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Naldemedine (opioid-induced constipation) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
SPC	Summary of Product Characteristics

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 naldemedine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 May 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of naldemedine in comparison with the appropriate comparator therapy (ACT) in adult patients with opioid-induced constipation who received prior laxative treatment.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of naldemedine

Research question	Therapeutic indication	ACT[a]
1	Adult patients with opioid-induced constipation and prior laxative treatment[b]	Another non-prescription laxative (in accordance with the Medicinal Products Directive (AM-RL Annex I, No. 1) [1]) or a prescribable medical device for treating constipation (in accordance with AM-RL Section J and Annex V [2])
2	Adult patients with opioid-induced constipation who received prior laxative treatment and are no longer suited for a non-prescription laxative or prescribable medical device for treating constipation.	Methylnaltrexone, prucalopride, or naloxegol

a. Presented is the respective ACT specified by the G-BA.
b. On the basis of the specification of the ACT, these patients are suited for another non-prescription laxative or prescribable medical device for treating constipation.

ACT: appropriate comparator therapy; AM-RL: Medicinal Products Directive; G-BA: Federal Joint Committee

To simplify and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients who are suited for another laxative
- Research question 2: Patients who are no longer suited for another laxative

Departing from the G-BA's specification of the ACT, the company did not categorize the population into patients who are suited for another laxative versus those who are not any longer. Instead, in Module 3 A of the dossier, the company defines naloxegol or methylnaltrexone as the comparator therapy. It argues that conventional laxatives are indicated merely as first-line therapy and that naloxegol and methylnaltrexone, as representatives of peripherally acting μ-opioid receptor antagonists (PAMORAs), are therefore ACTs for all patients with the therapeutic indication.

Deviating from the company's approach, the present assessment was conducted using the ACT specified by the G-BA and the associated categorization of patient groups. Various current national and international guidelines support the G-BA's specification on key aspects. For instance, the current guideline issued by the Association of the Scientific Medical Societies in Germany (AWMF) on palliative care of patients with incurable cancer recommends the use of PAMORAs as third-line treatment after various laxatives have been tried. All things considered, the guidelines do not provide sufficient justification for deviating from the specification of the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Results

In agreement with the company's findings, the check of completeness of the study pool did not identify any relevant study for the direct comparison of naldemedine with the ACT.

Evidence presented by the company

Since no directly comparative data are available, the company additionally searched for studies to be used in an adjusted indirect comparison of naldemedine versus naloxegol via the common comparator of standard therapy. For this purpose, it identified 1 study on each side: COMPOSE 3 on the naldemedine side and KODIAC-08 on the naloxegol side. The choice of naloxegol as a comparator therapy means that the data submitted by the company are potentially relevant only for the assessment of research question 2. The company does not provide any data for assessing research question 1.

COMPOSE 3 is an RCT comparing naldemedine with placebo. The study included 1246 patients. The patient population is therapeutically indicated for naldemedine, except that only patients with non-cancer pain were included. Naldemedine treatment was administered in accordance with the Summary of Product Characteristics (SPC). In both the naldemedine arm and the comparator arm, patients who routinely or regularly took laxatives at baseline were to continue this stable laxative therapy, preferably for the entire study duration. Patients who were not on stable laxative therapy were allowed to use emergency medication as needed. In both arms, taking this emergency medication in addition to stable laxative therapy or naldemedine

treatment was allowed. Treatment with the study drug was continued despite the use of an emergency drug. The primary outcome of the study was adverse events.

KODIAC-08 is an RCT comparing naloxegol with standard therapy. The study included 844 adult patients with opioid-induced constipation who received opioid therapy of non-cancer pain. Prior laxative treatment was allowed, but was not a prerequisite for patient inclusion in the study. During a 2-week confirmation phase before randomization, patients had to discontinue all laxatives. Naloxegol treatment was administered in accordance with the SPC. In the comparator arm, patients received standard therapy with selected laxatives upon the investigator's discretion. The primary outcomes of the study were various adverse events.

Unsuitability of the data presented by the company for the benefit assessment

For research question 2, an adjusted indirect comparison on the basis of the COMPOSE 3 and KODIAC-08 studies is unsuitable for drawing conclusions on any added benefit of naldemedine due to the following reasons:

- The patient population of the KODIAC-08 study does not fully reflect the approved therapeutic indication of naldemedine since prior laxative treatment was not an inclusion criterion.
- In both COMPOSE 3 and KODIAC-08, the percentages of patients who are no longer suited for another laxative (research question 2) are unknown. Hence, at best, subpopulations of each of the studies are relevant for research question 2.
- The common comparator is insufficiently similar in the two studies since KODIAC-08 used newly defined laxative therapy as the standard therapy at the start of the study, whereas COMPOSE 3 did not.
- Weighing benefit and harm on the basis of the indirect comparison is impossible since KODIAC-08 is a study on long-term safety and provides results exclusively on AE outcomes.

No suitable data are available for assessing an added benefit of naldemedine in comparison with the ACT in patients with opioid-induced constipation who received prior laxative therapy. Consequently, there is no hint of an added benefit of naldemedine in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of naldemedine.

Table 3: Naldemedine – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with opioid-induced constipation and prior laxative treatment[b]	Another non-prescription laxative (in accordance with the Medicinal Products Directive (AM-RL Annex 1, No. 1) [1]) or a prescribable medical device for treating constipation (in accordance with AM-RL Section J and Annex V [2])	Added benefit not proven
2	Adult patients with opioid-induced constipation who received prior laxative treatment and are no longer suited for a non-prescription laxative or prescribable medical device for treating constipation.	Methylnaltrexone, prucalopride, or naloxegol	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. On the basis of the specification of the ACT, these patients are suited for another non-prescription laxative or prescribable medical device for treating constipation.

ACT: appropriate comparator therapy; AM-RL: Medicinal Products Directive; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of naldemedine in comparison with the ACT in adult patients with opioid-induced constipation who received prior laxative treatment.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

[3] 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). 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, added benefit not proven, or less benefit). For further details see [3,4].

Table 4: Research questions of the benefit assessment of naldemedine

Research question	Therapeutic indication	ACT[a]
1	Adult patients with opioid-induced constipation and prior laxative treatment[b]	Another non-prescription laxative (in accordance with the Medicinal Products Directive (AM-RL Annex I, No. 1) [1]) or a prescribable medical device for treating constipation (in accordance with AM-RL Section J and Annex V [2])
2	Adult patients with opioid-induced constipation who received prior laxative treatment and are no longer suited for a non-prescription laxative or prescribable medical device for treating constipation.	Methylnaltrexone, prucalopride, or naloxegol

a. Presented is the respective ACT specified by the G-BA.
b. On the basis of the specification of the ACT, these patients are suited for another non-prescription laxative or prescribable medical device for treating constipation.

ACT: appropriate comparator therapy; AM-RL: Medicinal Products Directive; G-BA: Federal Joint Committee

To simplify and improve readability, the running text of this benefit assessment uses the following designations for the research questions:

- Research question 1: Patients who are suited for another laxative
- Research question 2: Patients who are no longer suited for another laxative

In a departure from the ACT specified by the G-BA, the company did not categorize the population into patients who are suited for another laxative versus those who are not any longer. Instead, in Module 3 A of the dossier, the company defines naloxegol or methylnaltrexone as the comparator therapy. It argues that conventional laxatives are indicated merely as first-line therapy and that naloxegol and methylnaltrexone, as representatives of peripherally acting μ-opioid receptor antagonists (PAMORAs), are therefore an ACT for all patients with the therapeutic indication.

Deviating from the company's approach, the present assessment was conducted in comparison with the ACT specified by the G-BA and using the associated categorization of patient groups. Various current national and international guidelines support the G-BA's specification on key aspects [5-10]. For instance, the current AWMF guideline on palliative care of patients with incurable cancer recommends the use of PAMORAs as third-line treatment after various laxatives have been tried [6]. All things considered, the guidelines do not provide sufficient justification for deviating from the specification of the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on naldemedine (as of 16 March 2020)
- Bibliographic literature search on naldemedine (most recent search on 16 March 2020)
- Search in trial registries / study results databases on naldemedine (most recent search on 16 March 2020)
- Search on the G-BA website on naldemedine (most recent search on 16 March 2020)
- Bibliographic literature search on the ACT (most recent search on 16 March 2020)
- Search in trial registries or results databases on the ACT (most recent search on 16 March 2020)
- Search on the G-BA website on the ACT (most recent search on 16 March 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on naldemedine (most recent search on 18 May 2020)

In agreement with the company, the check of completeness of the study pool revealed no study for the direct comparison of naldemedine with the ACT.

In its inclusion criteria, the company used a minimum study duration of 24 weeks. For studies on opioid-induced constipation in patients with chronic non-cancer pain receiving opioid therapy, this duration is appropriate. Moreover, the check for completeness of the study pool did not reveal any shorter direct comparative studies on patients without chronic pain who also fall within the approved therapeutic indication of naldemedine (e.g. opioid-induced constipation in patients with cancer pain receiving opioid therapy).

Since no directly comparative data are available, the company additionally searched for studies to be used in an adjusted indirect comparison of naldemedine versus naloxegol via the common comparator of standard therapy. For this purpose, the company found 1 study each for naldemedine and naloxegol. However, the adjusted indirect comparison presented by the company is unsuitable for drawing conclusions on any added benefit of naldemedine in comparison with the ACT. The reasons are explained below.

Evidence presented by the company

For its adjusted indirect comparison, the company found the COMPOSE 3 study [11-16], which compares naldemedine with placebo, and the KODIAC-08 study [17-20], which compares naloxegol with standard therapy. Due to the choice of naloxegol as the comparator therapy, the data submitted by the company are potentially relevant for the assessment of research question 2

only (see Section 2.2). The company does not provide any data for assessing research question 1. However, an adjusted indirect comparison on the basis of these 2 studies is unsuitable for drawing conclusions on any added benefit of naldemedine regarding research question 2:

- The patient population of the KODIAC-08 study does not fully reflect the approved therapeutic indication of naldemedine since prior laxative treatment was not an inclusion criterion.
- In both COMPOSE 3 and KODIAC-08, the percentages of patients who are no longer suited for another laxative (research question 2) are unknown. Hence, at best, subpopulations of each of the studies are relevant for research question 2.
- The common comparator is insufficiently similar in the two studies since KODIAC-08 used newly defined laxative therapy as the standard therapy at the start of the study, whereas COMPOSE 3 did not.
- Weighing benefit and harm on the basis of the indirect comparison is impossible since KODIAC-08 is a study on long-term safety and provides results exclusively on AE outcomes.

Both the studies and the unsuitability of the indirect comparison for the assessment of benefit are described in more detail below. Further information on study and intervention characteristics of the COMPOSE 3 and KODIAC-08 studies are presented in tabular form in Appendix A of the full report.

COMPOSE 3 study on naldemedine

The COMPOSE 3 study is a double-blind, randomized, multicentre study comparing naldemedine with placebo. The study included adult patients with opioid-induced constipation receiving opioid treatment for chronic non-cancer pain. Patients had to have received prior treatment with at least 1 laxative.

Worldwide, a total of 1246 patients were allocated in a 1:1 ratio to treatment with naldemedine (N = 623) or placebo (N = 623). Patients received 1 tablet daily of 200 µg naldemedine or placebo to be taken at any time of day. Hence, the study treatment corresponds to the specifications of the naldemedine SPC [21]. In both the naldemedine arm and the comparator arm, patients who routinely or regularly took laxatives at baseline were to continue this stable laxative therapy, preferably for the entire study duration. Dose adjustments (increases or decreases) during the treatment phase were allowed. Patients who were not on stable laxative therapy were allowed to use emergency medication as needed. In both arms, taking this emergency medication in addition to stable laxative therapy or naldemedine treatment was allowed. Drug intake had to be documented, and treatment with the study drug was continued even when using an emergency drug.

After a 2-to-4-week screening period, patients were treated for 52 weeks and followed up for 2 weeks.

The primary outcome of the study was adverse events. Patient-relevant secondary outcomes were further outcomes from the adverse events category as well as outcomes from the categories of health-related quality of life and symptoms.

KODIAC-08 study on naloxegol

KODIAC-08 is an open-label, randomized, multicentric study comparing naloxegol with standard therapy. The study included adult patients with opioid-induced constipation receiving opioid therapy for non-cancer pain. Prior laxative treatment was allowed, but it was not a prerequisite for patient inclusion in the study.

A total of 844 patients were allocated in a 2:1 ratio to treatment with naloxegol (N = 563) or standard therapy (N = 281). In a prior 2-week phase, patients had to discontinue all laxatives in order to confirm the diagnosis of opioid-induced constipation (confirmation phase). Subsequently, patients in the naloxegol arm received 25 mg naloxegol daily. Concomitant laxative treatment was disallowed in the naloxegol arm. Hence, the study treatment was in accordance with the naloxegol SPC [22]. Patients in the comparator arm received standard therapy with selected laxatives upon the investigator's discretion. They could be either new laxatives or laxatives already taken before the study.

After a 2-week screening period, patients were treated for 52 weeks and followed up for 2 weeks.

The primary outcomes of the study were various adverse events. Patient-relevant secondary outcomes were further outcomes from the adverse events category.

Unsuitability of the data presented by the company for the benefit assessment

Patient population of the KODIAC-08 study only partially corresponds to the research questions of the benefit assessment

The population investigated in the COMPOSE 3 study represents a subpopulation for the therapeutic indication of naldemedine and hence the research questions of the present dossier assessment. The study included adult patients with opioid-induced constipation who received prior therapy with at least 1 laxative. While the COMPOSE 3 study provides results on the opioid therapy of non-cancer pain, the research questions of the dossier assessment also include cancer pain. The KODIAC-08 study included adult patients with opioid-induced constipation receiving opioid therapy of non-cancer pain. The KODIAC-08 study allowed prior laxative treatment, but, unlike the COMPOSE 3 study, it did not require it. The presented data show that in the KODIAC-08 study, only about two thirds of patients received prior laxative therapy. However, these data apply only to the 2 weeks prior to screening. Hence, only a subpopulation of unknown size in the KODIAC-08 study fits the approved therapeutic indication of naldemedine and therefore the research questions of the present dossier assessment.

Unknown percentage of patients relevant for research question 2

Naloxegol is an ACT option only for patients who are no longer suited for another laxative (research question 2). However, since the company departed from the ACT specified by the G-BA by not distinguishing between the 2 research questions, it did not specify how many, if any, patients in either study (COMPOSE 3 and KODIAC-08) can be used to answer research question 2. The study-related data found in Module 4 do not provide this information either.

For instance, laxative-refractory patients could be allocated to research question 2. As defined in guidelines issued by the European Medicines Agency and American Gastroenterological Association, for instance, these patients insufficiently responded to at least 2 different laxatives [7,8].

According to the inclusion criteria of the COMPOSE 3 study, all patients had received prior treatment with at least 1 laxative. In its dossier, the company also reports that about half of all patients had received stable laxative therapy within the 28 days before screening until the last dose of the study drug of the COMPOSE 3 study. However, these data do not indicate whether these patients are suited for another laxative therapy. This equally applies to patients who did not receive stable laxative therapy at study start. There are no further data on COMPOSE 3 and no data on KODIAC-08 which would allow estimating how many patients, if any, can be allocated to research question 2.

In consideration of the above, at best, COMPOSE 3 and KODIAC-08 subpopulations of an unknown size would therefore be relevant for research question 2.

The data presented by the company on the total study populations of COMPOSE 3 and KODIAC-08 are therefore unsuitable for the benefit assessment of naldemedine in the context of research question 2. However, even if suitable subpopulations could be operationalized from the two studies, an adjusted indirect comparison would be inappropriate on the basis of the two arguments listed below.

Insufficiently similar common comparator of the two studies

The COMPOSE 3 study is placebo controlled. Both study arms allow standard treatment with laxatives only in the form of concomitant treatment consisting of continuation of insufficient laxative therapy which existed at baseline. The treatment was not reviewed and optimized by the investigator at the start of the study. About half of all patients received this type of concomitant treatment for the entire treatment duration.

The KODIAC-08 study, in contrast, compares naloxegol with standard therapy. Patients taking laxatives at study start were to discontinue them during the confirmation phase. After randomization, about 80% of patients in the comparator arm received laxative therapy selected by the investigator; this therapy could generally also include laxatives which were new to the patient. Unlike patients in the COMPOSE 3 study, patients in the KODIAC-08 study therefore received standard therapy which was newly defined by the investigator at study start.

The difference in laxative therapies used in the two comparator arms of the studies renders the common comparator insufficiently similar. For this reason, once again, the prerequisites of an adjusted indirect comparison are not met.

No weighing of benefit and harm possible

KODIAC-08 is a study assessing the long-term safety of naloxegol. It therefore primarily investigated outcomes from the adverse events category. Thus, the company conducted the indirect comparison exclusively on the basis of AE outcomes. The symptoms of opioid-induced constipation (particularly the intended symptom improvement) were not recorded and cannot be derived from the AE outcomes. Therefore, at best, data on AE outcomes would be available for the indirect comparison, thus rending it impossible to weigh benefit and harm.

All things considered, contrary to the company's assessment, the presented adjusted indirect comparison is unsuitable for assessing an added benefit of naldemedine over the ACT.

2.4 Results on added benefit

No suitable data are available for assessing an added benefit of naldemedine in comparison with the ACT in patients with opioid-induced constipation who received prior laxative therapy. Consequently, there is no hint of an added benefit of naldemedine in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the result of the benefit assessment of naldemedine in comparison with the ACT.

Table 5: Naldemedine – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with opioid-induced constipation and prior laxative treatment[b]	Another non-prescription laxative (in accordance with the Medicinal Products Directive (AM-RL Annex I, No. 1) [1]) or a prescribable medical device for treating constipation (in accordance with AM-RL Section J and Annex V [2])	Added benefit not proven
2	Adult patients with opioid-induced constipation who received prior laxative treatment and are no longer suited for a non-prescription laxative or prescribable medical device for treating constipation.	Methylnaltrexone, prucalopride, or naloxegol	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. On the basis of the specification of the ACT, these patients are suited for another non-prescription laxative or prescribable medical device for treating constipation.

ACT: appropriate comparator therapy; AM-RL: Medicinal Products Directive; G-BA: Federal Joint Committee

The above-described assessment departs from that of the company, which derives a hint of at least minor added benefit for the entire population on the basis of the indirect comparison of the COMPOSE 3 and KODIAC-08 studies.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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