Common Drug Review

Clinical Review Report (Resubmission)

January 2014

Drug	lurasidone hydrochloride (Latuda)
Indication	Management of manifestations of schizophrenia
Listing request	Management of manifestations of schizophrenia
Manufacturer	Sunovion Pharmaceuticals Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
AAP	atypical antipsychotic
BPRSd	Brief Psychiatric Rating Scale derived
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
DB	double blind
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
MADRS	Montgomery–Asberg Depression Rating Scale
MD	mean difference
NMA	network meta-analysis
PANSS	Positive And Negative Syndrome Scale
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SSO	Schizophrenia Society of Ontario
SMD	standardized mean differences
TEAE	treatment emergent adverse event
WMD	weighted mean differences
XR	extended release

EXECUTIVE SUMMARY

Introduction

Lurasidone (Latuda) is an atypical antipsychotic (AAP) indicated for the management of patients with clinical manifestations of schizophrenia. The manufacturer has submitted a resubmission requesting reimbursement for the 40 mg, 80 mg, and 120 mg strengths for the management of the manifestations of schizophrenia; the original approved indication and listing request for lurasidone when the drug was initially submitted to the Common Drug Review (CDR) in 2012 was for the acute treatment of patients with schizophrenia.

In January 2013, the Canadian Drug Expert Committee (CDEC) issued a recommendation that lurasidone not be listed.[1] The key reason for the recommendation was a lack of evidence from randomized controlled trials (RCTs) to establish the comparative efficacy of lurasidone relative to other AAPs for the acute treatment of schizophrenia.[1] The original CDR review included nine RCTs investigating the efficacy and safety of lurasidone for the treatment of schizophrenia. Seven of the trials were placebo-controlled, acute-treatment trials of six weeks duration designed to assess the efficacy of various doses of lurasidone ranging from 20 mg to 160 mg daily (Studies: 6 [N = 149], 196 [N = 180], 229, [N = 500], 231 [N = 478], 233 [N = 488], 2 [N = 460], and 49 [N = 356]). The remaining two trials (Study 237 and Study 254) were performed in stable patients. Four of the acute-treatment trials (Studies 2, 49, 231, and 233) included active comparators to verify assay sensitivity, but none were designed to compare lurasidone with the active treatments.

In May 2013, the manufacturer resubmitted lurasidone seeking a listing recommendation for the acute treatment of schizophrenia. The basis of the resubmission is: an indirect comparison (IDC) of lurasidone, aripiprazole, and ziprasidone; an open-label study of patients switched to lurasidone from another antipsychotic; the publication of Study 234, an open-label extension study of Study 233 (reviewed as a Supplemental Issue in the original CDR review based on unpublished information); Study 231E, an open-label extension of Study 231; and a lower confidential price.

Indication under review
Management of the manifestations of schizophrenia.
Listing criteria requested by sponsor
Management of the manifestations of schizophrenia.

Results and Interpretation

In this updated review, no additional RCTs met the inclusion criteria compared with the original CDR review. However, the main elements forming the basis of the resubmission were reviewed and appraised in detail. As well, the issue of comparative efficacy and safety of lurasidone and other AAPs was carefully considered based on available published evidence from systematic reviews and meta-analyses.

Indirect Treatment Comparisons

Without adequate direct comparative trials, the manufacturer submitted three indirect treatment comparisons: lurasidone flexibly dosed (40 mg to 120 mg) versus ziprasidone, using risperidone as the

common comparator; lurasidone 40 mg versus aripiprazole 15 mg to 30 mg, using olanzapine as the common comparator; and lurasidone 120 mg versus aripiprazole 15 mg to 30 mg, using olanzapine as the common comparator. Both acute and stable treatment trials were included in the IDCs. Results for five outcomes were reported: Positive and Negative Syndrome Scale (PANSS) total score, PANSS negative subscale, PANSS positive subscale, Clinical Global Impression – Severity of Illness Scale (CGI-S), and the Montgomery-Asberg Depression Rating Scale (MADRS). No safety outcomes were assessed. Analyses were performed using the Canadian Agency for Drugs and Technologies in Health (CADTH) IDC calculator (which employs the Bucher method).

Overall, there were no statistically significant differences in efficacy outcomes between lurasidone and ziprasidone or aripiprazole. However, several shortcomings that limit the interpretation of these results were noted, primarily the restricted focus to aripiprazole and ziprasidone as comparators, the lack of a systematic literature search, and the apparent absence of methods for considering heterogeneity across studies. The lack of information on comparative safety was also a limitation.

CDR also identified a recent comprehensive network meta-analysis by Leucht et al. (2013)[2] of 15 orally administered antipsychotic drugs (including lurasidone) for acute treatment of schizophrenia. The results suggested that there were no statistically significant differences on PANSS total score between lurasidone and aripiprazole, haloperidol, quetiapine, ziprasidone, chlorpromazine, or asenapine. However, lurasidone demonstrated statistically significantly lower efficacy than clozapine, olanzapine, risperidone, and paliperidone. Among lurasidone, aripiprazole, and ziprasidone, lurasidone was ranked lowest in terms of efficacy. Lurasidone was associated with statistically higher risks of all-cause discontinuation compared with olanzapine and risperidone, but there were no significant differences between lurasidone and quetiapine, aripiprazole, or ziprasidone.

Unlike the manufacturer-submitted indirect comparison (IDC), Leucht et al. also reported on comparative safety across AAPs. The degree of weight change was similar across aripiprazole, ziprasidone, and lurasidone compared with placebo. The effect estimate for lurasidone indicated a non-significant change in body weight compared with placebo. Olanzapine, quetiapine, and risperidone were associated with significantly more weight gain than lurasidone. No information was available on other relevant metabolic outcomes such as blood glucose and lipid parameters. In line with the results of the CDR review of lurasidone trials, the risk of extrapyramidal symptoms (EPS) reported by Leucht et al. was higher with lurasidone than placebo and several other AAPs, and lurasidone was one of the least tolerated drugs in this respect. The comparison of lurasidone with aripiprazole on EPS was statistically significant in favour of the latter drug.

Extension Studies

The only comparative RCTs of lurasidone with other AAPs in the stable treatment setting are Studies 254 and 237 (both included in the original CDR review), in which the comparators were ziprasidone and risperidone, respectively. Study 237 was specifically designed to compare treatments on time to relapse using a non-inferiority design, but failed to confirm the non-inferiority hypothesis.

The only other study providing comparative evidence in the stable treatment setting was Study 234, the extension of Study 233. This study was reviewed in the original CDR review based on unpublished information, and the manufacturer submitted the peer-reviewed publication of this study as part of the resubmission. This study confirmed the a priori non-inferiority hypothesis for time to relapse against quetiapine, and no new harms were identified. However, interpretation of these results is limited by concerns that the original randomization performed in Study 233 may have been compromised in the

extension, since not all patients completing Study 233 consented to participate in 234 and there were high rates of withdrawal from both studies. Thus, similar to the results of the original CDR review, the comparative long-term efficacy and safety of lurasidone versus other AAPs remains uncertain.

The resubmission also contained a six-month, open-label extension study of Study 231, Study 231E. The original trial was a six-week double-blind (DB), randomized controlled trial (RCT) in which the efficacy of lurasidone 40 mg, lurasidone 120 mg, and olanzapine 15 mg were compared with placebo. In the extension, all patients were switched to open-label lurasidone. Efficacy data were only reported for the subset of patients who completed the full extension phase. Improvements from extension phase baseline were observed in PANSS (–8.7) and CGI-S (–0.4). No new safety events were observed in the extension study compared with the core RCT. Without a comparator group (e.g., patients randomized to olanzapine continuing on olanzapine in the extension), Study 231E does not provide information regarding relative long-term efficacy and safety. Discontinuation rates in the extension study were high (> 50%), suggesting that most patients will require alternative antipsychotic therapy within months of initiating lurasidone.

Switching Study

McEvoy et al.[3] reported the results of an open-label, multi-centre, randomized, parallel-group, six-week study in which patients were switched from previous treatment with antipsychotics to lurasidone, using three different dosing strategies (starting with lurasidone 40 mg for two weeks, lurasidone 40 mg for one week, then 80 mg for one week; or lurasidone 80 mg for two weeks). No significant differences were observed across treatment groups on the primary outcome of time to treatment failure. Without a comparator group consisting of an AAP other than lurasidone, the McEvoy et al. study does not elucidate the comparative efficacy and safety of lurasidone and other AAPs for patients requiring treatment switch.

Pharmacoeconomic Summary

Lurasidone (Latuda) is available as 40 mg, 80 mg, and 120 mg tablets at a confidential flat price of [redacted] per tablet ([redacted] per day). The manufacturer submitted a cost-minimization analysis that compared lurasidone with other AAPs, and focused on the metabolically neutral drugs, aripiprazole and ziprasidone.[4] At the submitted price of [redacted], lurasidone ([redacted] per year) is less expensive than aripiprazole ($1,509 to $1,746 per year) and ziprasidone ($1,448 per year). Therefore, lurasidone would generate modest cost savings for public plans were it to be used instead of aripiprazole or ziprasidone. By contrast, lurasidone is more expensive than quetiapine ($352 to $705) and risperidone ($443 to $665), regardless of dose. Therefore, lurasidone would incur additional costs to public plans if it were used instead of quetiapine or risperidone. Whether lurasidone is more or less expensive than other AAPs (olanzapine, risperidone orally disintegrating tablet (ODT), quetiapine extended release (XR), paliperidone) depends on the dose considered and prices within individual public plans.

Conclusions

The main reason for the original CDEC recommendation of "Do Not List" was a lack of sufficient evidence to establish the comparative efficacy of lurasidone against other AAPs. In this updated review, no additional RCTs meeting the inclusion criteria have been identified since the original CDR review of lurasidone. Without direct comparative trials, a recently published network meta-analysis provided important insights into the comparative efficacy and safety of AAPs, including lurasidone, in the acute-treatment setting. The results indicated that lurasidone was associated with lower efficacy, in terms of PANSS total score, than olanzapine and risperidone. Although there were no significant differences in efficacy between lurasidone and aripiprazole, quetiapine, or ziprasidone, lurasidone was ranked as least

efficacious among these drugs. Weight changes with lurasidone were similar in magnitude to aripiprazole and ziprasidone, and less than with older AAPs. There was no information regarding relative effects on other metabolic parameters. Compared with the original CDR review, there was no additional information regarding the relative long-term efficacy and safety of lurasidone compared with other AAPs. An important context for interpreting the available evidence for lurasidone is patient group input, indicating the need for additional therapeutic options for schizophrenia.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Schizophrenia is a mental illness that requires lifelong treatment[5] and is associated with symptoms that include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and amotivation.[6] Its worldwide prevalence is 0.5 to 1.5%[7] and in Canada it affects about 1% of the population[6] or about 234,000 people (2004 data).[8] Schizophrenia is a chronic or recurrent illness and patients are at an increased risk for numerous other medical illnesses, suicide and substance abuse, homelessness, and unemployment.[9]

Antipsychotic medications form the cornerstone of treatment for schizophrenia[6] because they target the characteristic symptoms of the disease.[7] These symptoms can be positive or negative in nature[7] whereby positive symptoms reflect a distortion or abundance of normal functions and negative symptoms reflect a loss or restriction of normal function.[10] The underlying principles for the administration of pharmacotherapy include the individualization of medication (including patient preferences), simple medication regimens, appropriate dosing, attention to side effect profiles, regular evaluation of responses (including adverse events),[9] and short- and long-term clinical efficacy, safety, and tolerability.[5]

1.2 Standards of Therapy

Existing antipsychotic therapies fall into one of two classes. The typical antipsychotics (TAs) (also known as conventional antipsychotics or neuroleptics) are of the first-generation antipsychotic (FGA) class. These drugs have antagonistic activity at dopamine D_2 receptors[11] and are associated with an increased incidence of extrapyramidal (EPS) side effects.[5] The atypical antipsychotics (AAPs) or second-generation antipsychotics have antagonistic activity at both D_2 receptors and serotonin 5-hydroxytryptamine ($5\text{-}HT_{2a}$) receptors. The risk of EPS incidence appears reduced with AAPs; however, differences between TAs and AAP drugs can be variable in this respect.[12,13] Both classes are considered to be equally effective in the treatment of positive symptoms. AAPs appear to be more effective in the treatment of negative symptoms;[5] however, an increased risk of weight gain and metabolic side effects is also associated with their use.[9]

Treatment of schizophrenia is typically divided into three phases: acute, stabilization, and maintenance. In the acute phase, the patient is routinely experiencing psychotic or positive symptoms, with pharmacotherapy being initiated or adjusted as soon as possible.[14-16] Oral medications represent first-line treatment although the formulations administered may differ under certain circumstances (e.g., non-adherence or need for rapid control of symptoms). Examples of alternative formulations that may be used in these situations include rapidly dissolving tablets of olanzapine or risperidone, sublingual asenapine, liquid haloperidol, intravenous or intramuscular (IM) haloperidol, IM loxapine, or IM zuclopenthixol acetate.

Non-emergent acute presentations still have a degree of urgency as a delay in treatment may lead to patient distress and/or harm to themselves or others; moreover, a longer time to treatment has been linked to a less favourable outcome.[17-19] Current guidelines favour the use of an AAP in patients experiencing a first episode of psychosis as these individuals are more sensitive to side effects such as EPS,[20,21] which can be uncomfortable, potentially life-threatening (e.g., acute laryngeal-pharyngeal dystonia), and contribute to non-adherence. Patients who experience multiple episodes are, as a rule, offered a trial of another antipsychotic.[14-16,22] AAPs are again the treatment of choice unless the patient prefers a TA or has had a good prior response to a TA.

1.3 Drug

Lurasidone (Latuda) is an AAP approved by Health Canada for treatment of the clinical manifestations of schizophrenia.[23] The product monograph further indicates that "the efficacy of Latuda for long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled studies."[23] The indication for lurasidone has been revised since the initial submission was reviewed by the Canadian Drug Expert Committee (CDEC) in January 2013 — the initial indication was for the acute treatment of schizophrenia.[1] The efficacy of lurasidone in managing schizophrenia is thought to be mediated predominantly through a combination of central D_2 and 5-HT_{2a} receptor antagonisms. However, interactions with other receptor types such as 5-HT_{1A} and 5-HT_7 may play roles in efficacy while activity at other receptors may play a role in the drug's tolerability profile.[24]

The recommended starting dose for lurasidone is 40 mg once daily.[23] Patients should be treated with the lowest effective dose for optimal clinical response and tolerability, expected to be 40 mg or 80 mg once daily for most patients. Doses above 80 mg may be considered for certain patients based on individual clinical judgment.[23] The strengths of lurasidone currently marketed in Canada are 40 mg, 80 mg, and 120 mg. The manufacturer has indicated that a 160 mg strength dose will be marketed in the future.

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Management of the manifestations of schizophrenia
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Management of the manifestations of schizophrenia

TABLE 1: KEY CHARACTERISTICS OF ORALLY ADMINISTERED AAPS AVAILABLE IN CANADA

	Lurasidone[23]	Aripiprazole[25]	Ziprasidone[26]	Asenapine[27]	Olanzapine[28]	Risperidone[29]	Quetiapine[30]	Clozapine[31]	Paliperidole[32]
Mechanism of Action	Unknown	Unknown	Unknown	Unknown	Unknown	A benzisoxazole derivative, binds with high affinity to serotonin type 2 (5-HT2), dopamine type 2 (D2), and alpha 1-adrenergic receptors. Risperidone binds with a lower affinity to the alpha 2-adrenergic and histamine H1 receptors	Unknown	Not reported	Unknown
Indication[a]	Management of the manifestations of schizophrenia	Treatment of schizophrenia and related psychotic disorders in adults	Treatment of schizophrenia and related psychotic disorders	Treatment of schizophrenia	The acute and maintenance treatment of schizophrenia and related psychotic disorders	Indicated for the acute treatment and maintenance treatment of schizophrenia and related psychotic disorders	Indicated for the management of the manifestations of schizophrenia	Management of symptoms of treatment-resistant schizophrenia	Treatment of schizophrenia and related psychotic disorders
Route of Administration	Oral	Oral	Oral	Sublingual	Oral	Oral	Oral	Oral	Oral
Recommended Dose	40 mg or 80 mg o.d.	10 mg or 15 mg o.d.	40 mg b.i.d.	5 mg or 10 mg b.i.d.	10 mg o.d.	4 mg to 6 mg per day (o.d. or b.i.d.)	300 mg/day (150 b.i.d.)	300 mg to 600 mg/day	6 mg o.d.
Serious Side Effects/Safety Issues	NA	NA	Rash, urticaria	hypersensitivity reactions	NA	NA	NA	NA	NA
Other	NA	NA	NA	NA	Gain of ≥ 25% from baseline body weight with long-term exposure was very common (≥ 10%).	NA	NA	NA	NA

AAP = atypical antipsychotic; b.i.d = twice daily; o.d. = once daily; NA = not applicable.
[a]Health Canada indication.

2. SUBMISSION HISTORY

In January 2013, CDEC issued a recommendation that lurasidone not be listed.[1] The key reason for the recommendation was a lack of evidence from RCTs to establish the comparative efficacy of lurasidone relative to other AAPs for the acute treatment of schizophrenia.[1]

The original Common Drug Review (CDR) review included nine RCTs investigating the efficacy and safety of lurasidone for the treatment of schizophrenia. Seven of the trials were placebo-controlled, acute treatment trials of six-week duration designed to assess the efficacy of various doses of lurasidone ranging from 20 mg to 160 mg daily (Studies: 6 [N = 149], 196 [N = 180], 229, [N = 500], 231 [N = 478], 233 [N = 488], 2 [N = 460], and 49 [N = 356]). Four of the acute-treatment trials (Studies 2, 49, 231, and 233) included the following active comparators to verify assay sensitivity: risperidone, haloperidol, olanzapine, and quetiapine XR. However, these trials were not designed to assess the comparative efficacy of lurasidone and the active comparators. The manufacturer classified two of these trials (Studies 2 and 49) as failed trials because the active comparator failed to differentiate from placebo on one or more of the key efficacy outcomes. One 52-week non-inferiority RCT compared lurasidone with risperidone (Study 237; N = 629) in stable patients, and one three-week RCT compared lurasidone with ziprasidone (Study 254; N = 307) in stable patients.

CDEC considered the following outcomes during their deliberations: Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale derived (BPRSd), CGI-S, adverse events (AEs), and serious adverse events (SAEs). CDR conducted meta-analyses to assess the efficacy outcomes and change in body weight reported in the seven acute-treatment trials. The failed trials, 2 and 49, were excluded from the reference case meta-analyses of efficacy outcomes; however, sensitivity analyses were conducted by including these studies. In the meta-analysis for change in body weight, all six-week studies were pooled.

In the meta-analysis of non-failed acute-treatment trials, the weighted mean differences (WMDs) in change from baseline in PANSS total score relative to placebo were –6.2 (95% CI, –11.1 to –1.3) for 40 mg lurasidone, –8.9 (95% CI, –12.2 to –5.7) for 80 mg lurasidone, –6.7 (95% CI, –10.9 to –2.5) for 120 mg lurasidone, and –16.2 (95% CI, –21.1 to –11.2) for 160 mg lurasidone. The inclusion of the failed studies (2 and 49) in the meta-analyses did not appreciably alter the effect sizes, although the estimate for lurasidone 40 mg was no longer statistically significant.

In the two stable treatment trials (Studies 254 and Study 237), there were no statistically significant differences between lurasidone and ziprasidone (80 mg twice daily) or risperidone (2 mg/day to 6 mg/day) in change from baseline total PANSS scores. Lurasidone failed to demonstrate non-inferiority to risperidone for time to relapse in Study 237. There was no statistically significant difference between lurasidone (40 mg to 120 mg) and risperidone (2 mg to 6 mg) in this study for time to relapse (hazard ratio (HR) = 1.30; 95% CI, 0.87 to 1.96); however, the non-inferiority criterion (i.e., upper limit of 1.6 for the 95% CI) was exceeded.

Akathisia and parkinsonism were the most frequently reported extrapyramidal symptoms for lurasidone-treated patients. In the acute-treatment trials, the proportion of patients experiencing akathisia and parkinsonism increased with increasing doses of lurasidone up to 120 mg (akathisia ranged from 11% with 40 mg to 22% with 120 mg, and parkinsonism ranged from 4% with 40 mg to 9% with 120 mg). In meta-analyses of change from baseline in body weight, only lurasidone 80 mg demonstrated a statistically significant increase compared with placebo (WMD = 0.59 kg; 95% CI, 0.27 to 0.91).

Among the active comparators, olanzapine and quetiapine XR were associated with statistically significant increases in body weight when compared with placebo (mean difference = 3.53 kg and 1.96 kg respectively). A weight gain of at least 7% occurred in a higher proportion of patients treated with olanzapine (34%) and quetiapine XR (15%) compared with lurasidone (4% to 9% across doses of 40 mg to 160 mg).

Although not included in CDR's systematic review of lurasidone, Study 234, a 12-month double-blind (DB) extension study of Study 233, was also summarized and appraised in detail by CDR and discussed by CDEC.

2.1 Basis of Resubmission

The basis of this resubmission, as described by the manufacturer, is as follows:

- indirect comparisons of lurasidone to aripiprazole and ziprasidone
- a revised (lower) confidential price
- an open-label study of patients switched to lurasidone from another antipsychotic
- publication of Study 234, a DB extension of Study 233 that compared lurasidone to quetiapine XR (Study 234 was reviewed as a Supplemental Issue in the original CDR review based on unpublished information)
- publication of Study 231E, an open-label extension of Study 231.

3. OBJECTIVES AND METHODS

3.1 Objectives

To perform an updated systematic review of the beneficial and harmful effects of lurasidone 40 mg, 80 mg, and 120 mg for the treatment of adults with schizophrenia.

3.2 Methods

The literature search employed in the original CDR review was updated for APPENDIX 2: LITERATURE SEARCH STRATEGY. Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 2. As the original review was sufficiently broad in scope to cover both acute and chronic/stable treatment, the original literature search strategy and selection criteria were appropriate for this update despite the change in the approved indication for lurasidone since the original review. Hence, no changes to the review protocol were made compared with the protocol for the original CDR review. Studies were only considered for inclusion if they were not included in the original CDR review.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	• Adults with schizophrenia	
	Subgroups: • Resistance to other AAPs • Drug naive versus second-line treatment • Acute versus maintenance	
Intervention	Lurasidone at approved dosages (40 mg, 80 mg, and 120 mg daily)	
Comparators	**Atypical APs:** • clozapine • risperidone • quetiapine • olanzapine • paliperidone • ziprasidone • aripiprazole • asenapine	**Typical APs:** • chlorpromazine • fluphenazine • flupentixol • haloperidol loxapine • pericyazine • perphenazine • pimozide • prochlorperazine • thioridazine • trifluoperazine • thiothixene • zuclopenthixol • pipotiazine palmitate **Other** • placebo
Outcomes	**Key efficacy outcomes:** Global symptoms, mortality (including suicide), relapse **Other efficacy outcomes:** Hospitalization, suicidality , quality of life, functional capacity (e.g., employment), clinical remission, relapse, positive symptoms, negative symptoms, cognition, persistence with therapy **Harms outcomes:** Serious AEs , non-serious AEs , WDAEs, weight gain, EPS-related AEs, cardiovascular AEs	
Study Design	Published and unpublished DB RCTs	

AAP = atypical antipsychotics; AE = adverse event; AP = antipsychotic; DB = double blind; EPS = extrapyramidal symptoms; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified in the original CDR review of lurasidone by searching the following bibliographic databases in July 2012: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; PsycINFO (1967–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was lurasidone (Latuda).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. For the current updated review, database searches were rerun on July 8, 2013 to capture any articles published since the original Latuda CDR search from July 2012.

Regular alerts were established to update the search until the meeting of CDEC on November 20, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. The grey literature search was also updated to include documents made available since July 2012.

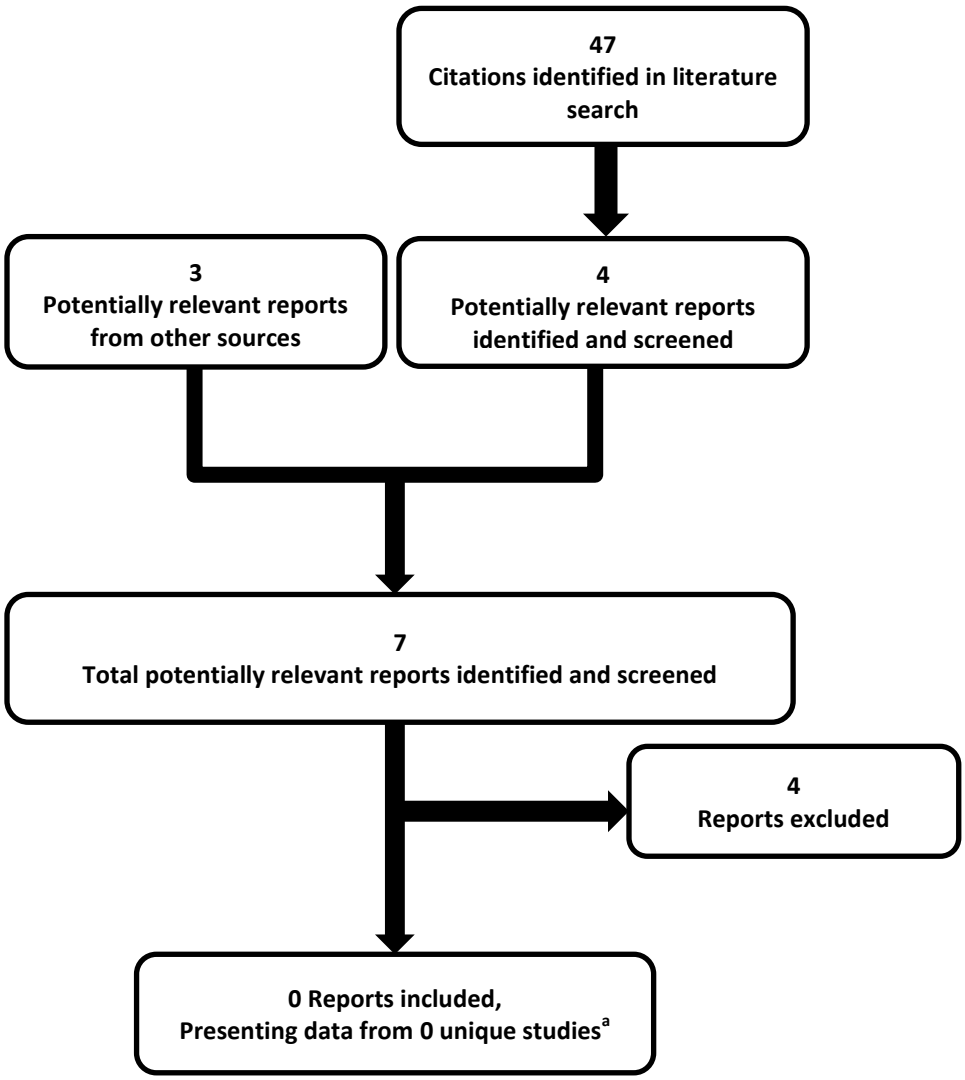
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

4. RESULTS

4.1 Findings from the Literature

No studies were identified from the literature search for inclusion in the systematic review (Figure 1). A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



FDA = Food and Drug Administration; QUOROM = quality of reporting of meta-analyses.
[a]Additional documents were reviewed in relation to the studies included in the original CDR review: Manufacturer's resubmission binder,[33] FDA medical review,[34] and FDA statistical review.[35]

4.2 Key Clinical Issues

Although no trials met the inclusion criteria for the updated systematic review, the main elements forming the basis of the resubmission are reviewed and appraised in detail in this section. As well, the issue of comparative efficacy and safety of lurasidone and other AAPs was carefully considered based on available published evidence from systematic reviews and meta-analyses.

4.2.1 Manufacturer-Submitted Indirect Treatment Comparisons

a) Objective

Without direct comparative trials, the manufacturer conducted IDCs to assess the efficacy of lurasidone against ziprasidone and aripiprazole.

b) Rationale

The IDC was conducted as part of the manufacturer's approach to addressing the CDR recommendation of "Do Not List" for lurasidone because of "insufficient evidence from RCTs to establish the comparative efficacy of lurasidone relative to other less costly antipsychotics for the acute treatment of schizophrenia."[33] The manufacturer's rationale for the selection of aripiprazole and ziprasidone as comparators for the IDCs was that they were considered to be "new, metabolically and weight neutral entrants to the market," similar to lurasidone.[33]

c) Methods

Eligibility Criteria

The inclusion criteria for the IDCs were the following: studies of aripiprazole and ziprasidone included in CDR's systematic reviews of these drugs that were available in the public domain and accessible for analysis. Lurasidone studies were drawn from the original CDR review of this drug. In addition, to be eligible for inclusion the studies required an active comparator group.

Intervention and Comparators

The interventions included in the IDC were lurasidone 40 mg, 120 mg, and 40 mg to 120 mg (flexibly dosed); aripiprazole 15 mg to 30 mg; ziprasidone 40 mg to 80 mg; risperidone 2 mg to 6 mg; risperidone 3 mg to 5 mg; olanzapine 15 mg; and olanzapine 10 mg to 20 mg. Risperidone and olanzapine acted as the common comparators in the IDCs.

Outcomes

The outcomes of interest in the IDC included the PANSS total score; PANSS subscale scores (positive or negative scores); Brief Psychiatric Rating Scale derived (BPRSd) extracted from the PANSS; CGI-S; Clinical Global Impression-Improvement Scale (CGI-I); Montgomery–Asberg Depression Rating Scale (MADRS); Negative Symptom Assessment (NSA) Scale and Global Assessment of Functioning (GAF). Of these, results for five outcomes were reported in the IDCs (PANSS total score, PANSS negative subscale, PANSS positive subscale, CGI-S, and MADRS). No safety outcomes were assessed.

Analysis

Data for the efficacy measures were presented as a mean followed by standard deviation (SD). In cases where the SD was not available, it was derived from the 95% CI or standard error of the mean, whichever was available. The mean difference (MD) between treatment and comparator in change from baseline was calculated if it was not readily available. The IDC authors used Revman 5.0 for direct meta-analyses when two or more RCTs were available for a given comparison. The direct comparison results were used as inputs into an IDC between lurasidone and aripiprazole conducted by the manufacturer. The CADTH IDC calculator (which employs the Bucher method) was used for the IDCs.

There were three distinct IDC models created: lurasidone flexibly dosed (40 mg to 120) versus ziprasidone, using risperidone as the common comparator, lurasidone 40 mg versus aripiprazole 15 mg to 30 mg, using olanzapine as the common comparator, and lurasidone 120 mg versus aripiprazole 15 mg to 30 mg, using olanzapine as the common comparator.

d) Results

A summary of study characteristics is provided in Table 3. There were five included studies in three IDCs. All studies were DB RCTs. The IDC comparing flexibly dosed lurasidone to ziprasidone included trials of acute and stable patients; sample sizes ranged from 296 to 1,090 patients, and study durations ranged from 8 to 52 weeks.[36,37] The IDCs comparing lurasidone 40 mg or 120 mg with aripiprazole 15 mg to 30 mg included trials of acute patients as well as patients switched from prior treatment with olanzapine.[38-40] The sample sizes of the trials ranged from 173 to 566. Study duration varied from 6 to 28 weeks.

Study and Patient Characteristics

Study and patient characteristics were reported in the form of summary tables based on the inclusion criteria for the five included studies. Study-level data for study and patient characteristics were not reported. A written summary of selected inclusion criteria was provided for each study. In all of the included studies, patients were required to be at least 18 years of age and not more than 64, 65, or 75 years old. All patients were required to meet Diagnostic and Statistical Manual (DSM) criteria for schizophrenia or schizoaffective disorder; duration of illness of at least one year was required in two studies. Inclusion criteria for PANSS total ranged from a minimum of 60 to 80 for the three studies where this was reported. CGI-S of $\leq$ 4 was required in two studies, and $\geq$ 4 was required in another study.

Results of the IDC

The IDC results are presented in Table 4. There was no statistically significant difference on the CGI-S between lurasidone flexibly dosed (40 mg to 120 mg) compared with ziprasidone (2 mg to 6 mg) (MD [95% CI] = 0.30 [–0.06 to 0.66]). There was also no statistically significant difference between lurasidone and ziprasidone on the MADRS scale (MD [95% CI] = –0.30 [95% CI, –2.91 to 2.31]). Results for PANSS total score were not reported for this comparison.

Lurasidone 40 mg was associated with no statistically significant difference in PANSS total score compared with aripiprazole (15 mg to 30 mg) (MD [95% CI],–1.60 [–8.08 to 4.88]). Similarly, lurasidone 120 mg was associated with no statistically significant difference in PANSS total score compared with aripiprazole (15 mg to 30 mg) (MD [95% CI] = 0.50 [95% CI, –6.39 to 7.39]). There were also no significant differences between lurasidone 40 mg or 120 mg and aripiprazole (15 to 30 mg) on the CGI-S (MD [95% CI] = –0.08 [95% CI, –0.40 to 0.24]) and 0.02 (95% CI, –0.29 to 0.34) for the lurasidone 40 mg and 120 mg comparisons respectively].

Critical Appraisal

The quality of the manufacturer's indirect treatment comparisons was assessed according to the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on indirect treatment comparisons.[41] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 20.

There were numerous limitations to the IDC. The strategy for identifying potential studies for inclusion was not based on a systematic search of the literature; only those studies referred to in previous CDR recommendations for lurasidone, aripiprazole, and ziprasidone were included. It is possible that potentially relevant studies could have been excluded, particularly for aripiprazole and lurasidone, since these CDR reviews were completed several years ago. Additional limitations included lack of reporting on baseline and disease characteristics, no clearly articulated research questions, and no apparent assessment of the scientific quality of the included studies. In addition, it is unclear why placebo was not selected as a common comparator to allow the inclusion of more studies to create more comprehensive IDC models or network meta-analyses. Moreover, the reasons for excluding some trials were unclear, and exclusions do not appear to entirely align with the stated inclusion/exclusion criteria.

Another important limitation was uncertainty as to whether and how clinical and methodological heterogeneity were assessed prior to performing IDCs. Indeed, based on the reported inclusion criteria, there is some evidence to suggest the presence of clinical heterogeneity in terms of baseline disease characteristics (e.g., PANSS total score, CGI-S, and duration of illness). Study-level data on baseline characteristics were not reported, therefore it is unclear if the studies were similar enough to be included in IDCs. Studies ranging in duration from 6 to 28 weeks were combined in one of the IDCs, and in another IDC studies ranging from 8 to 52 weeks were combined. It is also noteworthy that both acute and stable treatment trials were combined in the IDCs. These sources of heterogeneity may introduce bias in IDC results if they are independently associated with treatment outcomes, for example if changes from baseline in efficacy measures vary by study duration.

An additional issue was the identification of outcome measures for the IDCs. Outcomes included in the IDCs were selected based on whether outcomes were "common," but no definition was provided for this criterion. From a list of nine efficacy outcomes, four outcomes were reported in the IDCs (PANSS total score, PANSS negative subscale, PANSS positive subscale, and MADRS), with no rationale provided as to why the remaining outcomes were not reported. Thus, the reporting of efficacy outcomes appears to be somewhat selective. The IDCs were also limited by the lack of analyses on safety outcomes. Tolerability concerns (e.g., weight gain or EPS) can be key considerations for the selection of treatment, and a key putative benefit of lurasidone is the relative lack of metabolic adverse effects. However, the IDC analyses provide no evidence regarding the relative risks of such events compared with aripiprazole and ziprasidone. The dosages of lurasidone assessed in the IDC were an issue as well; the analysis was conducted for lurasidone 40 mg and 120 mg but not lurasidone 80 mg. The Canadian product monograph suggests lurasidone 40 mg or 80 mg will be the optimal dose for most patients,[23] hence the exclusion of the 80 mg dose somewhat limits generalizability to the Canadian context.

e) Summary

Without adequate head-to-head trial data, the manufacturer conducted three indirect treatment comparisons using study-level data for lurasidone 40 mg and 120 mg; lurasidone 40 mg to 120 mg (flexibly dosed); aripiprazole 15 mg to 30 mg; ziprasidone 40 to 80 mg; risperidone 2 mg to 6 mg; and olanzapine 10 mg, 15 mg, and 20 mg. Five RCTs were included in the three indirect comparisons. No statistically significant differences were reported between lurasidone and aripiprazole or lurasidone and ziprasidone with respect to efficacy. However, numerous limitations were noted. A network meta-analysis approach incorporating all of the available evidence (including placebo-controlled trials) could have provided a more robust platform for assessing comparative efficacy and safety than separate IDCs. Furthermore, incorporation of other atypical antipsychotics available in Canada would have provided a more complete assessment of comparative efficacy and safety. A comprehensive and systematic literature search and selection methodology, appraisal of study quality, and assessment of clinical and

methodological heterogeneity across studies are crucial elements of a reliable IDC, yet none of these are described in the submitted analysis. Indeed, the analysis was limited to trials identified in the CDR reviews of aripiprazole, ziprasidone, and lurasidone, and it is possible that not all potentially relevant trials were included. Furthermore, substantial heterogeneity was noted across trials in baseline characteristics and study duration. Another limitation was that safety results were not assessed in the IDC. Given these concerns, the results of the IDC are of uncertain validity.

TABLE 3: SUMMARY OF THE INCLUDED TRIALS

Author and Year	Study Design	Treatment	Comparator	Study Duration and Sample Size
Meltzer et al. (2011)[38]	R, DB, MC	Lurasidone 40 mg, 120 mg Olanzapine, 15 mg (included to establish assay sensitivity)	Placebo	6 weeks N = 478
Citrome et al. (2012)[37]	R, DB, MC	Lurasidone (40 mg to 120 mg)	Risperidone (2 mg to 6 mg)	52 weeks N = 629
Addington et al. (2004)[36]	R, DB	Ziprasidone 40 mg to 80 mg (once daily)	Risperidone 3 mg to 5mg (once daily)	8 weeks N = 269
Kane et al. (2009)[40]	R, DB	Aripiprazole 15 mg to 30 mg	Olanzapine 10 mg to 20 mg	28 weeks N = 566
Newcomer et al. (2008)[39]	R, DB, MC	Aripiprazole 15 mg to 30 mg	Olanzapine 10 mg to 20 mg	16 weeks N = 173

DB = double blind; MC = multi-centre; R = randomized.

TABLE 4: SUMMARY OF IDC RESULTS

Comparison Results: MD [95% CI]			
Efficacy Measures (change from baseline)	**Direct Comparison MD (95% CI)**		**Indirect Treatment Comparison**
	Lurasidone versus Risperidone	**Risperidone versus Ziprasidone**	**Lurasidone versus Ziprasidone**
CGI-S	0.00 [–0.18 to 0.18]	0.30 [–0.01 to 0.61]	0.30 [–0.06 to 0.66]
MADRS	1.60 [0.33 to 2.87]	–1.9 [–4.17 to 0.37]	–0.30 [–2.91 to 2.31]
	Lurasidone (40 mg) versus Olanzapine	**Olanzapine versus Aripiprazole**	**Lurasidone (40 mg) versus Aripiprazole**
PANSS Total Score	3.00 [–2.41 to 8.41]	–4.60 [–8.18 to –1.02]	–1.60 [–8.08 to 4.88]
PANSS Positive Score	1.60 [–0.34 to 3.54]	–0.80 [–1.55 to –0.05]	0.80 [–1.28 to 2.88]
PANSS Negative Score	0.20 [–1.19 to 1.59]	–1.60 [–2.88 to –0.32]	–1.40 [–3.29 to 0.49]
CGI-S	0.00 [–0.28 to 0.28]	–0.08 [–0.23 to 0.08]	–0.08 [–0.40 to 0.24]
	Lurasidone (120 mg) versus Olanzapine	**Olanzapine versus Aripiprazole**	**Lurasidone (120 mg) versus Aripiprazole**
PANSS Total Score	5.10 [–0.45 to 10.65]	–4.60 [–8.18 to –1.02]	0.50 [–6.39 to 7.39]
PANSS Positive Score	1.00 [–0.94 to 2.94]	–0.80 [–1.55 to –0.05]	0.20 [–1.88 to 2.28]
PANSS Negative Score	1.00 [–0.53 to 2.53]	–1.60 [–2.88 to –0.32]	–0.60 [–2.59 to 1.39]
CGI-S	0.10 [–0.18 to 0.38]	–0.08 [–0.23 to 0.08]	0.02 [–0.29 to 0.34]

CGI-S = clinical global impression – severity; CI = confidence interval; IDC = indirect treatment comparison; MADRS = Montgomery-Asberg Depression Scale; MD = mean difference; PANSS = Positive and Negative Syndrome Scale.
Data from Qi (2013).[42]

4.2.2 Summary and Critical Appraisal of Network Meta-Analyses by Leucht et al. (2013)[2]

a) Objective

CDR performed a literature search to identify published systematic reviews and meta-analyses relevant to understanding the comparative efficacy and safety of lurasidone and other AAPs. A recent network meta-analysis (NMA) by Leucht et al.[2] of antipsychotic drugs in the treatment of schizophrenia was identified. A critical appraisal and summary of the results for lurasidone are presented in this section.

Rationale

Leucht et al. described the need for an evidence-based hierarchy of comparative efficacy and tolerability of AAP drugs in schizophrenia. The authors conducted an NMA to overcome the limitations of existing pairwise meta-analyses, which cannot be used to establish a hierarchy due to the lack of head-to-head studies for some comparisons, and because all available evidence cannot be incorporated in these models.

Methods

Eligibility Criteria: The report included published and unpublished, single or DB RCTs of acute antipsychotic treatment (six weeks) in patients with schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder). The review excluded studies in patients with predominantly negative symptoms, concomitant medical illness, treatment resistance, or those with stable illness (i.e., relapse-prevention trials). For the analysis of extrapyramidal side effects, studies where antiparkinson drugs were given prophylactically were excluded.

Interventions and Comparators: The NMA included 15 orally administered antipsychotic drugs used as monotherapy (fixed and flexible- dosing regimens) (Table 5). The criteria for the dosages included in the analysis were established a priori and based on the International Consensus Study of Antipsychotic Dosing. In addition, variability in dosing across studies was addressed by several meta-regression and sensitivity analyses.

TABLE 5: INTERVENTIONS AND OUTCOMES ASSESSED IN THE LEUCHT ET AL. NETWORK META-ANALYSIS

Interventions		Outcomes
• placebo • amisulpride • aripiprazole • asenapine • chlorpromazine • clozapine • haloperidol • iloperidone	• lurasidone • olanzapine • paliperidone • quetiapine • risperidone • sertindole • ziprasidone • zotepine	• PANSS total score • all-cause discontinuation • weight gain • use of antiparkinson drugs (measure of extrapyramidal side effects) • prolactin increase • QTc prolongation • sedation

PANSS = Positive and Negative Syndrome Scale; QTc = QT corrected.
Source: Leucht et al.[2]

Outcomes: The primary efficacy outcome was PANSS total score (change from baseline). If the PANSS score was not available, then the BPRSd was included (change from baseline), or values of these scales at study end point. Harms outcomes were included as secondary outcomes. Outcomes measured at six weeks were used; however, data from four to 12 weeks were accepted if six-week data were unavailable.

Analysis: A random effects Bayesian hierarchical model was employed to combine direct and indirect evidence using WinBUGS software. Key aspects of the analysis were as follows:

- Normal vague priors.
- Standardized mean differences (MDs) were estimated for continuous outcomes.
- Odds ratios (OR) were estimated for dichotomous outcomes.
- Ranking was estimated using the surface under the cumulative ranking (SUCRA) probabilities.
- Meta-regression was used to examine the effects of: unfair dose comparisons; haloperidol dose; chlorpromazine dose; different olanzapine dose equivalents; study sponsorship; mean age of patients; year of publication; study duration; small sample size; and overall percentage of withdrawals.

- Sensitivity analyses were conducted by excluding: studies that compared a high dose of one drug with a low dose of another; single-blind trials; trials that included patients with first-episode psychosis; haloperidol trials; placebo-controlled trials; trials with missing SDs or with no intention-to-treat analysis; and failed studies (i.e., active treatment did not differ from placebo). In addition, an analysis was conducted that included some fixed-dosage regimens that were excluded in the primary analysis.
- Inconsistency was assessed by comparing model fit of consistency and inconsistency models, and through examination of all closed loops for inconsistency between direct and indirect evidence.

Results

Study and Patient Characteristics: A total of 212 studies were included (N = 43,049 patients). The mean age of participants was 38.4 years (SD 6.9), and the mean duration of illness was 12.4 years (SD 6.6).

Among the included RCTs, approximately one-third had unclear allocation concealment or unclear random sequence generation methods; the remainder had a low risk of bias on these parameters. Half the studies had an unclear or high risk of bias related to blinding of subjective outcomes and all had low risk of bias due to blinding of objective outcomes. Approximately half the studies had high risk of bias related to attrition bias or reporting bias, and approximately 10% had a high risk of other biases.

Results of the Network Meta-Analysis: The efficacy and all-cause discontinuation results from the NMA for lurasidone are presented in Table 6. In this table the treatments are listed in order of rank based on efficacy. Specific AE data are presented in Table 7 for lurasidone compared with placebo, and five key active comparators: aripiprazole, asenapine, olanzapine, risperidone, and ziprasidone.

Lurasidone was statistically significantly more effective than placebo as measured by the PANSS or BPRSd, but was significantly less effective than clozapine, amisulpride, olanzapine, risperidone, and paliperidone. There were no statistically significant efficacy differences between lurasidone and the other active comparators. However, based on probability ranking, lurasidone was ranked 14, which was lower than all other active therapies except iloperidone. The differences in effect size (Hedge's g SMD) between lurasidone and active comparators ranged from 0.0 to 0.55. In general, an SMD of 0.2 is considered small, 0.5 is medium, and 0.8 is a large effect size.

The results of the analysis of all-cause discontinuations were similar. Lurasidone was associated with statistically significantly fewer discontinuations than placebo, and more discontinuations than clozapine, amisulpride, olanzapine, risperidone, and paliperidone. No statistically significant differences were found between lurasidone and other active comparators.

TABLE 6: EFFICACY AND DISCONTINUATION OUTCOMES FOR LURASIDONE

LUR versus Control	SUCRA Rank	Efficacy (PANSS) SMD (95% CrI)[a]	All-Cause Discontinuation OR (95% CrI)[b]
CLO	1	**0.55 (0.36 to 0.74)**	**1.64 (1.11 to 2.56)**
AMI	2	**0.33 (0.16 to 0.50)**	**1.79 (1.27 to 2.56)**
OLA	3	**0.26 (0.13 to 0.39)**	**1.64 (1.30 to 2.13)**
RIS	4	**0.23 (0.10 to 0.37)**	**1.43 (1.12 to 1.89)**
PAL	5	**0.17 (0.00 to 0.33)**	**1.59 (1.18 to 2.13)**
ZOT	6	0.16 (–0.06 to 0.37)	1.10 (0.68 to 1.96)
HAL	4	0.12 (–0.01 to 0.25)	0.94 (0.75 to 1.22)
QUE	8	0.11 (–0.03 to 0.25)	1.23 (0.97 to 1.64)
ARI	9	0.10 (–0.05 to 0.25)	1.25 (0.95 to 1.67)
SER	10	0.06 (–0.11 to 0.24)	0.98 (0.72 to 1.37)
ZIP	11	0.07 (–0.09 to 0.22)	1.06 (0.81 to 1.43)
CPZ	12	0.05 (–0.14 to 0.25)	1.16 (0.84 to 1.64)
ASE	13	0.05 (–0.12 to 0.23)	1.10 (0.82 to 1.56)
ILO	15	0.00 (–0.16 to 0.16)	1.12 (0.83 to 1.50)
PBO	16	**–0.33 (–0.45 to –0.21)**	**0.77 (0.61 to 0.96)**

AMI = amisulpride; ARI = aripiprazole; ASE = asenapine; CLO = clozapine; CPZ = chlorpromazine; CrI = credible interval; HAL = haloperidol; ILO = iloperidone; LUR = lurasidone; OLA = olanzapine; OR = odds ratio; PAL = paliperidone; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; QUE = quetiapine; RIS = risperidone; SER = sertindole; SMD = standardized mean difference; SUCRA = surface under the cumulative ranking curve; ZIP = ziprasidone; ZOT = zotepine.
[a]SMD greater than 0 favours the control over lurasidone.
[b]OR less than 1 favour lurasidone over the control. Statistically significant results in bold.

With regard to specific AEs, lurasidone was not statistically significantly different from placebo in weight gain and QTc prolongation, but was associated with increased risks for extrapyramidal side effects (measured by the need for antiparkinson drugs) and sedation, and greater mean increases in prolactin.

Use of lurasidone resulted in significantly less weight gain than 9 of the 15 drugs, including olanzapine and risperidone, and no statistically significant differences versus aripiprazole, asenapine, ziprasidone, and haloperidol (Table 7). Other comparisons that showed statistically significant differences were:

- increased risk of extrapyramidal side effects with lurasidone compared with aripiprazole, olanzapine, quetiapine, and clozapine, and less compared with haloperidol
- more prolactin increase with lurasidone versus aripiprazole and quetiapine, and less versus risperidone, paliperidone, and haloperidol
- less QTc prolongation with lurasidone compared with asenapine, olanzapine, risperidone, ziprasidone, quetiapine, and haloperidol
- less sedation than chlorpromazine and clozapine.

TABLE 7: ADVERSE EVENT OUTCOMES FOR LURASIDONE VERSUS KEY COMPARATORS

LUR versus Control	Weight Gain SMD (95% CrI)[a]	Extrapyramidal Side Effects (OR 95% CrI)[b]	Prolactin Increase (SMD 95% CrI)[a]	QTc Prolongation (SMD 95% CrI)[a]	Sedation (OR 95% CrI)[b]
PBO	0.10 (–0.02 to 0.21)	**2.46 (1.55 to 3.72)**	**0.34 (0.11 to 0.57)**	–0.10 (–0.21 to 0.01)	**2.45 (1.31 to 4.24)**
ARI	–0.07 (–0.23 to 0.10)	**1.96 (1.10 to 3.85)**	**0.56 (0.23 to 0.88)**	–0.11 (–0.28 to 0.07)	1.43 (0.60 to 2.89)
ASE	–0.13 (–0.32 to 0.05)	1.41 (0.71 to 3.23)	0.22 (–0.11 to 0.55)	**–0.40 (–0.77 to –0.04)**	0.68 (0.29 to 2.08)
OLA	**–0.64 (–0.77 to –0.51)**	**2.38 (1.47 to 4.00)**	0.20 (–0.05 to 0.45)	**–0.32 (–0.45 to –0.18)**	0.68 (0.38 to 1.32)
RIS	**–0.32 (–0.46 to –0.19)**	1.12 (0.70 to 1.92)	**–0.89 (–1.16 to –0.61)**	**–0.35 (–0.50 to –0.21)**	0.92 (0.51 to 1.85)
ZIP	0.00 (–0.16 to 0.16)	1.59 (0.85 to 2.71)	0.09 (–0.24 to 0.42)	**–0.51 (–0.66 to –0.38)**	0.59 (0.32 to 1.23)

ARI = aripiprazole; ASE = asenapine; CrI = credible interval; LUR = lurasidone; OLA = olanzapine; OR = odds ratio; PBO = placebo; RIS = risperidone; SMD = standardized mean difference; ZIP = ziprasidone.
[a]SMD lower than 0 favours lurasidone.
[b]OR less than 1 favours lurasidone; Statistically significant results in bold.

The assumption of consistency was generally supported, with consistency models showing lower deviance information criterion (DIC) values than the inconsistency model. When the differences between direct and indirect estimates were calculated (i.e., inconsistency factor [IF]) for each outcome, 0% to 9% of loops showed statistically significant inconsistency. One significant inconsistent loop included lurasidone (weight gain for lurasidone-olanzapine-placebo: IF 0.49; 95% CI, 0.15 to 0.83).

The effect estimates and ranking for lurasidone versus placebo were similar across sensitivity analyses and meta-regression analyses for the efficacy outcome. For the movement disorder adverse outcome, additional sensitivity analyses and meta-regressions related to dose were conducted. These also showed consistent effect estimates as in the primary analysis for lurasidone versus placebo.

Critical Appraisal of Network Meta-Analysis

The quality of the NMA was assessed according to the recommendations provided by the ISPOR Task Force on Indirect Treatment Comparisons.[41,43] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 21.

Strengths: The Leucht et al. paper appears to represent a well-conducted and reported NMA according to the ISPOR criteria. The report is based on a systematic review that was conducted using accepted methods for the literature search, study selection, extraction, and quality assessment of studies. The authors used focused eligibility criteria limited to short-term treatment of acute schizophrenia in order to improve homogeneity of included studies. Detailed information on the methods used for the NMA was provided, including justification for decisions. The Bayesian random effects model selected was appropriate for the analysis, and numerous sensitivity and meta-regression analyses were conducted. The outcomes selected were relevant, and included both efficacy and important harms. The model results were reported clearly and in detail.

Limitations: Few details of the individual study characteristics were reported, and no individual study results were available. Thus, limited study data are available to readers to assess if the similarity assumption was met. However, the authors did conduct several sensitivity and meta-regression analyses to assess the impact of potential effect modifiers.

The authors report several limitations. First, they included only two of the older antipsychotics (haloperidol and chlorpromazine), although they state that these are the most commonly used high and low-potency drugs. Second, the reporting of AEs was poor in the RCTs and not all side effects were reported for some drugs. Third, meta-regression with the percentage of withdrawals as an effect modifier cannot control for all bias associated with high attrition.

The authors report that the results are not generalizable to populations excluded from the analysis (i.e., younger patients, those with predominantly negative symptoms, and refractory or stable patients). Further, the analysis was restricted to short-term trials (six weeks). Finally, some funnel plot asymmetry was noted, which the authors state may be explained by other factors, and is not necessarily due to publication bias.

Summary

Leucht et al.[2] conducted an NMA on 15 antipsychotic drugs, including lurasidone, for the acute (six-week) treatment of patients with schizophrenia or related disorders. The analysis was based on a systematic review that included 212 RCTs with data from 43,049 participants and used a Bayesian random effects model. The results of the NMA indicated that lurasidone was less effective in controlling symptoms of schizophrenia and associated with more all-cause discontinuation than clozapine, olanzapine, risperidone, and paliperidone. There were no significant differences between lurasidone and other antipsychotics. Lurasidone was associated with less weight gain and less QTc prolongation than a number of drugs, and increased risk of extrapyramidal side effects than some key comparators. Lurasidone showed more sedation than placebo but was not statistically significantly different from most other antipsychotics for this outcome. The increase in prolactin levels was higher with lurasidone than placebo, aripiprazole, and quetiapine, but less than with risperidone, paliperidone, and haloperidol. The assumption of consistency was generally supported, and effect estimates and rankings were similar across the sensitivity analyses and meta-regression analyses conducted. The overall quality of the NMA was high according to the ISPOR criteria.

4.2.3 Summary of Study 234

a) Objective

To summarize efficacy and safety evidence from Study 234, the extension of Study 233 (PEARL-3).

Study Characteristics

Study 234 was a 12-month, DB, extension study comparing lurasidone 40 mg/day to 160 mg/day versus quetiapine XR 200 mg/day to 800 mg/day.[44] Placebo and lurasidone-treated patients who completed Study 233, a six-week DB RCT, and who elected to continue in the extension phase (Study 234), were treated with lurasidone 120 mg/day for one week and flexibly dosed lurasidone thereafter. Those who were treated with quetiapine XR 600 mg in Study 233 were treated with quetiapine XR 600 mg/day for the first week of Study 234, and flexibly dosed quetiapine XR for the remainder of the study.

At baseline in Study 234, patients were similar in terms of average age (37 years to 39 years), duration of illness (10 years to 13 years), duration of current episode (30 days to 35 days), CGI-S (3 points to 4 points), and MADRS (6 points to 7 points). However, at 12-month baseline (i.e., Study 234 baseline),

patients switched from placebo to flexibly dosed lurasidone (40 mg to 160 mg), had higher mean PANSS scores than the continuous lurasidone and quetiapine/lurasidone groups (76 versus 67 and 68 respectively). The primary efficacy end point of Study 234 was time-to-relapse analyzed through a Cox proportional hazards model. Lurasidone was considered to be non-inferior to quetiapine XR in preventing relapse if the upper limit of the 95% CI for the HR was no greater than 1.93. The non-inferiority margin was based on a meta-analysis of placebo-controlled relapse-prevention studies of AAPs, which reported a 30% difference between AAP and placebo. To preserve a minimum 30% relapse-prevention effect of AAPs compared with placebo, an absolute margin of 15% was selected and relapse rates of 35% for lurasidone and 20% for quetiapine XR were assumed.[44]

Analyses of PANSS subscores and total scores, CGI-S, MADRS, and 16-item Negative Symptom Assessment Scale (NSA-16) were based on mixed-model repeated-measures analysis.

Patient Disposition: A summary of patient disposition is provided in Table 8. In Study 233, 488 patients were randomized to four treatment groups: lurasidone 80 mg, lurasidone 160 mg, placebo, and quetiapine XR 600 mg. Of these, 353 (72%) patients completed the study; across treatment groups the proportion ranged from 61% (placebo group) to 81% (quetiapine). Out of the completers, 292 (60%) patients entered the 12-month, DB extension phase. Patients treated with 80 mg lurasidone or 160 mg lurasidone during Study 233 were collapsed in Study 234 into a single, flexibly dosed lurasidone group treated with 40 mg to 160 mg daily. Across treatment groups the proportions of patients who entered the extension phase ranged from 46% (placebo switched to lurasidone group) to 71% (continuous quetiapine). Overall, 140 (29%) patients completed the extension study; across treatment groups, the range was 24% (placebo switched to lurasidone group) to 32% (continuous lurasidone). Overall, 152 (31%) patients discontinued the extensions. Across treatment groups, discontinuations ranged from 22% (placebo switched to lurasidone) to 43% (continuous quetiapine). The most frequently cited reason for discontinuation was withdrawal of consent (12%) with similar proportions across treatment groups (10% to 16%).

TABLE 8: SUMMARY OF PATIENT DISPOSITION

Disposition – n (%)	Study 234 (Overall)	LUR 80 mg/ 40 mg to 160 mg	LUR 160 mg/ 40 mg to 160 mg[a]	Placebo/ LUR 40 mg to 160 mg	QXR 600 mg/ QUE 200 mg to 800 mg
Randomized in core RCT	488	125	121	122	120
Completed core RCT	353 (72.3)	89 (71.2)	93 (76.9)	74 (60.7)	97 (80.8)
Entered extension	292 (59.8)	151 (61.3)		56 (45.9)	85 (70.8)
Completed extension	140 (47.9)	78 (51.6)		29 (51.9)	33 (38.9)
Discontinued extension	152 (31.1)	73 (29.7)		27 (22.1)	52 (43.3)
Withdrew consent	60 (39.4)	29 (19.2)		12 (21.4)	19 (22.4)
Insufficient clinical response	37 (24.3)	14 (9.3)		5 (8.9)	18 (21.2)
Adverse event	17 (11.1)	10 (6.6)		3 (5.4)	4 (4.7)
Lost to follow-up	21 (13.8)	10 (6.6)		2 (3.6)	9 (10.6)
Protocol violation	NR	NR		NR	NR
Miscellaneous	17 (11.1)	10 (6.6)		5 (8.9)	2 (2.4)

Data proportions for the sections in italics were calculated by CDR along with the overall n (%) in the same sections.
Data from Stahl et al.(2013).[45]
LUR = lurasidone; NR = not reported; QUE = quetiapine; QXR = quetiapine extended release; RCT = randomized controlled trial.
[a]Lurasidone 80 mg and 160 mg groups from Study 233 were collapsed into a single flexibly dosed lurasidone 40 mg to 160 mg group for Study 234.

Efficacy Outcomes: The manufacturer conducted two analyses of efficacy for lurasidone-treated patients:

- All patients who received lurasidone in the extension phase (including those who were treated with placebo in the initial six-week study).
- Only patients who received lurasidone in both the initial and extension phases (i.e., not including patients who were treated with placebo in the initial six-week study).

The primary efficacy end point of Study 234 was time to relapse. The population for the relapse analysis included those patients who demonstrated clinical response (a CGI-S score ≤ 4 and at least a 20% improvement in PANSS total score from baseline) at six weeks with either lurasidone or quetiapine XR in the core study (i.e., Study 233), and then took at least one dose of either lurasidone (n = 79) or quetiapine XR (n = 139) in the extension study. Relapse was defined as any one of the following: the earliest occurrence of a worsening of ≥ 30% on the PANSS total score and CGI-S ≥ 3; re-hospitalization for worsening of psychosis; or the emergence of suicidal ideation, homicidal ideation, and/or risk of harm to self or others.

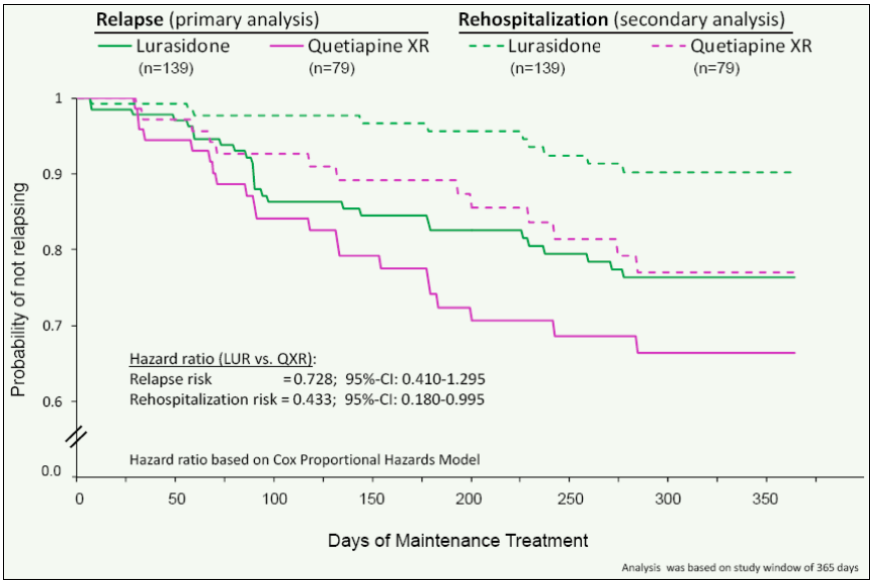
Kaplan-Meier curves showing time to relapse and re-hospitalization in the lurasidone and quetiapine XR groups are displayed in Figure 2. The relapse HR comparing lurasidone versus quetiapine was 0.73 (95% CI, 0.41 to 1.30) (an HR of < 1 favours lurasidone), which satisfied the manufacturer's predefined non-inferiority margin (i.e., the upper bound of the 95% CI was less than 1.93) (see Table 9). For both treatment groups, the Kaplan-Meier probabilities for relapse were less than 0.5 at Month 12; therefore, median time to relapse was not available for either treatment group.

TABLE 9: RISK OF RELAPSE OR RE-HOSPITALIZATION

	Lurasidone (%)	Quetiapine (%)	Lurasidone versus QXR	
			HR (95% CI)	*P* value
Proportion of Relapse	23.7	33.6	0.73 (0.41, 1.30)	0.280
Proportion of Hospitalization	9.8	33.1	0.43 (0.19, 0.99)	NR

CI = confidence interval; HR = hazard ratio; NR = not reported; QXR = quetiapine extended release.

FIGURE 2: TIME TO RELAPSE OR RE-HOSPITALIZATION IN STUDY 234



LUR = lurasidone; QXR = quetiapine extended release.
Figure from Clinical Summary from original submission.[24]

Secondary efficacy end points in Study 234 included change from baseline in PANSS, CGI-S, and MADRS. Each of these end points was calculated using two methods: change from the extension study baseline; and change from core study baseline. The difference in change from baseline for each end point is displayed in Table 10 for the extension study baselines. Lurasidone was favoured over quetiapine for change in PANSS from both the extension study baseline (*P* = 0.010) and from the core study baseline (*P* = 0.006).

TABLE 10: SUMMARY OF SECONDARY EFFICACY END POINTS

End Point	Acute Study Baseline LS Mean (SE)	12-Month Study Baseline LS Mean (SE)	LUR versus QXR – Difference in Δ from Baseline	
			Δ from Extended Study Baseline	
			MD (95% CI)	*P* Value
Change in PANSS	−34.6 (1.8)	−5.0 (1.4)	–6.7 (–11.7 to –1.7)	0.010
Change in CGI-S	−1.9 (0.1)	0.0 (0.1)	–0.2 (–0.4 to 0.1)	0.266
Change in MADRS	−6.0 (0.6)	0.1 (0.6)	–1.3 (–3.3 to 0.7)	0.216

CGI-S = clinical global impression – severity of illness; CI = confidence interval; LS = least squares; LUR = lurasidone; MADRS = Montgomery–Asberg Depression Rating Scale; MD = mean difference; PANSS = positive and negative syndrome scale; QXR = quetiapine extended release; SE = secondary efficacy.
Data from Study 234 Clinical Study Report.[46]

Harms Outcomes: A summary of AEs reported in Study 234 is shown in Table 11. The proportion of patients who experienced at least one AE was similar in the lurasidone (64%) and quetiapine groups (72%). A greater proportion of lurasidone-treated patients reported EPS-related AEs (11.9%) compared with the quetiapine group (3.5%). A smaller proportion of lurasidone-treated patients reported one or more SAEs compared with quetiapine (9.9% vs. 20.0%). The proportion of patients who discontinued treatment due to an AE was also smaller in the lurasidone group (12.6%) compared with the quetiapine XR group (23.5%). The most frequently reported AEs in lurasidone-treated patients were: akathisia, headache, insomnia, anxiety, and parkinsonism. Akathisia and parkinsonism were reported in a higher proportion of lurasidone-treated patients than quetiapine XR-treated patients (12.1% versus 2.4% and 8.7% versus 0% respectively). Overall, the adverse event profile in Study 234 was similar to that reported for the core RCT.

Body weight increased in a similar proportion of patients in all treatment groups, with the highest incidence in the continuous quetiapine group (8.2%) and the lowest incidence in the placebo/lurasidone switched group (1.8%).

TABLE 11: SUMMARY OF ADVERSE EVENTS IN STUDY 234

Adverse Events	Patients – n (%)	
	Lurasidone	QXR
≥ 1 AE	97 (64.2)	61 (71.8)
EPS-related AE	18 (11.9)	3 (3.5)
Metabolic AE	11 (7.3)	9 (10.6)
Discontinuation due to AE	23 (15.2)	20 (23.5)

AE = adverse event; EPS = extrapyramidal symptoms; QXR = quetiapine extended release.
Data from Study 234 Clinical Study Report[46] and Loebel et al. (2013).[44]

TABLE 12: ADVERSE EVENTS REPORTED IN ≥ 5% OF PATIENTS DURING THE 12-MONTH DOUBLE-BLIND TREATMENT IN RELAPSE-PREVENTION STUDY

Adverse Events	Patients – n (%)		
	LUR to LUR	QXR to QXR	PL to LUR
≥ 1 AE	97 (64.2)	61 (71.8)	35 (62.5)
Akathisia	19 (12.6)	2 (2.4)	6 (10.7)
Headache	16 (10.6)	8 (9.4)	3 (5.4)
Insomnia	12 (7.9)	8 (9.4)	3 (5.4)
Anxiety	9 (6.0)	3 (3.5)	2 (3.6)
Parkinsonism	9 (6.0)	0.0	9 (16.1)
Weight increase	9 (6.0)	7 (8.2)	1 (1.8)
Nausea	7 (4.6)	2 (2.4)	6 (10.7)
Schizophrenia	7 (4.6)	13 (15.3)	2 (3.6)
Agitation	6 (4.0)	5 (5.9)	0.0
Psychotic Disorder	6 (4.0)	7 (8.2)	0.0
Vomiting	6 (4.0)	4 (4.7)	3 (5.4)
Diarrhea	4 (2.6)	4 (4.7)	4 (7.1)

AE = adverse event; LUR = lurasidone; PL = placebo; QXR = quetiapine extended release.
Data from Loebel et al. (2013).[44]

Limitations

The primary limitation of Study 234 is the high rate of discontinuation. Only 140 patients completed the extension study from the 292 who were enrolled in the extension phase (48%) and 488 who were originally randomized (29%). Furthermore, not all patients completing Study 233 consented to participation in 234, and it is unlikely that non-consent occurred in a random manner. Hence, randomization performed for the original study (233) may have been compromised in Study 234, and there may have been differences between treatment groups in the distribution of potential confounding factors. High rates of discontinuation may also obscure true differences between treatments, thus increasing the probability of demonstrating non-inferiority.

Although the justification for the non-inferiority margin of 1.93 in Study 234 was based on previous literature, the clinical acceptability of the margin is uncertain. Indeed, the margin appears generous since it represents a near doubling of relapse risk; although the actual upper 95% CI limit was considerably lower (1.30). In addition, there were no power calculations reported to indicate the required sample size to demonstrate non-inferiority.

Summary

Study 234 was a 12-month, DB, extension study comparing lurasidone 40 mg/day to 160 mg/day versus quetiapine XR 200 mg/day to 800 mg/day. The study was the extension of Study 233 (PEARL-3), a six-week, DB, placebo-controlled trial that compared lurasidone 80 mg, lurasidone 160 mg, and quetiapine XR 600 mg with placebo. Discontinuation rates were high (approximately 50%) in all treatment groups, suggesting that a substantial proportion of patients requires alternative antipsychotic therapy within months of treatment initiation regardless of the drug chosen. Lurasidone was deemed to be non-inferior to quetiapine based on the primary outcome, time to relapse. There were no statistically significant differences on secondary efficacy outcomes, except that lurasidone was favoured on PANSS total score at 12 months. AEs occurred in a similar proportion of patients across treatment groups, although the frequency of akathisia was higher for patients treated with lurasidone continuously or switched from placebo to lurasidone compared with quetiapine XR. No new harms were identified during the extension phase. Interpretation of the results of Study 234 requires caution due to the possibility of imbalances between treatment groups, and high rates of treatment discontinuation.

4.2.4 Summary of Study 231E

a) Objective

To summarize efficacy and safety evidence from Study 231 E, the extension phase of Study 231.

b) Findings

Study Characteristics

Study 231E was a six-month, open-label extension phase of Study 231. In Study 231, patients were randomly assigned to treatment with lurasidone 40 mg daily, lurasidone 120 mg daily, olanzapine 15 mg daily, or placebo. Eligible patients who completed the six-week DB phase entered a three-day placebo washout, and then switched to open-label lurasidone 80 mg daily. The dose of lurasidone could be titrated to 40 mg or 120 mg. At Study 231E baseline, the mean duration of illness for patients in the trial was approximately 12 years. At baseline, mean PANSS and CGI-S scores were approximately 67 and 3 respectively.

Patient Disposition

A summary of patient disposition is provided in Table 13. Of the 254 patients who entered the open-label extension phase of Study 231E, 113 (44%) completed the full six-month extension study. The most frequently reported reason for discontinuation from the extension study was withdrawal of consent (16%).

TABLE 13: SUMMARY OF PATIENT DISPOSITION

Disposition	Study 231E N (%)
Randomized in core RCT	478
Completed core RCT	298 (62)
Entered extension	254 (87)
Completed extension	113 (44)
Discontinued extension	141 (56)
Withdrew consent	41 (29)
Insufficient clinical response	17 (12)
Adverse event	32 (23)
Lost to follow-up	29 (21)
Protocol violation	12 (8)
Other	10 (7)

RCT = randomized controlled trial.
Data from Stahl et al. (2013).[45]

Efficacy Outcomes

Efficacy data were only reported for the subset of patients (n = 117) who completed the full extension phase (see Table 14). Improvements from extension phase baseline were observed in PANSS (–8.7) and CGI-S (–0.4). There was no difference in the MADRS scores (–0.0). Efficacy results were not reported according to original treatment assignment in Study 231.

TABLE 14: SUMMARY OF EFFICACY END POINTS IN OPEN-LABEL STUDIES

End Point	Study 231E N	Δ from OL Baseline
Change in PANSS	117	–8.7 (–11.3, –6.1)
Change in CGI-S	117	–0.4 (–0.6, –0.2)

Δ = increase; CGI-S = clinical global impression – severity; N = total sample size; OL = open label; PANSS = Positive and Negative Syndrome Scale.
Data from Clinical Trial Synopses for Study 231E and Stahl et al. (2013).[45,47]

Harms

Adverse events (AEs) reported in Study 231E are summarized in Table 15 and Table 16. Sixty-six per cent of patients experienced at least one AE. The most frequent AEs were akathisia (10% to 15%), insomnia (8% to 15%), nausea (6% to 11%), somnolence (7% to 11%), and parkinsonism (8% to 10%). The only clinically meaningful changes in body weight were for patients who had received olanzapine (15 mg) during the DB phase. These patients demonstrated a mean decrease in body weight of –1.80 kg ± 4.93 kg from open-label baseline to end point. Overall, the manufacturer did not identify any new safety concerns.

TABLE 15: SUMMARY OF ADVERSE EVENTS IN OPEN-LABEL STUDIES

Adverse Events	Study 231E n (%)
≥ 1 AE	162 (65.9)
SAEs	28 (11.4)
WDAEs	30 (12.2)
Deaths	NR
Suicide attempts	NR

AE = adverse event; NR = not reported; SAEs = serious adverse event; WDAEs = withdrawal due to adverse event.
Data from Stahl et al. (2013).[45]

TABLE 16: ADVERSE EVENTS REPORTED IN ≥ 5% OF PATIENTS DURING OPEN-LABEL TREATMENT WITH LURASIDONE, SAFETY POPULATION

Adverse Events	Patients – n (%)		
	LUR to LUR	OLN to LUR	PL to LUR
Akathisia	12 (10.4)	11 (5.9)	9 (14.5)
Insomnia	9 (7.8)	10 (14.5)	8 (12.9)
Somnolence	12 (10.4)	5 (7.2)	7 (11.3)
Nausea	7 (6.1)	5 (7.2)	12 (19.4)
Parkinsonism	11 (9.6)	6 (8.7)	6 (9.7)
Headache	9 (7.8)	2 (2.9)	7 (11.3)
Vomiting	7 (6.1)	5 (7.2)	4 (6.5)
Anxiety	9 (7.8)	2 (2.9)	4 (6.5)
Weight increase	7 (6.1)	2 (2.9)	4 (6.5)

LUR = lurasidone; OLN = olanzapine; PL = placebo.
Data from Stahl et al. (2013).[45]

Summary

Based on the results of Study 231E, the efficacy and safety of lurasidone appear to be maintained over six months among patients who continue with therapy, and no new safety concerns were identified. Without a comparator group (e.g., patients randomized to olanzapine continuing on olanzapine in the extension), the study does not provide any information regarding relative long-term efficacy and safety. Discontinuation rates in the extension study were high (> 50%), suggesting that most patients will require alternative antipsychotic therapy within months of initiating lurasidone.

4.2.5 Switching Study

a) Objective

The purpose of this study (McEvoy et al. 2013)[3] was to examine the efficacy of switching patients from other antipsychotics to lurasidone using three dosing strategies.

b) Findings

Study Characteristics

A phase III, open-label, multi-centre, randomized, parallel-group, six-week switching study was conducted at multiple sites across the USA. The inclusion criteria for the trial incorporated the following: adults (≥ 18 years of age), Diagnostic and Statistical Manual of Mental Disorders (DSM) DSM-IV schizophrenia or schizoaffective disorder, illness ≥ 1 year, appropriate candidate for switching due to inefficacy and/or safety or tolerability concerns, clinically stable (at least 8 weeks with CGI-S ≤ 4). The exclusion criteria were as follows: axis I or II disorder other than schizophrenia or schizoaffective disorder that was the primary focus of pre-screening treatment; antipsychotic medications not exceeding the following doses 28 days prior to screening: aripiprazole 30 mg, asenapine 20 mg, iloperidone 24 mg, olanzapine 20 mg, paliperidone 12 mg, quetiapine 800 mg, risperidone 8 mg, or ziprasidone 160 mg; dose of FGAs must not have exceeded the equivalent of haloperidol 12 mg/day.

Patients were switched from a wide variety of antipsychotics; they were gradually tapered off prior antipsychotics and completely discontinued by day 14. At baseline, the majority of patients were previously treated with quetiapine, risperidone, or aripiprazole.

Patients were randomly assigned to one of three treatment groups stratified based on treatment with a sedating antipsychotic (olanzapine or quetiapine) or non-sedating antipsychotic drug (all others):

- lurasidone 40 mg per day for 14 days, followed by flexible dosing between 40 mg and 120 mg per day for 4 weeks.
- lurasidone 40 mg per day for 7 days, followed by 80 mg for seven days, ending with flexible dosing between 40 mg and 120 mg for 4 weeks.
- lurasidone 80 mg per day for 14 days, followed by flexible dosing between 40 mg and 120 mg per day for 4 weeks.

A summary of patient disposition is provided in Table 17. Initially, 377 patients were screened, of whom 133 patients were deemed ineligible for various reasons; the most frequently cited reason was meeting at least one exclusion criterion. As a result, 244 patients were randomized. Patients were allocated in similar numbers to each treatment group (40 mg for two weeks (40 mg), n = 74; 40 mg one week/80 mg one week (40 mg/80 mg), n = 88; 80 mg two weeks (80 mg), n = 82. Across treatment groups similar proportions of patients completed the trial (78% to 83%). The most frequently cited reason for discontinuation across treatment groups was AEs (6% to 7%).

TABLE 17: SUMMARY OF PATIENT DISPOSITION

Disposition – n (%)	LUR 40 mg/ 40 mg[a]	LUR 40 mg/80 mg[b]	LUR 80 mg/ 80 mg[c]
Assessed for eligibility	377		
Total randomized	244		
Allocated to each treatment	74	88	82
Completed extension	58 (78.4)	73 (83.0)	67 (81.7)
Discontinued extension	16 (21.6)	15 (17.0)	15 (18.3)
Withdrew consent	4 (5.4)	3 (3.4)	3 (3.7)
Insufficient clinical response	0	2 (2.3)	1 (1.2)
Adverse event	5 (6.8)	6 (6.8)	5 (6.1)
Lost to follow-up	2 (2.7)	3 (3.4)	4 (4.9)
Protocol violation	2 (2.7)	0.0	0.0
Non-compliance with study drug	0.0	1 (1.1)	1 (1.2)
Administrative	1 (1.4)	0.0	0.0
Principal investigator decision	2 (2.7)	0.0	1 (1.2)

LUR = lurasidone.
[a]Lurasidone 40 mg/day for 14 days, followed by flexible dosing between 40 mg/day and 120 mg/day for four weeks.
[b]Lurasidone 40 mg/day for 7 days, then 80 mg/day for 7 days, followed by flexible dosing between 40 mg/day and 120 mg/day for four weeks.
[c] Lurasidone 80 mg/day 14 days, followed by flexible dosing between 40 mg/day and 120 mg/day for four weeks.
Data from McEvoy et al.[3]

Efficacy Outcomes

The primary outcome was time to treatment failure, defined as any occurrence of: insufficient clinical response; exacerbation of underlying disease; or discontinuation due to an AE, as determined by the investigator. Secondary outcomes included discontinuations, change in body weight, PANSS total score (not reported), and CGI-S (not reported).

There were two patient populations for the efficacy and safety analyses:

- The intention-to-treat population (used for the efficacy analysis) was defined as all patients who were randomized and received at least one dose of lurasidone at baseline and at least one post-baseline efficacy measurement.
- The safety population was defined as any patient who received at least one dose of lurasidone.

The proportion of patients experiencing treatment failure was similar across treatment groups, ranging from 7% to 9% (lurasidone 40 mg group to lurasidone 80 mg group respectively). A log-rank test for time to treatment failure demonstrated no statistically significant differences among the three groups (P = 0.861) Table 18.

Median time to treatment failure was similar across treatment groups, ranging from 18.5 days to 23 days (lurasidone 40 mg/80 mg to lurasidone 40 mg). The proportion of patients who discontinued due to any cause was similar across treatment groups, ranging from 17% to 18%. The median time to all-cause discontinuation was lowest in the lurasidone 40 mg/80 mg group at 16 days and highest in the lurasidone at 40 mg at 22 days. Within group measures of change from baseline PANSS, total scores generated statistically significant differences in all treatment groups ranging from –5 to –7 points (lurasidone 40 mg group to lurasidone 80 mg group).

TABLE 18: SUMMARY OF KEY EFFICACY OUTCOMES

Outcome	LUR 40 mg	LUR 40 mg/80 mg	LUR 80 mg
Treatment failures n (%)	5 (6.9)	8 (9.2)	6 (7.4)
Time to treatment failure (d) Median Mean (SD)	 23 23.8 (12.1)	 18.5 16.9 (11.6)	 20.5 17.3 (8.9)
Log-rank test, *P* value	0.861		
All-cause discontinuation n (%)	13 (18.1)	15 (17.2)	14 (17.3)
Time to all-cause discontinuation (d) Median 25th to 75th percentiles	 22 6 to 34	 16 3 to 30	 20 13 to 21
Log-rank test, *P* value	.989		
Change from baseline PANSS total score LS Mean (95% CI)	–5.2 (–7.5 to –2.8)	–5.0 (–7.1 to –2.8)	–6.8 (–7.9 to –3.5)
P value (within group)	< 0.0001	< 0.0001	< 0.0001
Change from baseline CGI-S			
LS Mean (95% CI)	–0.2 (–0.4 to –0.1)	–0.3 (0.4 to –0.1)	–0.2 (0.4 to –0.1)
P value (within group)	0.0014	< 0.0001	0.0004

CGI-S = clinical global impressions – severity; CI = confidence interval; LS = least squares; LUR = lurasidone; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
Data from McEvoy et al.[3]

Harms Outcomes

A summary of AEs is reported in Table 19. Limited data were reported for common treatment emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs). Among all treated patients, the most frequent TEAEs included nausea, insomnia, and akathisia.

TABLE 19: SUMMARY OF ADVERSE EVENTS

Adverse Events	LUR 40 mg	LUR 40 mg/80 mg	LUR 80 mg
Most Common TEAEs (≥ 5%)			
Nausea	10 (13.9)	8 (9.2)	15 (8.5)
Insomnia	3 (4.2)	16 (18.4)	12 (14.8)
Akathisia	6 (8.3)	13 (14.9)	11 (13.6)
Headache	7 (9.7)	10 (11.5)	6 (7.4)
Vomiting	4 (5.6)	6 (6.9)	7 (8.6)
Somnolence	7 (9.7)	7 (8.0)	2 (2.5)
Dry mouth	3 (4.2)	9 (10.3)	2 (2.5)

LUR = lurasidone; TEAE = treatment-emergent adverse event.

Summary

An open-label, multi-centre randomized, parallel-group six-week study of patients switched to lurasidone from previous treatment with antipsychotics demonstrated no statistically significant differences for time to treatment failure when dose escalation started with lurasidone 40 mg then 80 mg, or lurasidone 80 mg. The most frequent TEAEs were nausea, insomnia, and akathisia in all treatment groups. Without a comparator group consisting of an AAP other than lurasidone, the comparative efficacy and safety of lurasidone and other AAPs for patients requiring a treatment switch is uncertain.

5. DISCUSSION

No RCTs met the inclusion criteria for the updated review of lurasidone. Nevertheless, the key elements forming the basis of the manufacturer's resubmission have been summarized and appraised in detail in this report.

The main reason for CDEC's recommendation of "Do Not List" for lurasidone was a lack of evidence from RCTs to establish the comparative efficacy of lurasidone relative to other AAPs for the acute treatment of schizophrenia.[1] As discussed at length in CDR's original review, direct comparative evidence for lurasidone against other AAPs is sparse. In the acute-treatment trials, risperidone, olanzapine, and quetiapine were incorporated as active comparators for the purpose of assay sensitivity, but these trials were not designed for comparisons against lurasidone. In fact, the only study designed to assess non-inferiority of lurasidone with another AAP was a 52-week stable treatment trial that failed to confirm non-inferiority against risperidone on time to relapse.

Broadly speaking, there is a considerable body of evidence regarding the comparative efficacy of AAPs. Findings from the large clinical antipsychotic trial of intervention effectiveness (CATIE)[48,49] suggested that olanzapine was more effective than risperidone and quetiapine, as indicated by time to treatment discontinuation, with a similar trend favouring olanzapine over ziprasidone. Lurasidone was not studied in this trial. Olanzapine was also shown to be superior to aripiprazole, quetiapine, risperidone, and ziprasidone for a change in PANSS scores in a systematic review and meta-analysis of blinded, head-to-head studies comparing second-generation antipsychotics (78 studies, N = 13,558).[50]

Without direct comparative evidence, well-conducted indirect comparisons can aid the assessment of relative efficacy and safety. The manufacturer submitted the IDCs separately, comparing lurasidone with aripiprazole and with ziprasidone. Overall, no statistically significant differences in efficacy were noted in these comparisons. However, several shortcomings were noted that limit the interpretation of these results, primarily the restricted focus to aripiprazole and ziprasidone as comparators, the lack of a systematic literature search, and the apparent absence of methods for considering heterogeneity across studies.

Recently, Leucht et al. (2013)[2] conducted a comprehensive NMA that integrated direct and indirect comparisons of 15 orally administered antipsychotic drugs (including lurasidone) for acute-treatment of schizophrenia (defined as six weeks duration). The primary outcome was change in overall symptoms from baseline to end point, measured by the PANSS total score. The results suggested that there were no statistically significant differences in efficacy between lurasidone and aripiprazole, zotepine, haloperidol, quetiapine, sertindole, ziprasidone, chlorpromazine, asenapine, or iloperidone. However, lurasidone demonstrated statistically significantly lower efficacy than clozapine, amisulpride, olanzapine, risperidone, and paliperidone. Compared with placebo, the SMD in symptom improvement for the four

newest AAP drugs available in Canada were similar: aripiprazole (0.43); ziprasidone (0.39); asenapine (0.38); and lurasidone (0.33). The older AAPs tended to be associated with larger SMDs: olanzapine (0.59); risperidone (0.56); paliperidone (an active metabolite of risperidone) (0.50); and quetiapine (0.44). These results were robust even when adjustments were made for known confounders such as year of publication. Lurasidone ranked second-last in terms of efficacy (after iloperidone), and lower than aripiprazole and ziprasidone. The results were broadly similar for the outcome of all-cause discontinuation, such that lurasidone had the third-highest risk of discontinuation after sertindole and haloperidol. Lurasidone was associated with statistically higher risks of all-cause discontinuation compared with olanzapine and risperidone, but there were no significant differences between lurasidone and quetiapine, aripiprazole, or ziprasidone.

Unlike the manufacturer-submitted IDCs, Leucht et al. also reported on comparative safety across AAPs. Lurasidone is purported to have a relatively neutral metabolic profile, similar to the other newer AAPs (i.e., aripiprazole and ziprasidone). The only metabolic outcome reported in the Leucht et al. paper was weight gain. Based on SMDs, the degree of weight change was similar across aripiprazole (0.17), ziprasidone (0.10), and lurasidone (0.10) compared with placebo. The effect estimate for lurasidone indicated a non-significant change in body weight compared with placebo. Olanzapine, quetiapine, and risperidone were associated with significantly more weight gain than lurasidone. For example, the effect estimate for weight change with olanzapine versus placebo was an SMD of 0.74. However, no information was available on other relevant metabolic outcomes, such as blood glucose and lipid parameters. A recent meta-analysis by De Hert et al. (2012)[51] compared the body weight and metabolic AEs of newer second-generation AAPs (lurasidone, asenapine, iloperidone, and paliperidone) based on the changes in numerous metabolic measures, including weight change from placebo-controlled clinical trials. The authors reported that lurasidone was associated with a statistically significant increase in weight gain when compared with placebo (WMD = 0.49 kg), and it was concluded that this drug was similar to aripiprazole and ziprasidone in this respect.

In line with the results of the CDR review of lurasidone trials, the risk of EPS reported by Leucht et al. was higher with lurasidone than placebo and several other AAPs, and lurasidone was one of the least tolerated drugs in this respect. The odds ratio (OR) for this outcome against placebo was 2.46 and statistically significant for lurasidone, compared with 1.20 and non-significant for aripiprazole, and 1.00 for olanzapine. The comparison of lurasidone with aripiprazole was statistically significant in favour of the latter drug.

Another adverse effect reported by Leucht et al. was QTc prolongation, which occurred to a lesser degree with lurasidone than olanzapine and other older AAPs. The comparison of lurasidone with aripiprazole was statistically non-significant; whereas, lurasidone was associated with a significantly lower degree of QTc prolongation compared with ziprasidone. Increases in prolactin were larger with lurasidone than with aripiprazole, but there was no significant difference between lurasidone and either olanzapine or ziprasidone. With respect to sedation, there were no significant differences between lurasidone and aripiprazole, ziprasidone, olanzapine, risperidone, or quetiapine.

The Leucht et al. study provides important information regarding comparative efficacy and safety across AAPs in the acute-treatment setting (initial six weeks). However, a similar analysis is not available for stable patients. The only comparative RCTs of lurasidone with other AAPs in this setting are Studies 254 and 237 (both included in the original CDR review), in which the comparators were ziprasidone and risperidone respectively. Study 237 was a one-year trial specifically designed to compare treatments on time to relapse using a non-inferiority design, but failed to confirm the non-inferiority hypothesis. The

only other study providing comparative evidence in the stable treatment setting was Study 234, the extension of Study 233. While this study confirmed the a priori non-inferiority hypothesis for time to relapse against quetiapine, interpretation of these results is limited by concerns that the original randomization performed in Study 233 may have been compromised in the extension. Such concerns arise because not all patients completing Study 233 consented to participating in Study 234 and there were high rates of withdrawal from both studies. Thus, similar to the results of the original CDR review, the comparative long-term efficacy and safety of lurasidone versus other AAPs remains uncertain.

The clinical context of antipsychotic therapy for schizophrenia is an important consideration in evaluating the available comparative efficacy and safety evidence for lurasidone. Patient group input received by CDR indicated the need for additional antipsychotic treatment options for patients with schizophrenia, and an individualized approach to treatment. Two main reasons were cited for this. First, there is variability in individual patient response, so that a particular drug may not be effective for all patients, and a trial and error approach to identifying optimal therapy is common. Second, AEs, particularly metabolic effects such as weight gain, can be very problematic for patients because of their impact on self-esteem, as well as the associated risks of diabetes and cardiovascular disease. Neurological adverse effects such as drowsiness and akathisia can also impair quality of life and result in treatment discontinuation. While there may be concerns regarding the comparative efficacy of lurasidone versus other commonly used antipsychotic drugs, it is possible that its observed AE profile may be advantageous for some patients, particularly with respect to its low propensity for causing weight gain.

6. CONCLUSIONS

The main reason for the original CDEC recommendation of “Do Not List” was a lack of sufficient evidence to establish the comparative efficacy of lurasidone against other AAPs. In this updated review, no additional RCTs meeting the inclusion criteria have been identified since the original CDR review of lurasidone. Without direct comparative trials, a recently published NMA provided important insights into the comparative efficacy and safety of AAPs, including lurasidone, in the acute-treatment setting. The results indicated that lurasidone was associated with lower efficacy in terms of PANSS total score than olanzapine and risperidone. Although there were no significant differences in efficacy between lurasidone and aripiprazole, quetiapine, or ziprasidone, lurasidone was ranked as least efficacious among these drugs. Weight changes with lurasidone were similar in magnitude to aripiprazole and ziprasidone, and less than with older AAPs. There was no information regarding relative effects on other metabolic parameters. Compared with the original CDR review, there was no additional information regarding the relative long-term efficacy and safety of lurasidone compared with other AAPs. An important context for interpreting the available evidence for lurasidone is patient group input, indicating the need for additional therapeutic options for schizophrenia.

APPENDIX 1: PATIENT INPUT SUMMARY

1. Brief Description of Patient Groups Supplying Input

The Schizophrenia Society of Canada exists to improve the quality of life for those affected by schizophrenia and psychosis through public education, support, advocacy, and research. The Society has received funding this year from Sunovion, Eli Lilly, Janssen, Roche, Bristol-Myers Squibb, and Pfizer.

The British Columbia Schizophrenia Society (BCSS) is a family-based organization with 27 branches and over 2,500 members, with the mission to improve the quality of life for those affected by schizophrenia and psychosis through education, support, public policy, and research. BCSS declared funding from Bristol-Myers Squibb, Janssen, Novartis, Otsuka, Pfizer, and Mylan Pharmaceuticals.

The Schizophrenia Society of Ontario (SSO) is a non-profit charitable organization dedicated to making a positive difference in the lives of people, families, and communities affected by schizophrenia and psychotic illnesses. SSO has five regional offices, over 300 active volunteers, and provides programs and services throughout the province to assist, inform, and support individuals and families affected by these conditions. SSO declared funding from Janssen, Eli Lilly, Novartis, Bristol-Myers Squibb, Sunovion, Lundbeck, Mylan Pharmaceuticals, AstraZeneca, Pfizer, and Hoffmann-La Roche.

The three submitting groups declared no conflicts in the preparation of their submissions.

2. Condition and Current Therapy Related Information

Information was gathered through surveys conducted by SSO in May 2010 (49 patients, 101 family members) and March 2013 (79 patients, 201 family members); the former included questions on the impact of living with schizophrenia and experience with medications, and the latter on experiences with schizophrenia and the mental health system. Information was also based on previously gathered personal experience; focus groups; one-on-one conversations with members, board members, and staff; and published literature.

Schizophrenia affects 1 in 100 people worldwide and more than 300,000 Canadians. It generally strikes people aged 15 to 24 and is lifelong; there is no cure. Even with no family history of mental illness, a young person is six times more likely to develop schizophrenia than insulin dependent diabetes, and 60 times more likely to develop schizophrenia than muscular dystrophy. In 2004, it was estimated that 85% of patients with schizophrenia were unable to work and that the economic burden of the disease in Canada was $6.85 billion per year.

For some, the dominant symptoms are distressing voices, delusions, and paranoia (positive symptoms). For others, symptoms affecting cognition, especially those limiting executive skills, memory, and verbalization, are the most problematic (negative symptoms). Schizophrenia interferes with identity formation, socialization, maturation, and acceptance. Many patients report difficulty determining what is real and what is not. Maintaining relationships and working or continuing one's education can be nearly impossible without effective treatments, and there is significant social stigma.

In the 2010 SSO survey, 63% of patients and 87% of family members felt that schizophrenia affects quality of life a lot, while 21% and 12% respectively, felt it had somewhat of an impact. Almost all respondents were currently taking antipsychotic medications, but many were still experiencing symptoms such as hallucinations, delusions, paranoia, low energy, lack of motivation, social withdrawal, lack of insight, poor concentration, memory or attention problems, disorganized speech, depression,

anxiety, and blunted emotions. Weight gain was added as an adverse effect by several respondents. Most family members believed schizophrenia affected day-to-day life a lot, including sleep, work, attending school, socializing with friends, living independently, driving a car, and self-care. Child raising and family relationships were also affected. Patients mentioned that schizophrenia has changed their life for the worse, that they have no hope for the future, and that they can't make future plans. The 2013 SSO survey results showed that 41% of individuals with schizophrenia were on public disability and 31% were not working, on long-term disability, or unemployed. Only 13% were working full time and 63% had annual incomes of less than $25,000. Twenty-five per cent reported living with a disability and only 38% rated their physical health as good. The top five comorbidities were obesity, high cholesterol, diabetes, drug or alcohol dependence, and high blood pressure.

Current therapies include antipsychotics, antidepressants, benzodiazepines, cognitive behavioural therapy (CBT), and psychiatric rehabilitation. Twenty-five per cent of patients are considered treatment-resistant. For many, medications are helpful in managing their illness, but individual responses vary. Medications generally help reduce, not eliminate, positive symptoms, but do not adequately address negative symptoms. There are also significant concerns regarding side effects, particularly weight gain — which has physical health consequences such as type 2 diabetes and additionally can erode self-esteem — and drowsiness. Other side effects include neurological effects: akathisia, blurred vision, excess salivation, body tremors, nervousness, sleeplessness, tardive dyskinesia, and blood disorders. Such side effects limit adherence or require discontinuation of the medication in question. Finding the right medication is a trial and error process, but can reduce psychotic episodes and hospitalizations, and improve the ability to lead a meaningful, peaceful life.

Because schizophrenia has a profound impact on employment and income, medications that are not covered by public drug plans become inaccessible or are a major financial burden. Additionally, regional barriers such as living in rural or northern communities can reduce access to medications, psychiatrists, CBT, and psychiatric rehabilitation. It can be very difficult to finally find the right medication and then not be able to afford it; the cost of an unlisted medication can take up a major part of an already low income, which deters compliance. One individual stated "Prevention (such as subsidized drugs and therapies) is a better investment than too-late public spending on the effects of untreated mental illness (unemployment, jail, violence, etc.)."

Families are the primary caregivers and support for those living with schizophrenia. Seventy per cent of those living with schizophrenia live with their families, often due to lack of appropriate housing and services. The SSO 2013 survey showed that 96% of caregivers provided emotional support on a weekly basis, 85% helped with transportation, 71% with meal preparations, 65% with scheduling, 63% with banking, 54% with medication, 48% with home maintenance, and 12% with personal care. Only 30% of caregivers received professional support for these tasks and the majority received no assistance from the health care system or from other family and friends. Patients and caregivers carry a significant burden rooted in social prejudice against those with mental illness. They feel shamed and are often frustrated by the "mental health maze" in accessing treatment. Families worry about side effects affecting quality of life and personal goals, compliance, and their loved one becoming so ill that she or he becomes homeless or imprisoned. There is no respite and little hope. In order to provide optimal treatment for schizophrenia in Canada, caregivers believe physicians must have the ability to individualize treatment.

3. Related Information About the Drug Being Reviewed

It is expected that the lives of some patients will be improved by using lurasidone, the most desperate of whom are the 25% who are currently considered treatment-resistant. Some patients also anticipate fewer metabolic side effects with lurasidone, an important consideration for those whose current medication may be effective but causes significant weight gain, sometimes over 45 kilograms (100 pounds). Whether a patient is willing to put up with any given side effect depends on the patient and his or her personal goals.

While experience with lurasidone was limited, family members of those who took it noted advantages such as more control in taking their medication, greater control of symptoms, and considerable improvements in mood. The majority of survey respondents would prefer medications to be easier to access and be much less expensive.

Most antipsychotic medications have similar efficacy on average, but individual patients may respond differently to a particular medication. It can take years to learn the unique advantages of specific antipsychotic medications; at one time even clozapine was considered a classic “me too” drug. The long-term economic benefits of allowing patients access to the medication that is right for them include reduced relapse rates, reduced hospitalizations, reduced use of emergency and community services, and better patient outcomes. Schizophrenia and psychosis are treatable and recovery of quality of life is possible when people are able to find the right options for treatment and support; thus, allowing patients to have hope.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations PsycINFO 1967 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 8, 2013
Alerts:	Weekly search updates until November 20, 2013 (date of CDEC meeting)
Study Types:	No search filters were applied
Limits:	Date limit: citations added to databases since date of original Latuda submission search (July 2012) No language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
.ed	Entry date [MEDLINE only]
.ep	Electronic date of publication [MEDLINE only]
.dd	Date delivered [Embase only]
.em	Entry week [Embase only]
.up	Update code [PsycINFO only]
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(lurasidone* or latuda* or SM 13496 or SM13496).ti,ot,ab,sh,rn,hw,nm.
2	(367514-88-3 or 367514-87-2 or 441351-20-8).rn,nm.
3	or/1-2
4	3 use pmez,psyb
5	(lurasidone* or latuda* or SM 13496 or SM13496).ti,ab.
6	*lurasidone/
7	or/5-6
8	conference abstract.pt.
9	7 not 8
10	9 use oemezd
11	4 or 10
12	exp animals/
13	exp animal experimentation/
14	exp models animal/
15	exp animal experiment/
16	nonhuman/
17	exp vertebrate/
18	animal.po.
19	or/12-18
20	exp humans/
21	exp human experiment/
22	human.po.
23	or/20-22
24	19 not 23
25	11 not 24
26	(201207* or 201208* or 201209* or 20121* or 2013*).ed,ep.
27	25 and 26
28	27 use pmez
29	(201207* or 201208* or 201209* or 20121* or 2013*).dd.
30	("201227" or "201228" or "201229" or 20123* or 20124* or 20125* or 2013*).em.
31	29 or 30
32	25 and 31
33	32 use oemezd
34	("201227" or "201228" or "201229" or 20123* or 20124* or 20125* or 2013*).up.
35	25 and 34
36	35 use psyb
37	28 or 33 or 36
38	remove duplicates from 37

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for search:	July 2013
Keywords:	Latuda, lurasidone, schizophrenia
Limits:	Date limit: anything made available since date of original Latuda submission grey literature search (July 2012). No language limits used.

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Loebel et al. (2013)[52]	Found in original submission
Nasrallah et al. (2013)[53]	Found in original submission
Ogasa et al.[54]	Found in original submission
Loebel et al.[44]	Extension study / Not randomized

APPENDIX 4: APPRAISAL OF MANUFACTURER-SUBMITTED INDIRECT TREATMENT COMPARISION

TABLE 20: APPRAISAL OF INDIRECT TREATMENT COMPARISONS USING ISPOR CRITERIA[41,43]

ISPOR Checklist Item		Details and Comments
1.	Is the rationale for the study and the objectives stated clearly?	• Study objective stated • No rationale was provided within the document for the IDC.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity/quality assessment of individual studies	• Eligibility criteria are unclear and seemingly incomplete (i.e., patients suffering a relapse, mixed population of patients undergoing chronic maintenance treatment. • Database searches were not conducted. • A systematic approach to searching the literature was not used. An explicit search strategy was not reported. • Study selection involved identifying trials cited in the aripiprazole, ziprasidone, and lurasidone CDR recommendations. • Outcomes extracted from the included studies are clearly described. • Validity/quality assessment of the included studies not reported.
3.	Are the outcome measures described?	• A broad list of outcomes of interest is provided, with a statement that outcomes common to the included studies were pooled for indirect treatment comparison.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical methods was provided. The methods for modelling direct and indirect comparisons were reported. CADTH's indirect comparison calculator using the Bucher Method was used for the indirect treatment comparison. • No methods for handling potential bias or inconsistencies were reported. • It is unclear if covariates were built into the models.
5.	Are sensitivity analyses presented?	• No sensitivity analyses results were presented.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with study-level patient characteristics was not provided. • Trial duration of all included studies was reported to range from 6 to 28 weeks. • A figure showing the network of studies was not provided. • It is unclear at what time point outcomes in the IDC were assessed (e.g., PANSS at 6 weeks).
7.	Does the study describe an assessment of model fit?	• No description of assessment of model fit is provided.
8.	Are the results of the evidence synthesis presented clearly?	• Yes, the results are presented numerically but there are no figures or plots.
9.	Are there sensitivity/scenario analyses	• No sensitivity analyses were reported.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research.

APPENDIX 5: APPRAISAL OF LEUCHT ET AL. (2013) NMA

TABLE 21: APPRAISAL OF LEUCHT ET AL. (2013)[2] NMA USING ISPOR CRITERIA[41,43]

ISPOR Checklist Item		Details and Comments
1.	Is the rationale for the study and the objectives stated clearly?	• The rationale for conducting an NMA and the study objectives was clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity/quality assessment of individual studies	• Eligibility criteria of RCTs were clear and focused. • Literature search included multiple databases, clinical trial register, reference lists, and information from the FDA and manufacturers. • Detailed search strategy was not provided. • Study selection, data extraction, and validity assessment were done independently by two researchers. • Outcomes extracted from the included studies are clearly described. • Validity/quality assessment of the included studies was completed using the Cochrane risk of bias method.
3.	Are the outcome measures described?	• The outcomes of interest are described and include efficacy and harms.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the Bayesian NMA statistical methods was provided for continuous and dichotomous outcomes. Rationale for methods used was listed. • Meta-regression was used to examine possible effect modifiers. • Consistency and inconsistency models were compared for model fit and consistency of direct and indirect evidence was examined.
5.	Are sensitivity analyses presented?	• The rationale for the numerous sensitivity analyses was presented.
6.	Do the results include a summary of the studies in the network of evidence? • Individual study data? • Network of studies?	• Study selection flowchart was provided. • A table with study-level characteristics was provided, but with limited study details. • No individual study outcome data were provided. • Figures showing the network of studies for each outcome were provided.
7.	Does the study describe an assessment of model fit?	• Model fit was assessed comparing consistency and inconsistency models.
8.	Are the results of the evidence synthesis presented clearly?	• The NMA results were presented numerically (all comparisons) and in figures (versus placebo) and included point estimates and 95% credible intervals. • Ranking curves were provided in the appendix.
9.	Are there sensitivity/scenario analyses?	• Data for sensitivity analyses and meta-regression models were reported in the appendix.
10.	Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• The discussion included a summary of findings, internal validity, external validity, and implications for the target audience.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; RCT = randomized controlled trials.

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