REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Latuda
37 mg film-coated tablet x 28
lurasidone

Therapeutic indications	Indicated for the treatment of schizophrenia in adults aged 18 years and over.
Start/end date of procedure	30.05.2019 - 20.12.2019
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Latuda

Health problem

Schizophrenia is a neurodegenerative disease of the CNS, combining a number of genetic predispositions, non-specific clinical manifestations and diagnostically significant behaviors and variants of disease outcome, affecting social functioning as a chief criterion for prognosis. Regardless of the type of symptoms manifestation in their negative or positive forms, of crucial importance for psychiatric morbidity is the huge impact of symptoms on the social roles of the individual. Unlike other morbidities in humans, usually involving the individual and the immediate environment, in schizophrenic psychoses and associated deviant behavior the social repercussions can be enormous, including the potential to influence public attitude and directly affect unrelated individuals. This specific model of illness is at the core of stigmatization of psychiatric illness and the mentally ill and requires active measures both in terms of prevention and treatment of patients and in terms of public attitudes.

Epidemiological data

There are insufficient data on the epidemiology of schizophrenic psychoses in Bulgaria. Numerous studies in the field show a high degree of stability of epidemiological indicators for schizophrenic psychosis, regardless of social or climatic factors. Schizophrenic psychoses are widespread throughout the world. The prevalence varies in international aspect by about 1%. The incidence for a one-year period is 1.5% per 10,000 people. The onset of disease is usually in young adulthood, a little earlier in men, around 18-25 years, in women after the age of 25-30 years. Instances of onset in childhood and after the age of 45 are relatively rare. Men are diagnosed more often than women in a 1.4: 1 ratio. There is uncertain evidence of a more unfavorable course of disease in men. The mortality rate from natural causes is 2-8 times higher than that of the rest of the population.

For a period of 20 years, 50% of schizophrenics would attempt suicide, 10% of which are completed. Schizophrenia affects all segments of society, but tends to be more common in the lower strata. This phenomenon is explained by the so-called "down drifting", a characteristic of schizophrenic psychosis - patients lose their social status, descending to lower social strata; another possible explanation being increased tolerance and lower requirements towards unacceptable behavior of poorer communities.

Schizophrenic symptoms are viewed as two counterpoints:

Positive - delusions of control, reference or other persistent delusions that are culturally inappropriate or improbable; "insertion" or withdrawal of thoughts, transmission of thoughts, thought “echo”, interruptions or insertions in the flow of thinking, leading to torn or

incoherent speech; hallucinatory voices, commenting or discussing the patients or voices coming from a body part, persisting hallucinations in any modality; catatonic behavior - agitation, posturing or waxy flexibility, negativism, mutism or stupor.
Negative - apathy, poverty of speech, dullness or discrepancy of emotional responses, inability to make decisions, lack of intention, social withdrawal and reduced social functioning.

There are no pathognomonic symptoms for schizophrenia. The symptoms observed in a given patient can change over time and to some extent depend on the intellectual abilities, educational level and cultural characteristics of the community to which the patient belongs.

The development of disease includes prodromal manifestations and a psychotic episode. It consists of exacerbations and relative improvements (remissions), but unlike affective disorders, after a psychotic episode in most cases patients with schizophrenia cannot live and work as prior to the attack (a worsened social functioning).
The types of schizophrenia are:

- Paranoid - delusions, hallucinations and thought disorders predominate in the symptoms (the most common form).
- Catatonic - with manifestations of catatonic stupor (complete immobilization in embryonic or bizarre posture, negativism or automatic obedience, mutism, waxy flexibility) or catatonic arousal (impulsive, unmotivated, often stereotyped movements).
- Disorganized type (hebephrenic) - mannerisms, unpredictable behavior, inconsistency of affect, transient delusions and hallucinations predominate. The onset is in adolescence.
- Undifferentiated - conditions that meet criteria for schizophrenia, but it is impossible to refer to any of the described forms (excluding residual schizophrenia).
- Simple form - the negative symptoms with odd behavior and a collapse in social functioning prevail.
- Residual - the first five forms are based on the specifics of the clinical picture and the predominant symptoms, this form practically has the symptoms described in the prodromal period of schizophrenia, but unlike it there is a clear psychotic episode in the history.

Convenient for practice and therapy is the presentation of the course of disorder in phases:

- Acute phase: It is characterized by pronounced positive symptoms and requires active treatment.
- Stabilization phase: Reduction in positive symptoms. Lasts about six months.
- Stability phase: Symptoms are under control, there is some critical thinking.

- Deterioration phase (relapse): Occurs due to intrinsic or environmental factors. The frequency depends on the form of the disease, the quality of treatment, environmental factors.

Antipsychotic treatment is the leading pharmacotherapy recommendation. In the course of treatment of schizophrenia, psychotic symptoms may vary in manifestations or intensity, and decisions for use and the dosage of antipsychotics are determined by the response to therapy, side effects, and the stage of the disease. Latuda (lurasidone) shows a different pharmacological and receptor profile, compared to the spectrum of antipsychotics currently available in therapeutic practice, making Latuda (lurasidone) a medicinal product with a unique profile of efficacy and tolerability.

Efficacy data

PEARL 1 clinical trial to evaluate the therapeutic efficacy and safety profile of lurasidone (40 mg/day, 80 mg/day and 120 mg/day) in patients with acute schizophrenia.
Therapeutic efficacy outcomes, assessed by the change in the total score on PANSS and CGI-S are summarized in the following tables.

Table. 1: Mean (LS) change from baseline to week 6 in the PANSS score:

	Lurasidone 80 mg	Placebo
Analyzed patients	90	90
Mean (LS) change from baseline through week 6 in PANSS score (95% CI)	-14.1 (-18.3 до -9.9)	-5.5 (-9.8 до -1.2)

Table. 2: Mean (LS) change from baseline to week 6 in the MADRS score:

	Lurasidone 80 mg	Placebo
Analyzed patients	86	83
Mean (LS) change from baseline through week 6 in MADRS score (95% CI)	-2.9 (-4.6 до -1.3)	-0.1 (-1.9 до 1.6)

PEARL 2 clinical trial to evaluate the therapeutic efficacy and safety profile of lurasidone (40 mg/day and 120 mg/day) in patients with acute schizophrenia. Treatment with lurasidone (40

mg/day and 120 mg/day) or olanzapine 15 mg/day was associated with a significantly greater improvement in the overall PANSS score and CGI-S score, compared to placebo. No statistically significant differences were observed in the overall PANSS score or CGI-S score between the lurasidone group and the olanzapine group.

PEARL 3 clinical trial to evaluate the therapeutic efficacy and safety profile of lurasidone (80 mg/day and 160 mg/day) in patients with acute schizophrenia. In this study, quetiapine XR at a dose of 600 mg/day was used as an active comparator to confirm the sensitivity of the study. Treatment with lurasidone (80 mg and 160 mg/day) or quetiapine XR (600 mg/day) was associated with significantly greater improvement at week 6 in the overall score, PANSS scores for positive and negative symptoms, and CGI-S scores compared to placebo.

Clinical study D1050006 examined the efficacy of lurasidone compared to placebo, with the highest rate of dropouts due to lack of efficacy in the placebo group (32% compared to 22% of patients in the lurasidone (40 mg/day) group and 12% in the group with lurasidone 120 mg/day). Despite the significant proportion of dropouts, lurasidone (40 mg/day and 120 mg/day) was more effective than placebo on day 3 and at each subsequent visit.

Clinical study D1050196: Secondary endpoint results (PANSS score) show a superiority of lurasidone 20 mg, 40 mg and 80 mg over 10 mg haloperidol and placebo.

Clinical study D-1050234 demonstrated non-inferior efficacy of lurasidone compared to quetiapine XR in relapse prevention. In addition, lurasidone treatment was associated with a significantly greater improvement compared to quetiapine XR in the overall PANSS score at month 12, with a lower likelihood of recurrence (23.7% vs. 33.6%) and a significantly higher remission rate (61.9% vs. 46.3%). In addition, the incidence of hospitalization was lower with lurasidone treatment (9.8% vs. 23.1%). The incidence of withdrawal due to ADRs was similar in both groups (7% vs. 5%).

Clinical study D-1050238 shows that patients treated with lurasidone had a longer time to relapse than patients treated with placebo. The probability of recurrence at week 28, as assessed by Kaplan-Meier, was 42.2% with lurasidone and 51.2% with placebo. The probability of treatment discontinuation for any reason at week 28 was 58.2% with lurasidone and 69.9% with placebo.
Data analysis from a study conducted in 2014 shows a consistent and statistically significant decrease in the total score on PANSS (mean change -8.2), in the score on CGI-S (-0.39) and CDSS (-8.2) in the treatment with flexible doses of lurasidone. Similar results were obtained from the scales for suicidal ideation and assessment of depression, which showed an overall

improvement in lurasidone-treated patients. The frequency of treatment discontinuation is low.
From the cumulative analysis of the short-term studies it is evident that lurasidone administration results in a markedly greater improvement in symptoms compared with placebo at all doses studied (between 40 mg and 160 mg/day). When analyzing data from the individual studies, a significantly greater efficacy of lurasidone was seen compared to placebo, as assessed by the PANSS scale and the PANSS positive and negative symptoms subscales.

Analysis of five aspects of schizophrenia, with pooled data on the efficacy of lurasidone versus placebo from short-term studies.
The analysis was performed on a sample of 1525 patients (n = 1209 on lurasidone, at doses of 40 to 160 mg/day and 496 on PLACEBO), using a model examining five established factors of positive and negative symptoms on the PLACEBO scale (positive symptoms, negative symptoms, disorganized thinking, hostility/agitation and depression/anxiety). During 6-month treatment, lurasidone shows a significantly greater improvement over placebo in the overall PANSS score (-22.6 for lurasidone versus -12.8 for placebo) ($p < 0.001$), as well as in each of the assessed factors. The mean reduction in the positive symptom score (PANSS) is -8.4 for lurasidone compared to -6.0 for placebo; for negative symptoms it is -5.2 versus -3.3; for the disorganized thinking factor the average decrease is -4.9 compared to -2.8; for the hostility/ agitation factor it is -2.7 versus -1.6, for depression/anxiety factor it is -3.2 versus -2.3. For all factors, the difference between lurasidone and placebo was statistically significant. The magnitude of the effect at week 6 was consistent in all factors at lurasidone doses of 40 mg/ day and 120 mg/day, but it was not more reliable at 160 mg/ day. Lurasidone is more effective than placebo, beginning on the first day of treatment for the factors positive symptoms, disorganized thinking and hostility/agitation. Beginning at week 2, lurasidone was more effective than placebo in terms of negative symptoms and depression/anxiety factors (excluding the 120 mg/day dose).
The response to lurasidone shows some dose-response dependence, although not completely linear.

Combined analysis of four short-term, placebo-controlled studies of the efficacy of lurasidone in the treatment of depressive symptoms in schizophrenia
The predominance of clinically relevant depressive symptoms affects between 10% and 60% of patients with schizophrenia. The presence of depressive symptoms can have a significant negative outcome, as it is associated with lower job satisfaction, higher risk of unemployment, worsened social functioning, worse quality of life and increased health care costs. In addition, the presence of depressive symptoms is associated with a significantly higher risk of psychotic relapse, further increasing the risk of suicide in these patients.

Four of the studies examined the effectiveness of lurasidone (40 to 160 mg/day) compared with placebo using the MADRS (Montgomery-Åsberg Depression Rating Scale). Patients treated with lurasidone showed a significant reduction in the MADRS scale compared to placebo, regardless of the severity of depressive symptoms. In patients with a baseline MADRS score ≥12 points, remission of depressive symptoms was reported in 45% of lurasidone-treated patients and 36.3% of placebo-treated patients, with statistically significant differences. In addition, most of the changes in MADRS were not related to changes in PANSS, indicating a significant effect of lurasidone on depressive symptoms in patients with schizophrenia.

Although baseline depression was not extremely severe in all patients enrolled in these studies, the results of the post hoc analysis show that treatment with lurasidone achieved a significant improvement in depressive symptoms compared with placebo, regardless of their severity.

Studies with data from real clinical practice

One study with actual clinical practice data compared adherence to lurasidone treatment with other oral antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone).

Data for MPR (Medication possession ratio) at month 6 of initiation of oral atypical antipsychotics show greater and more significant adherence to lurasidone treatment than to aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone. In addition, patients treated with lurasidone show a lower rate of discontinuation (49.3%) compared to other antipsychotics (62.3-68.3%). The mean duration of maintenance treatment with lurasidone was significantly longer than with ziprasidone.

Analysis of data reported by patients shows that the median time to discontinuation of treatment was longer with lurasidone than with other antipsychotics, both for insured and uninsured patients.

Safety data

The safety of lurasidone has been evaluated at doses of 18.5 - 148 mg in clinical trials in patients with schizophrenia, treated for up to 52 weeks, as well as in post-marketing surveillance. The most common adverse reactions (ADR) (≥ 10%) were akathisia and somnolence, which were dose-dependent through 111 mg daily.

Summary of the safety profile from clinical trials:

The safety data for lurasidone were collected from 52 clinical trials with the medicinal product; 30 of them are phase 1, with 9 for schizophrenia. There were 22 phase 2 and 3 studies with 5068 patients with schizophrenia, of which 3502 were treated with lurasidone, 724 with placebo and 842 with other drugs. The duration of the studies ranged from 3 weeks to 22 months; doses of lurasidone from 20 mg to 160 mg/day were assessed.

Extrapyramidal symptoms: Data on extrapyramidal ADR from all clinical trials indicate that they occur in 24.4% of lurasidone patients. This percentage is similar to the one seen with olanzapine (23%) and risperidone (27.7%), much lower than haloperidol (54.2%) and higher compared with patients on placebo (9.2%) or quetiapine XR (7.6%).).

Metabolic parameters: An important aspect of lurasidone is its good tolerability in relation to metabolic and endocrine effects. As opposed to other antipsychotics, lurasidone has been shown to be neutral in terms of body weight, lipid profile and glucose metabolism.

Dyslipidemia: Lurasidone demonstrated a neutral effect on lipid parameters, which is supported by data from the lurasidone clinical program. This is of particular interest, because both schizophrenia and treatment with some second-generation antipsychotics are associated with dyslipidemia, manifested by increased levels of triglycerides, LDL-cholesterol and total cholesterol and reduced levels of HDL-cholesterol. This dyslipidemia is often associated with weight gain, but is sometimes a separate ADR resulting from antipsychotic treatment.

Glucose metabolism: Analysis of all phase 2 and 3 studies with lurasidone confirmed that there was no significant change in glucose-related ADR. Treatment with lurasidone resulted in an increase in blood sugar in 0.7% and in glycated hemoglobin in 0.2% of patients. Lurasidone caused hyperglycaemia in 0.2%, glucose intolerance, glucosuria and diabetes mellitus in <0.1% of patients.

Cardiovascular ADR: ECG abnormalities and significant QT-interval deviations were not observed in short- and long-term studies with lurasidone, even at higher doses of lurasidone.

Data on comparators

Latuda (lurasidone) is indicated for the treatment of schizophrenia in adult patients 18 years of age and older.
Based on the treatment recommendations published in the Bulgarian Pharmacotherapeutic Guide on Mental Illness, the following alternatives registered in Bulgaria have been selected for comparison, which could be partially or completely replaced by the introduction of the new technology: aripiprazole, olanzapine, quetiapine, risperidone, cariprazine.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

Health technology assessments have been performed by government institutions in the United Kingdom (NICE, 2014), Sweden (TLV), France (HAS, 2014), Germany (G-BA, 2015), Scotland (SMC, 2016), and Wales (AWMSG). All evaluations for Latuda are positive, it is listed as an additional treatment option along with existing alternatives. Only the German assessment indicated that the medicinal product did not show any additional benefits compared to the alternatives.

Applied analysis

Minimum cost and cost-benefit pharmacoeconomic analysis with a quality-of-life (QALY) outcome measure have been applied. The time trade-off technique was employed to measure health-related quality of life (HRQoL). As comparative alternative, cariprazine, olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone were used, currently included in PDL. The analysis is from the NHIF, the paying institution perspective for a time horizon of 10 years with a discount of 3.5%. Sensitivity analysis was performed.
To model the cost-benefit ratio, a Markov model is applied with five health conditions.

The cycle duration is 6 weeks, according to short-term studies with lurasidone. Extrapolation of data in the model used shows that the relapse-free period was longer with olanzapine and cariprazine (compared to lurasidone), while compared to quetiapine, aripiprazole and risperidone and ziprasidone, a higher proportion of patients had no recurrence with lurasidone therapy. Regarding the frequency of therapy discontinuation, extrapolated data show a higher frequency for quetiapine, ziprasidone, aripiprazole and risperidone; the frequency was similar with lurasidone and cariprazine, and lower with olanzapine than with lurasidone.

A minimum cost analysis based on similarities in QALY has been used. Lurasidone was compared to each product separately and shows a higher cost per patient per year compared to aripiprazole, risperidone, ziprasidone. When comparing lurasidone and cariprazine, lurasidone leads to savings when comparing costs of therapy for one year.

In the cost-benefit analysis, olanzapine has been used as a reference and an incremental ratio of all alternatives was presented. In this case, all alternatives are cost-effective, with the exception of cariprazine and lurasidone.
The results show that lurasidone therapy is value effective compared to cariprazine; lurasidone therapy has a higher cost and more health benefits than olanzapine and quetiapine; lurasidone therapy has a higher annual cost than aripiprazole, ziprasidone and risperidone, but is expected to lead to a higher adherence to therapy and reduce healthcare costs associated with the disease.
Sensitivity analysis was performed using Monte Carlo simulation.

Costs for the assessed health technology

Costs for one year of treatment for one patient with Latuda and with therapeutic alternatives have been presented. Additionally, costs for control of adverse reactions and costs for activities in the specialized outpatient health care, paid by the NHIF, have been included, as well as costs of the Ministry of Health for subsidizing the activities of health care institutions.

Budget impact analysis

The analysis of the budget impact has been prepared from the National Health Insurance Fund perspective, the time horizon is 5 years. The estimated number of patients eligible for treatment with Latuda for the analyzed future period of 5 years is projected to be 270 in the first year through 690 in the fifth year.

A sensitivity analysis has been performed with +/- 20% variation of costs of alternatives and number of patients from NHIF perspective. The presented Tornado diagram shows that the budget impact is most significantly affected by the cost of therapy with alternatives and with Latuda.

The introduction of Latuda in therapeutic practice is associated with an increase in costs from the payer's perspective, the NHIF.

Conclusion

Latuda (lurasidone) has a different pharmacological profile compared to the available antipsychotics, currently employed in therapeutic practice, representing a product with a unique profile of efficacy and tolerability. The outcome of short-term studies, as well as the pooled analyses of these studies, demonstrate the superiority of lurasidone over placebo and various active comparators. The reported results of studies of actual therapeutic practice show a high degree of adherence to therapy compared to other oral antipsychotics. Latuda (lurasidone) has a favorable and manageable safety profile with improved characteristics in terms of key indicators such as extrapyramidal symptoms, metabolic changes, dyslipidemias, glucose metabolism and cardiovascular ADR. The conducted pharmacoeconomic analysis demonstrates the value efficacy of lurasidone compared to some of the alternatives, and due to the higher degree of adherence to therapy, it is expected to reduce the cost of disease-associated health care. The analysis of the budget impact shows that the introduction of Latuda in the therapeutic practice is associated with an increase in costs from the perspective of the payer, the NHIF.