IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Natalia Wolfram
- Gertrud Egger
- Sibylle Sturtz
- Beate Wieseler

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

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CGI-S	Clinical Global Impression Scale of Severity
CI	confidence interval
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MADRS	Montgomery-Åsberg Depression Rating Scale
NNT	number needed to treat
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor

1 Background

On 8 September 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-16 (Vortioxetine – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In the dossier on vortioxetine for the assessment of the acute treatment of patients with moderate and severe major depressive episodes, the pharmaceutical company (hereinafter referred as "the company") had presented an adjusted indirect comparison in comparison with the selective serotonin reuptake inhibitor (SSRI) citalopram using a common comparator placebo [2]. The dossier assessment on vortioxetine showed that the results presented by the company were unsuitable for the assessment of the added benefit of vortioxetine. This was largely due to the fact that the company made an inadequate limitation of the study pool for the meta-analyses of the indirect comparison and did not consider the available evidence completely [1].

In its comment, the company submitted supplementary analyses on the indirect comparison, which went beyond the information provided in the dossier. Moreover, the company in its comments referred to a study of direct comparison of vortioxetine versus the SSRI escitalopram (study 318) [3], which the company had not included in the dossier for the assessment of the added benefit. The G-BA commissioned IQWiG with the assessment of the additional data on the indirect comparison and of study 318.

In accordance with the commission, both research questions are assessed separately in the following Chapter 2.

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 of the data submitted with the comment

2.1 Additional analyses on the indirect comparison submitted

The company had initially included 14 studies on vortioxetine and 10 studies on citalopram in the initial study pool for the indirect comparison in its assessment in the dossier. Subsequently, the company made a choice of studies on the basis of its considerations on the heterogeneity of the study results on vortioxetine in the outcome "change in symptoms of depression". The company only included studies with mainly European patients (studies with ≥ 80% Europeans in the total population) in the indirect comparison. As a result, the evidence was limited to a relevant degree, and only 3 of the 12 potentially relevant studies on vortioxetine (11492, 305, 13267A) and 4 of the 8 potentially relevant studies on citalopram (899003, 89303, 89306, Gastpar 2006) were considered [2]. Four studies included by the company (2 studies on vortioxetine and 2 on citalopram) were not relevant because of dosages that did not comply with the approval [1].

The indirect comparison of the company was not considered for the assessment of the added benefit in the dossier assessment. It was particularly criticized that the company's investigation on heterogeneity was insufficient and was only limited to the factors dose and region. Irrespective of the question whether the limitation of the study pool to studies with mainly European patients was justified, the company included no results of the subpopulations of European patients from the studies with a relevant proportion of Europeans (between 50 and 70%) in its analyses, although individual patient data were available to the company [1].

With its comment, the company presented additional indirect comparisons, which, from the company's point of view, should support the conclusions in the dossier:

- Analysis 1: Analyses of the outcomes "response" and "remission" using the 3 studies on vortioxetine with ≥ 80% Europeans and 8 potentially relevant studies on citalopram. In contrast to the analyses presented in the dossier, this analysis contained data from 4 additional studies on citalopram (studies 99007, 91206, 99008, 29060/785); the study pool on vortioxetine was not enlarged.
- Analysis 2: Calculations of the absolute risk reduction and number needed to treat (NNT) for the outcomes "response" and "remission" from the indirect comparison. These indirect comparisons were based on the same limited and therefore unsuitable study pool as the analyses in the dossier.
- Analysis 3: Analysis on the outcome "change in cognitive function" (factor analysis on cognition). This analysis was based on the same limited and therefore unsuitable study pool as the analyses in the dossier.

Irrespective of the fact that the company presented its additional analyses for the indirect comparison only for selected benefit outcomes (and that these analyses are therefore

incomplete regarding the outcomes investigated), these analyses are still not evaluable for the assessment of the added benefit of vortioxetine. Their substantial flaws, which were explicitly pointed out in the dossier assessment, remain unchanged, and they provide no additional data that can lead to a consideration of the indirect comparison presented by the company in the dossier.

Despite the criticism in the dossier assessment, the company in its comments submitted no additional analyses that investigate in how far other factors (particularly disease severity) can explain the heterogeneity and justify the limitation to the European population.

It is also not comprehensible that the company still included no data from European patients from other studies in its analyses. All additional analyses were still conducted using the 3 studies on vortioxetine that mainly investigated European patients (≥ 80% of the total population). The company did not include the data from studies on vortioxetine with a relevant proportion of Europeans (between 50 and 70%), for which, at the latest for the comment, it was able to calculate corresponding subgroup analyses using the individual patient data. Sensitivity analyses approximating this problem were also missing.

Following criticism in the dossier assessment that the company had included studies with citalopram with only European patients in its analyses, the company only calculated an additional analysis (analysis 1) that additionally contained 4 potentially relevant studies on citalopram with non-European patients. However, this analysis was also unsuitable for the assessment of the added benefit because it was not expanded on the vortioxetine side and, as before, was based on a choice of data from the studies on vortioxetine.

Summary

Due to the still inadequate approach of the company in the choice of the studies for the indirect comparison, the analyses subsequently submitted by the company were not evaluable for the benefit assessments. They provided no data that can lead to a consideration of the indirect comparison presented by the company in the dossier.

There was therefore no hint of an added benefit of vortioxetine in comparison with the ACT in the acute treatment of patients with major depression. The added benefit is therefore not proven. The G-BA decides on the added benefit.

2.2 Assessment of study 318

2.2.1 Research question

In accordance with the G-BA commission, the 318 study of direct comparison of vortioxetine versus escitalopram was assessed under the research question of a possible added benefit of vortioxetine in adult patients with major depressive episodes.

It can be inferred from the division of the treatment of depression into different treatment phases (acute treatment, maintenance treatment and relapse prevention) [4] and the Summary of Product Characteristics (SPC) of vortioxetine [5] that vortioxetine can be used in 2 different treatment phases. On the one hand, these are the treatment of acute symptoms (acute treatment) and, on the other, relapse prevention after remission (relapse prevention under maintenance treatment). Different study designs are recommended for the different treatment phases of depression to generate conclusive data for the respective treatment goal. Study 318 was assessed regarding its potential suitability for assessing the different treatment phases.

The assessment was conducted based on patient-relevant outcomes. A minimum study duration of 6 weeks was considered adequate to investigate acute treatment. In accordance with recommendations by the European Medicines Agency (EMA) [6], studies with a minimum duration of ≥ 6 months were considered for studies investigating relapse prevention, in which, after a (controlled or uncontrolled) treatment phase of about 8 to 12 weeks, patients are (re)randomized .

2.2.2 Description of the study

Table 1 and Table 2 describe study 318. Figure 1 shows a schematic presentation of the study design.

Table 1: Characteristics of the study assessed – RCT, direct comparison: vortioxetine vs. escitalopram

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study 318	RCT, double-blind, parallel	Treatment-experienced[b] adults (18–55 years) with stable MDD (according to DSM-IV-TR) and treatment-emergent sexual dysfunction, CGI-S ≤ 3 at baseline	Vortioxetine 10–20 mg/day (N = 225) escitalopram 10–20 mg/day (N = 222)	Screening: 2 weeks Treatment phase: 8 weeks Taper-down phase: 1 week Follow-up phase: 3 weeks	9 centres in Canada, 57 centres in the USA 6/2011–12/2013	Primary: change in CSFQ-14 Secondary: symptoms, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Pretreated with an SSRI (citalopram, paroxetine or sertraline) for ≥ 8 weeks.

AE: adverse event; CGI-S: Clinical Global Impression Scale of Severity; CSFQ-14: Sexual Functioning Questionnaire Short-Form; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MDD: major depressive disorder; N: number of randomized patients; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor; vs.: versus

Table 2: Characteristics of the interventions – RCT, direct comparison: vortioxetine vs. escitalopram

Study	Intervention	Comparison	Non-permitted concomitant treatment
Study 318	Pretreatment with an SSRI (citalopram, paroxetine or sertraline) for ≥ 8 weeks discontinuation of pretreatment on the day of randomization		
	Vortioxetine oral ▪ week 1: 10 mg/day ▪ week 2: 20 mg/day ▪ week 3–8: 10–20 mg/day, depending on response and if tolerated ▪ week 9 (taper-down phase): placebo	Escitalopram oral ▪ week 1: 10 mg/day ▪ week 2: 20 mg/day ▪ week 3–8: 10–20 mg/day, depending on response and if tolerated ▪ week 9 (taper-down phase): 10 mg/day	▪ The following psychoactive drugs within 8 weeks before screening: mood stabilizers (including anticonvulsants), antipsychotics or other antidepressants except the allowed SSRI monotherapy ▪ Non-drug interventions: ▫ formal cognitive therapy or behavioural therapy, systemic psychotherapy within < 6 months before screening or intention to start this therapy during the study ▫ electroconvulsive therapy, vagus nerve stimulation, repeat transcranial magnetic stimulation within 6 months before screening
RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor; vs.: versus			

Study 318 was a randomized, active-controlled, double-blind phase 3 study exclusively conducted in Canada and the USA. Men and women with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (4th Edition [DSM-IV-TR]) who were treated with an SSRI (citalopram, paroxetine or sertraline) for at least 8 weeks before the start of the study and who were experiencing sexual dysfunction attributable to this treatment were included in the study. The symptoms of depression had to be stable in the physician's assessment. The severity grade had to correspond to a Clinical Global Impression Scale of Severity (CGI-S) score of ≤ 3 (at most "mildly ill"). According the investigator, the patients had to be suitable to switch treatments because of their sexual dysfunction.

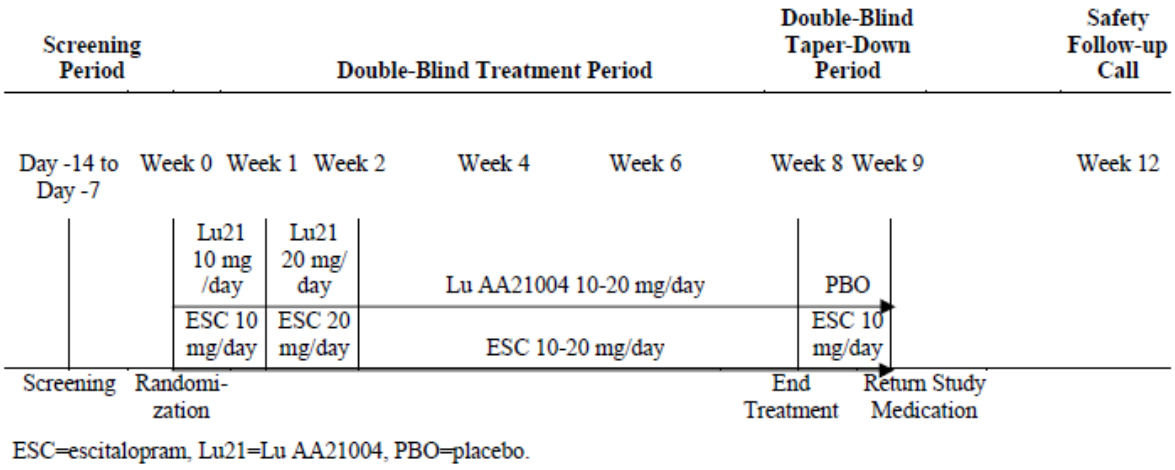

Figure 1: Schematic presentation of the study design of study 318

The study comprised a 2-week screening phase, an 8-week treatment phase, a one-week taper-down phase and follow-up. On the day of randomization, the patients discontinued their respective SSRI treatment and were randomly assigned to either vortioxetine or escitalopram. The dosage of both drugs was 10 mg daily in the first week; starting in the second week, the dosage was increased to 20 mg. Starting in the third week and until the end of treatment, the drugs were dosed at 10 mg or at 20 mg at the investigator's discretion.

Overall, the study investigated a population of patients for whom vortioxetine [5] and escitalopram [7] are approved. The study also essentially complied with the specifications of the respective SPCs regarding dosage, even though the SPCs specify no mandatory dose increase after the first treatment week. According to the approval, the dose of vortioxetine can also be lowered to 5 mg, which was not envisaged in the study 318. Psychotherapy was prohibited during the study.

Nonetheless, study 318 could not be used for the assessment of the added benefit of vortioxetine in comparison with escitalopram because it was unsuitable for the investigation both of the acute phase and of relapse prevention. This is justified below.

Table 3 shows the characteristics of the patients in study 318.

Table 3: Characteristics of the study populations – RCT, direct comparison: vortioxetine vs. escitalopram

Study Characteristics Category	Vortioxetine N = 225[a]	Escitalopram N = 222[a]
Study 318		
Age [years], mean (SD)	39 (10)	40 (10)
Sex [F/M], %	57/43	61/39
Origin (%)		
Caucasian[b]/other	79/21[c]	82/18[c]
MADRS before the start of prior therapy with SSRI, mean (SD)	ND	ND
MADRS at baseline, mean (SD)	7.9 (6.3)	8.3 (6.5)
Number of prior MDEs (%)		
0	19.1[c]	19.4[c]
1–3	64.0	67.1
4–6	14.7	13.1
> 6	2.2	0.5
Duration of current MDE [weeks], median [min; max]	59 [0; 1683]	46 [0; 938]
Duration of prior SSRI therapy [weeks], median [min; max]	ND	ND
Study discontinuations, n (%)	56 (24.9)	43 (19.4)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Or whites including Latin Americans.
c: Institute's calculation.
F: female; M: male; MADRS: Montgomery-Åsberg Depression Rating Scale; max: maximum; MDE: major depressive episode; min: minimum; N: number of randomized patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SSRI: selective serotonin reuptake inhibitor; vs.: versus

It was clear from the inclusion criteria of the study on the one hand, and from the characteristics of the patients included on the other, that patients in the study had already responded to their prior therapy with an SSRI. The mean Montgomery-Åsberg Depression Rating Scale (MADRS) score at the start of the study was 8.1 (SD 6.40), which corresponds to a mild severity grade of the disease (MADRS 7-19) [4]. Also according to direct information provided in the clinical study report (CSR), 98.4% of the patients had responded to their prior therapy with SSRI. Hence at study inclusion, the majority of the patients investigated were no longer in a disease phase that allows investigation of the acute treatment. There were no analyses for those patients who had not responded to prior therapy and would have therefore allowed investigating acute treatment with vortioxetine or escitalopram in study 318.

Hence the patient population in the study was more suitable to investigate maintenance treatment. However, the treatment duration in the randomized treatment phase of the study

(8 weeks) was too short to investigate whether there is an added benefit of vortioxetine in comparison with escitalopram in the maintenance treatment. In particular, no conclusions on maintaining the improvement of symptoms of depression can be drawn on the basis of this study. It remained unclear whether the positive effect regarding symptom reduction after switching to vortioxetine or escitalopram observed at the start of the study was maintained over a longer period of time and under which drug fewer relapses occurred. Even if it was possible to evaluate the results on adverse events from this study, no adequate balancing of benefits and harm would be possible to draw an overall conclusion on the added benefit of vortioxetine in maintenance treatment.

It should be noted as additional information that is unclear which severity grade of the disease patients were in before starting their SSRI treatment. It was also not clear whether the switch to vortioxetine or escitalopram because of sexual dysfunction was necessary at all: According to the information provided in the CSR, 96.6% of the patients had tolerated their prior therapy with SSRI.

Irrespective of the suitability of the study it should be noted that the study showed no relevant differences between vortioxetine and escitalopram regarding sexual dysfunction. There was a statistically significant difference between the treatment groups for the continuous data of the Sexual Functioning Questionnaire Short-Form (CSFQ-14) (group difference for the mean change from baseline to week 8 in the total score: 2.2; 95% confidence interval [CI] [0.48-4.02], p = 0.013). However, it could not be derived from the assessment of the effect size based on Hedges' g that the effect was relevant because the 95% CI was not fully above the irrelevance threshold of 0.2 (standardized mean difference 0.26, 95% CI [0.05-0.48], p = 0.016). Responder analyses of the patients who reported no sexual dysfunction at the end of the study (OR 1.37, 95% CI [0.93-2.03], p = 0.112) and of the patients with a prespecified improvement in total score by ≥ 3 points, which was considered relevant by the company (OR 1.50, 95% CI [0.99-2.29], p = 0.057) showed no statistically significant difference between the treatment groups.

Summary

Study 318 is unsuitable for the assessment of the added benefit of vortioxetine in comparison with escitalopram. The patients included in the study were unsuitable to investigate the acute treatment of depression. The study was too short to assess the phase of relapse prevention.

There was no hint of an added benefit of vortioxetine in comparison with escitalopram. The added benefit is therefore not proven. The G-BA decides on the added benefit.

2.2.3 List of sources for the study assessed

Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton A. Effect of vortioxetin vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induces sexual dysfunction [submitted manuscript]. 2015.

Takeda. A randomized, double-blind, parallel-group, active-controlled, flexible-dose study evaluatinf the effect of Lu AA21004 vs Escitalopram on sexual dunctioning in adults with well-treated mejor depressive disorder experiencing selective serotonin reuptake inhibitor-induced sexual dysfunction. Lu AA21004 10 and 20 mg for treatment of major depressive disorder with sexual dysfunction; protocol [unpublished]. 2011.

Takeda. A randomized, double-blind, parallel-group, active-controlled, flexible-dose study evaluating the effect of Lu AA21004 vs Escitalopram on sexual dunctioning in adults with well-treated mejor depressive disorder experiencing SSRI-induced sexual dysfunction; statistical analysis plan [unpublished]. 2011.

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