IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-42

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Lurasidon – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 January 2015). 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 his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: lurasidone, schizophrenia, benefit assessment

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BAS	Barnes Akathisia Scale
CGI-S	Clinical Global Impression Scale of Severity
CI	confidence interval
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PANSS	Positive and Negative Syndrome Scale
PT	Preferred Term
QTc	corrected QT interval
RCT	randomized controlled trial
SAE	serious adverse event
SAS	Simpson-Angus Scale
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics

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 lurasidone. 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 3 November 2014.

Research question

The aim of this report was to assess the added benefit of lurasidone compared with the appropriate comparator therapy (ACT) in adult patients with schizophrenia.

The G-BA specified amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone as ACTs. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. The company planned no summarizing analysis for all drugs. In the present benefit assessment, a summarizing assessment of the added benefit is conducted versus the drugs named by the G-BA.

Two research questions resulted for the assessment, which are derived from the different treatment goals in the treatment of patients with schizophrenia. On the one hand, this is the treatment of acute symptoms (e.g. after exacerbation or first diagnosis), on the other hand the prevention of relapse of a stable disease.

- Research question 1: acute treatment of patients with schizophrenia
- Research question 2: prevention of relapse in patients with schizophrenia

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Research question 1: acute treatment of patients with schizophrenia

The company identified 3 studies in which lurasidone was compared with risperidone (Study D1001002), olanzapine (Study D1050231) or extended-release quetiapine (quetiapine XR; Study D1050233) respectively.

In the studies in which the acute treatment of patients with schizophrenia was investigated, there were major uncertainties regarding the influence of the applied dosages of lurasidone and of the comparator therapies risperidone, olanzapine and quetiapine XR on the study results. However, the company derived an added benefit in this research question only on the basis of the reduction in adverse events (AEs). However, it could not be inferred from the available data on the studies 002, 231 and 233 that the effect of lurasidone on schizophrenia

symptoms was at least similarly large as the one of the ACT. Even under the company's assumption that fewer AEs occurred under lurasidone, overall no added benefit could be derived from this. Hence irrespective of the question whether the 3 studies were suitable for the benefit assessment at all, there is no proof of added benefit of lurasidone versus the ACT.

Research question 2: prevention of relapse in patients with schizophrenia

Study characteristics and risk of bias

One relevant study (D1050237, hereinafter referred to as "237") was available for the benefit assessment.

Study 237 was a randomized, double-blind, active-controlled study, in which lurasidone was compared with risperidone. Adult patients with schizophrenia were enrolled. The treatment duration was 12 months. The dose of the study medication was flexible in both treatment arms. Beginning with the second treatment week, lurasidone could be administered in dose range between 40 and 120 mg/day. The dose in the risperidone arm was up-titrated to 4 mg/day within the first treatment week according to a fixed regimen. Thereafter, the patients received an individual dose, which could be adjusted to between 2 and 6 mg/day. Patients with a score of ≤ 4 on the Positive and Negative Syndrome Scale (PANSS) for the symptoms "delusions", "conceptual disorganization", "hallucinations" and "unusual thought content", and concurrent Clinical Global Impression Scale of Severity (CGI-S) score of ≤ 4 could be enrolled in the study. The patients were not hospitalized. The primary objective of the study was to evaluate the long-term effects of lurasidone. It could be inferred from the sample size planning of the study that the proof of the non-inferiority of lurasidone in comparison with risperidone for the outcome "relapse rate" was a key objective.

The mean PANSS total score of the patients was approximately 65, which indicates a disease severity of no more than moderate. Approximately one third of the patients had been hospitalized for schizophrenia 4 times or more before enrolment in the study. Over 10% of the patients in both study arms received other antipsychotics and/or anticholinergics as concomitant medication.

The study was mainly conducted outside Europe, with the majority of the patients being from North America (66%), followed by Africa (15%) and South America (14%). Only 2% of the study participants were from Europe (Croatia); the study was not conducted in German study centres. The company's documents contained no information on further care pathways, particularly psychotherapeutic care. The transferability of the study results to the German health care context is therefore questionable.

The risk of bias at study level (and consequently also at outcome level) was rated as high. The reason for this is the high rate of patients who discontinued the study (approximately 60%) and the difference regarding the time point of discontinuation between the study arms.

Results

Mortality

Two patients died in the course of the study. Both were treated with lurasidone. There was no statistically significant difference between the treatment groups. An added benefit or greater harm of lurasidone compared with risperidone for mortality is therefore not proven.

Morbidity – relapse rate

The company operationalized the relapse rate as composite outcome, but presented separate data for only 1 of the 3 components of the outcome (rehospitalization for worsening of psychosis). The outcome could therefore be interpreted only to a limited extent.

Proving the non-inferiority of lurasidone versus risperidone based on the relapse rate was the study objective of Study 237. The non-inferiority threshold was a hazard ratio of 1.6. The study objective was not achieved. The company operationalized the relapse rate as composite outcome, but presented results for only 1 of the 3 components of the outcome (rehospitalization for worsening of psychosis).

Morbidity – schizophrenia symptoms

The severity of the schizophrenia symptoms was assessed with the PANSS. Besides the total score, the scores of the 3 subscales on positive symptoms, negative symptoms, and general psychopathology were evaluated.

The result was not statistically significant in the total score or in the 3 subscales. Hence an added benefit of lurasidone regarding schizophrenia symptoms is not proven. Due to the upper limit of the 95% confidence interval (CI) it is uncertain, however, whether the effects of lurasidone are of a similar size as the ones of risperidone in the total score and in the subscale "psychopathology symptoms". This concurs with the missing proof of non-inferiority in the outcome "relapse rate".

Morbidity – rehospitalization for worsening of psychosis

There was no statistically significant difference between the treatment groups for the rate of rehospitalizations for worsening of psychosis. An added benefit of lurasidone in comparison with risperidone for this outcome is therefore not proven.

Health-related quality of life

Health-related quality of life was not recorded in Study 237. An added benefit for this outcome is therefore not proven.

Adverse events

Overall rate of serious AEs (SAEs): There was no statistically significant difference between the treatment groups for this outcome. Greater or lesser harm from lurasidone than from risperidone is therefore not proven.

Treatment discontinuations due to AEs: There was a statistically significant difference in favour of risperidone for this outcome. This results in a hint of greater harm from lurasidone in comparison with risperidone.

Vomiting: There was a statistically significant difference between the treatment groups in favour of risperidone for this outcome. This results in a hint of greater harm from lurasidone in comparison with risperidone.

Constipation: There was a statistically significant difference between the treatment groups in favour of lurasidone for this outcome. This results in a hint of lesser harm from lurasidone in comparison with risperidone.

Reproductive system and breast disorders: There was a statistically significant difference between the treatment groups in favour of lurasidone for this outcome. This results in a hint of lesser harm from lurasidone in comparison with risperidone.

Akathisia: The outcome "akathisia", on the one hand, was operationalized as the rate of patients in whom akathisia was recorded as an AE, and on the other, the severity of akathisia induced by antipsychotic medication was measured with the Barnes Akathisia Scale (BAS). There was a statistically significant difference between the treatment groups in favour of risperidone regarding the akathisia recorded as AEs. The extent of this effect was no more than marginal, however, because the upper limit of the 95% CI, with reversed direction of effect, was larger than the threshold value of 0.90. In the assessment of the BAS, there was a statistically significant difference in favour of risperidone for the total score. The standardized mean difference (SMD) in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD did not lie completely above the irrelevance threshold of 0.2. Hence an irrelevant effect cannot be excluded. Greater harm from lurasidone for this outcome is therefore not proven. There was no statistically significant difference between the treatment groups for the item of global clinical assessment of the BAS. Greater or lesser harm from lurasidone than from risperidone is therefore not proven regarding the outcome "akathisia".

Parkinsonism: The severity of parkinsonism induced by antipsychotic medication was measured with the Simpson-Angus Scale (SAS). There was no statistically significant difference between the treatment groups for the SAS total score. Greater or lesser harm from lurasidone than from risperidone is therefore not proven regarding the outcome "parkinsonism".

Prolongation of QT interval (QTc interval > 500 ms): No patients had corrected QT intervals of greater than 500 ms (Fridericia's correction). Greater or lesser harm from lurasidone than from risperidone is therefore not proven regarding this outcome.

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

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

In the studies included by the company in which the acute treatment of patients with schizophrenia was investigated, there were major uncertainties regarding the influence the dosages of lurasidone used in the studies and of the comparator therapies risperidone, olanzapine and quetiapine XR had on the study results. However, it could not be inferred from the available data that the effect of lurasidone on schizophrenia symptoms was at least similarly large as the one of the ACT. Hence the differences in AEs and body weight postulated by the company are also irrelevant. The added benefit of lurasidone versus the ACT in the acute treatment is not proven.

In the overall assessment of Study 237 on the prevention of relapse, there were statistically significant effects only for the outcomes from the category "non-serious/non-severe AEs", both in favour and to the disadvantage of lurasidone. Overall, neither an advantage nor a disadvantage of lurasidone results from this. In addition, it is uncertain whether the effect of lurasidone on schizophrenia symptoms is at least similar in size as the one of risperidone. The added benefit of lurasidone versus the ACT in the prevention of relapse is not proven.

Table 2 presents a summary of the extent and probability of the added benefit of lurasidone.

Table 2: Lurasidone – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Extent and probability of added benefit**
Schizophrenia ▪ acute treatment ▪ prevention of relapse	Amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. 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), 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 aim of this report was to assess the added benefit of lurasidone compared with the ACT in adult patients with schizophrenia.

The G-BA specified amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone as ACTs. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. The company planned no summarizing analysis for all drugs. In the present benefit assessment, a summarizing assessment of the added benefit is conducted versus the drugs named by the G-BA.

Two research questions resulted for the assessment, which are derived from the different treatment goals in the treatment of patients with schizophrenia. On the one hand, this is the treatment of acute symptoms (e.g. after exacerbation or first diagnosis), on the other hand the prevention of relapse of a stable disease.

- Research question 1: acute treatment of patients with schizophrenia
- Research question 2: prevention of relapse in patients with schizophrenia

The studies presented by the company were also designed in such a way that they either investigated the first (acute treatment) or the second (prevention of relapse) research question. Below, the 2 research questions are therefore presented separately in Section 2.3 (acute treatment) and 2.4 (prevention of relapse).

The assessment was based on patient-relevant outcomes. Direct comparative RCTs were included in the assessment.

2.3 Research question 1: acute treatment of patients with schizophrenia

2.3.1 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 list on lurasidone (studies completed up to 24 September 2014)
- bibliographical literature search on lurasidone (last search on 26 September 2014)
- search in trial registries for studies on lurasidone (last search on 24 September 2014)

To check the completeness of the study pool:

- bibliographical literature search on lurasidone (last search on 14 November 2014)
- search in trial registries for studies on lurasidone (last search on 14 November 2014)

This check produced no additional relevant studies for the benefit assessment.

From the steps of information retrieval mentioned, the company identified 3 studies in which lurasidone was compared with risperidone (Study D1001002, hereinafter "002"), olanzapine (Study D1050231, hereinafter "231") or quetiapine XR (Study D1050233, hereinafter "233").

In these studies, lurasidone and the comparator therapies used were partly administered at dosages that deviate from treatment recommendations and do not comply with the respective Summaries of Product Characteristics (SPCs). In general, dose adjustments were not possible. This applied to the 3 studies to different extents. The treatment effect of an antipsychotic can be overestimated or underestimated, depending on the choice of dosage, the dose escalation or the lack of possibility for titration [3]. It is therefore doubtful whether the studies presented by the company can answer the research question of the benefit assessment.

However, the company based its conclusion on the added benefit exclusively on results on AEs and changes in body weight. It could not be inferred from its data that the effect on schizophrenia symptoms was of a similar size as the one of the ACT. Hence irrespective of the question whether the 3 studies were suitable for the benefit assessment at all, there is no proof of added benefit of lurasidone versus the ACT.

The 3 studies are described in the following sections, particularly addressing the problem of dosage mentioned. Subsequently, the effect of lurasidone on schizophrenia symptoms in comparison with the other drugs investigated in the studies will be addressed.

Description of the studies D1001002, D1050231 and D1050233

The characteristics of the studies 002, 231 and 233 are presented in Table 3 and Table 4.

Table 3: Characteristics of the studies included – RCT, direct comparison lurasidone vs. risperidone, olanzapine or quetiapine XR (acute treatment)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
D1001002	RCT, double-blind, multicentre, parallel, placebo-controlled, active-controlled	Hospitalized adult patients with schizophrenia[b] PANSS total score ≥ 70 and score ≥ 4 for at least 1 item on the positive scale at screening and start of treatment	1) lurasidone 40 mg/day[c] + placebo (N = 131) 2) lurasidone 80 mg/day[c,d] + placebo (N = 131) 3) placebo (N = 133)[e] 4) risperidone 4 mg/day[d] + placebo (N = 65)	Screening phase: day 21 to day 4 before baseline Observation phase: 3 days to 1 week Treatment phase: 6 weeks Follow-up: 6-17 days after completion of treatment	92 centres in Japan, Korea, Taiwan 6/2008-4/2010	Primary outcome: schizophrenia symptoms (PANSS total score) Secondary outcomes: schizophrenia symptoms (PANSS positive and negative scales), adverse events, suicidality
D1050231	RCT, double-blind, multicentre parallel, active-controlled, placebo-controlled	Hospitalized[f] adult patients with acute schizophrenia[g] PANSS total score ≥ 80 at screening and start of study, and score ≥ 4 (moderate) for at least 2 of the following symptoms: delusions, conceptual disorganization, hallucinations, unusual thought content, suspiciousness CGI-S score ≥ 4 at screening and start of study	1) lurasidone 40 mg/day[c] + placebo (N = 120) 2) lurasidone 120 mg/day[c,d] + placebo (N = 119) 3) olanzapine 15 mg/day[d] + placebo (N = 123) 4) placebo (N = 116)[e]	Screening phase: up to 14 days Wash-out phase: 3-7 days Treatment phase: 6 weeks Follow-up: 14 days after completion of treatment or open-label six-month extension phase	52 centres in India, Columbia, Lithuania, Philippines, United States 1/2008-6/2009	Primary outcome: schizophrenia symptoms (PANSS total score) Secondary outcomes: schizophrenia symptoms (PANSS positive and negative scales), adverse events, suicidality

(continued)

Table 3: Characteristics of the studies included – RCT, direct comparison lurasidone vs. risperidone, olanzapine or quetiapine XR (acute treatment) (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
D1050233	RCT, double-blind, multicentre parallel, active-controlled, placebo-controlled	Hospitalized[f] adult patients with acute schizophrenia[g] PANSS total score ≥ 80 at screening and start of study, and score ≥ 4 (moderate) for at least 2 of the following symptoms: delusions, conceptual disorganization, hallucinations, unusual thought content[h] CGI-S score ≥ 4 at screening and start of study	1) lurasidone 80 mg/day[c] + placebo (N = 125) 2) lurasidone 160 mg/day[c, d] + placebo (N = 121) 3) quetiapine XR 600 mg/day[d] + placebo (N = 120) 4) placebo (N = 122)[e]	Screening phase up to 14 days Wash-out phase (with placebo): 3-7 days Treatment phase: 6 weeks Follow-up: 14 days or double-blind 12-month extension study (D1050234)	63 centres in India, Columbia, Rumania, Russia, Ukraine, United States 10/2008–6/2010	Primary outcome: schizophrenia symptoms (PANSS total score) Secondary outcomes: schizophrenia symptoms (PANSS positive and negative scales), health-related quality of life, adverse events, suicidality

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: Based on the inclusion criteria it was assumed that these were patients with acute schizophrenia because they had to present with marked positive symptoms.
c: Lurasidone hydrochloride; 40 mg lurasidone hydrochloride are equivalent to 37 mg pure lurasidone.
d: In this treatment arm, the study medication was not administered from the beginning at the dose shown, but was up-titrated. Details on this are presented in Table 4.
e: The placebo arm is not relevant for the assessment and is no longer shown in the following tables.
f: Patients who fulfilled the criteria for stable disease could be discharged after 3 weeks of treatment.
g: Acute exacerbation of psychotic symptoms (no longer than 2 months) and marked worsening of disease state in comparison with patient's history, or hospitalization for treating an acute psychotic exacerbation for 2 weeks or less immediately before screening.
h: The symptom "suspiciousness" is also mentioned in Module 4A of the dossier. This is not contained in the CSR.
CGI-S: Clinical Global Impression Scale of Severity; CSR: clinical study report; N: number of randomized patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; vs.: versus

Study design

The studies 002, 231 and 233 were randomized, double-blind, active-controlled and placebo-controlled studies. Hospitalized patients aged 18 years or older with moderate to high severity of their schizophrenia who required acute treatment were enrolled. Depending on the study, the severity grade had to be determined by a total score of ≥ 70 or ≥ 80 and a score of 4 or higher on 1 or 2 PANSS items. For the studies 231 and 233, a CGI-S score of ≥ 4 was an additional prerequisite for inclusion in the study. The treatment duration in all 3 studies was 6 weeks, preceded by a 2-week screening phase and an observation or wash-out phase of up to 7 days. Patients received placebo for 3 to 7 days between screening and randomization.

In all 3 studies, 2 dosages of lurasidone were compared with an active comparator and placebo. All studies aimed to prove the superiority of lurasidone versus placebo. The placebo arms were not relevant for the assessment of the added benefit and are not further commented on.

Influence of starting dosages and specifications for titration in the studies 002, 231 and 233

The dosages and dosage regimens used in the individual studies are presented in Table 4.

Table 4: Characteristics of the interventions – RCT, direct comparison lurasidone vs. risperidone, olanzapine or quetiapine XR (acute treatment)

Study	Intervention	Comparison	Non-permitted concomitant medication
D1001002	Lurasidone 40 mg/day (fixed dosage), orally + placebo, fixed dose lurasidone, orally + placebo dosing regimen: day 1–7: 40 mg/day, day 8–14: 60 mg/day, thereafter 80 mg/day	Risperidone, orally + placebo dosing regimen: day 1–7: 2 mg/day, day 8–14: 3 mg/day, thereafter 4 mg/day	▪ antipsychotics not permitted except in cases when treatment was started before the study ▪ antimanic drugs and antiepileptics ▪ MAO inhibitors, CYP3A4 inhibitors (except dermatological drugs for external use) ▪ epinephrine ▪ electroconvulsive therapy
D1050231	Lurasidone 40 mg/day (fixed dosage), orally + placebo, fixed dose lurasidone 120 mg/day (fixed dosage), orally + placebo	Olanzapine, orally + placebo dosing regimen: day 1–7: 10 mg/day, thereafter 15 mg/day	▪ premedication with antidepressants, mood stabilizers, MAO inhibitors, other antipsychotics and psychotropic drugs (exceptions are shown in "restricted concomitant medication") were to be discontinued before the study ▪ CYP3A4 inhibitors, herbal or alternative remedies
D1050233	Lurasidone 80 mg/day (fixed dosage), orally + placebo, fixed dose lurasidone, orally + placebo dosing regimen: day 1 and 2: 120 mg/day, thereafter 160 mg/day	Quetiapine XR, orally + placebo dosing regimen: day 1-2: 300 mg/day, thereafter 600 mg/day	▪ psychotropic drugs including antipsychotics ▪ MAO inhibitors, CYP3A4 inhibitors, herbal or alternative remedies ▪ antidepressants, mood stabilizers
CGI-S: Clinical Global Impression Scale of Severity; CSR: clinical study report; CYP3A4: cytochrome P450 3A4; MAO: monoamine oxidase; N: number of randomized patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; vs.: versus			

Deviations from the SPCs regarding dosages both for the lurasidone and for the respective comparator arms occurred in all 3 studies. These differed in importance depending on the study.

Among other things, the deviations occurred in the initial dosing of lurasidone, which was higher in 2 study arms of the studies 231 and 233 (120 mg) than recommended in the SPC (40 mg) [4-6]. In the comparator arms, in contrast, there was potential underdosing. Patients in study 002 could receive risperidone in a daily dosage of no more than 4 mg, whereas, according to the SPC, most patients benefit from daily doses between 4 and 6 mg, and a

maximum dose of 16 mg risperidone per day is approved [7]. In Study 231, the maximum daily dose of olanzapine was 15 mg, whereas a maximum dose of 20 mg is approved [8].

Furthermore, no individual optimization of treatment was possible in the studies. All drugs were either used in fixed dosages, or fixed time points in the course of the study were specified at which dose adjustments of the drugs (in the intervention and in the treatment arm) for the patients had to be conducted. The extent of dose adjustment within the studies was also specified a priori for all patients equally. The S3 guideline for the treatment of schizophrenia (Gaebel 2006) [9] recommends to generally choose the lowest possible dosage of antipsychotics. Furthermore, the dose recommendations in the guideline are 3 to 6 mg/day (or even up to 10 mg/day for patients with multiple episodes) for risperidone, 5 to 20 mg/day for olanzapine, and 300 to 750 mg/day for quetiapine. The guideline also explicitly states that the reasonable dose in an individual case cannot be predicted with certainty, and that therefore often further dose adjustments have to be conducted after titration.

It is known that the treatment effect can be overestimated or underestimated, depending on the choice of dosage, the dose escalation or the lack of possibility for titration of the antipsychotics used (Heres 2006) [3]. It is stated in Heres 2006 that, in studies with olanzapine as comparator therapy, the upper dose is often limited to 15 mg/day, thus excluding the most effective dosage of 20 mg/day. In Study 231 included by the company, olanzapine was also exclusively administered at a fixed dosage of 15 mg/day. The lower efficacy of olanzapine in this dosage can lead to biased conclusions in favour of the intervention treatment [3]. Regarding the use of antipsychotics in fixed dosages, Heres 2006 concluded that this does not reflect the therapeutic flexibility required in the treatment of schizophrenia.

Comparison of the effect on schizophrenia symptoms

The comparison of the effect on schizophrenia symptoms was conducted under consideration of the different lurasidone dosages used in the studies.

To do this, the study arms of the 3 studies were categorized as “low”, “medium” and “high” depending on the lurasidone dosages used, and then pooled in a meta-analysis. The meta-analysis comprised the 3 comparator therapies risperidone, olanzapine and quetiapine XR. The category “low daily dose of lurasidone” contained the 40 mg arms of the studies 002 and 231. The category “medium daily dose of lurasidone” contained the 80 mg arms of the studies 002 and 233. This category was chosen for Study 002 because the patients received 40 mg or 80 mg lurasidone/day in the first or second week, but received 80 mg for a comparably longer period of time (4 weeks). The category “high daily dose of lurasidone” contained the 120 mg arm of Study 231 and the 160 mg arm of Study 233. The patients in Study 233 also received a dose of 120 mg only for the first 2 days.

The analyses mentioned were conducted for the PANSS total score and for the 3 PANSS subscales (positive scale, negative scale, general psychopathology scale) on the basis of the

continuous values. It was clear from the further study documents that responder analyses were also conducted for the 3 studies, but only for the PANSS total score. In addition, the response criteria were not consistent in the studies, and were 20% improvement in the PANSS total score in Study 002, and 20%, 30%, 40% and 50% in the studies 231 and 233. The European Medicines Agency (EMA) recommends a threshold value of 30% as response criterion, which may need adjustment in patients with higher severity [10]; the EMA guideline contains no details on necessary adjustments, however. The company did not mention these responder analyses in Module 4A of the dossier and also did not explain why the chosen threshold values were so different in the studies. Since responder analyses for the recommended threshold value of 30% were not available in all studies, the suitability of other threshold values was unclear, and the responder analyses for the PANSS subscales were not presented at all, the mean differences were primarily considered for the comparison of the effects, and the results on the available responder analyses are presented as additional information.

Figure 1 to Figure 4 show the meta-analyses for the PANSS total score and the PANSS subscales in the 3 studies considered. The results are presented in table form in Appendix B of the full dossier assessment.

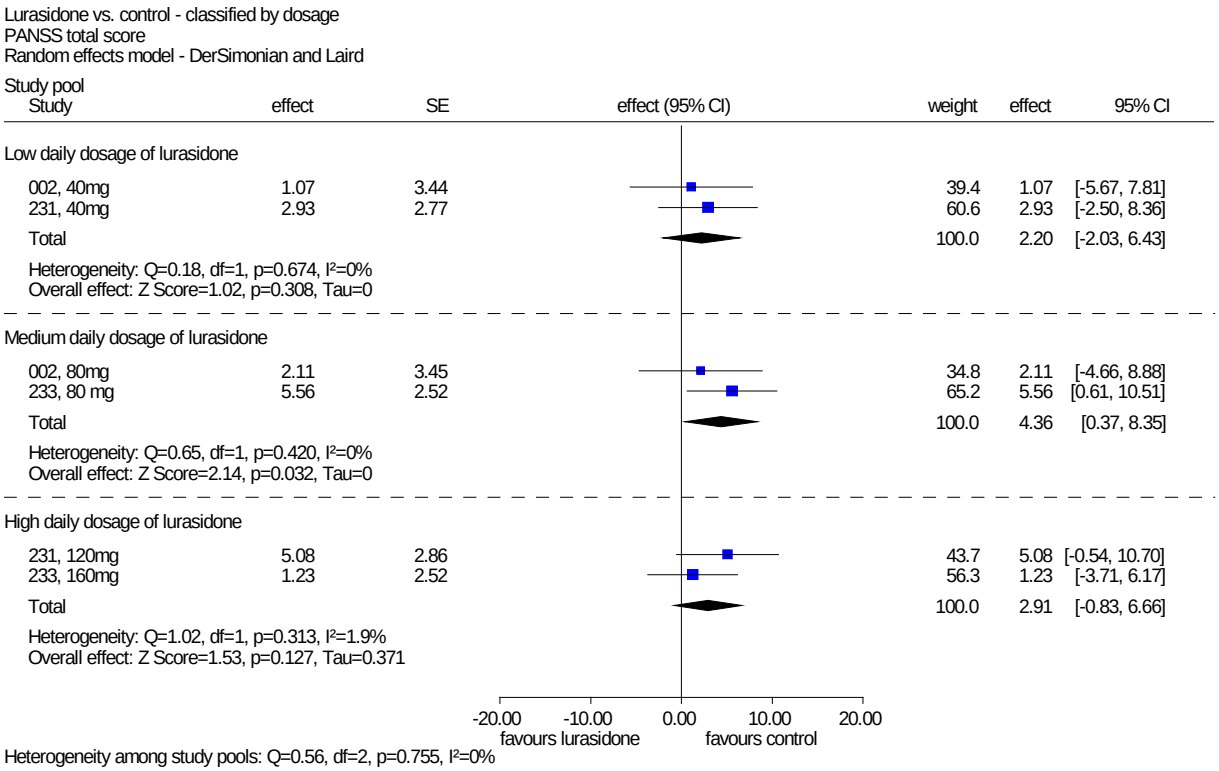

Figure 1: Meta-analysis, PANSS total score, lurasidone versus risperidone (Study 002), olanzapine (Study 231) and quetiapine XR (Study 233), classified according to low, medium and high daily dose; effect estimate: mean difference

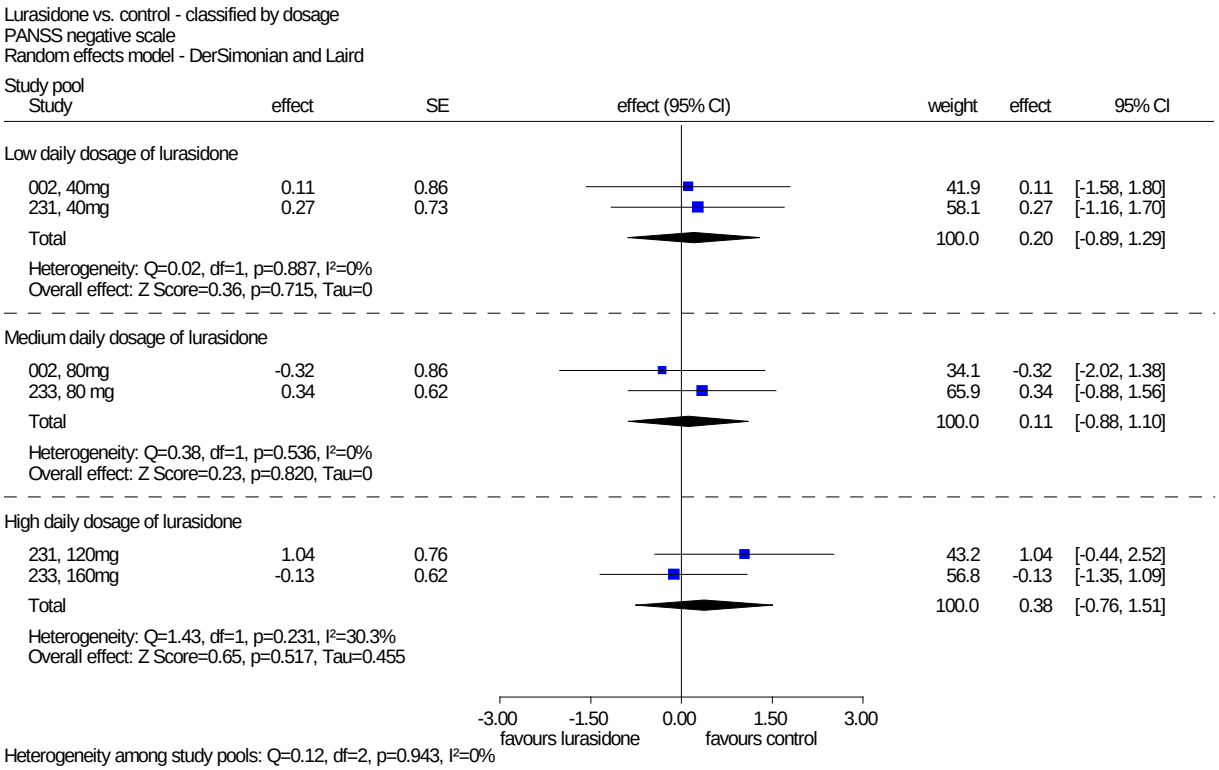

Figure 2: Meta-analysis, PANSS negative scale, lurasidone versus risperidone (Study 002), olanzapine (Study 231) and quetiapine XR (Study 233), classified according to low, medium and high daily dose; effect estimate: mean difference

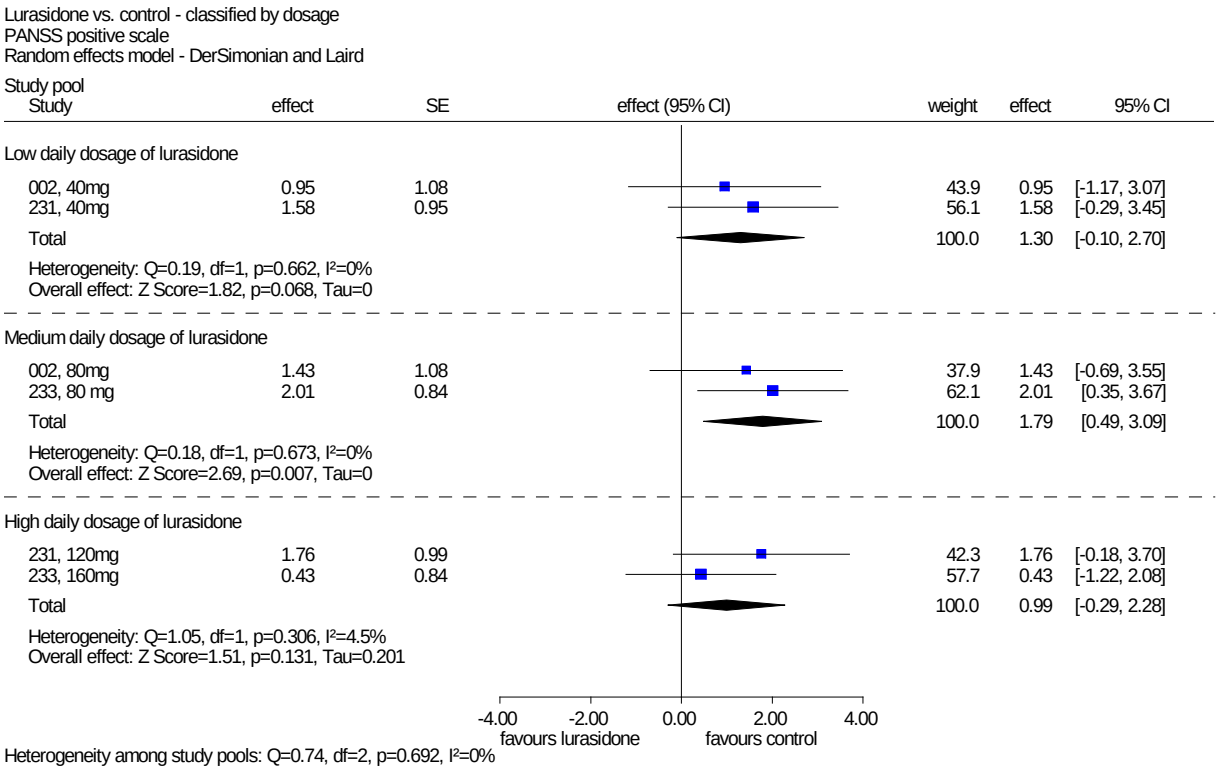

Figure 3: Meta-analysis, PANSS positive scale, lurasidone versus risperidone (Study 002), olanzapine (Study 231) and quetiapine XR (Study 233), classified according to low, medium and high daily dose; effect estimate: mean difference

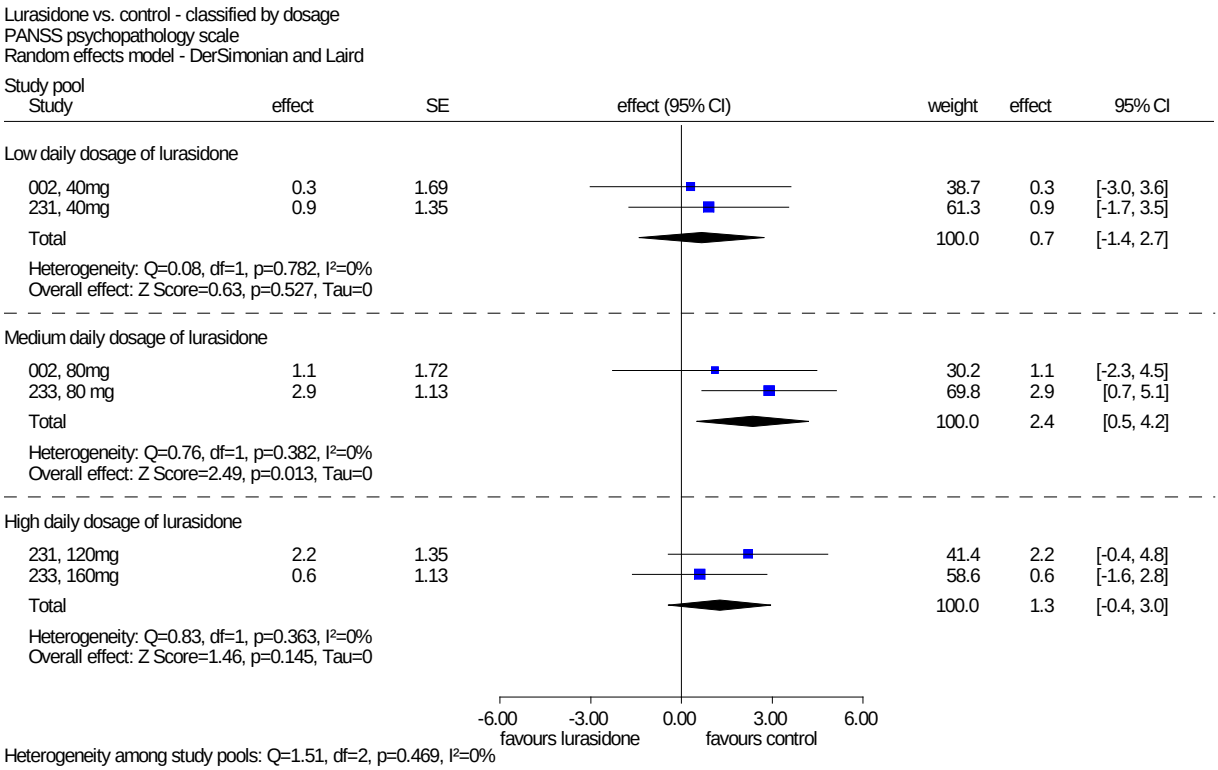

Figure 4: Meta-analysis, PANSS general psychopathology scale, lurasidone versus risperidone (Study 002), olanzapine (Study 231) and quetiapine XR (Study 233), classified according to low, medium and high daily dose; effect estimate: mean difference

The effect estimate in all lurasidone dosages showed a direction of effect to the disadvantage of lurasidone both in PANSS total score and in the PANSS subscales "positive scale" and "psychopathology symptoms". The effect for the PANSS total score and the PANSS subscales "positive scale" and "psychopathology symptoms" was statistically significant for the dosage of lurasidone 80 mg. In contrast, the effect estimates for the negative scale also pointed in the same direction, but they were so close to 0 that no clear directed effect could be assumed.

The company's documents contained no information on a non-inferiority threshold for the PANSS scales. In all 3 scales, the upper limit of the 95% CI was (sometimes markedly) in an area in which a relevant effect to the disadvantage of lurasidone cannot be excluded (see Appendix B, Figure 6 to Figure 9, of the full dossier assessment). This was confirmed by the responder analyses on the PANSS total score (which, as described, were only available to a limited extent). These partly showed a statistically significant difference to the disadvantage of lurasidone (response criterion 30%, see Appendix B, Figure 10. of the full dossier assessment).

Overall, it could not be inferred from the studies presented by the company that the effect of lurasidone on schizophrenia symptoms was at least similarly large as the one of the ACT.

Summary and consequences

In the studies included by the company in which the acute treatment of patients with schizophrenia was investigated, there were major uncertainties regarding the influence the dosages of lurasidone used in the studies and of the comparator therapies risperidone, olanzapine and quetiapine XR had on the study results. However, the company derived an added benefit in this research question only on the basis of the reduction in AEs. However, it could not be inferred from the available data on the studies 002, 231 and 233 that the effect of lurasidone on schizophrenia symptoms was at least similarly large as the one of the ACT. Even under the company's assumption that fewer AEs occurred under lurasidone, overall no added benefit could be derived from this.

Hence an added benefit of lurasidone in the acute treatment of patients with schizophrenia versus the ACT specified by the G-BA is not proven.

2.3.2 Extent and probability of added benefit (research question 1)

The result of the assessment of the added benefit of lurasidone in comparison with the ACT for the research question "acute treatment of schizophrenia" is summarized in Table 5.

Table 5: Lurasidone – extent and probability of added benefit (acute treatment)

Research question	**ACT**[a]	**Extent and probability of added benefit**
Acute treatment of schizophrenia	Amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

Overall, there is no proof of an added benefit of lurasidone in comparison with the ACT specified by the G-BA (amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone). Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's approach, which, in the overall assessment of all 5 studies it included without differentiation of the treatment goals of acute treatment or prevention of relapse, claimed an added benefit of lurasidone. There was deviating information on the extent of added benefit in the dossier: The company described proof of minor added benefit in Module 1 and in Sections 4.1 and 4.4.3 of Module 4A, and considerable added benefit in Section 4.4.2 of Module 4A. The company derived proof of a minor added benefit for the comparison of lurasidone with risperidone, and an indication of a minor added benefit in the comparison with quetiapine XR. For the comparison of lurasidone with olanzapine, the

company stated in Section 4.1 of Module 4A that it considered there to be an indication of a minor or of no added benefit.

2.3.3 List of included studies

D1001002

Dainippon Sumitomo Pharma. Randomized, placebo-controlled, double-blind, parallel-group, confirmatory study of SM-13496 (lurasidone HCl) in patients with schizophrenia <phase III study>: study D1001002; clinical study report [unpublished]. 2011.

Sumitomo Dainippon Pharma. Study of SM-13496 (lurasidone HCl) in patients with schizophrenia: full text view [online]. In: Clinicaltrials.gov. 11 June 2012 [accessed: 14 November 2014]. URL: http://ClinicalTrials.gov/show/NCT00711269.

D1050231

Dainippon Sumitomo Pharma. A phase 3 randomized, placebo- and active comparator-controlled clinical trial to study the safety and efficacy of two doses of lurasidone HCL in acutely psychotic patients with schizophrenia: study D1050231; clinical study report [unpublished]. 2009.

Dainippon Sumitomo Pharma America. A phase 3 randomized, placebo- and active comparator-controlled clinical trial to study the safety and efficacy of two doses of lurasidone HCl in acutely psychotic patients with schizophrenia [online]. In: EU Clinical Trials Register. [accessed: 14 November 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-003820-40.

Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry 2011; 168(9): 957-967.

Stahl SM, Cucchiaro J, Simonelli D, Hsu J, Pikalov A, Loebel A. Effectiveness of lurasidone for patients with schizophrenia following 6 weeks of acute treatment with lurasidone, olanzapine, or placebo: a 6-month, open-label, extension study. J Clin Psychiatry 2013; 74(5): 507-515.

Sunovion. Lurasidone HCl: a phase 3 study of patients with acute schizophrenia; full text view [online]. In: Clinicaltrials.gov. 9 April 2013 [accessed: 14 November 2014]. URL: http://ClinicalTrials.gov/show/NCT00615433.

Sunovion. Lurasidone HCl: a phase 3 study of patients with acute schizophrenia; study results [online]. In: Clinicaltrials.gov. 9 April 2013 [accessed: 14 November 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00615433.

D1050233

Harvey PD, Siu CO, Hsu J, Cucchiaro J, Maruff P, Loebel A. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. Eur Neuropsychopharmacol 2013; 23(11): 1373-1382.

Loebel A, Cucchiaro J, Sarma K, Xu L, Hsu C, Kalali AH et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res 2013; 145(1-3): 101-109.

Loebel AD, Siu CO, Cucchiaro JB, Pikalov AA, Harvey PD. Daytime sleepiness associated with lurasidone and quetiapine XR: results from a randomized double-blind, placebo-controlled trial in patients with schizophrenia. CNS Spectr 2014; 19(2): 197-205.

Sunovion. Lurasidone HCL: a 6-week phase 3 study of patients with acute schizophrenia; full text view [online]. In: Clinicaltrials.gov. 9 April 2013 [accessed: 14 November 2014]. URL: http://ClinicalTrials.gov/show/NCT00790192.

Sunovion. Lurasidone HCL: a 6-week phase 3 study of patients with acute schizophrenia; study results [online]. In: Clinicaltrials.gov. 9 April 2013 [accessed: 14 November 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00790192.

Sunovion Pharmaceuticals. A phase 3 randomized, doubel-blind, placebo- and active comparator-controlled clinical trial to study the efficacy and safety of two doses of lurasidone in acutely psychotic patients with schizophrenia: study D1050233; clinical study report [unpublished]. 2011.

2.4 Research question 2: prevention of relapse in patients with schizophrenia

2.4.1 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 list on lurasidone (studies completed up to 24 September 2014)
- bibliographical literature search on lurasidone (last search on 26 September 2014)
- search in trial registries for studies on lurasidone (last search on 24 September 2014)

To check the completeness of the study pool:

- bibliographical literature search on lurasidone (last search on 14 November 2014)
- search in trial registries for studies on lurasidone (last search on 14 November 2014)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 6: Study pool – RCT, direct comparison lurasidone vs. risperidone, olanzapine or quetiapine XR

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D1050237	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

Besides Study D1050237 (hereinafter referred to as “237”) relevant for the present benefit assessment, the company included another 12-month study, which investigated the research question on prevention of relapse (Study D1050234, hereinafter referred to as “234”). The study was not relevant for the benefit assessment however because the study design did not guarantee structural equality between the treatment groups.

Study D1050234 was a 2-arm study with a lurasidone and a quetiapine XR treatment arm. The dosing of the drugs could be chosen flexibly in both treatment arms, with allowed dose ranges between 40 and 160 mg in the lurasidone arm, and between 200 and 800 mg in the quetiapine arm.

Only those patients were included in Study 234 for whom a complete data set on all planned examinations was available at the last visit of Study 233. Hence no re-randomization was conducted at enrolment in Study 234. Since only 61% and 71% of the patients originally randomized to the lurasidone and quetiapine XR arms of Study 233 were included in Study 234, structural equality between the patient populations of the 2 treatment arms of Study 234 was not guaranteed. Hence the 234 extension study was unsuitable for the derivation of an added benefit of lurasidone versus the ACT and was not used for the benefit assessment.

Section 2.4.4 contains a reference list for the 237 study included.

2.4.1.2 Study characteristics

Table 7 and Table 8 describe the studies used for the benefit assessment.

Table 7: Characteristics of the studies included – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
D1050237	RCT, double-blind, multicentre parallel, active-controlled	not-hospitalized adult patients with stable chronic schizophrenia or schizoaffective disorder severity at most moderate: PANSS scores ≤ 4 for the symptoms "delusions", "conceptual disorganization", "hallucinations" and "unusual thought content", and CGI-S ≤ 4 at screening and start of treatment	1) lurasidone 40-120 mg/day + placebo (N = 427) 2) risperidone 2-6 mg/day + placebo (N = 202)	Screening phase: 2 weeks Transition phase: 1 to 7 days Treatment phase: 12 months	68 centres in Argentina, Brazil, Chile, Croatia, Israel, South Africa, Thailand, United States 3/2008 – 7/2010	Primary outcome: not explicitly stated in the study protocol[b] Secondary outcomes: relapse rate[c], schizophrenia symptoms, suicidality

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: The study objective was to evaluate the safety and tolerability of lurasidone; in Module 4A of the dossier, mortality, AEs, SAEs and treatment discontinuation due to AEs were named as primary treatment objectives.
c: Presented as secondary outcome in Module 4A of the dossier. No primary outcome was explicitly mentioned in the CSR, but the sample size in the statistical analysis plan was calculated on the basis of the relapse rate.

AE: adverse event; CGI-S: Clinical Global Impression Scale of Severity; CSR: clinical study report; N: number of randomized patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 8: Characteristics of the interventions – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study	Intervention	Comparison	Non-permitted concomitant medication
D1050237	Lurasidone 40–120 mg/day[a], orally+ placebo dosing regimen: day 1-7: 80 mg/day, thereafter individual dose, administration once daily dose adjustments could be performed in 40 mg steps at weekly intervals	Risperidone 2–6 mg/day, orally + placebo dosing regimen: day 1-2: 2 mg/day, day 3-7: 4 mg/day, thereafter individual dose, administration once daily	▪ psychotropic drugs including antipsychotics ▪ MAO inhibitors, CYP3A4 inhibitors, herbal or alternative remedies ▪ typical or atypical antipsychotics, D2 agonists, D2 antagonists or stimulants (exceptions are shown in "allowed concomitant medication")
a: The data refer to lurasidone hydrochloride; this corresponds to 37-111 mg pure lurasidone. CYP3A4: cytochrome P450 3A4; MAO: monoamine oxidase; N: number of randomized patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; vs.: versus			

Study 237 was a randomized, double-blind, active-controlled study, in which lurasidone was compared with risperidone. Adult patients with schizophrenia were enrolled. The treatment duration was 12 months. The dose of the study medication was flexible in both treatment arms. In the lurasidone arm, lurasidone could be administered in a dose range of 40 to 120 mg/day; the dose could be changed in 40 mg steps (only in the first treatment week, a stable dose of 80 mg/day lurasidone was administered). The dose in the risperidone arm was up-titrated to 4 mg/day within the first treatment week according to a fixed regimen (see Table 8). Thereafter, the patients received an individual dose. This could be adjusted to a dose between 2 and 6 mg/day with available dose steps of 2 mg. In both treatment arms, dose adjustments only be performed at intervals of at least 1 week and then only by one dose step at a time. The company's documents contained no defined criteria as to when the dose of the study medication was to be changed.

Patients with a PANSS score of ≤ 4 for the symptoms "delusions", "conceptual disorganization", "hallucinations" and "unusual thought content", and concurrent CGI-S score of ≤ 4 could be enrolled in the study. The patients were not hospitalized. According to the company, the patients included are to be considered clinically stable.

The dosing of the study medication partly deviated from the recommendations in the SPCs on lurasidone [4-6] and risperidone [7]. On the one hand, lurasidone should be administered at an initial dose of 40 mg/day, according to the SPC. The initial dose in Study 237 was 80 mg/day. This dose was only administered for the duration of one week, however. Then the dose could be reduced to 40 mg/day. Furthermore, the maximum daily dose of lurasidone according to the approval is 160 mg/day. In Study 237, a maximum of 120 mg/day was permitted. The influence of these deviations was considered to be minor.

The dose of risperidone in Study 237 was 2 to 6 mg/day. According to the SPC [7], higher dosages are not excluded, but it is assumed that most patients will benefit from 4 to 6 mg/day. A dose below 4 mg/day is regarded useful in individual cases. Hence the dosages in the study were largely in compliance with the approval.

The patients and the treating staff were blinded with regard to the type of study medication, but not to possible dose adjustments.

The primary objective of the study was to evaluate the long-term effects of lurasidone. It could be inferred from the sample size planning of the study that the proof of the non-inferiority of lurasidone in comparison with risperidone for the outcome “relapse rate” was a key objective.

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study characteristics category	Lurasidone N[a] = 427	Risperidone N[a] = 202
D1050237		
Age [years], mean (SD)	41.7 (11.3)	41.6 (11.3)
Sex [F/M], %	28/72	38/62
PANSS total score at the start of the study, mean (SD)	65.0 (12.3)	65.2 (12.3)
Disease duration: time between first diagnosis and randomization [years], mean (SD)	16.5 (11.2)	17.3 (11.4)
Number of previous hospitalizations, n (%)		
0	90 (21)	39 (19)
1	71 (17)	36 (18)
2	61 (15)	32 (16)
3	58 (14)	22 (11)
≥ 4	139 (33)	73 (36)
Comedication: antipsychotics	48 (11.5)	22 (10.9)
Comedication: anticholinergics	46 (11.0)	30 (14.9)
Ethnicity, n (%)		
white	151 (36)	88 (44)
non-white	268 (64[b])	114 (56[b])
Geographical region, n (%)		
Europe	7 (2)	5 (2)
non-Europe[c]	412 (98[b])	197 (98[b])
Treatment discontinuations, n (%)	277 (65)	105 (52)

a: Number of randomized patients; values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b: Institute's calculation.
c: The group of non-Europeans is composed as follows: North America (66%), South America (14%), Africa (15%), Asia (3%).
F: female; M: male; N: number of randomized patients; n: number of patients in the category; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patients in the 2 treatment arms of Study 237 were comparable with regard to age, severity of their schizophrenia symptoms, disease duration, number of previous hospitalizations, and origin. Both groups contained more men than women with 28% women and 72% men in the lurasidone group, and 38% women and 62% men in the risperidone group. The groups differed by approximately 8 percentage points regarding skin colour (white or non-white).

The mean PANSS total score of the patients was approximately 65, which, according to Leucht 2005, indicates a disease severity of no more than moderate [11]. Approximately one

third of the patients had been hospitalized for schizophrenia 4 times or more before enrolment in the study. Over 10% of the patients in both study arms received antipsychotics and/or anticholinergics as concomitant medication.

The study was mainly conducted outside Europe, with the majority of the patients being from North America (66%), followed by Africa (15%) and South America (14%). Only 2% of the study participants were from Europe (Croatia); the study was not conducted in German study centres. The company's documents contained no information on further care pathways, particularly psychotherapeutic care. The transferability of the study results to the German health care context is therefore questionable.

With 65% in the lurasidone arm and 52% in the risperidone arm, the number of patients who discontinued treatment was high. This affected the risk of bias at study level. The consequences are described in Section 2.4.2.2.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
D1050237	Yes	Yes	Yes	Unclear	Yes	No[a]	High[a]

a: High proportion of patients who discontinued the study prematurely and large difference in the median time to study discontinuation.
RCT: randomized controlled trial; vs.: versus

The risk of bias at study level was rated as high. The reason for this is the high rate of missing observations in the course of the study, which was up to over 60% at the end of the study, and the difference regarding the time point of discontinuation between the study arms. Half the patients discontinued the study after 5.9 months (lurasidone arm) and 9.6 months (risperidone arm).

This deviates from the company's evaluation, which assumed a low risk of bias at study level.

Moreover, the transferability of the results to the German health care context is questionable because the study was not conducted in Germany and there was no information on further care pathways such as psychotherapeutic care.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - relapse rate
  - schizophrenia symptoms (measured with PANSS)
  - rehospitalization for worsening of psychosis
- Health-related quality of life: no data available
- Adverse events
  - overall rate of SAEs
  - overall rate of treatment discontinuations due to AEs
  - vomiting (Preferred Term [PT])
  - constipation (PT)
  - reproductive system and breast disorders (SOC)
  - suicidality
  - akathisia
    - measured with total score and global clinical assessment of the BAS
    - recorded as AE (PT)
  - parkinsonism (measured with total score of the SAS)
  - QT interval prolongation (QTc interval > 500ms)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4A) (see Section 2.6.2.4.3 of the full dossier assessment).

Table 11 shows for which outcomes data were available in the studies included.

Table 11: Matrix of outcomes – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study	Outcomes													
	All-cause mortality	Schizophrenia symptoms[a]	Relapse rate	Rehospitalization for worsening of psychosis	Health-related quality of life	SAEs	Discontinuation due to AEs	Akathisia[b]	Parkinsonism[c]	Suicidality	Vomiting	Constipation	Reproductive system and breast disorders	QT interval prolongation (QTc interval > 500 ms)
D1050237	Yes	Yes	Yes[d]	Yes	–[e]	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes

a: Measured with the PANSS symptom scales: total score, positive scale, negative scale and general psychopathology scale.
b: Measured with the BAS symptom scale (total score of the items 1 to 3 and global clinical assessment) and recorded as MedDRA PT.
c: Measured with the SAS symptom scale (total score).
d: Operationalized as composite outcome, but only data for 1 of the 3 components (rehospitalization for worsening of psychosis) is shown; the outcome can therefore only be interpreted to a limited extent.
e: The outcome was not recorded in the study.
f: No evaluable data available.

AE: adverse event; BAS: Barnes Akathisia Scale; MedDRA: Medical Dictionary for Regulatory Activities; PANSS: Positive and Negative Syndrome Scale; PT: Preferred Term; QTc: corrected QT interval; RCT: randomized controlled trial; SAE: serious adverse event; SAS: Simpson-Angus Scale; vs.: versus

2.4.2.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study	Study level	Outcomes													
		All-cause mortality	Schizophrenia symptoms[a]	Relapse rate	Rehospitalization for worsening of psychosis	Health-related quality of life	SAEs	Discontinuation due to AEs	Akathisia[b]	Parkinsonism[c]	Suicidality	Vomiting	Constipation	Reproductive system and breast disorders	QT interval prolongation (QTc interval > 500 ms)
D1050237	H	H	H	-[d]	H	–[e]	H	H	H	H	-[f]	H	H	H	H

a: Measured with the PANSS symptom scales: total score, positive scale, negative scale and general psychopathology scale.
b: Measured with the BAS symptom scale (total score of the items 1 to 3 and global clinical assessment) and recorded as MedDRA PT.
c: Measured with the SAS symptom scale (total score).
d: Operationalized as composite outcome, but only data for 1 of the 3 components (rehospitalization for worsening of psychosis) is shown; the outcome can therefore only be interpreted to a limited extent.
e: The outcome was not recorded in the study.
f: No evaluable data available

AE: adverse event; BAS: Barnes Akathisia Scale; H: high; MedDRA: Medical Dictionary for Regulatory Activities; PANSS: Positive and Negative Syndrome Scale; PT: Preferred Term; QTc: corrected QT interval; RCT: randomized controlled trial; SAE: serious adverse event; SAS: Simpson-Angus Scale; vs.: versus

The risk of bias at outcome level was rated as high for all outcomes. The reasons for assuming a high risk of bias at study level also lead to assuming a high risk of bias for all outcomes considered here. For none of the outcomes used were the bias aspects at study level negligible, which would have led to assuming an outcome-specific low risk of bias.

This deviates from the company's assessment, which only assumed a high risk of bias for the outcome schizophrenia symptoms.

Since only one study was relevant for the assessment and the certainty of results was considered to be moderate for all outcomes, no more than hints of an added benefit can be derived.

2.4.2.3 Results

Table 13, Table 14 and Table 15 summarize the results on the comparison of lurasidone with risperidone in patients with schizophrenia. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 13: Results (continuous outcomes – benefit) – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study outcome category outcome	Lurasidone			Risperidone			Lurasidone vs. risperidone
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	Mean difference [95% CI]; p-value
D1050237							
Morbidity							
Schizophrenia symptoms							
PANSS total score[c]	410	65.0 (12.3)	-4.7 (0.9)	197	65.3 (12.3)	-6.5 (1.1)	1.9 [-0.9; 4.6]; 0.181 Hedges' g: 0.12 [-0.05; 0.29]
PANSS positive scale[c]	410	15.1 (4.0)	-1.6 (0.3)	197	15.1 (4.1)	-1.9 (0.3)	0.3 [-0.5; 1.1]; 0.488 Hedges' g: 0.06 [-0.11; 0.23]
PANSS negative scale[c]	410	18.8 (4.6)	-1.3 (0.3)	197	19.0 (4.4)	-1.4 (0.4)	0.0 [-0.9; 1.0]; 0.948 Hedges' g: 0.00 [-0.17; 0.17]
PANSS general psychopathology scale[c]	410	31.3 (6.9)	-2.3 (0.4)	197	31.2 (7.0)	-3.6 (0.6)	1.3 [-0.1; 2.7]; 0.072 Hedges' g: 0.16 [-0.01; 0.33]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, MMRM analysis of the ITT population.
c: Higher scores on the scales indicate a higher severity grade.
CI: confidence interval; ITT: intention to treat; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 14: Results (dichotomous outcomes) – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study outcome category outcome	Lurasidone		Risperidone		Lurasidone vs. risperidone
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
D1050237					
Mortality					
All-cause mortality	419	2 (0.5)	202	0 (0)	2.42 [0.12; 50.11][a]; 0.356[b]
Morbidity					
additional: Relapse rate	410	82 (20.0)	198	32 (16.2)	1.31[c] [0.87; 1.97]; 0.194
Rehospitalization	410	27 (6.6)	198	13 (6.6)	0.97[c] [0.50; 1.89]; 0.924
Health-related quality of life	Outcome not recorded				
Adverse events					
AEs	419	354 (84.5)	202	171 (84.7)	
SAEs	419	46 (11.0)	202	20 (9.9)	1.11 [0.67; 1.82]; 0.684
Discontinuation due to AEs[e]	419	46 (11.0)	202	10 (5.0)	2.22 [1.14; 4.30]; 0.014[b]
QTc interval prolongation > 500 ms	419	0 (0)	202	0 (0)	NC; > 0.999[a]
Headache	419	42 (10.0)	202	30 (14.9)	0.67 [0.44; 1.05][d]; 0.081[b]
Akathisia	419	60 (14.3)	202	16 (7.9)	1.81 [1.07; 3.06][d]; 0.023[b]
Gastrointestinal disorders	419	137 (32.7)	202	54 (26.7)	1.22 [0.94; 1.60][d]; 0.135[b]
Nausea	419	70 (16.7)	202	22 (10.9)	1.53 [0.98; 2.40][d]; 0.057[b]
Vomiting	419	42 (10.0)	202	7 (3.5)	2.89 [1.32; 6.32][d]; 0.005[b]
Constipation	419	8 (1.9)	202	14 (6.9)	0.28 [0.12; 0.65][d]; 0.002[b]
Reproductive system and breast disorders	419	19 (4.5)	202	19 (9.4)	0.48 [0.26; 0.89][d]; 0.045[b]
additional: Weight increase ≥ 7%	410	30 (7.3)	197	27 (13.7)	0.53 [0.33; 0.87]; p = 0.01

a: Institute's calculation, asymptotic, with a correction term of 0.5 added to each cell frequency of the 2x2 table.
b: Institute's calculation, unconditional exact test (CSZ method [12]).
c: Hazard ratio.
d: Institute's calculation, asymptotic.
e: Data excluding SOC "psychiatric disorders" because these are symptoms of the underlying disease.
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; NC: not calculable; QTc: corrected QT interval (Fridericia's correction); RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 15: Results (continuous outcomes – harm) – RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study outcome category outcome	Lurasidone			Risperidone			Lurasidone vs. risperidone
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	Mean difference [95% CI]; p-value
D1050237							
Adverse events							
Akathisia (BAS, global clinical assessment[c])	410	0.18 (0.56)	0.04 (0.02)	198	0.15 (0.46)	-0.02 (0.04)	0.06 [-0.02; 0.15]; 0.126
Akathisia (BAS; total score[c])	410	0.28 (0.90)	0.12 (0.04)	198	0.23 (0.69)	-0.07 (0.06)	0.18 [0.04; 0.32]; 0.012 Hedges' g: 0.22 [0.05; 0.32][d]
Parkinsonism (SAS; total score[c])	410	0.09 (0.19)	0.00 (0.01)	198	0.13 (0.27)	-0.02 (0.01)	0.02 [-0.02; 0.05]; 0.332
additional: Dyskinesia (AIMS; total score[c])	410	0.62 (1.59)	-0.05 (0.05)	198	0.51 (1.38)	-0.03 (0.08)	-0.02 [-0.20; 0.16]; 0.819
additional: Change in body weight at month 12	410	82.96 (18.43)	-0.97 (5.06)[d]	197	80.99 (16.54)[d]	1.47 (5.03)	ND [ND]; p < 0.001

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, LOCF analysis of the ITT population.
c: Higher scores on the scales indicate a higher severity grade.
d: Institute's calculation.
AIMS: Abnormal Involuntary Movement Scale; BAS: Barnes Akathisia Scale; CI: confidence interval; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAS: Simpson-Angus Scale; SD: standard deviation; SE: standard error; vs.: versus

Mortality

Two patients died in the course of the study. Both were treated with lurasidone. There was no statistically significant difference between the treatment groups. An added benefit or greater harm of lurasidone compared with risperidone for mortality is therefore not proven. This concurs with the company's assessment.

Morbidity

Relapse rate

The company operationalized the relapse rate as composite outcome, but presented separate data for only 1 of the 3 components of the outcome (rehospitalization for worsening of

psychosis) (see Section 2.6.2.4.3 of the full dossier assessment). The outcome could therefore be interpreted only to a limited extent.

Proving the non-inferiority of lurasidone versus risperidone based on the relapse rate was the study objective of Study 237. The non-inferiority threshold was a hazard ratio of 1.6. The study objective was not achieved because the upper limit of the 95% CI of the hazard ratio was 1.97. This was also determined by the EMA in the framework of the Public Assessment Report on lurasidone [13]. Hence the non-inferiority of lurasidone is not proven.

Schizophrenia symptoms

The severity of the schizophrenia symptoms was assessed with the PANSS. Results were only available for the mean difference. The company presented no responder analyses.

The result was not statistically significant in the total score or in the 3 subscales. Due to the upper limit of the 95% CI it is uncertain, however, whether the effects of lurasidone are of a similar size as the ones of risperidone in the total score and in the subscale "psychopathology symptoms". This concurs with the missing proof of non-inferiority in the outcome "relapse rate".

Rehospitalization rate for worsening of psychosis

There was no statistically significant difference between the treatment groups for the rate of rehospitalizations for worsening of psychosis. An added benefit of lurasidone in comparison with risperidone for this outcome is therefore not proven. This concurs with the company's assessment. Since there were no noteworthy numerical differences between the treatment groups, no relevant effect to the disadvantage of lurasidone is assumed.

Health-related quality of life

Health-related quality of life was not recorded in Study 237. An added benefit for this outcome is therefore not proven.

Adverse events

Serious adverse events

There was no statistically significant difference between the treatment groups for the overall rate of SAEs. There was no noteworthy numerical difference between the treatment groups for other SAEs. Mainly symptoms of the underlying disease were included in the overall rate of SAEs. Greater or lesser harm from lurasidone than from risperidone is therefore not proven.

Discontinuation due to adverse events

There was a statistically significant difference in favour of risperidone for the overall rate of treatment discontinuations due to AEs. This was mainly caused by discontinuations due to AEs that could not be categorized as symptoms of the underlying disease. The result remained statistically significant in an analysis without discontinuations due to symptoms of the

underlying disease (i.e. excluding the SOC "psychiatric disorders"). This results in a hint of greater harm from lurasidone in comparison with risperidone.

Vomiting

There was a statistically significant difference between the treatment groups in favour of risperidone for the outcome "vomiting". This results in a hint of greater harm from lurasidone in comparison with risperidone. The company did not consider the outcome "vomiting" in Module 4A of the dossier.

Constipation

There was a statistically significant difference between the treatment groups in favour of lurasidone for the outcome "constipation". This results in a hint of lesser harm from lurasidone in comparison with risperidone. The company did not consider the outcome "constipation" in Module 4A of the dossier.

Reproductive system and breast disorders

There was a statistically significant difference between the treatment groups in favour of lurasidone for the outcome "reproductive system and breast disorders". This results in a hint of lesser harm from lurasidone in comparison with risperidone. The company did not consider the outcome "reproductive system and breast disorders" in Module 4A of the dossier.

Akathisia

The outcome "akathisia" was recorded as the rate of patients in whom akathisia was recorded as AE. In addition, the severity of akathisia induced by antipsychotic medication was measured with the BAS.

Rate of patients in whom akathisia was recorded as AE

There was a statistically significant difference between the treatment groups in favour of risperidone for the outcome "akathisia". The extent of this effect was no more than marginal, however, because the upper limit of the 95% CI, with reversed direction of effect, was larger than the threshold value of 0.90 (see also the *General Methods* of the Institute [1]). Greater or lesser harm from lurasidone in comparison with risperidone is therefore not proven regarding this outcome. The company did not consider the outcome "akathisia" in Module 4A of the dossier.

BAS (global clinical assessment)

There was no statistically significant difference between the treatment groups for the item of clinical global assessment using the BAS. Greater or lesser harm from lurasidone in comparison with risperidone is therefore not proven regarding this outcome. This concurs with the company's assessment.

BAS (total score)

There was a statistically significant difference in favour of risperidone for the BAS total score. It is to be noted that a higher BAS score reflects a worse state. The SMD in the form of Hedges' g was considered to check the relevance of this result. The 95% CI of the SMD did not lie completely above the irrelevance threshold of 0.2. Hence an irrelevant effect cannot be excluded. Greater harm from lurasidone for this outcome is therefore not proven. The company did not consider the BAS total score in Module 4A of the dossier.

Parkinsonism

The severity of parkinsonism induced by antipsychotic medication was measured with the SAS. There was no statistically significant difference between the treatment groups for the SAS total score.

Prolongation of QT interval (QTc interval > 500 ms)

No patients had QTc intervals of greater than 500 ms (Fridericia's correction). Greater or lesser harm from lurasidone than from risperidone is therefore not proven regarding this outcome. This concurs with the company's assessment, which used a different operationalization of this outcome, however.

2.4.2.4 Subgroups and other effect modifiers

Below, only the results for subgroups and outcomes are presented in which there were at least indications of an effect modification between treatment effect and subgroup.

In addition, there must be a statistically significant effect in at least one of the subgroups. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Table 16 summarizes the subgroup results on the comparison of lurasidone with risperidone in patients with schizophrenia. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 16: Subgroups (continuous outcomes) parkinsonism by ethnicity, RCT, direct comparison lurasidone vs. risperidone (prevention of relapse)

Study outcome characteristic subgroup	Lurasidone			Risperidone			Lurasidone vs. risperidone
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SE)	Mean difference [95% CI]; p-value
D1050237							
Parkinsonism (SAS; total score)[c]							
Ethnicity						Interaction:	p-value = 0.090[c]
white	149	0.13 (0.23)	-0.03[e] (0.02)	86	0.16 (0.31)	-0.01[e] (0.03)	-0.02 [-0.08; 0.04]; 0.554
non-white	261	0.07 (0.16)	0.01[e] (0.01)	112	0.10 (0.23)	-0.03[e] (0.02)	0.04 [0.00; 0.07]; 0.030
							Hedges' g: 0.25 [0.03; 0.47][d]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Unless stated otherwise, MMRM analysis of the ITT population.
c: Higher scores on the scales indicate a higher severity grade.
d: Institute's calculation.
e: ANCOVA-LOCF analysis of the ITT population.
ANCOVA: analysis of covariance; CI: confidence interval; ITT: intention to treat; LOCF: last observation carried forward; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PANSS: Positive and Negative Syndrome Scale; RCT: randomized controlled trial; SAS: Simpson-Angus Scale; SD: standard deviation; SE: standard error; vs.: versus

There was an indication of an effect modification by the characteristic "ethnicity" for the SAS. There was no statistically significant difference between the treatment groups for white patients.

There was a statistically significant difference in favour of risperidone for non-white patients. It is to be noted that higher SAS scores reflect a worse state. The 95% CI of Hedges' g did not lie completely above the irrelevance threshold of 0.2. Hence an irrelevant effect cannot be excluded.

Overall, the effect modification on the outcome "parkinsonism" did not influence the overall result so that it was not considered further.

2.4.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subquestion is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 on the one hand resulted in hints of greater harm from lurasidone than from risperidone for the outcomes "vomiting" and "discontinuations due to AEs", and on the other, in hints of lesser harm for the outcomes "constipation" and "reproductive system and breast disorders". The extent of the respective added benefit at outcome level was estimated from these results (see Table 19). With regard to schizophrenia symptoms, it could not be inferred that the effect of lurasidone is at least similar in size to the one of risperidone.

Table 17: Extent of added benefit at outcome level: lurasidone vs. risperidone (prevention of relapse)

Outcome category **outcome**	**Lurasidone vs. risperidone** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.5% vs. 0% RR: 2.42 [0.12; 50.11][c] p = 0.356[d]	Added benefit not proven
Morbidity (schizophrenia symptoms)		
PANSS total score	MD: 1.9 [-0.9; 4.6] p = 0.181	Added benefit not proven
PANSS positive scale	MD: 0.3 [-0.5; 1.1] p = 0.488	Added benefit not proven
PANSS negative scale	MD: 0.0 [-0.9; 1.0] p = 0.948	Added benefit not proven
PANSS general psychopathology scale	MD: 1.3 [-0.1; 2.7] p = 0.072	Added benefit not proven
Rehospitalization	6.6% vs. 6.6% HR: 0.97 [0.50; 1.89] p = 0.924	Added benefit not proven
additional presentation: Relapse rate	20.0% vs. 16.2% HR: 1.31[c] [0.87; 1.97] p = 0.194	
Adverse events		
SAEs	11.0% vs. 9.9% RR: 1.11 [0.67; 1.82] p = 0.684	Greater/lesser harm not proven
Discontinuations due to AEs	11.0% vs. 5.0% RR: 2.22 [1.14; 4.30] 0.45 [0.23; 0.88][f] p = 0.014[d] probability: “hint”	Outcome category: non-serious/non-severe AEs $CI_u < 0.90$ greater harm, extent: “minor”
Vomiting	10.0 % vs. 3.5 % RR: 2.89[e] [1.32; 6.32] 0.35 [0.16; 0.76][f] p = 0.005[d] probability: “hint”	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: “considerable”

(continued)

Table 17: Extent of added benefit at outcome level: lurasidone vs. risperidone (prevention of relapse) (continued)

Outcome category **outcome**	**Lurasidone vs. risperidone** **proportion of events** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Constipation	1.9% vs. 6.9% RR: 0.28[e] [0.12; 0.65] p = 0.002[d] probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm, extent: "considerable"
Reproductive system and breast disorders	4.5% vs. 9.4% RR: 0.48[e] [0.26; 0.89] p = 0.045[d] probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.90$ lesser harm, extent: "minor"
Akathisia (AE)	14.3% vs. 7.9% RR: 1.81[e] [1.07; 3.06] 0.55 [0.33; 0.94][f] p = 0.023[d]	Outcome category: non-serious/non-severe AEs $0.90 < CI_u$ Greater/lesser harm not proven
Akathisia (BAS total score)	MD: 0.18 [0.04; 0.32] p = 0.012 Hedges' g: 0.22 [0.05; 0.32]	Greater/lesser harm not proven
Akathisia (BAS, global clinical assessment)	MD: 0.06 [-0.02; 0.15] p = 0.126	Greater/lesser harm not proven
Parkinsonism (SAS total score)	MD: 0.02 [-0.02; 0.05] p = 0.332	Greater/lesser harm not proven
QTc interval > 500 ms	0% vs. 0% RR: NC p > 0.999[d]	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, asymptotic, with a correction term of 0.5 added to each cell frequency of the 2x2 table.
d: Institute's calculation, unconditional exact test (CSZ method according to [12]).
e: Institute's calculation, asymptotic.
f: Proportion of events lurasidone vs. risperidone (reversed direction of effect to enable direct use of limits to derive the extent of added benefit).
AE: adverse event; BAS: Barnes Akathisia Scale; CI: confidence interval; CI_u: upper limit of CI; CSZ: convexity, symmetry, z score; HR: hazard ratio; MD: mean difference; NC: not calculable; PANSS: Positive and Negative Syndrome Scale; QTc: corrected QT interval (Fridericia's correction); RR: relative risk; SAE: serious adverse event; SAS: Simpson-Angus Scale; SE: standard error; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of lurasidone in comparison with risperidone (prevention of relapse)

Positive effects	**Negative effects**
Hint of lesser harm – extent: "considerable" (non-serious/non-severe adverse events: constipation)	Hint of greater harm – extent: "considerable" (non-serious/non-severe adverse events: vomiting)
Hint of lesser harm – extent: "minor" (non-serious/non-severe adverse events: reproductive system and breast disorders)	Hint of greater harm - extent "minor" (non-serious/non-severe adverse events: discontinuations due to adverse events)

In the overall assessment of Study 237, there were statistically significant effects only for the outcomes from the category "non-serious/non-severe AEs", both in favour and to the disadvantage of lurasidone. Overall, neither an advantage nor a disadvantage of lurasidone results from this.

In addition, it is uncertain whether the effect of lurasidone on schizophrenia symptoms is at least similar in size as the one of risperidone.

In summary, there is no proof of an added benefit of lurasidone versus the ACT for patients with schizophrenia.

The result of the assessment of the added benefit of lurasidone in comparison with the ACT is summarized in Table 19.

Table 19: Lurasidone – extent and probability of added benefit

Research question	**ACT**[a]	**Extent and probability of added benefit**
Prevention of relapse in patients with schizophrenia	Amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine and ziprasidone	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from the company's approach, which, in the overall assessment of all 5 studies it included without differentiation of the treatment goals of acute treatment or prevention of relapse, claimed an added benefit of lurasidone. A detailed description of the company's approach can be found in Section 2.3.2 of the present benefit assessment.

2.4.4 List of included studies

D1050237

Citrome L, Cucchiaro J, Sarma K, Phillips D, Silva R, Tsuchiya S et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. Int Clin Psychopharmacol 2012; 27(3): 165-176.

Sunovion. Lurasidone HCl: a long term safety phase 3 study of patients with clinically stable schizophrenia; full text view [online]. In: Clinicaltrials.gov. 29 October 2013 [accessed: 14 November 2014]. URL: http://ClinicalTrials.gov/show/NCT00641745.

Sunovion. Lurasidone HCl: a long term safety phase 3 study of patients with clinically stable schizophrenia; study results [online]. In: Clinicaltrials.gov. 29 October 2013 [accessed: 14 November 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT00641745.

Sunovion Pharmaceuticals. Long-term safety, tolerability, and effectiveness of lurasidone in subjects with schizophrenia or schizoaffective disorder: a randomized, active comparator-controlled trial (double-blind phase): study D1050237; clinical study report [unpublished]. 2011.

2.5 Extent and probability of added benefit – summary

Table 20 summarizes the extent and probability of the added benefit of lurasidone for both research questions.

Table 20: Lurasidone – extent and probability of added benefit in adult patients with schizophrenia

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Schizophrenia ▪ acute treatment ▪ prevention of relapse	Amisulpride, aripiprazole, olanzapine, paliperidone, risperidone, quetiapine or ziprasidone	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. The company followed this specification in principle. Instead of choosing a drug however, it presented the result versus those drugs for which direct comparative studies were available. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from the company's approach, which, in the overall assessment of all 5 studies it included without differentiation of the treatment goals of acute treatment or prevention of relapse, claimed an added benefit of lurasidone. A detailed description of the company's approach can be found in Section 2.3.2 of the present benefit assessment.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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