Gadopiclenol (contrast-enhanced magnetic resonance imaging)

Benefit assessment according to §35a SGB V[1] contrast-enhanced magnetic resonance imaging

EXTRACT

Project: A24-37 Version: 1.0 Status: 27 Jun 2024 DOI: 10.60584/A24-37_en

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Gadopiclenol (kontrastverstärkte Magnetresonanztomografie) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Gadopiclenol (contrast-enhanced magnetic resonance imaging) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

02 April 2024

Internal Project No.

A24-37

DOI-URL

https://doi.org/10.60584/A24-37_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Udo Ehrmann.

IQWiG thanks the respondent and Bundesverband Prostatakrebs Selbsthilfe for participating in the written exchange and for their support. The respondent and Bundesverband Prostatakrebs Selbsthilfe were not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Anja Reinartz
- Dorothee Ehlert
- Petra Kohlepp
- Mattea Patt
- Daniela Preukschat
- Claudia Selbach
- Dorothea Sow
- Pamela Wronski

Keywords

Gadopiclenol, Magnetic Resonance Imaging, Child, Adolescent, Adult, Benefit Assessment

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BW	body weight
CNS	central nervous system
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug gadopiclenol. 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 02 April 2024.

Research question

Aim of the present report is the assessment of the added benefit of gadopiclenol in comparison with the appropriate comparator therapy (ACT) in patients aged 2 years and older, for whom contrast-enhanced magnetic resonance imaging (MRI) is indicated to obtain diagnostic information, in order to better recognize and visualize pathologies with a disrupted blood-brain barrier and/or vascular anomalies in the following areas: brain, spine and associated tissues of the central nervous system (CNS) as well as liver, kidneys, pancreas, breast, lung, prostate and musculoskeletal system.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of gadopiclenol

Therapeutic indication	**ACT**[a, b]
Adults and children from 2 years of age for contrast-enhanced MRI in order to better recognize and visualize pathologies with a disrupted blood-brain barrier and/or vascular anomalies in the following areas: ▪ the brain, spine, and associated tissues of the CNS ▪ the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system It should be used only when diagnostic information is essential and not obtainable with unenhanced MRI[b]	Gadoteric acid or gadobutrol or gadoteridol
a. Presented is the ACT specified by the G-BA. b. The G-BA points out that the benefit assessment procedure according to Section 35a SGB V has only been opened for those sub-areas of the therapeutic indication for which MRI is included in the EBM as a billable service at the relevant time point according to Chapter 5, Section 8 Rules of Procedure. This also applies to the drugs of the ACT. The G-BA points out that it must be ensured that the diagnostic quality and the quality of the imaging in both study arms are sufficiently comparable within the framework of a clinical study and that this must be presented in the dossier. CNS: central nervous system; G-BA: Joint Federal Committee; MRT: Magnetic Resonance Imaging; SGB: German Social Code Book; UVS: Uniform Value Scale; VerfO: rules of procedure	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) on the

diagnostic-therapeutic chain are used to derive the added benefit. Only in these studies can the benefit or harm of the new diagnostic agent shown by the subsequent therapeutic consequences/follow-up treatments (i.e. indirectly) be investigated with regard to patient-relevant outcomes.

Based on the information available, it is assumed that the new diagnostic agent will replace the old one in this research question without changing the treatment decision. The new diagnostic agent should therefore identify or exclude the same patients as the old one and have direct patient-relevant advantages, i.e. be less burdensome, for example. In this constellation, RCTs on direct patient-relevant effects alone can also be considered in combination with studies that address a concordance question. The prerequisite for the (possibly also sole) consideration of studies on a concordance question requires sufficient certainty that the new diagnostic agent provides direct patient-relevant advantages. The company did not address a concordance question explicitly.

Results

The check of the information retrieval did not identify any RCT on the diagnostic-therapeutic chain. The company identified the studies PICTURE and PROMISE, but only presents these two studies in Module 4 A as supplementary information with the justification "missing patient-relevant outcomes". Although the RCTs PICTURE and PROMISE are basically suitable for providing results on both the direct advantages of gadopiclenol compared to gadobutrol and the results on the concordance, overall the necessary requirements for the consideration of a concordance question are not met. The company did not consider the possibility of a concordance question in its dossier and accordingly did not conduct any information retrieval that would be suitable to ensure that all studies for answering a concordance question are fully identified. Whether other studies are available that are suitable for a concordance question was not examined.

The studies PICTURE and PROMISE presented as supplementary information by the company

The studies PICTURE and PROMISE have an almost identical design and are described together below. Both studies are blinded RCTs in a cross-over design comparing gadopiclenol with gadobutrol. The PICTURE study included adult patients with known lesion(s) or highly suspected lesion(s) in the CNS with a disrupted blood-brain barrier in the focal area. The PROMISE study included adult patients with known abnormality(ies) or lesion(s) or suspected contrast-enhanced abnormality(ies) or lesions in at least one of the following body regions: Head and neck, thorax (including chest), abdomen (including liver, pancreas and kidneys), pelvis (including uterus, ovaries and prostate) and musculoskeletal regions (including extremities). In both studies, the assessment of the lesion(s) was based on the results of previous imaging procedures such as computed tomography or MRI within 12 months prior

to study inclusion. Patients had to be members of a national health insurance fund and a contrast-enhanced MRI for the corresponding body region had to be planned for clinical reasons.

The studies PICTURE and PROMISE included a total of 256 or 304 patients who were randomly assigned in a 1:1 ratio to two alternating treatment arms. They either received gadopiclenol as the first contrast agent and gadobutrol for the subsequent MRI, or the treatment sequence was reversed. A so-called safety follow-up was carried out at a one-day interval to record short-term adverse events (AEs). The second MRI visit took place 2 to 14 days after the first MRI visit.

The primary outcome of each study was the visualization of the lesions with regard to the assessment of the demarcation of the margin, the internal morphology and the degree of contrast enhancement. Side effects were recorded as patient-relevant secondary outcomes. In addition, the influence of contrast-enhanced MRI compared to native MRI on the treatment plan (surgery, biopsy, chemotherapy, radiotherapy, other treatment) of the patients was investigated as a secondary outcome.

Recording of side effects in the studies PICTURE and PROMISE

As for all other gadolinium-containing contrast agents, various specific side effects such as adverse reactions of the immediate type, nephrogenic systemic fibrosis and gadolinium deposits in the CNS and other body regions have been described for gadopiclenol. Only short-term AEs can be recorded due to the study design of the studies PICTURE and PROMISE. Long-term AEs, which may occur months or years after application or after repeated administration of the contrast agent, are not recorded due to the short follow-up period of a maximum of 14 days. Irrespective of this, due to the cross-over design, it is not possible to clearly assign AEs to the intervention or comparator therapy after the 2nd administration of contrast medium.

Studies are not suitable for mapping the diagnostic-therapeutic chain

Gadopiclenol is an approved drug used as a diagnostic agent. As a rule, a distinction must be made between direct effects of diagnostic interventions on patient-relevant outcomes in the benefit assessment of diagnostic agents, i.e. those caused by the diagnostic intervention itself, and indirect effects, i.e. those caused by the subsequent therapeutic consequences / follow-up treatments. Only in studies on the diagnostic-therapeutic chain can the benefit or harm caused by the subsequent therapeutic consequences/subsequent treatments be investigated with regard to patient-relevant outcomes. However, due to the study design, the studies PICTURE and PROMISE are not suitable for depicting the diagnostic-therapeutic chain with gadopiclenol in comparison to the diagnostic-therapeutic chain with gadobutrol.

Requirements for concordance question also not met

Taking into account the information provided by the company, the approval of gadopiclenol and the guidelines on the use of gadolinium-containing contrast agents for MRI, it can be assumed that gadopiclenol as a new contrast agent is merely intended to replace the established contrast agents specified in the ACT, without gadopiclenol as a new diagnostic agent identifying or excluding additional or different patients. If the therapeutic consequences resulting from the use of gadopiclenol did not differ significantly from those of the established contrast agent (concordance), and if it were also shown or sufficiently certain that gadopiclenol had direct patient-relevant advantages over the established contrast agent, it would not be necessary to investigate the entire diagnostic-therapeutic chain. If these conditions are met, the studies PICTURE and PROMISE could in principle be suitable for answering a concordance question.

Direct benefits of gadopiclenol unclear

Based on the available data, the direct benefits of gadopiclenol are unclear. On the one hand, the studies PICTURE and PROMISE showed no advantage of gadopiclenol over gadobutrol in short-term AEs. On the other hand, the study design does not allow conclusions about the long-term AEs that can be directly attributed to gadopiclenol or gadobutrol. Moreover, the gadolinium-specific AE of nephrogenic systemic fibrosis occurs very rarely and may occur as late as years after application. Furthermore, the clinical significance or the direct patient-relevant effects and the extent of gadolinium deposits in the body are unclear. In principle, gadopiclenol and the macrocyclic drugs of the ACT have a low risk regarding these deposits and nephrogenic systemic fibrosis anyway and are predominantly excreted unchanged. The company's argument that the benefit can be derived solely based on the lower dose of gadopiclenol is therefore not sufficiently certain. In summary, the available data did not show the direct patient-relevant benefit of gadopiclenol (fewer AEs). This does not fulfil the prerequisite that data on the concordance of the two contrast agents (gadopiclenol vs. gadobutrol) can be used. If the direct patient-relevant advantage was proven, the sufficient concordance of the two diagnostic agents could be demonstrated in a concordance study and would be sufficient to answer the research question. Irrespective of the missing prerequisite, the company does not sufficiently prepare the data to answer the concordance question. The data presented by the company on the "non-inferiority of diagnostic performance" (company's term) are not suitable to answer the concordance question.

Summary

The studies PICTURE and PROMISE presented by the company as supplementary information are not suitable for depicting the diagnostic-therapeutic chain due to the study design and thus do not allow conclusions on benefit or harm based on patient-relevant outcomes. The direct patient-relevant advantages of gadopiclenol compared to gadobutrol and the

concordance with regard to a treatment decision following the diagnosis were not shown. In summary, no suitable data are available to answer the present research question.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of gadopiclenol 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 shows a summary of probability and extent of the added benefit of gadopiclenol.

Table 3: Gadopiclenol – probability and extent of added benefit

Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
Adults and children from 2 years of age for contrast-enhanced MRI in order to better recognize and visualize pathologies with a disrupted blood-brain barrier and/or vascular anomalies in the following areas: ▪ the brain, spine, and associated tissues of the CNS ▪ the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system It should be used only when diagnostic information is essential and not obtainable with unenhanced MRI[b]	Gadoteric acid or gadobutrol or gadoteridol	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. The G-BA points out that the benefit assessment procedure according to Section 35a SGB V has only been opened for those sub-areas of the therapeutic indication for which MRI is included in the EBM as a billable service at the relevant time point according to Chapter 5, Section 8 Rules of Procedure. This also applies to the drugs of the ACT. The G-BA points out that it must be ensured that the diagnostic quality and the quality of the imaging in both study arms are sufficiently comparable within the framework of a clinical study and that this must be presented in the dossier. CNS: central nervous system; G-BA: Joint Federal Committee; MRT: Magnetic Resonance Imaging; SGB: German Social Code Book; UVS: Uniform Value Scale; VerfO: rules of procedure		

The G-BA decides on the added benefit.

[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 [1,2].

I 2 Research question

The aim of the present report is the assessment of the added benefit of gadopiclenol in comparison with the ACT in patients for patients from 2 years of age. Gadopiclenol is a diagnostic agent that is used for contrast-enhanced MRI in order to better recognize and visualize pathologies with a disruption of the blood-brain barrier and/or vascular anomalies in the following areas: brain, spine and associated tissues of the CNS as well as liver, kidney, pancreas, breast, lung, prostate and musculoskeletal system.

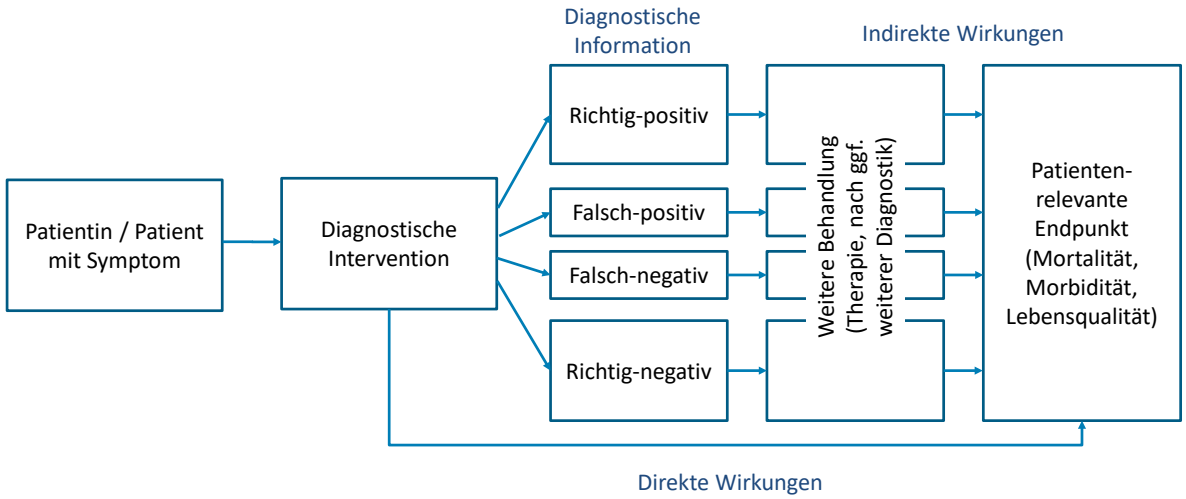
The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of gadopiclenol

Therapeutic indication	**ACT**[a, b]
Adults and children from 2 years of age for contrast-enhanced MRI in order to better recognize and visualize pathologies with a disrupted blood-brain barrier and/or vascular anomalies in the following areas: ▪ the brain, spine, and associated tissues of the CNS ▪ the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system It should be used only when diagnostic information is essential and not obtainable with unenhanced MRI[b]	Gadoteric acid or gadobutrol or gadoteridol
a. Presented is the ACT specified by the G-BA. b. The G-BA points out that the benefit assessment procedure according to Section 35a SGB V has only been opened for those sub-areas of the therapeutic indication for which MRI is included in the EBM as a billable service at the relevant time point according to Chapter 5, Section 8 Rules of Procedure. This also applies to the drugs of the ACT. The G-BA points out that it must be ensured that the diagnostic quality and the quality of the imaging in both study arms are sufficiently comparable within the framework of a clinical study and that this must be presented in the dossier. CNS: central nervous system; G-BA: Joint Federal Committee; MRT: Magnetic Resonance Imaging; SGB: German Social Code Book; UVS: Uniform Value Scale; VerfO: rules of procedure	

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs on the diagnostic-therapeutic chain are used to derive the added benefit. Only in these studies can the benefit or harm of the new diagnostic agent caused by the subsequent therapeutic consequences/follow-up treatments (i.e. indirectly) be investigated with regard to patient-relevant outcomes (see Figure 1).



Diagnostische Information:	diagnostic information
Richtig-positiv:	true positive
Falsch-positiv:	false positive
Falsch-negativ:	false negative
Richtig-negativ:	true negative
Indirekte Wirkungen:	indirect effects
Weitere Behandlung …:	further treatment (therapy after further diagnosis if necessary)
Patienten-relevante Endpunkte …:	patient-relevant outcomes (mortality, morbidity, quality of life)
Direkte Wirkungen:	direct effects
Patient/Patientin mit Symptom:	patient with symptom
Diagnostische Intervention:	diagnostic intervention

Figure 1: Direct and indirect effects of diagnostic interventions

Based on the information available, it is assumed that the new diagnostic agent will replace the old one in this research question without changing the treatment decision. The new diagnostic agent should therefore identify or exclude the same patients as the old one and have other direct patient-relevant advantages, i.e. be less burdensome, for example. In this constellation, RCTs on direct patient-relevant effects alone can also be considered in combination with studies that address a concordance question (see also Chapter I 3). The prerequisite for the (possibly also sole) consideration of studies on a concordance question requires sufficient certainty that the new diagnostic agent provides direct patient-relevant advantages [1]. The company did not address a concordance question explicitly.

I 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 gadopiclenol (status: 02 February 2024)
- bibliographical literature search on gadopiclenol (last search on 02 February 2024)
- search in trial registries/trial results databases for studies on gadopiclenol (last search on 02 February 2024)
- search on the G-BA website for gadopiclenol (last search on 05 February 2024)

To check the completeness of the study pool:

- search in trial registries for studies on gadopiclenol (last search on 24 April 2024); for search strategies, see I Appendix A of the full dossier assessment

This check of the information retrieval identified no RCTs on the diagnostic-therapeutic chain. The company identified the RCTs PICTURE [3] and PROMISE [4], but only presents these two studies in Module 4 A as supplementary information with the justification "missing patient-relevant outcomes". Although the RCTs PICTURE and PROMISE are basically suitable for providing results on both the direct advantages of gadopiclenol compared to gadobutrol and the results on the concordance, overall the necessary requirements for the consideration of a concordance question are not met. The studies are described below and their unsuitability for answering the present research question is justified. The company did not consider the possibility of a concordance question in its dossier and accordingly did not conduct any information retrieval that would be suitable to ensure that all studies for answering a concordance question are fully identified. Whether other studies are available that are suitable for a concordance question was not examined.

The studies PICTURE and PROMISE presented as supplementary information by the company

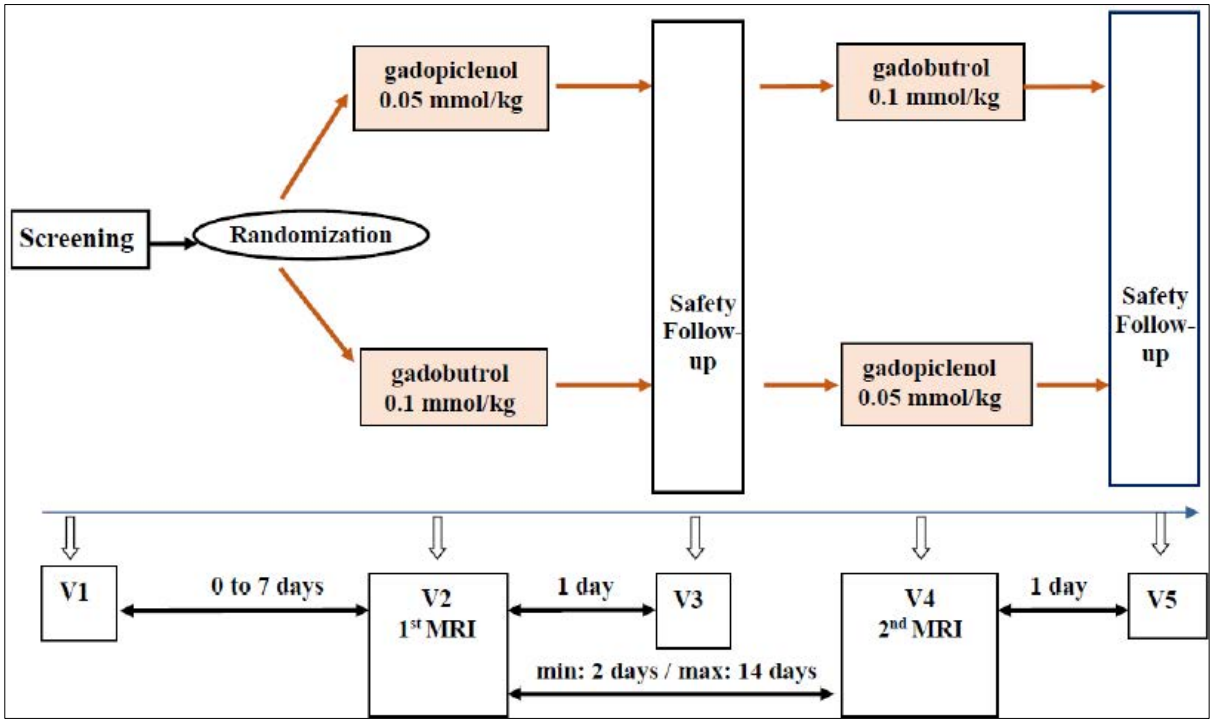
The studies PICTURE and PROMISE have an almost identical design and are described together below. Both studies are blinded RCTs in a cross-over design comparing gadopiclenol with gadobutrol. Both studies were conducted in the years 2019 - 2020 and are completed. The PICTURE study included adult patients with known lesion(s) or highly suspected lesion(s) in the CNS with a disrupted blood-brain barrier in the focal area. The PROMISE study included adult patients with known abnormality(ies) or lesion(s) or suspected contrast-enhanced abnormality(ies) or lesions in at least one of the following body regions: Head and neck, thorax (including chest), abdomen (including liver, pancreas and kidneys), pelvis (including uterus,

ovaries and prostate) and musculoskeletal regions (including extremities). In both studies, the assessment of the lesion(s) was based on the results of previous imaging procedures such as computed tomography or MRI within 12 months prior to study inclusion. Patients had to be members of a national health insurance fund and a contrast-enhanced MRI for the corresponding body region had to be planned for clinical reasons. In addition, they should be willing to undergo a further contrast-enhanced MRI scan at an interval of at most 14 days. Patients with stage III or IV heart failure according to the classification of the New York Heart Association or with acute or chronic renal insufficiency were excluded from both studies. In addition, patients with extracranial and/or extradural lesions and patients whose lesion(s) were due to an acute flare of multiple sclerosis were excluded from the PICTURE study. Patients with known or suspected lesion(s) and planned contrast-enhanced MRI of the CNS or the heart, or MRI angiography were excluded from the PROMISE study.

The studies PICTURE and PROMISE included a total of 256 or 304 patients who were randomly assigned in a 1:1 ratio to two alternating treatment arms. They either received gadopiclenol as the first contrast agent and gadobutrol for the subsequent MRI, or the treatment sequence was reversed (see Figure 2). For each MRI visit, a native MRI (without contrast agent) was performed first and then a contrast-enhanced MRI after contrast agent administration. A so-called safety follow-up was carried out at a one-day interval to record short-term AEs. The second MRI visit took place 2 to 14 days after the first MRI visit.

Gadopiclenol and gadobutrol were each administered according to the SPC [5,6]. Gadopiclenol was administered at a dose of 0.05 mmol/kg BW and gadobutrol with 0.1 mmol/kg BW. Administration was carried out at the corresponding MRI visit as a single intravenous bolus injection.

The primary outcome of each study was the visualization of the lesions with regard to the assessment of the demarcation of the margin, the internal morphology and the degree of contrast enhancement. Side effects were recorded as patient-relevant secondary outcomes. In addition, the influence of contrast-enhanced MRI compared to native MRI on the treatment plan (surgery, biopsy, chemotherapy, radiotherapy, other treatment) of the patients was investigated as a secondary outcome.



MRI: magnetic resonance imaging; V: visit

Figure 2: Design of the studies PICTURE and PROMISE [7]

Approach of the company

The company only presents the studies as supplementary information with the justification "missing patient-relevant outcomes", but derives a hint of non-quantifiable added benefit of gadopiclenol over the ACT due to the lower dosage of gadopiclenol. In this context, it refers to the better long-term tolerability with regard to the specific side effect of nephrogenic systemic fibrosis and other adverse clinical effects of the accumulation and retention of gadolinium in the body. In its argumentation, the company also refers to the non-inferior diagnostic performance based on the outcomes on radiographic imaging compared to gadobutrol.

Recording of side effects in the studies PICTURE and PROMISE

In the studies PICTURE and PROMISE, outcomes in the side effects category were recorded as part of the safety follow-up. AEs that occurred during and after the 1st administration of the contrast agent but before the 2nd treatment period were assigned to the 1st administration of the contrast agent. AEs that occurred during and after the 2nd administration of the contrast agent were assigned to the 2nd treatment period. The follow-up period for AEs therefore was at most 14 days after the 1st treatment period (see Figure 2) and 1 day after the 2nd treatment period.

As for all other gadolinium-containing contrast agents, various specific side effects such as adverse reactions of the immediate type, nephrogenic systemic fibrosis and gadolinium deposits in the CNS and other body regions have been described for gadopiclenol [8,9].

- Adverse reactions of the immediate type are categorized as anaphylactoid (e.g. urticaria, itching, oedema, bronchospasm, hypotensive shock) and physiological reactions (e.g. nausea, vomiting, arrhythmias, cerebral seizures) and usually occur within a short time after the administration of the contrast medium. In rare or very rare cases, severe reactions such as hypotensive shock, respiratory arrest, cardiac arrest or cerebral seizure may also occur.
- Nephrogenic systemic fibrosis is a systemic disease characterized by fibrotic skin and organ changes and has so far only been described in patients with chronic severe renal insufficiency or acute renal failure. A possible association with gadolinium-containing contrast agents was established in 2006 and led to warnings by the regulatory authorities [10]. The disease occurs months to years after application of the contrast medium and has been described in particular for gadolinium-containing contrast media with a linear structure. Since macrocyclic contrast agents such as gadopiclenol, gadobutrol, gadoteric acid and gadoteridol make it very difficult for gadolinium to dissociate from the chelate complex, they have a low risk of developing nephrogenic systemic fibrosis [9,10].
- Gadolinium deposits in the brain and other areas of the body are recognizable as regions of increased signal intensity in native imaging procedures. A connection between these changes and contrast agents containing gadolinium was first reported in 2014 and also led to warnings and approval restrictions by the regulatory authorities [11]. The risk of gadolinium deposition depends on the dose and the number of applications. Macrocyclic contrast agents are also assigned to the low-risk class here. No neurological or clinical symptoms have been described to date, so the clinical relevance of gadolinium deposits is currently still unclear [8,9].

Only short-term AEs can be recorded due to the study design of the studies PICTURE and PROMISE. Long-term AEs, which may occur months or years after application or after repeated administration of the contrast agent, are not recorded due to the short follow-up period of a maximum of 14 days. Irrespective of this, due to the cross-over design, it is not possible to clearly assign AEs to the intervention or comparator therapy after the 2nd administration of contrast medium.

Studies are not suitable for mapping the diagnostic-therapeutic chain

Gadopiclenol is an approved drug used as a diagnostic agent. As a rule, a distinction must be made between direct effects of diagnostic interventions on patient-relevant outcomes in the

benefit assessment of diagnostic agents, i.e. those caused by the diagnostic intervention itself, and indirect effects, i.e. those caused by the subsequent therapeutic consequences/follow-up treatments. Only in studies on the diagnostic-therapeutic chain can the benefit or harm caused by the subsequent therapeutic consequences/subsequent treatments be investigated with regard to patient-relevant outcomes. However, due to the study design, the studies PICTURE and PROMISE are not suitable for depicting the diagnostic-therapeutic chain with gadopiclenol in comparison to the diagnostic-therapeutic chain with gadobutrol.

Requirements for concordance question also not met

Taking into account the information provided by the company, the approval of gadopiclenol [5] and the guidelines on the use of gadolinium-containing contrast agents for MRI [9], it can be assumed that gadopiclenol as a new contrast agent is merely intended to replace the established contrast agents specified in the ACT, without gadopiclenol as a new diagnostic agent identifying or excluding additional or different patients.

If the therapeutic consequences resulting from the use of gadopiclenol did not differ significantly from those of the established contrast agent (concordance), and if it were also shown or sufficiently certain that gadopiclenol had direct patient-relevant advantages over the established contrast agent, it would not be necessary to investigate the entire diagnostic-therapeutic chain. If these conditions are met, the studies PICTURE and PROMISE could in principle be suitable for answering a concordance question.

Direct benefits of gadopiclenol unclear

Based on the available data, the direct benefits of gadopiclenol are unclear. On the one hand, the studies PICTURE and PROMISE showed no advantage of gadopiclenol over gadobutrol in short-term AEs. On the other hand, the study design does not allow conclusions about the long-term AEs that can be directly attributed to gadopiclenol or gadobutrol. Moreover, the gadolinium-specific AE of nephrogenic systemic fibrosis occurs very rarely and may occur as late as years after application. Furthermore, the clinical significance or the direct patient-relevant effects and the extent of gadolinium deposits in the body are unclear. In principle, gadopiclenol and the macrocyclic drugs of the ACT have a low risk regarding these deposits and nephrogenic systemic fibrosis anyway and are predominantly excreted unchanged [8]. The company's argument that the benefit can be derived solely based on the lower dose of gadopiclenol is therefore not sufficiently certain.

In summary, the available data did not show the direct patient-relevant benefit of gadopiclenol (fewer AEs). This does not fulfil the prerequisite that data on the concordance of the two contrast agents (gadopiclenol vs. gadobutrol) can be used. If the direct patient-relevant advantage was proven, the sufficient concordance of the two diagnostic agents could

be demonstrated in a concordance study and would be sufficient to answer the research question.

Irrespective of the missing prerequisite, the company does not sufficiently prepare the data to answer the concordance question. The data presented by the company on the "non-inferiority of diagnostic performance" (company's term) are not suitable to answer the concordance question. Firstly, it would be necessary for the company to explain why the concordance values achieved between the old and new diagnostic agent are sufficient to show a concordance between the two diagnostic agents. Secondly, it should be described which outcome is used in practice to determine the indication for a particular therapy. This outcome should be decisive for the assessment of concordance or the concordance should be considered with regard to the therapeutic consequence resulting from gadopiclenol-enhanced MRI on the patient's treatment plan compared with the contrast-enhanced MRI with the drugs of the ACT. Data on therapeutic consequences were collected in the studies PICTURE and PROMISE, but were not analysed corresponding to a concordance question.

Summary

The studies PICTURE and PROMISE presented by the company as supplementary information are not suitable for depicting the diagnostic-therapeutic chain due to the study design and thus do not allow conclusions on benefit or harm based on patient-relevant outcomes. The direct patient-relevant advantages of gadopiclenol compared to gadobutrol and the concordance with regard to a treatment decision following the diagnosis were not shown. In summary, no suitable data are available to answer the present research question.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of gadopiclenol compared to the ACT in patients aged 2 years and older for whom contrast-enhanced MRI is indicated to obtain diagnostic information, in order to better recognize and visualize pathologies with a disruption of the blood-brain barrier and/or vascular anomalies in various areas (brain, spine and associated tissues of the CNS as well as liver, kidneys, pancreas, breast, lungs, prostate and musculoskeletal system). There is no hint of an added benefit of gadopiclenol in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of gadopiclenol in comparison with the ACT is summarized in Table 5.

Table 5: Gadopiclenol – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Adults and children from 2 years of age for contrast-enhanced MRI in order to better recognize and visualize pathologies with a disrupted blood-brain barrier and/or vascular anomalies in the following areas: ▪ the brain, spine, and associated tissues of the CNS ▪ the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system It should be used only when diagnostic information is essential and not obtainable with unenhanced MRI[b]	Gadoteric acid or gadobutrol or gadoteridol	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The G-BA points out that the benefit assessment procedure according to Section 35a SGB V has only been opened for those sub-areas of the therapeutic indication for which MRI is included in the EBM as a billable service at the relevant time point according to Chapter 5, Section 8 Rules of Procedure. This also applies to the drugs of the ACT. The G-BA points out that it must be ensured that the diagnostic quality and the quality of the imaging in both study arms are sufficiently comparable within the framework of a clinical study and that this must be presented in the dossier.

CNS: central nervous system; G-BA: Joint Federal Committee; MRT: Magnetic Resonance Imaging; SGB: German Social Code Book; UVS: Uniform Value Scale; VerfO: rules of procedure

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit of gadaopiclenol compared with the ACT due to the lower gadaopiclenol dosage.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Loevner LA, Kolumban B, Hutóczki G et al. Efficacy and Safety of Gadopiclenol for Contrast-Enhanced MRI of the Central Nervous System: The PICTURE Randomized Clinical Trial. Invest Radiol 2023; 58(5): 307-313. https://doi.org/10.1097/rli.0000000000000944.

4. Kuhl C, Csőszi T, Piskorski W et al. Efficacy and Safety of Half-Dose Gadopiclenol versus Full-Dose Gadobutrol for Contrast-enhanced Body MRI. Radiology 2023; 308(1): e222612. https://doi.org/10.1148/radiol.222612.

5. Guerbet. Elucirem 0,5 mmol/ml Injektionslösung [online]. 2023 [Accessed: 27.05.2024]. URL: https://www.fachinfo.de.

6. Bayer Vital. Gadovist 1,0 mmol/ml Injektionslösung [online]. 2024 [Accessed: 27.05.2024]. URL: https://www.fachinfo.de.

7. Guerbet. Gadopiclenol (Elucirem); Dossier zur Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1069/#dossier].

8. Bauerle T, Saake M, Uder M. Gadolinium-based contrast agents: What we learned from acute adverse events, nephrogenic systemic fibrosis and brain retention. Rofo 2021; 193(9): 1010-1018. https://doi.org/10.1055/a-1328-3177.

9. European Society of Urogenital Radiology. ESUR Leitlinien für Kontrastmittel 10.0 [online]. 2018 [Accessed: 27.05.2024]. URL: https://www.esur.org/wp-content/uploads/2022/03/ESUR-V0-Deutsch.pdf.

10. European Medicines Agency. Gadolinium-containing contrast agents - referral [online]. 2010 [Accessed: 27.05.2024]. URL: https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents-0.

11. Bundesinstitut für Arzneimittel und Medizinprodukte. Rote-Hand-Brief zu gadoliniumhaltigen Kontrastmitteln: Aktualisierte Empfehlung zur Anwendung [online]. 2018 [Accessed: 27.05.2024]. URL: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2018/rhb-gadolinium.html.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-37.html.