IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ospemifene (vulvovaginal atrophy) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ospemifen (vulvovaginale Atrophie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 July 2016). 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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[2] Due to legal data protection regulations, employees have the right not to be named.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MBS	most bothersome symptom
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VVA	vulvovaginal atrophy

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 ospemifene. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 26 April 2016.

Research question

The aim of the present report was to assess the added benefit of ospemifene in comparison with the appropriate comparator therapy (ACT) in postmenopausal women with moderate to severe symptomatic vulvovaginal atrophy (VVA) who are not candidates for local vaginal oestrogen therapy.

Table 2 shows the research question and the ACT specified by the G-BA for the benefit assessment.

Table 2: Research question of the benefit assessment of ospemifene

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment of moderate to severe symptomatic vulvovaginal atrophy in postmenopausal women who are not candidates for local vaginal oestrogen therapy	**BSC[b]** or systemic hormonal therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

Initially claiming to follow the G-BA's specification, the company chose best supportive care (BSC) as comparator therapy. In contrast to the G-BA, the company then further specified that non-hormonal vaginal lubricants were the only BSC remaining in the present therapeutic indication, however. This limitation of the BSC, which, for example, did not consider possible hormonal non-vaginal treatments, was inadequate. The specification by the G-BA was therefore used for the present assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum study duration of 24 weeks were to be used for the derivation of the added benefit.

Results

The company identified 3 RCTs for the present research question: study 15-50310 ("310" for short), study 15-50718 ("718" for short), and study 15-50821 ("821" for short). Two extension studies were available for study 310: the controlled study 15-50310x ("310x" for short) and the one-arm study 15-50312 ("312" for short), both of which were irrelevant, however.

None of the studies presented by the company was suitable to draw conclusions on the added benefit of ospemifene in comparison with the ACT.

Target population of ospemifene not included in the studies presented

Ospemifene is approved for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal oestrogen therapy. Lack of suitability for local vaginal oestrogen therapy can be operationalized as the presence of specific contraindications to such treatment (women with a history of breast cancer) and women who had discontinued previous local vaginal hormonal therapy because of side effects. These women were not specifically included in the 3 RCTs 310, 718, and 821, and they only constituted a small proportion of the study populations, however. In addition, moderate to severe VVA symptoms were no inclusion criterion of study 718.

Study duration too short

Besides the reasons mentioned above, the studies 310 and 821 were unsuitable for the assessment of the added benefit of ospemifene because of the short study duration of only 12 weeks each.

Implementation of BSC treatment not ensured

In both study arms (ospemifene and placebo) of each of the studies 310 and 821, only as-needed use of a lubricant specified in the study was additionally allowed. Use of other non-hormonal treatments, such as local vaginal moisturizers, was not allowed. Furthermore, ongoing systemic hormonal therapy also had to be discontinued, even if this therapy had been necessary for symptom relief of the individual patient before. Hence BSC treatment was not ensured in any of the 3 studies.

Summary

No suitable data were available for the assessment of the added benefit of ospemifene in postmenopausal women with moderate to severe symptomatic VVA who are not candidates for local vaginal oestrogen therapy. This resulted in no hint of an added benefit; an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Table 3: Ospemifene – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Treatment of moderate to severe symptomatic vulvovaginal atrophy in postmenopausal women who are not candidates for local vaginal oestrogen therapy	**BSC**[b] or systemic hormonal therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report was to assess the added benefit of ospemifene in comparison with the ACT in postmenopausal women with moderate to severe symptomatic VVA who are not candidates for local vaginal oestrogen therapy.

Table 4 shows the research question and the ACT specified by the G-BA for the benefit assessment.

Table 4: Research question of the benefit assessment of ospemifene

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Treatment of moderate to severe symptomatic vulvovaginal atrophy in postmenopausal women who are not candidates for local vaginal oestrogen therapy	**BSC[b]** or systemic hormonal therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

Initially claiming to follow the G-BA's specification, the company chose BSC as comparator therapy. In contrast to the G-BA, the company then further specified that non-hormonal vaginal lubricants were the only BSC remaining in the present therapeutic indication, however (see Section 2.7.1 of the full dossier assessment). This limitation of the BSC was inadequate. The specification by the G-BA was therefore used for the present assessment.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum study duration of 24 weeks were to be used for the derivation of the added benefit. This deviated from the company's approach, which specified no minimum study duration.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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 ospemifene (status: 4 February 2016)
- bibliographical literature search on ospemifene (last search on 3 February 2016)
- search in trial registries for studies on ospemifene (last search on 5 February 2016)

To check the completeness of the study pool:

- bibliographical literature search on ospemifene (last search on 19 May 2016)
- search in trial registries for studies on ospemifene (last search on 23 May 2016)

No relevant study was identified from the check.

2.3.2 Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified 3 RCTs for the present research question:

- study 15-50310 (referred to as "310" in the present report) [3]
- study 15-50718 ("718" for short) [4]
- study 15-50821 ("821" for short) [5,6]

Two extension studies were available for study 310: the controlled study 15-50310x ("310x" for short) [7] and the one-arm study 15-50312 ("312" for short) [8]. Both extension studies were unsuitable for the benefit assessment, however, and are therefore not considered further (see Section 2.7.2.3.2 of the full dossier assessment).

None of the studies presented by the company was suitable to draw conclusions on the added benefit of ospemifene in comparison with the ACT. On the one hand, the patients for whom ospemifene is approved were not investigated: It was not clear in any of the 3 studies that vaginal oestrogen therapy was not an option for the patients included; and in study 718, moderate to severe symptoms were not an inclusion criterion. On the other, the implementation of the BSC treatment was not ensured in the comparator arms of the studies. Moreover, the observation period was too short in 2 of the 3 studies.

The 3 studies included by the company and the reasons mentioned for their irrelevance are described in detail below.

2.3.3 Assessment of the studies presented by the company

Tables presenting the study characteristics of the 3 studies presented by the company can be found in Appendix A of the full dossier assessment.

Postmenopausal women aged 40 to 80 years with VVA were included in the 3 RCTs 310, 718, and 821. The women in the studies 310 and 821 had to report an at least moderate to severe symptom of their VVA; with vaginal dryness or dyspareunia being reported as the most bothersome symptom (MBS) in study 821. Study 718, in contrast, only included women with an intact uterus, without symptoms being a criterion for study inclusion.

Ospemifene 60 mg (and 30 mg in study 310) was compared with placebo in each of the 3 RCTs. Ospemifene is approved in a dosage of 60 mg so that only this study arm is considered below. In studies 310 and 821, as-needed use of a vaginal non-hormonal lubricant specified in the study was additionally allowed in both treatment groups. In study 718, vaginal non-hormonal lubricants and moisturizers were allowed to be used freely (without specification of a certain agent) not before week 12. Further treatments considered as BSC (hormonal non-vaginal treatment or non-hormonal treatment of symptoms) were not explicitly mandated in the studies.

The 3 RCTs included 544 women (study 310), 426 women (study 718), and 919 women (study 821).

The women were treated for 12 weeks in the studies 310 and 821, and 52 weeks in study 718. Patient-relevant outcomes in the studies 310 and 821 were change in symptoms and side effects. Only side effects were recorded in study 718.

Women in study 310 could continue treatment in 2 extension studies. Both of these studies are described in Section 2.7.2.3.2 of the full dossier assessment. They are not considered further because the original study 310 was already irrelevant for the present benefit assessment due to the population.

Operationalization of the lacking suitability for vaginal oestrogen therapy

Ospemifene is approved for the treatment of symptomatic VVA in women who are not candidates for local vaginal oestrogen therapy. The Summary of Product Characteristics (SPC) of ospemifene does not specify the lack of suitability for vaginal oestrogen therapy. The company therefore defined the following reasons why local vaginal oestrogen therapy might not be an option:

1) contraindications to local oestrogens that present no contraindications to ospemifene:
   - history of breast cancer or endometrial cancer
   - mild or moderate liver disease

2) physical limitations, e.g. due to stroke, which make local vaginal oestrogen therapy impossible
3) local oestrogens have caused a side effect

Re 1: The company's approach to define a target population of ospemifene using contraindications to local oestrogens is generally comprehensible. However, except "history of breast cancer", the criteria mentioned by the company are not contraindications to all available hormonal vaginal treatments. Active endometrial cancer or suspected active endometrial cancer is a contraindication to hormonal vaginal treatments (as is the case for ospemifene), but not a history of endometrial cancer [9-11]. Mild or moderate liver disease also is not a contraindication to estriol, for example [9].

Re 2: As another target population for treatment with ospemifene the company named women with physical limitations that make local oestrogen therapy impossible. Except for "e.g. stroke", the company did not further specify the limitations so that it remained unclear which limitations were meant exactly. It is inadequate to generally assume such severe physical limitation in patients after stroke that vaginal hormonal therapy would be no longer possible. In addition, the SPC on ospemifene contains a warning on a possibly increased risk of cerebrovascular events particularly for women with stroke, which should be considered when prescribing ospemifene [11] so that it is doubtful that these patients are candidates for ospemifene treatment to a major extent. Furthermore, since non-hormonal vaginal lubricants or moisturizers were used in the comparator groups of the company's studies, patients with relevant physical limitations regarding the local application were excluded by definition. The criterion "physical limitation" is therefore not considered further.

Re 3: Not every side effect per se results in the unsuitability of a specific drug treatment. It depends on the side effect and the benefit of treatment. If the concrete side effects are very bothersome for the individual patient or if they cause an unfavourable individual benefit-risk relation leading to treatment discontinuation due to a side effect, this can be considered a lack of suitability for a treatment.

In summary, the reasons mentioned by the company were only partly adequate for characterizing the criterion "lack of suitability for local oestrogen therapy". The remaining criteria are "history of breast cancer" and "treatment discontinuation due to a side effect in a previous vaginal hormonal therapy".

Comparison of the populations in the studies presented by the company with the target population of ospemifene

Women with a history of breast cancer

Women with a history of a tumour (in the last 10 years) were generally excluded in the studies presented. This also applied to patients with breast cancer in this period. The company provided no information on whether women who had had a tumour in the period of > 10 years

were included in the study and whether this would have been relevant. The study documents on the studies 718 and 821 showed that only fewer than 1.5% of the women in each study had documented breast cancer. No such information was available for study 310.

Women who had discontinued previous treatment with local vaginal oestrogens because of side effects

Treatment discontinuation due to side effects of a previous vaginal hormonal therapy was no inclusion criterion in any of the 3 studies. Depending on the study, between about 20% and about 40% of the patients were receiving vaginal hormonal therapy at enrolment in the study, which was discontinued before the treatment phase for reasons of the study design, but not because of side effects. About 60% to 80% of the patients had not received any vaginal hormonal therapy at all before the start of the study; there was no information about any vaginal hormonal therapy in the past (> 6 months before the start of the study).

Overall, there was no sign that a relevant proportion of the patients included in the company's studies fulfilled the criterion "treatment discontinuation due to side effects of previous treatment with local vaginal oestrogens".

Study 718: moderate to severe symptoms no inclusion criterion

One of the preconditions for approval-compliant use of ospemifene is moderate to severe symptoms of VVA.

Study 718 included postmenopausal women with VVA. VVA was defined only with the following criteria:

- ≤ 5% superficial cells confirmed with maturation index of the vaginal smear
- vaginal pH > 5.0

Symptoms, particularly moderate to severe symptoms, were not an explicit inclusion criterion, however. The company did not address this issue in its dossier. Hence, there was no evidence that a relevant proportion of the population of study 718 was relevant for the present research question regarding symptoms.

Studies 310 and 821: study duration too short

A study duration of at least 24 weeks was considered necessary for the assessment of the added benefit of ospemifene (see also Section 2.7.2.1 of the full dossier assessment). Besides the reasons mentioned above, the studies 310 and 821 were therefore unsuitable for the assessment of the added benefit of ospemifene because of the short study duration of only 12 weeks each.

Notes on the implementation of the BSC in the company's studies

In both study arms (ospemifene and placebo) of each of the studies 310 and 821, only as-needed use of a lubricant specified in the study was additionally allowed. Use of other non-

hormonal treatments, such as local vaginal moisturizers, was not allowed. The company referred to this as BSC. It was not clear from the dossier whether lubricants were the individually optimized supportive treatment for all women in both studies mentioned above. Elsewhere in the dossier, the company explicitly described that lubricants only aim to relieve symptoms associated with sexual intercourse. Moisturizers explicitly prohibited (in the studies 310 and 812 for the total study period, in study 718 until week 12) are used to relieve symptoms such as itching, a symptom analysed by the company in the studies 310 and 821 as an outcome, however. In addition, any ongoing systemic hormonal therapy had to be discontinued even if it had been required for symptom relief before, which also contradicts the definition of BSC ("best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life").

Hence BSC treatment was not ensured in any of the 3 studies.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of ospemifene in postmenopausal women with moderate to severe symptomatic VVA who are not candidates for local vaginal oestrogen therapy. This resulted in no hint of an added benefit; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of ospemifene. An added benefit of ospemifene is therefore not proven.

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

Table 5: Ospemifene – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy[a]**	**Extent and probability of added benefit**
Treatment of moderate to severe symptomatic vulvovaginal atrophy in postmenopausal women who are not candidates for local vaginal oestrogen therapy	**BSC[b]** or systemic hormonal therapy (in women with an intact uterus [oestrogen/gestagen combination] or in women without uterus [only oestrogen])	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: BSC refers to the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

This deviates from the company's approach, which derived proof of considerable added benefit of ospemifene on the basis of the data presented by the company.

The G-BA decides on the added benefit.

2.6 List of included studies

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

References for English extract

Please see full dossier assessment for full reference list.

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