

IQWiG Reports – Commission No. A14-30

**Nalmefene –
Benefit assessment according
to §35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment *Nalmefen – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 November 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DRL	drinking risk level
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HDD	heavy drinking day
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SPC	Summary of Product Characteristics
WHO	World Health Organization

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nalmefene. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 1 September 2014.

Research question

The aim of this report was to assess the added benefit of nalmefene in comparison with the appropriate comparator therapy (ACT) in patients with alcohol dependence who have a high drinking risk level (DRL)⁴, without physical withdrawal symptoms and who do not require immediate detoxification. In accordance with the limitations specified in the approval, nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene should be initiated only in patients who continue to have a high DRL 2 weeks after initial assessment.

For this therapeutic indication, the G-BA specified the following ACT:

- naltrexone to support the reduction of alcoholism, according to the stipulations specified in the limitations of prescription in Appendix III Number 2 of the Pharmaceutical Directive, with psychosocial support according to the approval.

According to the Pharmaceutical Directive, agents for the reduction of alcohol consumption are reimbursable in patients who are to undergo abstinence treatment, but for whom no appropriate therapy options are currently available. These agents can be prescribed for up to 3 months; in justified exceptional cases for another 3 months at the most.

The company concurred with the G-BA’s specification on the ACT.

The present benefit assessment was conducted in comparison with the ACT naltrexone (in each case in conjunction with psychosocial support). The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 12 weeks. Analyses at time points between 12 and 24 weeks were primarily relevant because these reflect the stipulations specified in the Pharmaceutical Directive mentioned above and therefore also the use in patients insured in the statutory health insurance (SHI).

⁴ > 60 g alcohol/day for men and > 40 g alcohol/day for women according to the definition by the World Health Organization (WHO).

Results

Direct comparison

There were no direct comparative studies of nalmefene versus the ACT naltrexone.

Indirect comparison

The company presented an adjusted indirect comparison for the derivation of the added benefit of nalmefene versus naltrexone. The company chose placebo as common comparator. The company included a total of 11 studies for the indirect comparison. The indirect comparison presented by the company was unsuitable to draw conclusions on the added benefit of nalmefene versus naltrexone. This is justified below.

Nalmefene studies

On the nalmefene side, the company included 4 double-blind RCTs. These were the 3 approval studies 12014A, 12013A, and 12023A, as well as study CPH-101-0801. All 4 studies compared nalmefene with placebo with regard to the reduction of alcohol consumption in alcohol-dependent patients for 24 to 52 weeks. Data at 12 weeks were additionally available for all studies. Supportive psychosocial treatment was additionally conducted in all studies. The nalmefene dose used in the 3 approval studies 12014A, 12013A and 12023A was 20 mg/day as needed, which is in compliance with the approval. In the CPH-101-0801 study, however, the nalmefene dose could be adjusted from 20 mg/day to 40 mg/day or to 10 mg/day at the investigator's discretion. Over the entire course of the study, this dose adjustment was performed in at least 33% of the patients. This does not concur with the approval, which does not specify any dose adjustment. Hence at most 67% of the patients were treated in compliance with the approval so that, deviating from the company's approach, the CPH-101-0801 study could not be used for the benefit assessment.

Furthermore, only subpopulations of the nalmefene studies were relevant for the benefit assessment, namely patients with at least high DRL. The company submitted analyses of these subpopulations, which constituted between 28% and 58% of the patients in the 3 approval studies.

Overall, suitable data for an indirect comparison were available for 3 of the 4 studies on nalmefene submitted by the company.

Naltrexone studies

The company included 7 double-blind RCTs on the naltrexone side of the indirect comparison (Anton 2005, Balldin 2003, Heinälä 2001, Morris 2001, O'Malley 2003, O'Malley 2008, Volpicelli 1997). These 7 studies investigated the comparison of naltrexone versus placebo in alcohol-dependent patients with regard to abstinence, prevention of relapse, and reduction of alcohol consumption over 12 to 32 weeks. Supportive concomitant psychosocial treatment was additionally conducted in all naltrexone studies.

However, all 7 studies were unsuitable for answering the present research question for the following reasons:

- In 6 of the 7 studies, patients without high DRL were included. Hence the patients did not concur with the research question.
- In the remaining study Heinälä 2001, the use of naltrexone was not compliant with the approval over the total course of the study, and there were no suitable results for an indirect comparison.

Inclusion criterion abstinent patients

Whereas, according to the research question, from the studies on nalmefene plus placebo those patients were selected for the indirect comparison who continued to consume alcohol on a DRL that was at least high in the period between screening and randomization, this did not apply to the patients in 6 of the 7 studies on naltrexone versus placebo. In contrast to the nalmefene studies, only patients were included who had to be abstinent for several days before the start of the study. The patients in these studies therefore do not correspond to the present research question. Hence at randomization, the study populations (nalmefene versus naltrexone) differed notably with regard to their DRL and cannot be used for the assessment of the added benefit. Under this condition the results of an indirect comparison would also not be meaningfully interpretable with regard to outcomes like change in drinking behaviour because different populations would be compared with each other: alcohol-dependent patients who are already abstinent (naltrexone population) with alcohol-dependent patients with a DRL that is at least high at the start of the study (nalmefene population). Ultimately there are 2 different treatment goals: prevention of relapse in naltrexone patients versus reduction of a current high level of alcohol consumption in nalmefene patients. As a result, there would be opposing trends in drinking behaviour to be expected, which would bias the comparison in favour of nalmefene. Hence the 6 naltrexone studies described were neither relevant for the present research question nor for an indirect comparison with the nalmefene studies included.

Further reasons for exclusion

The study Heinälä 2001 was not relevant because the use of naltrexone was not compliant with the approval. According to the Summary of Product Characteristics (SPC), the recommended dose of naltrexone is one 50 mg tablet once daily. In the study Heinälä 2001, the patients received 50 mg once daily in the first 12-week study phase. In the subsequent 20-week main phase of the study, however, the drug was no longer taken daily, but only as needed. Depending on the study arm, patients were taking between 2.1 and 3.4 tablets weekly on average during this phase. This is less than half of the recommended dose and there is a risk that the effect of naltrexone is underestimated because of this underdosing. Hence only the first 12 weeks of the study would be relevant for this assessment. There were no relevant analyses for this period of time, however.

Summary

There were no direct comparative RCTs of nalmefene versus the ACT.

The adjusted indirect comparison presented by the company was not evaluable because particularly the studies on the naltrexone side were unsuitable to answer the research question. In 6 of 7 naltrexone studies, the patients included were already abstinent and therefore did not correspond to the research question. In the remaining study, naltrexone was not administered in accordance with the approval, or no relevant analyses were available. Overall there were therefore no suitable data for the assessment of the added benefit of nalmefene.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁵

On the basis of the results presented, the extent and probability of the added benefit of the drug nalmefene compared with the ACT is assessed as follows:

Table 2 presents a summary of the extent and probability of the added benefit of nalmefene.

Table 2: Nalmefene – extent and probability of added benefit

Therapeutic indication	ACT^a	Extent and probability of added benefit
Reduction of alcohol consumption in adult patients with alcohol dependence with high DRL	Naltrexone ^b	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: To support the reduction of alcohol consumption, according to the stipulations specified in the limitations of prescription in Appendix III Number 2 of the Pharmaceutical Directive, with psychosocial support according to the approval. ACT: appropriate comparator therapy; DRL: drinking risk level; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

⁵ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of this report was to assess the added benefit of nalmefene in comparison with the ACT in patients with alcohol dependence who have a high DRL⁶, without physical withdrawal symptoms and who do not require immediate detoxification. In accordance with the limitations specified in the approval, nalmefene should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene should be initiated only in patients who continue to have a high DRL 2 weeks after initial assessment.

For this therapeutic indication, the G-BA specified the following ACT:

- naltrexone to support the reduction of alcoholism, according to the stipulations specified in the limitations of prescription in Appendix III Number 2 of the Pharmaceutical Directive, with psychosocial support according to the approval

According to the Pharmaceutical Directive, agents for the reduction of alcohol consumption are reimbursable in patients who are to undergo abstinence treatment, but for whom no appropriate therapy options are currently available. These agents can be prescribed for up to 3 months; in justified exceptional cases for another 3 months at the most.

The company concurred with the G-BA's specification on the ACT.

The present benefit assessment was conducted in comparison with the ACT naltrexone (each in conjunction with psychosocial support). The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 12 weeks. Analyses at time points between 12 and 24 weeks were primarily relevant because these reflect the stipulations specified in the Pharmaceutical Directive mentioned above and therefore also the use in patients insured in the SHL. This deviates from the company's approach, which only considered categories of non-drug concomitant treatment chosen by the company, specified a study duration of 10 to 28 weeks, and limited the study design to double-blind RCTs.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nalmefene (studies completed up to 15 June 2014)
- bibliographical literature search on nalmefene (last search on 15 June 2014)
- search in trial registries for studies on nalmefene (last search on 15 June 2014)
- bibliographical literature search on the ACT (last search on 15 June 2014)

⁶ > 60 g alcohol/day for men and > 40 g alcohol/day for women according to the definition by the WHO.

- search in trial registries for studies on the ACT (last search on 15 June 2014)

To check the completeness of the study pool:

- search in trial registries for studies on nalmefene (last search on 12 September 2014)

No additional relevant study was identified from the check.

The data identified and presented by the company from the steps of information retrieval mentioned were unsuitable for the derivation of conclusions on the added benefit of nalmefene versus the ACT. This is justified below.

Direct comparison

There were no direct comparative studies of nalmefene versus naltrexone. This concurs with the company's assessment.

Indirect comparison

The company presented an adjusted indirect comparison according to Bucher [3] for the derivation of the added benefit of nalmefene versus naltrexone. The company chose placebo as common comparator.

The company included a total of 11 studies for the indirect comparison. The characteristics of these studies and of the interventions used in the studies can be found in Table 8 and Table 9 in Appendix A of the full dossier assessment.

Nalmefene studies

On the nalmefene side, the company included 4 double-blind RCTs. These were the 3 approval studies 12013A [4], 12014A [5], and 12023A [6], as well as study CPH-101-0801 [7]. All 4 studies compared nalmefene with placebo with regard to the reduction of alcohol consumption in alcohol-dependent patients. The studies 12014A, 12023A and CPH-101-0801 had a treatment duration of 24 or 28 weeks, study 12013A had a treatment duration of 52 weeks. The company also presented data at 12 weeks for each nalmefene study to consider the specifications of the limitations of prescription (see Section 2.2). Supportive psychosocial treatment was additionally conducted in all studies. The nalmefene dose used in the 3 approval studies 12014A, 12013A and 12023A was 20 mg/day as needed. "As needed" means that on each day the patient perceives a risk of drinking alcohol, one tablet should be taken, preferably 1 to 2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking the drug, the patient should take one tablet as soon as possible. This concurs with the approved use of nalmefene [8]. In the CPH-101-0801 study, however, the nalmefene dose could be adjusted from 20 mg/day to 40 mg/day or to 10 mg/day at the investigator's discretion. Over the entire course of the study, this dose adjustment was performed in at least 33% of the patients. This does not concur with the approval, which does not specify any dose adjustment. Hence at most 67% of the patients were treated in

compliance with the approval so that, deviating from the company's approach, the CPH-101-0801 study could not be used for the benefit assessment. In principle, the company could have analysed the subpopulation of the patients who were treated in compliance with the approval. It did not present this subpopulation, however.

Drinking risk level

The 3 approval studies of nalmefene included patients diagnosed with alcohol dependence. Furthermore, the studies 12014A and 12023A only included patients with a DRL that was at least medium (alcohol consumption > 20 g/day for women and > 40 g/day for men, according to the WHO [9]). In contrast, there was no criterion on the DRL in the 12013A study, but the limitation that the patients included had to have at least 6 heavy drinking days (HDDs) in the 4 weeks preceding screening. Hence the DRL of the patients included did not correspond to the approval of nalmefene in any of the 3 studies. This approval refers to patients with at least a high DRL (alcohol consumption > 40 g/day for women and > 60 g/day for men) [8]. Only the subpopulations of patients with at least a high DRL of the nalmefene studies were therefore relevant for the benefit assessment. The company submitted analyses of these subpopulations, which constituted between 28% and 58% of the patients in the 3 studies.

Overall, suitable data for an indirect comparison were available for 3 of the 4 studies on nalmefene submitted by the company.

Naltrexone studies

The company included 7 double-blind placebo-controlled RCTs on the naltrexone side of the indirect comparison (Anton 2005 [10], Balldin 2003 [11], Heinälä 2001 [12], Morris 2001 [13], O'Malley 2003 [14], O'Malley 2008 [15], Volpicelli 1997 [16]). The 7 naltrexone studies investigated the comparison of naltrexone versus placebo in alcohol-dependent patients with regard to abstinence, prevention of relapse, and reduction of alcohol consumption over 12 to 32 weeks. Supportive concomitant psychosocial treatment was additionally conducted in all naltrexone studies (for more detailed characteristics of the studies, see Table 8 and Table 9 in Appendix A of the full dossier assessment).

However, all 7 studies were unsuitable for answering the present research question:

- In 6 of the 7 studies, patients without high DRL were included. Hence the patients did not concur with the research question.
- In the remaining study Heinälä 2001, the use of naltrexone was not compliant with the approval over the total course of the study, and there were no suitable results for an indirect comparison.

An overview of the reasons for exclusion on the studies included by the company for the indirect comparison is provided in Table 3.

Table 3: Overview of the reasons for exclusion of the studies – indirect comparison: nalmefene vs. naltrexone

Study	Reasons for exclusion	
	Population	Use not in compliance with the approval
Nalmefene vs. placebo		
12013A		
12014A		
12023A		
CPH-101-0801		●
Naltrexone vs. placebo		
Anton 2005	●	
Ballidin 2003	●	
Heinäälä 2001		●
Morris 2001	●	
O'Malley 2003	●	
O'Malley 2008	●	
Volpicelli 1997	●	

The reasons for exclusion are explained below:

Inclusion criterion abstinent patients

Whereas, according to the research question, from the studies on nalmefene plus placebo those patients were selected for the indirect comparison who continued to consume alcohol on a DRL that was at least high in the period between screening and randomization, this did not apply to the patients in 6 of the 7 studies on naltrexone versus placebo. In contrast to the nalmefene studies, only patients were included who had to be abstinent for several days before the start of the study.

The duration of the patients' abstinence before the start of the study according to the inclusion criteria of the studies was defined differently in the naltrexone studies and ranged from at least 3 to at least 14 consecutive days of abstinence before the start of the study. In some studies, this duration was not to exceed a defined threshold of 28 to 30 days. In Volpicelli 1997, recently completed medical detoxification was required, with the length of abstinent days not exceeding 21 days. Hence the studies did not include patients with a current high DRL, but patients who are already abstinent and for whom the goal is to prevent relapse or repeated high alcohol consumption (see Table 8, Appendix A of the full dossier assessment). This is also reflected in the research questions and primary outcomes. Maintenance and extent of abstinence as well as relapse to heavy alcohol consumption were the primary outcomes in the studies Anton 2005, Morris 2001, O'Malley 2003, O'Malley 2008, and Volpicelli 1997.

Hence the patients in these studies did not concur with the present research question, which investigated patients who currently have a high DRL, and could not be used for the assessment of the added benefit. Hence the study populations (nalmefene versus naltrexone) differed notably with regard to their DRL at randomization. Under this condition the results of an indirect comparison would also not be meaningfully interpretable with regard to outcomes like change in drinking behaviour because different populations would be compared with each other: alcohol-dependent patients who are already abstinent (naltrexone population) with alcohol-dependent patients with a DRL that is at least high at the start of the study (nalmefene population). Ultimately there are 2 different treatment goals: prevention of relapse in naltrexone patients versus reduction of a current high level of alcohol consumption in nalmefene patients. As a result, there would be opposing trends in drinking behaviour to be expected, which would bias the comparison in favour of nalmefene. Hence the 6 naltrexone studies described were neither relevant for the present research question nor for an indirect comparison with the nalmefene studies included.

This deviates from the company's assessment, which regarded all 6 studies as being suitable for the research question. The company neither addressed the deviation of patients from the research question nor the differences between the populations of the nalmefene and the naltrexone studies.

Further reasons for exclusion

In contrast to the other studies on naltrexone, the study Heinälä 2001 included patients who had at least a high DRL at randomization (mean alcohol consumption before the start of the study of 5⁷ alcoholic drinks/day). Hence the investigated population concurs with the present research question. However, this study could also not be used for the indirect comparison because the use of naltrexone was not compliant with the approval. According to the SPC, the recommended dose of naltrexone is one 50 mg tablet once daily [17]. Other dosages or use as needed are not specified. In the study Heinälä 2001, the patients received 50 mg once daily in the first 12-week study phase. In the subsequent 20-week main phase of the study, however, the drug was no longer taken daily, but only as needed. Depending on the study arm, patients were taking between 2.1 and 3.4 tablets weekly on average during this phase. This is less than half of the recommended dose and there is a risk that the effect of naltrexone is underestimated because of this underdosing. Hence only the first 12 weeks of the study would be relevant for this assessment. There were no relevant analyses for this period of time, however.

Summary

There were no direct comparative RCTs of nalmefene versus the ACT.

⁷ At least 5 alcoholic drinks/day correspond to high DRL according to the WHO.

The adjusted indirect comparison presented by the company was not evaluable because particularly the studies on the naltrexone side were unsuitable to answer the research question. In 6 of 7 naltrexone studies, the patients included were already abstinent and therefore did not correspond to the research question. In the remaining study, naltrexone was not administered in accordance with the approval, or no relevant analyses were available. Overall there were therefore no suitable data for the assessment of the added benefit of nalmefene.

2.4 Results on added benefit

There were no suitable data for the assessment of the added benefit of nalmefene. Hence the added benefit of nalmefene versus the ACT is not proven. This result deviates from the company's assessment, which derived an added benefit on the basis of the results of the indirect comparison presented.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of nalmefene in comparison with the ACT is shown in Table 4.

Table 4: Nalmefene – extent and probability of added benefit

Therapeutic indication	ACT ^a	Extent and probability of added benefit
Reduction of alcohol consumption in adult patients with alcohol dependence with high DRL	Naltrexone ^b	Added benefit not proven
<p>a: Presentation of the ACT specified by the G-BA.</p> <p>b: To support the reduction of alcohol consumption, according to the stipulations specified in the limitations of prescription in Appendix III Number 2 of the Pharmaceutical Directive, with psychosocial support according to the approval.</p> <p>ACT: appropriate comparator therapy; DRL: drinking risk level; G-BA: Federal Joint Committee</p>		

This assessment deviates from that of the company, which derived proof of considerable added benefit of nalmefene in comparison with naltrexone.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as no studies were included in the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

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