IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pixantrone –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Pixantron – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27.02.2013). 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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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect her opinion.

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Keywords: pixantrone, lymphoma – B-cell, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DLBCL	diffuse large B-cell lymphoma
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
NHL	non-Hodgkin's lymphoma
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)

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 pixantrone. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 30.11.2012.

Research question

The assessment of the added benefit of pixantrone was conducted according to the approval status for the following therapeutic indication: monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (B-cell NHL). The approval is limited to third- and fourth-line therapy.

The appropriate comparator therapy (ACT) specified by the G-BA is the individual therapy assigned by the treating physician, particularly treatment containing bleomycin, cyclophosphamide, etoposide, ifosfamide, methotrexate, mitoxantrone, rituximab, trofosfamide, vinblastine, vincristine, or vindesine, provided that prior therapy allows further treatment with these drugs , and under consideration of the respective German approval status and the approved dosages.

The company cited the ACT specified by the G-BA, but did not state explicitly whether it concurred with this specification. On the basis of the study PIX301 presented by the company for a direct comparison it became clear that the company deviated from the G-BA's specifications. This deviation particularly concerns the approval status of the comparator therapy.

The randomized controlled trial (RCT) PIX301 compared pixantrone monotherapy with the individual monotherapy specified by the investigator, using one of 7 antineoplastic drugs specified in the protocol, in patients with aggressive non-Hodgkin's lymphoma (NHL) who had received at least 2 prior chemotherapeutic treatments (total population of 140 patients). The study included patients with both T-cell NHL and B-cell NHL, and patients with subsequent treatments after fourth-line therapy. Pixantrone, however, is only approved for the treatment of B-cell NHL in third- and fourth-line therapy. In its dossier, the company therefore presented an analysis of those patients for whom pixantrone is approved (subpopulation of 99 patients; pixantrone group: 50 patients; comparator treatment group: 49 patients).

4 of the 7 possible comparator therapies specified in the protocol of the study PIX301 comprise NHL in their approved therapeutic indication in Germany (etoposide, ifosfamide, mitoxantrone, and rituximab).

In its dossier, the company therefore presented a further evaluation of the subpopulation for whom pixantrone is approved, considering only those patients in the comparator group who had received one of the 4 substances mentioned (subpopulation: 73 patients; pixantrone group: 50 patients; comparator treatment group: 23 patients). Only 2 of these 4 drugs are approved for monotherapy in NHL, however (mitoxantrone and rituximab). In the study PIX301, rituximab was not used in any patients, mitoxantrone was only used in of 4 patients in the total population. Hence the vast majority of patients in the comparator arm, both of the entire study PIX301 and of the subpopulation described above, were not treated according to the German approval status.

According to the G-BA's specification on the ACT, however, the German approval status including the approved dosages is to be considered for the treatments chosen in the comparator group. Compliance with the approval status constitutes a necessary precondition for the ACT, pursuant to the G-BA's code of procedure.

This precondition (benefit assessment strictly within the German approval status) does not inevitably mean that studies in which patients were treated outside the valid approval status are not relevant for the assessment. It has to be examined for these studies whether the study results are applicable to a treatment situation within the German approval status, i.e. whether the effects of a treatment that is not approval-compliant are sufficiently comparable to treatment within the approval status. In such a case, it would therefore be conceivable that conclusions on the added benefit of a new drug in comparison with an (approval-compliant) ACT are based on data outside the German approval status. This requires plausible, data-based considerations on why the therapy chosen in the study is an adequate option for the patients, and is at least not inferior to the ACT.

For the benefit assessment of pixantrone, the company did not present any explanation for the applicability of the PIX301 study results to an approval-compliant treatment. Hence the study PIX301 presented by the company is unsuitable for answering the research question on the added benefit of pixantrone versus the ACT specified by the G-BA.

For the reasons stated above, the implementation of the ACT by the company was inadequate. For the benefit assessment, the ACT specified by the G-BA was used without reservation.

Results

No relevant data were available on the comparison of pixantrone with the ACT specified by the G-BA for the benefit assessment.

This deviated from the approach of the company, which presented the study PIX301 as a direct comparison, where pixantrone was compared with the monotherapy as appointed to the individual patient by the investigator. The data presented on this study are not relevant for the benefit assessment because the comparator therapy used was mainly outside the German

approval status, and because no reasons were given for the applicability of the results on treatment within the approval status.

In addition, the company presented further investigations. One was the study PIX203, an RCT on the comparison of 2 combination schemes using pixantrone in one of the treatment groups in therapy-naive patients with diffuse large B-cell lymphoma (DLBCL). The other was a compilation of Summaries of Product Characteristics by the company to compare possible harm from pixantrone with other drugs that, from the point of view of the company, could be used in Germany for the treatment of NHL. Overall, no sufficient reasons were given for the presentation of further investigations. Moreover, the further investigations were unsuitable to draw conclusions on the added benefit of pixantrone in comparison with the ACT. The population examined in the study PIX203 differed substantially from the patients in the target population, in particular because they lacked previous therapies. In addition, contrary to the approved therapeutic indication, pixantrone was given in combination with other chemotherapeutic drugs in this study. A comparison of Summaries of Product Characteristics is not relevant for the benefit assessment as it is basically unsuitable to demonstrate effects. The further investigations were therefore not relevant for this benefit assessment, either.

In summary, the dossier did not contain any relevant data for a benefit assessment of pixantrone. Hence there is no proof of added benefit of pixantrone versus the ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the drug pixantrone is assessed as follows:

No proof of added benefit of pixantrone versus the ACT specified by the G-BA could be derived from the data presented. Hence there is no patient group, for whom a therapeutically important added benefit could be derived.

The decision on added benefit is made 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 1-3 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 assessment of the added benefit of pixantrone was conducted according to approval status [5] for the following therapeutic indication: monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive B-cell NHL. The approval is limited to third- and fourth-line therapy.

The G-BA specified the following comparator therapy: the individual therapy specified by the treating physician, particularly treatment containing bleomycin, cyclophosphamide, etoposide, ifosfamide, methotrexate, mitoxantrone, rituximab, trofosfamide, vinblastine, vincristine, or vindesine, provided that prior therapy allows further treatment with these drugs , and under consideration of the respective German approval status and the approved dosages.

The company cited the ACT specified by the G-BA, but did not state explicitly whether it concurred with this specification. On the one hand, it questioned the G-BA's specification, but on the other hand, the company did not cite a deviating ACT. On the basis of the study PIX301 [6,7] presented by the company for a direct comparison it became clear that the company deviated from the G-BA's specifications. This deviation particularly refers to the approval status of the comparator therapy.

The RCT PIX301 compared pixantrone monotherapy with monotherapy individually assigned by the investigator from a choice of 7 antineoplastic drugs as defined per protocol, in patients with aggressive NHL who had received at least 2 prior chemotherapeutic treatments (total population of 140 patients).

The study included patients with both T-cell NHL and B-cell NHL, and patients with subsequent treatments after fourth-line therapy. Pixantrone, however, is only approved for the treatment of B-cell NHL in third- and fourth-line therapy. In its dossier, the company therefore presented an analysis of those patients for whom pixantrone is approved (subpopulation of 99 patients; pixantrone group: 50 patients; comparator treatment group: 49 patients).

4 of the 7 possible comparator therapies specified in the protocol of the study PIX301 comprise NHL in their approved therapeutic indication in Germany (etoposide, ifosfamide, mitoxantrone, and rituximab). In its dossier, the company presented a further evaluation of the subpopulation for whom pixantrone is approved, considering only those patients in the comparator group who had received one of the 4 substances mentioned (subpopulation: 73 patients; pixantrone group: 50 patients; comparator treatment group: 23 patients). Only 2 of these 4 drugs are approved for monotherapy in NHL (mitoxantrone and rituximab). But rituximab as monotherapy is only approved for a part of the therapeutic indication (stage III-IV therapy-refractory and relapsed follicular NHL) [6]. In the study PIX301, rituximab was not used in any patients, mitoxantrone was only used in 4 patients in the total population. Hence the majority of patients of this comparator group were treated with etoposide and ifosfamide [6]. However, in Germany, etoposide and ifosfamide are approved for the

therapeutic indication NHL only for use in combination chemotherapy [9-15]. Hence the vast majority of patients in the comparator arm of the study PIX301 were not treated according to the German approval status.

But according to the G-BA's specification on the ACT, the German approval status and the approved dosages are to be considered for the treatments chosen in the comparator group. Compliance with the approval status constitutes a necessary precondition for the ACT, pursuant to the G-BA's code of procedure [4].

This precondition (benefit assessment, as a principle, within the German approval status) does not inevitably mean that studies in which patients were treated outside the valid approval status, cannot be considered in the assessment. It has to be examined for these studies whether the study results are applicable to a treatment situation within the approval status, i.e. whether the effects of an approval-compliant treatment are sufficiently comparable to a treatment outside the approval status. In such a case, it would therefore be conceivable that conclusions on the added benefit of a new drug in comparison with an (approval-compliant) ACT are based on data outside the approval status. This requires plausible, data-based considerations on why the therapy chosen in the study is an adequate option for the patients, and is at least not inferior to the ACT.

For the benefit assessment of pixantrone, the company did not present any explanation for the applicability of the PIX301 study results to a treatment that is approval-compliant in Germany. Hence the study PIX301 presented by the company was unsuitable for answering the research question on the added benefit of pixantrone versus the ACT specified by the G-BA (see Section 2.7.1 of the full dossier assessment).

For the reasons described above, the implementation of the ACT by the company was inadequate. For the benefit assessment, the ACT specified by the G-BA was used without reservation.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

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

- Studies on pixantrone completed by the company up to 01.11.2012 (study list of the company)
- Results of a search in trial registries for studies on pixantrone (last search on 17.08.2012, searches by the company)
- Searches by the company for further investigations (see Section 2.7.2.3.1 of the full dossier assessment)

- A search by the Institute in trial registries for studies on pixantrone to check the search results of the company up to 13.12.2012

No direct comparative study relevant for the present research question was identified from the steps of information retrieval mentioned. The data on the study PIX301 presented by the company were not relevant for the benefit assessment because the comparator therapy used was mainly outside the German approval status, and because no reasons were given for the applicability of the results on treatment within the approval status (see Section 2.7.1 of the full dossier assessment).

In addition, the company presented further investigations. One was the study PIX203, an RCT on the comparison of 2 combination schemes using pixantrone in one of the treatment groups in therapy-naive patients with DLBCL. Furthermore, the company presented a compilation of Summaries of Product Characteristics to compare possible harm from pixantrone with other drugs that, from the point of view of the company, could be used in Germany for the treatment of NHL. Overall, no sufficient reasons were given for the presentation of further investigations. Moreover, the further investigations were unsuitable to draw conclusions on the added benefit of pixantrone in comparison with the ACT. The population examined in the study PIX203 differed substantially from the patients in the target population, particularly because they lacked prior therapies. In addition, contrary to the approved therapeutic indication, pixantrone was given in combination with other chemotherapeutic drugs in this study. A comparison of Summaries of Product Characteristics is not relevant for the benefit assessment as it is basically unsuitable to demonstrate effects. The further investigations were therefore also not relevant for this benefit assessment (see Section 2.7.2.6.2).

Overall, the company did not present any study data that were relevant for the research question of the benefit assessment.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results on added benefit

No relevant studies were available for the research question of the dossier assessment, neither for a direct comparison, nor from further investigations. Overall, there is no proof of added benefit of pixantrone versus the ACT specified by the G-BA.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

No proof of added benefit of pixantrone versus the ACT specified by the G-BA could be derived from the data presented. Hence there are no patient groups, for whom a therapeutically important added benefit could be derived.

This deviates from the company's assessment, which derived a hint of a non-quantifiable added benefit of pixantrone versus the ACT specified by the G-BA from the study PIX301 and the further investigations presented.

The decision on added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.5 of the full dossier assessment.

2.6 List of included studies

Not applicable as the company did not present any studies in its dossier from which an added benefit of pixantrone versus the ACT specified by the G-BA could be derived.

References for English extract

Please see full dossier assessment for full reference list.

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