospective, longitudinal, multi-	Factual error corrected

		centre study of real-life population characteristics and treatment practices in patients with suspected or diagnosed alcohol dependence in both primary care (GPs, in both UK and Germany) and specialised care (psychiatrists and outpatient alcohol specialists, only in Germany).	

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 106 The rationale for Scenario 8 is unclear, as nalmefene is only indicated to be prescribed in conjunction with continuous PI focused on treatment adherence and reducing alcohol consumption and the forms of PI recommended in NICE CG115 certainly incur costs.	Clarification: Scenario 8, which removed the cost of PI in the compared treatment arms, was aiming to demonstrate that the cost of PI is not a cost that drives the cost-effectiveness results. This means that the inclusion of the same treatment PI cost of any kind, in the compared treatment arm of the model, cannot change the cost-effectiveness conclusion.		Not a factual error. The clarification, if required, can be made to the Appraisal Committee.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 106 “There is a presumed typographical error in Scenario 8 with respect to life years, which the ERG believes should	We would propose correcting this sentence to read: “There is a presumed typographical error in Scenario 8 with respect to life years, which the ERG believes should	Clarification of the text to avoid misinterpretation.	Factual error corrected

be equal to those in Scenario 1."	be equal to those in the base case."		

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 110 "The clinical advisors to the ERG were also concerned that Scenario A could be misinterpreted to suggest that the PI regime recommended in NICE CG115 was not necessary. This potential misinterpretation was supported by a comment from the manufacturer in the clarification response that "This highlights that treatment with nalmefene gives the option not only of adding a pharmacological treatment to psychosocial intervention as first-line treatment (post brief intervention), but also gives the option of providing a psychosocial intervention of a lower intensity - with motivational support that can be given in either primary or secondary care as part of a usual medical consultation." There is no evidence base for this statement.	The manufacturer was not in any way suggesting or proposing that the PI regime recommended in NICE CG115 is unnecessary but, rather, that a treatment regimen of nalmefene + PI in the form of BRENDA is efficacious in a sub-group of patients with mild alcohol dependence who continue to drink at high or very high DRL two weeks after initial assessment. The evidence base for this assertion are the ESENSE1, ESENSE2 and SENSE studies, which in turn informed the nalmefene licence. The SPC/licence requires only that nalmefene be prescribed in conjunction with continuous psychosocial support, which the manufacturer maintains equates to PI of a similar intensity to BRENDA, and which is not at the level of intensity recommended in CG115. A PI *at this level of intensity* is capable of being delivered in primary or secondary care, and within the context of a usual medical consultation, in the same way that a	Clarification of the text to avoid misinterpretation.	Not a factual error. The clarification, if required, can be made to the Appraisal Committee.

	clinician might manage any other patient with a long-term medical condition. The regulatory authorities accepted that nalmefene treatment, in conjunction with continue psychosocial support, could be prescribed in primary care by GPs. The PI regime recommended in CG115 will still be appropriate for many patients and the manufacturer acknowledges that other forms of PI might be more suitable for delivery in a secondary care/specialist setting.		

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 114 "The clinical advisors to the ERG did not agree with the assumption that patients would remain on treatment (regardless of drinking risk level) for the full year. It was believed that GPs would not let patients drink at very-high risk levels for greater than 6 months without recommending intensification of treatment and additional specialist input, and that 3 months might be a more likely cut-off point. This point was discussed within the clarification round (Question A2) with the manufacturer maintaining that the 12 months' duration was appropriate as the patients were initially only mildly	We believe that further clarification of the text is required regarding duration of nalmefene treatment in the context of the treatment pathway in the health economic model.	We believe that further clarification is required regarding duration of nalmefene treatment in the context of the treatment pathway in the health economic model. The manufacturer does not assume that patients would remain on treatment continuously for a 12-month period if no response to treatment were observed during that time. Rather, and as shown in figure 4 of the ERG report (page 21), it is conceivable that a patient would show an initial response to nalmefene treatment, reduce his	Not a factual error. The clarification, if required, can be made to the Appraisal Committee. The ERG comment it is unclear how the statement in the justification for amendment that 'the manufacturer assumes that no patient would be eligible to receive nalmefene treatment for more than 12 months' meshes with the initial model where patients in a medium-risk drinking level continued to receive nalmefene treatment.

dependent with no features of withdrawal. This remains an issue of disagreement, and the manufacturer provides no evidence as to why the patients all meet the criteria for medically assisted withdrawal at 12 months rather than at 6 months or 60 months. This issue will add uncertainty to the cost-effectiveness ratio, although it is not clear whether such changes would be favourable or unfavourable to nalmefene. The ERG comment that it is highly unlikely to change the conclusion that nalmefene in addition to PI is cost-effective in Comparison 1.”		or her DRL, but then discontinue therapy and subsequently relapse back to high or very risk DRL, within a 12-month period. In this scenario, clinical experts advised the manufacturer that a clinician might wish to prescribe a second, or subsequent, course of nalmefene for a patient who had previously responded. It is not correct to say that the manufacturer assumes that all patients meet the criteria for medically-assisted withdrawal at 12 months. As the ERG is aware, however, there are no efficacy or safety data for nalmefene beyond a period of 12 months and the SPC advises caution in using nalmefene for more than 12 months. For these reasons, the manufacturer assumes that no patient would be eligible to receive nalmefene treatment for more than 12 months, at which point they would therefore become eligible for a further assessment (as shown on the right-hand side of Figure 4, top box).	

Appendix – Updated version of Table 13 (see Issue 8)

Table 13: Treatment-emergent adverse events with an incidence of ≥ 5% in either treatment group: Total population (Data derived from p130 of the MS and clarification response to question B19)

Adverse event	ESENSE1		ESENSE2		SENSE		Pooled	
	Nalmefene + PI (n=302)	Placebo + PI (n=296)	Nalmefene + PI (n=341)	Placebo + PI (n=337)	Nalmefene + PI (n=501)	Placebo + PI (n=164)	Nalmefene + PI (n=1144)	Placebo + PI (n=797)
Patients with treatment-emergent adverse events	246 (81.5%)	198 (66.9%)	232 (68.0%)	199 (59.1%)	377 (75.2%)	103 (62.8%)	855 (74.7%)	500 (62.7%)
Nausea	83 (27.5%)	18 (6.1%)	58 (17.0%)	20 (5.9%)	112 (22.4%)	9 (5.5%)	253 (22.1%)	47 (5.9%)
Dizziness	83 (27.5%)	23 (7.8%)	52 (15.2%)	15 (4.5%)	73 (14.6%)	6 (3.7%)	208 (18.2%)	44 (5.5%)
Insomnia	30 (9.9%)	10 (3.4%)	49 (14.4%)	22 (6.5%)	74 (14.8%)	11 (6.7%)	153 (13.4%)	43 (5.4%)
Headache	36 (11.9%)	27 (9.1%)	43 (12.6%)	26 (7.7%)	62 (12.4%)	13 (7.9%)	141 (12.3%)	66 (8.3%)
Nasopharyngitis	34 (11.3%)	37 (12.5%)	19 (5.6%)	17 (5.0%)	54 (10.8%)	19 (11.6%)	107 (9.4%)	73 (9.2%)
Vomiting	24 (7.9%)	8 (2.7%)	19 (5.6%)	8 (2.4%)	57 (11.4%)	2 (1.2%)	100 (8.7%)	18 (2.3%)
Fatigue	53 (17.5%)	25 (8.4%)	NR	NR	27 (5.4%)	3 (1.8%)	95 (8.3%)	37 (4.6%)
Somnolence	NR	NR	NR	NR	42 (8.4%)	8 (4.9%)	59 (5.2%)	23 (2.9%)
Sleep disorder	32 (10.6%)	1 (0.3%)	NR	NR	NR	NR	NR	NR
Hyperhidrosis	16 (5.3%)	5 (1.7%)	NR	NR	NR	NR	NR	NR
Decreased appetite	NR	NR	NR	NR	26 (5.2%) [a]	2 (1.2%) [a]	NR	NR
Diarrhoea	NR	NR	8 (2.3%)	17 (5.0%)	NR	NR	NR	NR
Accidental overdose	NR	NR	NR	NR	9 (1.8%) [a]	9 (5.5%) [a]	NR	NR
Fall	NR	NR	NR	NR	7 (1.4%) [a]	11 (6.7%) [a]	NR	NR

PI, Psychosocial Intervention, NR, not reported
[a] Data from Van den Brink *et al*.[34]