Palopegteriparatide (chronic hypoparathyroidism)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Petra Brügmann, Stefan Feiks, Simone Jentsch und Tanja Richter.

IQWiG thanks the respondents and the Network for Pituitary and Adrenal Diseases (Netzwerk Hypophysen- und Nebennierenerkrankungen e. V.), as well as the Hypopara network in the National Association of Thyroid Cancer Patients (Bundesverband Schilddrüsenkrebs “Ohne Schilddrüse Leben” e. V.) for participating in the written exchange and for their support. The respondents and the patient organizations were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CTCAE	Common Terminology Criteria for Adverse Events
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)

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 palopegteriparatide. 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 3 January 2024.

Research question

The aim of this report is to assess the added benefit of palopegteriparatide in comparison with parathyroid hormone as an appropriate comparative therapy (ACT) in adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy.

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

Table 2: Research question for the benefit assessment of palopegteriparatide

Therapeutic indication	**ACT**[a]
Adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy[b]	Parathyroid hormone[c]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that conventional therapy with calcium and vitamin D is not sufficient for patients in the present therapeutic indication and that parathyroid hormone replacement therapy is therefore an option for them. It is also assumed that in the present therapeutic indication patients will receive calcium and vitamin D substitution (calcitriol, alfacalcidol) in addition to parathyroid hormone replacement therapy, if indicated. c. Among the medicinal products authorised in Germany at the time of the dossier assessment, only parathyroid hormone (1-84), trade name Natpar, corresponds to the ACT. The G-BA would like to point out that a Direct Healthcare Professional Communication (DHPC) was published for the drug Natpar on 4 October 2022. It points out that the production of all dose strengths of Natpar is to be discontinued worldwide at the end of 2024. After 2024, the remaining doses are to be delivered until stocks are used up or expired. Currently (as of 15 March 2024), the drug Natpar is still listed in the Lauer-Taxe. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the specification of the G-BA.

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) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Results

In agreement with the company, the check of completeness of the information retrieval did not identify any relevant study for assessing the added benefit of palopegteriparatide in comparison with the ACT parathyroid hormone.

The company, however, supportively presented the RCT PaTHway for comparing palopegteriparatide with placebo in the dossier. The PaTHway study is not relevant for the research question of this dossier assessment, as the ACT defined by the G-BA was not implemented in the study. This is explained in the following Section.

Supportive evidence presented by the company – PaTHway study

The PaTHway study is a multicentre Phase 3 study of palopegteriparatide in adults with hypoparathyroidism who have been treated with vitamin D and calcium for at least 12 weeks prior to screening. The study is divided into an already completed, randomized, double-blind, placebo-controlled phase (RCT phase) of 26 weeks and a subsequent, still ongoing, single-arm, open-label extension phase of up to 156 weeks.

In the RCT phase, the study compared palopegteriparatide with placebo in addition to conventional therapy (calcium and vitamin D) each. Parathyroid hormone treatment was disallowed in the study. In its dossier, the company presents analyses of a prespecified data cut-off on the results of the RCT phase.

The primary outcome of the study was the response to treatment at week 26, operationalized as a composite outcome with components including serum calcium levels within the normal range, no intake of active vitamin D or calcium in therapeutic doses, and no dose increase of palopegteriparatide within 4 weeks before week 26. Patient-relevant additional outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Lack of implementation of the appropriate comparator therapy

The PaTHway study presented by the company as supportive evidence is unsuitable for assessing the added benefit of palopegteriparatide in comparison with the ACT. The reason for this is that the ACT defined by the G-BA, parathyroid hormone, was not implemented, as the patients in the comparator arm received placebo (in addition to a conventional therapy consisting of vitamin D and calcium). Conversely, parathyroid hormone treatment was disallowed in the study.

Results on added benefit

Since no relevant data are available for the benefit assessment, there is no hint of an added benefit of palopegteriparatide 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 palopegteriparatide.

Table 3: Probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy[b]	Parathyroid hormone[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that conventional therapy with calcium and vitamin D is not sufficient for patients in the present therapeutic indication and that parathyroid hormone replacement therapy is therefore an option for them. It is also assumed that in the present therapeutic indication patients will receive calcium and vitamin D substitution (calcitriol, alfacalcidol) in addition to parathyroid hormone replacement therapy, if indicated.
c. Among the medicinal products authorised in Germany at the time of the dossier assessment, only parathyroid hormone (1-84), trade name Natpar, corresponds to the ACT. The G-BA would like to point out that a Direct Healthcare Professional Communication (DHPC) was published for the drug Natpar on 4 October 2022. It points out that the production of all dose strengths of Natpar is to be discontinued worldwide at the end of 2024. After 2024, the remaining doses are to be delivered until stocks are used up or expired. Currently (as of 15 March 2024), the drug Natpar is still listed in the Lauer-Taxe.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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 this report is to assess the added benefit of palopegteriparatide in comparison with parathyroid hormone as an appropriate comparative therapy (ACT) in adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy.

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

Table 4: Research question for the benefit assessment of palopegteriparatide

Therapeutic indication	**ACT[a]**
Adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy[b]	Parathyroid hormone[c]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that conventional therapy with calcium and vitamin D is not sufficient for patients in the present therapeutic indication and that parathyroid hormone replacement therapy is therefore an option for them. It is also assumed that in the present therapeutic indication patients will receive calcium and vitamin D substitution (calcitriol, alfacalcidol) in addition to parathyroid hormone replacement therapy, if indicated.
c. Among the medicinal products authorised in Germany at the time of the dossier assessment, only parathyroid hormone (1-84), trade name Natpar, corresponds to the ACT. The G-BA would like to point out that a Direct Healthcare Professional Communication (DHPC) was published for the drug Natpar on 4 October 2022. It points out that the production of all dose strengths of Natpar is to be discontinued worldwide at the end of 2024. After 2024, the remaining doses are to be delivered until stocks are used up or expired. Currently (as of 15 March 2024), the drug Natpar is still listed in the Lauer-Taxe.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the specification of the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

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 palopegteriparatide (status: 17 October 2023)
- bibliographical literature search on palopegteriparatide (last search on 17 October 2023)
- search in trial registries/trial results databases for studies on palopegteriparatide (last search on 16 October 2023)
- search on the G-BA website for palopegteriparatide (last search on 16 October 2023)
- bibliographical literature search on the ACT (last search on 17 October 2023)
- search in trial registries / trial results databases for studies on the ACT (last search on 19 October 2023)
- search on the G-BA website for the ACT (last search on 16 October 2023)

To check the completeness of the study pool:

- search in trial registries for studies on palopegteriparatide (last search on 31 January 2024); for search strategies, see I Appendix A of the full dossier assessment

In agreement with the company, the check did not identify any relevant study for assessing the added benefit of palopegteriparatide in comparison with the ACT parathyroid hormone.

The company, however, supportively presented the RCT PaTHway [3] for comparing palopegteriparatide with placebo in the dossier. The PaTHway study is not relevant for the research question of this dossier assessment, as the ACT defined by the G-BA was not implemented in the study. This is explained below.

Furthermore, the company conducted research for indirect comparisons. The company is looking for RCTs with parathyroid hormone that are eligible for an indirect comparison with palopegteriparatide. In its information retrieval, the company identified the studies BALANCE and REPLACE (both parathyroid hormone vs. placebo) [4,5]. The completeness of the study pool for the indirect comparison was not checked. The company considered both studies to be unsuitable for conducting an indirect comparison in the present research question. It justified this with insufficient comparability of the study populations, the study designs and the outcomes on both sides of the indirect comparison.

Thus, for the present assessment, neither results from studies of direct comparisons nor from indirect comparisons are available.

Supportive evidence provided by the company

PaTHway study

The PaTHway study is a multicentre Phase 3 study of palopegteriparatide in adults with hypoparathyroidism who have been treated with vitamin D and calcium for at least 12 weeks prior to screening. The study is divided into an already completed, randomized, double-blind, placebo-controlled phase (RCT phase) of 26 weeks and a subsequent, still ongoing, single-arm, open-label extension phase of up to 156 weeks.

In the RCT phase, the study compared palopegteriparatide with placebo in addition to conventional therapy (calcium and vitamin D) each. Parathyroid hormone treatment was disallowed in the study. In its dossier, the company presents analyses of a prespecified data cut-off on the results of the RCT phase.

The primary outcome of the study was the response to treatment at week 26, operationalized as a composite outcome with components including serum calcium levels within the normal range, no intake of active vitamin D or calcium in therapeutic doses, and no dose increase of palopegteriparatide within 4 weeks before week 26. Patient-relevant additional outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

After the end of the RCT phase, patients were able to participate in the single-arm, open-label extension phase of the study, whereby patients in the comparator arm were switched to palopegteriparatide.

Lack of implementation of the appropriate comparator therapy

The PaTHway study presented by the company is unsuitable for assessing the added benefit of palopegteriparatide in comparison with the ACT. The reason for this is that the ACT defined by the G-BA, parathyroid hormone, was not implemented, as the patients in the comparator arm received placebo (in addition to a conventional therapy consisting of vitamin D and calcium). Conversely, parathyroid hormone treatment was disallowed in the study.

In the company's view, the PaTHway study also does not allow a comparison with the ACT parathyroid hormone, but in its opinion there is nevertheless a hint of a non-quantifiable added benefit, as palopegteriparatide meets the high therapeutic need within the target population due to its positive efficacy and safety profile.

In agreement with the company's assessment, the PaTHway study presented by the company as supportive evidence does not allow a comparison of palopegteriparatide with the ACT parathyroid hormone defined by the G-BA for adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of palopegteriparatide compared to parathyroid hormone in adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy. There is no hint of an added benefit of palopegteriparatide 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 palopegteriparatide in comparison with the ACT is summarized in Table 5.

Table 5: Probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with chronic hypoparathyroidism who are candidates for parathyroid hormone replacement therapy[b]	Parathyroid hormone[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that conventional therapy with calcium and vitamin D is not sufficient for patients in the present therapeutic indication and that parathyroid hormone replacement therapy is therefore an option for them. It is also assumed that in the present therapeutic indication patients will receive calcium and vitamin D substitution (calcitriol, alfacalcidol) in addition to parathyroid hormone replacement therapy, if indicated.
c. Among the medicinal products authorised in Germany at the time of the dossier assessment, only parathyroid hormone (1-84), trade name Natpar, corresponds to the ACT. The G-BA would like to point out that a Direct Healthcare Professional Communication (DHPC) was published for the drug Natpar on 4 October 2022. It points out that the production of all dose strengths of Natpar is to be discontinued worldwide at the end of 2024. After 2024, the remaining doses are to be delivered until stocks are used up or expired. Currently (as of 15 March 2024), the drug Natpar is still listed in the Lauer-Taxe.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit.

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.

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