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Ixekizumab (plaque psoriasis in children and adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ixekizumab (Plaque-Psoriasis bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 8 December 2020). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
(C)DLQI	(Children's) Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PUVA	Psoralen and ultraviolet-A light
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 ixekizumab. 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 27 July 2020.

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

Research question

The aim of the present report is the assessment of the added benefit of ixekizumab in comparison with the appropriate comparator therapy (ACT) in children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy.

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

Table 2: Research question of the benefit assessment of ixekizumab

Therapeutic indication	**ACT**[a]
Children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy	Adalimumab or etanercept or **ustekinumab**
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company chose ustekinumab from the presented treatment options of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company, the check of the completeness of the study pool for children and adolescents produced no relevant randomized controlled trials (RCTs) on the direct comparison of ixekizumab versus the ACT with a minimum duration of 24 weeks, which is the relevant study duration for the present research question.

For the derivation of the added benefit of ixekizumab in children and adolescents, the company transferred the added benefit of ixekizumab in the therapeutic indication from adults with plaque psoriasis. For this purpose, it used the results of the ixekizumab study IXORA-S in adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments. The IXORA-S study is already known from a previous benefit assessment of ixekizumab in adults (Commission for dossier assessment A17-07). For children and adolescents, the company used data on ixekizumab from the IXORA-PEDS study. This study included children and adolescents from 6 up to and including 17 years of age with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy, or who had treatment failure to topical therapy. This study recorded data comparing ixekizumab with etanercept only within the first 12 weeks. After 12 weeks, all children and adolescents were switched to an unblinded treatment with ixekizumab until week 60.

The company's approach of transferring the added benefit from adults because studies of direct comparisons of at least 24 weeks in children and adolescents were lacking for the benefit assessment is comprehensible.

The company's approach in transferring the added benefit in adults to children and adolescents is not appropriate for several reasons. An added benefit of ixekizumab in comparison with the ACT in children and adolescents in the present therapeutic indication cannot be derived from it. This is justified below.

Approach of the company in transferring the added benefit of ixekizumab in adults to children and adolescents

The aim of the company was to transfer the added benefit of ixekizumab versus ustekinumab from the adult population to the paediatric population, each with plaque psoriasis.

In Module 4 B, the company compared data from the randomized comparison of ixekizumab with ustekinumab in adults from the IXORA-S study and data on ixekizumab from the IXORA-PEDS study in children and adolescents, in each case at week 24. For this purpose, the company formed subpopulations from each of the 2 studies by defining criteria based on the inclusion criteria of the studies in order to obtain populations that are matched to each other and are thus sufficiently similar for a transfer. However, the company ultimately derived extent and probability of the added benefit of ixekizumab not on the basis of the subpopulations it had formed and the data it had compared, but in accordance with the decision of the G-BA in the assessment procedure for adults.

The company's approach in transferring the added benefit in adults to children and adolescents is not appropriate for the following reasons:

- The ACT specified by the G-BA in the therapeutic indication for children and adolescents was not investigated at all. The company conducted no information retrieval for the ACT in the therapeutic indication of the present research question for further investigations.

This resulted in a potential incompleteness of content. For example, the company did not identify 2 studies on ustekinumab that were identified by a specially conducted exploratory search for the comparator therapy. These studies were therefore not taken into account by the company in its data preparation.

Furthermore, the company's approach in selecting the option of the ACT was inconsistent. The company initially selected ustekinumab from the options of the ACT, but in its further procedure cited all 3 options of the ACT.

- The analyses submitted by the company for the transfer of the added benefit are not complete. The company presented results for the subpopulations only for some of the patient-relevant outcomes recorded in the studies. In particular, there are no results on patient-relevant symptom outcomes also recorded in the studies, such as itching and pain of skin. Furthermore, the company only prepared data at the analysis date week 24 for the comparison of the data from the studies IXORA-PEDS and IXORA-S. This is not appropriate because later analysis dates (week 48 and week 52) are also available for both studies. The company did not prepare these available data for the benefit assessment.
- The company's approach in processing the results and transferring the added benefit was inconsistent and not appropriate in terms of content. Although the company concluded that forming the subpopulations of the studies IXORA-S and IXORA-PEDS resulted in comparable populations that allowed a transfer of results, the company ultimately did not refer to these subpopulations, which it considered comparable, when transferring the added benefit of ixekizumab:
  - The company did not transfer the added benefit on the basis of the results in the subpopulation of adults from the IXORA-S study formed by the company, but in accordance with the decision by the G-BA in the assessment procedure for adults and thus on the basis of the results of the total population of adults.
  - The company did not transfer the added benefit to the population of children and adolescents defined by the company, but to all children and adolescents comprised by the therapeutic indication. This is not appropriate because the population of children and adolescents comprised by the approval of ixekizumab was severely limited by the formation of the subpopulation. A large proportion of the population comprised by the approval of ixekizumab was thus not taken into account.

Overall, the company's approach in transferring the added benefit from adults to children and adolescents is not adequate. The company's approach in retrieving information, processing the results and transferring the added benefit of ixekizumab was incomplete in terms of content and inconsistent, and therefore led to a data situation that cannot be interpreted.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug ixekizumab compared with the ACT is assessed as follows:

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

Table 3: Ixekizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy	Adalimumab or etanercept or **ustekinumab**	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**.

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

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of ixekizumab in comparison with the ACT in children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy.

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 4: Research question of the benefit assessment of ixekizumab

Therapeutic indication	**ACT**[a]
Children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy	Adalimumab or etanercept or **ustekinumab**
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT. The company chose ustekinumab from the presented treatment options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 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 lists on ixekizumab (status: 1 September 2020)
- bibliographical literature search on ixekizumab (last search on 1 September 2020)
- search in trial registries/trial results databases for studies on ixekizumab (last search on 25 May 2020)
- search on the G-BA website for ixekizumab (last search on 1 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 30 July 2020)
- exploratory search to find out whether there are studies on the ACT in the therapeutic indication (last search on 16 September 2020)

Concurring with the company, the check of the completeness of the study pool for children and adolescents produced no RCTs on the direct comparison of ixekizumab versus the ACT with a minimum duration of 24 weeks, which is the relevant study duration for the present research question.

For the derivation of the added benefit of ixekizumab in children and adolescents, the company transferred the added benefit of ixekizumab in the therapeutic indication from adults with plaque psoriasis. For this purpose, it used the results of the ixekizumab study IXORA-S [3] in adult patients with moderate to severe plaque psoriasis with inadequate response to other

systemic treatments. The IXORA-S study is already known from a previous benefit assessment of ixekizumab in adults [4,5] (see below for details). The company compared the results on adults with data on ixekizumab for children and adolescents from the IXORA-PEDS study [6-10].

The company's approach of transferring study results from adults because studies of direct comparisons of at least 24 weeks in children and adolescents were lacking is comprehensible. However, it is not comprehensible that such sufficiently long direct comparisons of ixekizumab with the ACT are not available in the present therapeutic indication, as such studies are conducted in the present therapeutic indication. For example, for the drug secukinumab, which was only recently approved in the population of the present research question, a study with a direct comparison of sufficient duration for a benefit assessment is available [11].

The company's approach in transferring the added benefit in adults to children and adolescents is not appropriate for several reasons. An added benefit of ixekizumab in comparison with the ACT in children and adolescents in the present therapeutic indication cannot be derived from it. This is justified below.

Evidence presented by the company for the transfer of the added benefit

Study IXORA-PEDS in children and adolescents

For children and adolescents, the company presented data from the IXORA-PEDS study. This is an ongoing study that included children and adolescents aged 6 to 17 years with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy, or who had treatment failure to topical therapy.

In the study, there was a randomization into 3 arms for the comparison of ixekizumab with etanercept or placebo, and a randomization into 2 arms for the comparison of ixekizumab with placebo. As etanercept is only approved in some countries for children and adolescents with severe plaque psoriasis [12], in these countries, only children and adolescents with severe plaque psoriasis were randomized for the comparison of ixekizumab with etanercept or placebo. Children and adolescents with moderate plaque psoriasis as well as children and adolescents with severe plaque psoriasis in countries without a corresponding approval of etanercept were randomized to the comparison of ixekizumab with placebo. After 12 weeks, all children and adolescents were switched to an unblinded treatment with ixekizumab until week 60. Thus, results for the direct comparison of ixekizumab with etanercept from the IXORA-PEDS study are available for only 12 weeks. The company did not use these results for the derivation of the added benefit because the duration of the direct comparison was too short for the benefit assessment. This is appropriate. However, the company presented the results as supplementary information (see below).

Results from the study arm of the IXORA-PEDS study in which children and adolescents were treated with ixekizumab are available for the analysis dates week 24 and week 48. The company only considered data on ixekizumab at week 24 in its approach. For week 48, it only presented

results on side effects, although results on benefit outcomes were also recorded. The results on side effects were presented by the company as supplementary information. It did not justify why it did not consider the available later analysis date week 48 for all relevant outcomes in its approach.

Details of the study design and study characteristics and of the intervention characteristics of the IXORA-PEDS study can be found in Appendix A of the full dossier assessment.

Study IXORA-S in adults

For adults, the company presented data from the IXORA-S study. The IXORA-S study is an RCT on the comparison of ixekizumab with ustekinumab already submitted by the company for benefit assessment A17-07. This study included adults with moderate to severe plaque psoriasis with treatment failure, contraindication or intolerance to at least one systemic treatment (including methotrexate, ciclosporin or phototherapy). A detailed description of the study design and the study results at week 24 can be found in dossier assessment A17-07 [4]. In the assessment procedure for adults with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA (Psoralen and ultraviolet-A light), or with contraindication or intolerance to such treatments, the G-BA determined an indication of a minor added benefit of ixekizumab [13].

At the time of the benefit assessment of ixekizumab in adults, the IXORA-S study was still ongoing. In the meantime, the study has been completed and results for the analysis date week 52 are available. For the present assessment, the company exclusively used results at week 24 for the transfer of the added benefit from the IXORA-S study. It did not justify why it did not take into account the later analysis date week 52, which had become available in the meantime.

Approach of the company in transferring the added benefit of ixekizumab in adults to children and adolescents

The aim of the company was to transfer the added benefit of ixekizumab versus ustekinumab from the adult population to the paediatric population, each with plaque psoriasis.

In Module 4 B, the company compared data from the randomized comparison of ixekizumab with ustekinumab in adults from the IXORA-S study and data on ixekizumab from the IXORA-PEDS study in children and adolescents, in each case at week 24. For this purpose, the company formed subpopulations from each of the 2 studies by defining criteria based on the inclusion criteria of the studies in order to obtain populations that are matched to each other and are thus sufficiently similar for a transfer. The company argued that the transfer of the results from adults to children and adolescents was meaningful because of the positive effects for ixekizumab in the same direction and a similar tolerability profile in both subpopulations formed by the company. In addition, the studies IXORA-S and IXORA-PEDS did not show any effect modification by the characteristic of age, the company stated. Furthermore, the company argued that there was similarity or agreement in terms of pharmacology, disease manifestation and

progression. It did not comment on the course of the disease in children and adolescents under the ACT.

From the company's point of view, the results presented for the transfer of the added benefit were additionally supported by the results from the IXORA-PEDS study on the randomized direct comparison of ixekizumab with etanercept at week 12, which the company presented as supplementary information.

However, the company ultimately derived extent and probability of the added benefit of ixekizumab not on the basis of the subpopulations it had formed and the data it had compared, but in accordance with the decision of the G-BA in the assessment procedure for adults (on the Commission for dossier assessment A17-07).

The company's approach in transferring the added benefit in adults to children and adolescents is not appropriate for the following reasons:

- The ACT specified by the G-BA in the therapeutic indication for children and adolescents was not investigated at all. The company conducted no information retrieval for the ACT in the therapeutic indication of the present research question for further investigations. This resulted in a potential incompleteness of content. For example, the company did not identify 2 studies on ustekinumab. Specifically, these are one placebo-controlled study on the treatment of adolescents aged 12 years and older with ustekinumab for 60 weeks and one single-arm study on ustekinumab in children aged 6 to 11 years for 56 weeks (CADMUS [14-16], CADMUS Jr [17,18]), which were identified in a specially conducted exploratory search for the comparator therapy. These studies were therefore not taken into account by the company in its data preparation.

  Furthermore, the company's approach in selecting the option of the ACT was inconsistent. It initially chose ustekinumab from the options of the ACT. In formulating its research question and defining the inclusion criteria, the company then no longer limited the ACT to ustekinumab, but cited all 3 options of the ACT (adalimumab, etanercept or ustekinumab).
- The analyses submitted by the company for the transfer of the added benefit are not complete.
  - The company presented results for the subpopulations only for a part of the patient-relevant outcomes recorded in the studies (for the outcomes "Psoriasis Area and Severity Index [PASI], "Nail Psoriasis Severity Index [NAPSI]", "[Children's] Dermatology Life Quality Index [(C)DLQI]" as well as analyses on the outcomes of the category of side effects). Results on further patient-relevant outcomes recorded in the studies, particularly on symptoms like itching and pain of skin, for example, were missing. The company did not address this issue.

- The company only prepared data at the analysis date week 24 for the comparison of the data from the studies IXORA-PEDS and IXORA-S. This is not appropriate because later analysis dates (week 48 and week 52) are also available for both studies. As already described above, for week 48 of the IXORA-PEDS study, the company only presented data on side effects as supplementary information in Module 4 B, although analyses on benefit outcomes were also planned for this time point in the study. In Module 4 B, the company cited 3 publications [19-21] that report 52-week data for the RCT in adults (IXORA-S), but did not process these data for the benefit assessment.

- The company's approach in processing the results and transferring the added benefit of ixekizumab was inconsistent and not appropriate in terms of content. Although the company concluded that forming the subpopulations of the studies IXORA-S and IXORA-PEDS resulted in comparable populations that allowed a transfer of results, the company ultimately did not refer to these subpopulations, which it considered comparable, when transferring the added benefit of ixekizumab:
  - The company did not transfer the added benefit on the basis of the results in the subpopulation of adults from the IXORA-S study formed by the company, but in accordance with the decision by the G-BA in the assessment procedure for adults and thus on the basis of the results of the total population of adults.
  - The company did not transfer the added benefit to the population of children and adolescents defined by the company, but to all children and adolescents comprised by the therapeutic indication. This is not appropriate because the population of children and adolescents comprised by the approval of ixekizumab was severely limited by the formation of the subpopulation. For example, the limited population only included adolescents who had been pretreated with at least one systemic therapy, from the age of 12 years and with a body weight of > 50 kg. However, the population comprised by the approval and relevant to the present research question also includes children and adolescents not pretreated with systemic therapy, as well as children and adolescents under 12 years of age and/or under 50 kg.
  - In connection with the transfer of the added benefit, the company argued that a transfer is also possible to children aged 6 to 11 years because no important effect modification for the characteristic of age was observed in the studies IXORA-PEDS and IXORA-S. However, this argumentation of the company is again not appropriate for the following 2 reasons:
    - The analyses on subgroup characteristics presented by the company for the IXORA-PEDS study refer to the randomized comparison of ixekizumab with etanercept at week 12 and thus to a comparison with a markedly too short treatment duration, which is why the company did not include this study in its benefit assessment. In addition, the ACT options etanercept and ustekinumab differ in their approval status. Ustekinumab is approved for the treatment of

children and adolescents with moderate to severe plaque psoriasis [22], whereas etanercept is approved only for the treatment of severe plaque psoriasis [12]. Therefore, only children and adolescents with severe plaque psoriasis were investigated for the comparison of ixekizumab with etanercept. The population relevant for the present research question also comprises children and adolescents with moderate plaque psoriasis, however. On the basis of the analyses on the comparison with etanercept, it is therefore not possible per se to draw conclusions on a lack of effect modification by the characteristic of age for the comparison of ixekizumab with ustekinumab, as well as for all children and adolescents comprised by the therapeutic indication of ixekizumab. It is therefore not possible to derive meaningful conclusions on the transferability of the added benefit from this.

- In the IXORA-S study on adults, it was only investigated for the age groups < 65 years and ≥ 65 years whether there was an effect modification by the characteristic of age. Due to the high cut-off value, it is not assumed that conclusions on the transferability of the added benefit to children and adolescents are possible on the basis of these analyses. The company did not provide any further justification for this.

Comparison of ixekizumab with etanercept at week 12 presented by the company as supplementary information cannot be interpreted for the present benefit assessment

As supplementary information, the company presented results at week 12 from the IXORA-PEDS study on the comparison of ixekizumab with etanercept, which it considered to support the transfer of the added benefit of ixekizumab. With 12 weeks, the treatment duration for the comparison was markedly shorter than the minimum duration of 24 weeks relevant for the benefit assessment in the present therapeutic indication. For this reason, the company did not use the results at week 12 for its assessment, but presented them as supplementary information.

It is appropriate that the company did not use the results at week 12 because the treatment duration was too short for the benefit assessment.

Moreover, the data submitted are not suitable to support the transfer of the added benefit of ixekizumab also for other reasons. The comparator therapy etanercept was not the option chosen by the company as ACT, i.e. ustekinumab. For the comparison of ixekizumab with etanercept, only children and adolescents with severe plaque psoriasis were included due to the different approval status of etanercept. Thus, on the basis of the results, no conclusions can be drawn regarding the transferability of the added benefit of ixekizumab compared with ustekinumab to all children and adolescents comprised by the present therapeutic indication.

Moreover, it is unclear whether etanercept was used in compliance with the approval in the IXORA-PEDS study. According to the approval of etanercept, patients must have intolerance or insufficient response to systemic therapy or phototherapy [12]. It is unclear whether the

children and adolescents included in the study were pretreated in compliance with the approval of etanercept. There is no information on how many of the children were pretreated with systemic therapy or phototherapy, but only separate information on pretreatment with systemic therapy and pretreatment with phototherapy. According to this, 53% of the children and adolescents in the etanercept arm were pretreated with systemic therapy and 43% with phototherapy. It remains unclear to what extent this includes multiple counts of patients. Overall, the proportion of children and adolescents without corresponding pretreatment can therefore be between 3% and 47%. Regardless of the reasons given above, the results for the comparison after 12 weeks are not interpretable.

Summary

Overall, the company's approach in transferring the added benefit from adults to children and adolescents is not adequate. The company's approach in retrieving information, processing the results and transferring the added benefit of ixekizumab was incomplete in terms of content and inconsistent, and therefore led to a data situation that cannot be interpreted.

2.4 Results on added benefit

In its dossier, the company did not provide any suitable data for the assessment of the added benefit of ixekizumab in comparison with the ACT in children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

Table 5: Ixekizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents with moderate to severe plaque psoriasis from the age of 6 years with a body weight of at least 25 kg who are candidates for systemic therapy	Adalimumab or etanercept or **ustekinumab**	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**.

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

The assessment described above deviates from that of the company, which derived an indication of minor added benefit.

The G-BA decides on the added benefit.

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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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