IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. 14-40

Addendum to Commission A14-19 (mirabegron)[1]

Addendum

Commission: A14-19
Version: 1.0
Status: 16 October 2014

[1] Translation of addendum A14-40 *Addendum zum Auftrag A14-19 (Mirabegron)* (Version 1.0; Status: 16 October 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Addendum to Commission A14-19 (mirabegron)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
7 October 2014

Internal Commission No.:
A14-40

Address of publisher:
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Keywords: mirabegron, urinary bladder – overactive, benefit assessment

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

Table of contents

List of abbreviations

Abbreviation	Meaning
ANCOVA	analysis of covariance
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward

1 Background

On 8 October 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A14-19 (benefit assessment of mirabegron [1]).

In the commenting procedure on the assessment of mirabegron, in its comment from 22 September 2014 [2], the pharmaceutical company (hereinafter abbreviated to "the company") submitted supplementary information for proving the added benefit to the G-BA that went beyond the information in the dossier [3]. These were further analyses on the outcomes "incontinence" and "urge incontinence" of the studies relevant for the assessment 178-CL-049 (TAURUS), 178-CL-044 (DRAGON), 178-CL-046 (SCORPIO), 178-CL-048, and 178-CL-090 on the comparison of mirabegron versus tolterodine. These studies were already contained in the company's dossier and were included as relevant in the dossier assessment A14-19. Hereinafter, they are referred to as studies "049", "044", "046", "048" and "090". The analyses for the 2 outcomes "incontinence" and "urge incontinence" presented in the dossier were based exclusively on those patients who already had incontinence or urge incontinence at the start of the study. These were considered to be not evaluable in the dossier assessment A14-19 because a relevant proportion of patients remained unconsidered in the analysis because of this, and there was also no information on whether patients without incontinence event at the start of the study had any such events in the course of the study. With its comment, the company presented supplementary analyses on the 2 outcomes based on the respective total populations of the studies, which, from the company's point of view, show that at least a disadvantage of mirabegron in these outcomes can be excluded.

The G-BA commissioned IQWiG to assess the analyses presented. The data were to be assessed under the research question of whether, under consideration of the analyses submitted by the company with the comment, an added benefit of mirabegron versus the appropriate comparator therapy tolterodine can be derived.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

In its comment [2], the company presented analyses on the outcomes "incontinence" and "urge incontinence" from the long-term study 049 as well as from the short-term studies 044, 046, 048 and 090, in each case based on the total population of the studies. A description of how the outcomes were recorded can be found in dossier assessment A14-19 (Section 2.7.2.4.3) [1]. The company presented the mean change in incontinence episodes per 24 hours at the end of the study compared with the start of the study as a result, and the mean difference of the change (including the 95% confidence interval [CI]) as estimate for the treatment effect as well as a p-value for the treatment difference.

Analyses presented not interpretable

It was notable in the results of the 049 long-term study, which was primarily relevant for the assessment, that the 95% CI presented for the treatment effect does not include the null effect for the outcome "incontinence" (CI [0.06; 0.37]) and for the outcome "urge incontinence" (CI [0.05; 0.34]), thus suggesting a statistically significant difference to the disadvantage of mirabegron. In contrast, the respective p-values of 0.45 (incontinence) and 0.74 (urge incontinence) indicate a difference between the treatment groups that is not statistically significant. These noticeable discrepancies between CI and p-value are not comprehensible on the basis of the information provided in the company's comment. The appendix to the comment and the oral hearing conducted on 6 October 2014 showed that the mean differences and the 95% CIs were based on a parametric analysis of covariance (ANCOVA) model adjusted for the baseline value. The p-values, however, were based on a non-parametric stratified rank ANCOVA. The difference between parametric and non-parametric methods is that in parametric methods, an underlying distribution of the data, e.g. normal distribution, is assumed.

The discrepancies suggest that the distributions of the change in incontinence or urge incontinence from the start to the end of the study in the treatment groups deviate greatly from the normal distribution. In such a data situation, parametric methods are usually no adequate analysis. The (adjusted) mean values in the respective treatment groups are not estimated correctly. As a result, the effect estimates (adjusted mean difference and standardized mean difference using Hedges' g) including the corresponding 95% CIs, estimated using parametric ANCOVA as in the present case, based on them are also not valid.

On the basis of the available information however, it cannot be assessed whether the non-parametric rank ANCOVA used for calculating the p-values constitutes an adequate type of analysis. The company did not present a specification of the concrete model with the comment. The rank ANCOVA used is not a standard method. The company also provided no information about the assumptions and preconditions of the model and in how far these were fulfilled. Moreover it is possible in the present case that a large number of patients had no incontinence at the start of the study or at the end of the study, and therefore were included in the analysis with a mean change of 0. In the analysis using a ranking method (as the company

did with the rank ANCOVA), the patients' values are ranked in ascending order. When several patients with the same values are included in the analysis, the same rank is allocated to these values, which is called "ties". Among other things, non-parametric methods differ in the way these ties are considered. The comment also contained no information by the company on how many ties occurred in the analyses and how such ties were dealt with in the analyses.

On the basis of the information provided by the company in the comment it cannot be estimated whether one of the statistical methods used constitutes an adequate analysis. In order to assess this, at least the following information, some of which was already addressed as lacking in dossier assessment A14-19, would have been required:

- descriptive presentation of the data that allow an assessment of the underlying distribution (e.g. histograms or box plots)
- exact description of the ANCOVA models used, including reasons for the choice and discussion of the model and the underlying assumptions
- information on the presence and the proportion of missing values in the analysis and discussion of whether, in this case, the last observation carried forward (LOCF) used constitutes an adequate imputation method

Hence overall, no meaningful interpretation is possible of the analyses presented on the 2 outcomes "incontinence" and "urge incontinence" - neither of the analyses based on parametric methods nor the ones based on non-parametric methods. This applies both to the results on the mean change per treatment group and on the respective effect estimates (including CIs) and p-values. Based on the available information it can also not be excluded that there is a statistically significant and also relevant effect to the disadvantage of mirabegron with regard to both outcomes.

For this reason the results are considered to be not evaluable for the benefit assessment. The results on the mean change per treatment group are also considered to be not interpretable and are therefore not presented either.

Possibility to use analyses on the proportion of patients without incontinence or urge incontinence at the end of the study

Independent from the considerations mentioned above, the company could have presented analyses based on the total populations of the studies, in which, for example, the proportions of patients without incontinence or urge incontinence at the end of the treatment are compared between the treatment groups. The necessary examination of model assumptions (e.g. normal distribution) in continuous outcomes can be avoided by dichotomization of the data. This kind of analyses would have been reasonable particularly against the background of the presumably noticeable deviation of the continuous data from the normal distribution in this case and of the presumably large proportion of ties. Moreover, the relevance of a treatment

effect could be directly estimated when using this kind of analyses. This is one of the reasons why the European Medicines Agency (EMA) also recommends respective analyses for the analysis of outcomes on the frequency of symptoms [4].

For individual outcomes (nocturia, incontinence and urgency), the clinical study reports of some of the relevant studies contained analyses in which the proportion of patients without event at the end of treatment was compared. However, for the outcome "incontinence", these were only available for the subpopulation of patients who already had incontinence at the start of the study. For the remaining outcomes, these analyses were considered to be relevant for the assessment A14-19 and therefore included in addition to the analyses of continuous outcomes presented in Module 4. Moreover, the relevance of this kind of analyses was pointed out in assessment A14-19. Hence the company could have presented corresponding analyses both for incontinence and for urge incontinence in its comment.

Summary and conclusion

In summary, the analyses on the outcomes "incontinence" and "urge incontinence" subsequently submitted by the company in the comment cannot be meaningfully interpreted on the basis of the available information. Lesser benefit of mirabegron with regard to these outcomes can also not be excluded.

Overall, also under consideration of the analyses subsequently submitted with the comment, an overall balancing on the added benefit for the total population is not possible. Hence the analyses subsequently submitted do not change the result of benefit assessment A14-19.

An added benefit of mirabegron in comparison with the appropriate comparator therapy is not proven for patients with overactive bladder symptoms.

The G-BA decides on the added benefit.

3 References

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