Approved acc to FDA

Novartis
~~19/11/2020~~
3/2/2020

Zetazolex tablets (brexpiprazole)

1 mg, 2 mg, 3 mg, 4 mg

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZETAZOLEX is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short-term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors. The safety and efficacy of ZETAZOLEX have not been established in pediatric patients *[see Warnings and Precautions (5.2), Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

ZETAZOLEX is indicated for:

- Adjunctive treatment of major depressive disorder (MDD) *[see Clinical Studies (14.1)]*.
- Treatment of schizophrenia *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adjunctive Treatment of Major Depressive Disorder

The recommended starting dosage for ZETAZOLEX as adjunctive treatment is 0.5 mg or 1 mg once daily, taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg. Periodically reassess to determine the continued need and appropriate dosage for treatment.

2.2 Treatment of Schizophrenia

The recommended starting dosage for ZETAZOLEX is 1 mg once daily on Days 1 to 4, taken orally with or without food *[see Clinical Pharmacology (12.3)]*.

The recommended target ZETAZOLEX dosage is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

2.3 Dosage Adjustments for Hepatic Impairment

For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 2 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.4 Dosage Adjustments for Renal Impairment

For patients with moderate, severe or end-stage renal impairment (creatinine clearance CLcr<60 mL/minute), the maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for CYP2D6 Poor Metabolizers and for Concomitant use with CYP Inhibitors or Inducers

Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). If the coadministered drug is discontinued, adjust the ZETAZOLEX dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the ZETAZOLEX dosage to the original level over 1 to 2 weeks *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 1: Dosage Adjustments of ZETAZOLEX for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 and CYP2D6 Inhibitors and/or CYP3A4 Inducers

Factors	Adjusted ZETAZOLEX Dosage
CYP2D6 Poor Metabolizers	
CYP2D6 poor metabolizers	Administer half of the usual dose
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors*	Administer half of the usual dose
Strong CYP3A4 inhibitors	Administer half of the usual dose
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

*In clinical trials examining the adjunctive use of ZETAZOLEX in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations and ZETAZOLEX may be administered without dosage adjustment in patients with MDD.

3 DOSAGE FORMS AND STRENGTHS

ZETAZOLEX tablets are available in 4 strengths (see Table 2).

Table 2: Zetazolex tablet strenghs and identifying features:

Tablet Strength	Tablet Color/ Shape
1 mg	Pale yellow to yellow round biconvex mottled tablets
2 mg	Red to crimson red round biconvex mottled tablets
3 mg	Blue round biconvex mottled tablets
4 mg	White to off white round biconvex tablets

4 CONTRAINDICATIONS

ZETAZOLEX is contraindicated in patients with a known hypersensitivity to brexpiprazole or any of its components. Reactions have included rash, facial swelling, urticaria, and anaphylaxis.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ZETAZOLEX is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients, and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater in antidepressant-treated patients than in placebo-treated patients.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antidepressant drug effect on suicide.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing ZETAZOLEX, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. ZETAZOLEX is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue ZETAZOLEX and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is unknown.
The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ZETAZOLEX should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and (2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment needed to produce a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on ZETAZOLEX, drug discontinuation should be considered.
However, some patients may require treatment with ZETAZOLEX despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs, including ZETAZOLEX, have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. Although all of the drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with ZETAZOLEX *[see Adverse Reactions (6.1)]*. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long-term treatment.

Major Depressive Disorder

In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with MDD, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with BREXPIPRAZOLE and placebo.

In the long-term, open-label depression studies, 5% of patients with normal baseline fasting glucose experienced a shift to high while taking BREXPIPRAZOLE+Antidepressant (ADT); 25% of subjects with borderline fasting glucose experienced shifts to high. Combined, 9% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term depression studies.

Schizophrenia

In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with schizophrenia, the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) or borderline (≥100 and <126 mg/dL) to high were similar in patients treated with BREXPIPRAZOLE and placebo.

In the long-term, open-label schizophrenia studies, 8% of patients with normal baseline fasting glucose experienced a shift from normal to high while taking BREXPIPRAZOLE, 17% of subjects with borderline fasting glucose experienced shifts from borderline to high. Combined, 10% of subjects with normal or borderline fasting glucose experienced shifts to high fasting glucose during the long-term schizophrenia studies.

Dyslipidemia

Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Major Depressive Disorder

In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with MDD, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in BREXPIPRAZOLE - and placebo-treated patients.

In the long-term, open-label depression studies, shifts in baseline fasting cholesterol from normal to high were reported in 9% (total cholesterol), 3% (LDL cholesterol), and shifts in baseline from normal to low were reported in 14% (HDL cholesterol) of patients taking BREXPIPRAZOLE. Of patients with normal baseline triglycerides, 17% experienced shifts to high, and 0.2% experienced shifts to very high. Combined, 0.6% of subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term depression studies.

Schizophrenia

In the 6-week, placebo-controlled, fixed-dose clinical trials in patients with schizophrenia, changes in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were similar in BREXPIPRAZOLE - and placebo-treated patients.

In the long-term, open-label schizophrenia studies, shifts in baseline fasting cholesterol from normal to high were reported in 6% (total cholesterol), 2% (LDL cholesterol), and shifts in baseline from normal to low were reported in 17% (HDL cholesterol) of patients taking BREXPIPRAZOLE. Of patients with normal baseline triglycerides, 13% experienced shifts to high, and 0.4% experienced shifts to very high triglycerides. Combined, 0.6% of subjects with normal or borderline fasting triglycerides experienced shifts to very high fasting triglycerides during the long-term schizophrenia studies.

Weight Gain

Weight gain has been observed in patients treated with atypical antipsychotics, including BREXPIPRAZOLE. Monitor weight at baseline and frequently thereafter.

Major Depressive Disorder

In the long-term, open-label depression studies, 4% of patients discontinued due to weight increase. BREXPIPRAZOLE was associated with mean change from baseline in weight of 2.9 kg at week 26 and 3.1 kg at week 52. In the long-term, open label depression studies, 30% of patients demonstrated a ≥7% increase in body weight and 4% demonstrated a ≥7% decrease in body weight.

Schizophrenia

In the long-term, open-label schizophrenia studies, 0.6% of patients discontinued due to weight increase. BREXPIPRAZOLE was associated with mean change from baseline in weight of 1.3 kg at week 26 and 2.0 kg at week 52. In the long-term, open label schizophrenia studies, 20% of patients demonstrated a ≥7% increase in body weight and 10% demonstrated a ≥7% decrease in body weight.

5.7 Pathological Gambling and Other Compulsive Behaviors

Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking BREXPIPRAZOLE. Other compulsive urges, reported less frequently, include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with ZETAZOLEX. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in this class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ZETAZOLEX at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ZETAZOLEX in patients with absolute neutrophil count <1000/mm^3 and follow their WBC until recovery.

5.9 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. In the short-term, placebo-controlled clinical studies of BREXPIPRAZOLE +ADT in patients with MDD, the incidence of orthostatic hypotension-related adverse reactions in BREXPIPRAZOLE +ADT-treated patients compared to placebo+ADT patients included: dizziness (2% vs. 2%) and orthostatic hypotension (0.1% vs. 0%). In the short-term, placebo-controlled clinical studies of BREXPIPRAZOLE in patients with schizophrenia, the incidence of orthostatic hypotension-related adverse reactions in BREXPIPRAZOLE-treated patients compared to placebo patients included: dizziness (2% versus 2%), orthostatic hypotension (0.4% versus 0.2%), and syncope (0.1% versus 0%).

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, (e.g., elderly patients, patients with dehydration, hypovolemia, concomitant treatment with antihypertensive medication), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. ZETAZOLEX has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

5.10 Falls

Antipsychotics, including ZETAZOLEX, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.11 Seizures

Like other antipsychotic drugs, ZETAZOLEX may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.12 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use ZETAZOLEX with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including ZETAZOLEX, should be used cautiously in patients at risk for aspiration.

5.14 Potential for Cognitive and Motor Impairment

ZETAZOLEX, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. In 6-week, placebo-controlled clinical trials in patients with MDD, somnolence (including sedation and hypersomnia) was reported in 4% for BREXPIPRAZOLE+ADT-treated patients compared to 1% of placebo+ADT patients.

In 6-week, placebo-controlled clinical trials in patients with schizophrenia, somnolence (including sedation and hypersomnia) was reported in 5% of BREXPIPRAZOLE-treated patients compared to 3% of placebo-treated patients.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that ZETAZOLEX therapy does not affect them adversely.

Lactose Warning: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosogalactose malabsorption should not take this medicine.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Falls *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Major Depressive Disorder

The safety of BREXPIPRAZOLE was evaluated 1,054 patients (18 to 65 years of age) diagnosed with MDD who participated in two 6-week, placebo-controlled, fixed-dose clinical trials in patients with major depressive disorder in which BREXPIPRAZOLE was administered at doses of 1 mg to 3 mg daily as adjunctive treatment to continued antidepressant therapy; patients in the placebo group continued to receive antidepressant therapy *[see Clinical Studies (14.1)]*.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

A total of 3% (17/643) of BREXPIPRAZOLE-treated patients and 1% (3/411) of placebo-treated patients discontinued due to adverse reactions.

Common Adverse Reactions

Adverse reactions associated with the adjunctive use of BREXPIPRAZOLE (incidence of 2% or greater and adjunctive BREXPIPRAZOLE incidence greater than adjunctive placebo) that occurred during acute therapy (up to 6-weeks in patients with MDD) are shown in Table 8.

Table 8: Adverse Reactions

Gastrointestinal disorders	Constipation.
General disorders and administration site conditions	Fatigue.
Infections and infestations	Nasopharyngitis.
Investigations	Weight increased. Blood cortisol decreased.
Metabolism and nutrition	Increased appetite.
Nervous system disorders	Akathisia. Headache. Somnolence. Tremor. Dizziness.
Psychiatric disorders	Anxiety. Restlessness.

Dose-Related Adverse Reactions in the MDD trials

In Studies 1 and 2, among the adverse reactions that occurred at ≥2% incidence in the patients treated with BREXPIPRAZOLE+ADT, the incidences of akathisia and restlessness increased with increases in dose.

Schizophrenia

The safety of BREXPIPRAZOLE was evaluated in 852 patients (18 to 65 years of age) diagnosed with schizophrenia who participated in two 6-week, placebo-controlled, fixed-dose clinical trials in which BREXPIPRAZOLE was administered at daily doses of 1 mg, 2 mg and 4 mg *[see Clinical Studies (14.2)]*.

Adverse reactions associated with BREXPIPRAZOLE (incidence of 2% or greater and BREXPIPRAZOLE incidence greater than placebo) during short-term (up to 6-weeks) trials in patients with schizophrenia are shown in Table 9.

Table 9: Adverse Reactions

Gastrointestinal disorders	Dyspepsia. Diarrhea.
Investigations	Weight increased. Blood creatinine phosphokinase increased.
Nervous system disorders	Akathisia. Tremor. Sedation.

Extrapyramidal Symptoms

Major Depressive Disorder

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 6% for BREXPIPRAZOLE+ADT-treated patients versus 3% for placebo+ADT-treated patients. The incidence of

athisia events for BREXPIPRAZOLE+ADT-treated patients was 9% versus 2% for placebo+ADT-treated patients.

In the 6-week, placebo-controlled MDD studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Score (AIMS) for dyskinesia. The mean change from baseline at last visit for BREXPIPRAZOLE+ADT-treated patients for the SAS, BARS and AIMS was comparable to placebo treated patients. The percentage of patients who shifted from normal to abnormal was greater in BREXPIPRAZOLE+ADT-treated patients versus placebo+ADT for the BARS (4% versus 0.6%) and the SAS (4% versus 3%).

Schizophrenia

The incidence of reported EPS-related adverse reactions, excluding akathisia, was 5% for BREXPIPRAZOLE-treated patients versus 4% for placebo-treated patients. The incidence of akathisia events for BREXPIPRAZOLE-treated patients was 6% versus 5% for placebo-treated patients.

In the 6-week, placebo-controlled, fixed-dose schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Rating Scale (BARS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia. The mean change from baseline at last visit for BREXPIPRAZOLE-treated patients for the SAS, BARS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in BREXPIPRAZOLE-treated patients versus placebo for the BARS (2% versus 1%) and the SAS (7% versus 5%).

Dystonia

Symptoms of dystonia may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Other Adverse Reactions Observed During the Premarketing Evaluation of BREXPIPRAZOLE

Other adverse reactions (≥1% frequency and greater than placebo) within the short-term, placebo-controlled trials in patients with MDD and schizophrenia are shown below. The following listing does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Eye Disorders: Vision Blurred

Gastrointestinal Disorders: Nausea, Dry Mouth, Salivary Hypersecretion, Abdominal Pain, Flatulence

Infections and Infestations: Urinary Tract Infection

Investigations: Blood Prolactin Increased

Musculoskeletal and Connective Tissue Disorders: Myalgia

Psychiatric Disorders: Abnormal Dreams, Insomnia

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

- Reporting any side effects to: PV.center@mohealth.gov.eg eda.

or PV@zeta-pharma.com

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ZETAZOLEX

Table 10: Clinically Important Drug Interactions with ZETAZOLEX

Strong CYP3A4 Inhibitors

Clinical Impact:	Concomitant use of ZETAZOLEX with strong CYP3A4 inhibitors increased the exposure of brexpiprazole compared to the use of ZETAZOLEX alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of ZETAZOLEX with a strong CYP3A4 inhibitor, reduce the ZETAZOLEX dosage *[see Dosage and Administration (2.5)]*
Examples:	itraconazole, clarithromycin, ketoconazole

Strong CYP2D6 Inhibitors*

Clinical Impact:	Concomitant use of ZETAZOLEX with strong CYP2D6 inhibitors increased the exposure of brexpiprazole compared to the use of ZETAZOLEX alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of ZETAZOLEX with a strong CYP2D6 inhibitor, reduce the ZETAZOLEX dosage *[see Dosage and Administration (2.5)]*
Examples:	paroxetine, fluoxetine, quinidine

Both CYP3A4 Inhibitors and CYP2D6 Inhibitors

Clinical Impact:	Concomitant use of ZETAZOLEX with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, increased the exposure of brexpiprazole compared to the use of ZETAZOLEX alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of ZETAZOLEX with 1) a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 2) a moderate CYP3A4 inhibitor and a strong CYP2D6 inhibitor; or 3) a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor; or 4) a moderate CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, decrease the ZETAZOLEX dosage *[see Dosage and Administration (2.5)]*
Examples:	1) itraconazole + quinidine 2) fluconazole + paroxetine 3) itraconazole + duloxetine 4) fluconazole + duloxetine

Strong CYP3A4 Inducers

Clinical Impact:	Concomitant use of ZETAZOLEX and a strong CYP3A4 inducer decreased the exposure of brexpiprazole compared to the use of ZETAZOLEX alone *[see Clinical Pharmacology (12.3)]*
Intervention:	With concomitant use of ZETAZOLEX with a strong CYP3A4 inducer, increase the ZETAZOLEX dosage *[see Dosage and Administration (2.5)]*
Examples:	rifampin, St. John's wort

*In clinical trials examining the adjunctive use of BREXPIPRAZOLE in the treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations and ZETAZOLEX may be administered without dosage adjustment in patients with MDD.

7.2 Drugs Having No Clinically Important Interactions with ZETAZOLEX

Based on pharmacokinetic studies, no dosage adjustment of ZETAZOLEX is required when administered concomitantly with CYP2B6 inhibitors (e.g., ticlopidine) or gastric pH modifiers (e.g., omeprazole). Additionally, no dosage adjustment for substrates of CYP2D6 (e.g., dextromethorphan), CYP3A4 (e.g., lovastatin), CYP2B6 (e.g., bupropion), BCRP (e.g., rosuvastatin), or P-gp (e.g., fexofenadine) is required when administered concomitantly with ZETAZOLEX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZETAZOLEX during pregnancy.

It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Risk Summary

Adequate and well-controlled studies have not been conducted with ZETAZOLEX in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like ZETAZOLEX, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical studies of the efficacy of ZETAZOLEX did not include any patients aged 65 or older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy.

Based on the results of a safety, tolerability and pharmacokinetics trial, the pharmacokinetics of once daily oral administration of brexpiprazole (up to 3 mg/day for 14 days) as an adjunct therapy in the treatment of elderly subjects (70 to 85 years old, N=11) with MDD were comparable to those observed in adults subjects with MDD.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. ZETAZOLEX is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers, because these patients have higher brexpiprazole concentrations than normal metabolizers of CYP2D6. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score ≥7). Patients with moderate to severe hepatic impairment (Child-Pugh score ≥7) generally had higher exposure to brexpiprazole than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of ZETAZOLEX-associated adverse reactions *[see Dosage and Administration (2.3)]*.

8.8 Renal Impairment

Reduce the maximum recommended dosage in patients with moderate, severe, or end-stage renal impairment (CLcr<60 mL/minute). Patients with impaired renal function (CLcr<60 mL/minute) had higher exposure to brexpiprazole than patients with normal renal function *[see Clinical Pharmacology (12.3)]*. Greater exposure may increase the risk of ZETAZOLEX-associated adverse reactions *[see Dosage and Administration (2.4)]*.

8.9 Other Specific Populations

No dosage adjustment for ZETAZOLEX is required on the basis of a patient's sex, race, or smoking status *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZETAZOLEX is not a controlled substance.

9.2 Abuse

Animals given access to ZETAZOLEX did not self-administer the drug, suggesting that ZETAZOLEX does not have rewarding properties.

9.3 Dependence

Humans and animals that received chronic ZETAZOLEX administration did not demonstrate any withdrawal signs upon drug discontinuation. This suggests that ZETAZOLEX does not produce physical dependence.

10 OVERDOSAGE

There is limited clinical trial experience regarding human overdosage with ZETAZOLEX.

Consult a Certified Poison Control Center for up-to-date guidance and advice regarding a ZETAZOLEX overdosage. Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting oral brexpiprazole, decreased brexpiprazole Cmax and area under the curve (AUC) by approximately 5% to 23% and 31% to 39% respectively; however, there is insufficient information available on the therapeutic potential of activated charcoal in treating an overdose with ZETAZOLEX.

Hemodialysis

There is no information on the effect of hemodialysis in treating an overdose with ZETAZOLEX; hemodialysis is unlikely to be useful because brexpiprazole is highly bound to plasma proteins.

11 DESCRIPTION

ZETAZOLEX tablets are for oral administration and are available in 1 mg, 2 mg, 3 mg and 4 mg strengths.

Zetazolex 1 mg:
Active Ingredient: 1 mg of Brexpiprazole.
Inactive ingredients: lactose monohydrate, microcrystalline cellulose PH 102, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, pregelatinized starch, colloidal silicon dioxide and Yellow Iron Oxide.

Zetazolex 2 mg:
Active Ingredient: 2 mg of Brexpiprazole.
Inactive ingredients: lactose monohydrate, microcrystalline cellulose PH 102, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, pregelatinized starch, colloidal silicon dioxide and Carmosine red.

Zetazolex 3 mg:

Active Ingredient: 3 mg of Brexpiprazole.

Inactive ingredients: lactose monohydrate, microcrystalline cellulose PH 102, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, pregelatinized starch, colloidal silicon dioxide and Brilliant Blue.

Zetazolex 4 mg:

Active Ingredient: 4 mg of Brexpiprazole.

Inactive ingredients: lactose monohydrate, microcrystalline cellulose PH 102, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, pregelatinized starch and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

12.2 Pharmacodynamics

Brexpiprazole has affinity (expressed as K_i) for multiple monoaminergic receptors including serotonin 5-HT_{1A} (0.12 nM), 5-HT_{2A} (0.47 nM), 5-HT_{2B} (1.9 nM), 5-HT_7 (3.7 nM), dopamine D_2 (0.30 nM), D_3 (1.1 nM), and noradrenergic α_{1A} (3.8 nM), α_{1B} (0.17 nM), α_{1D} (2.6 nM), and α_{2C} (0.59 nM) receptors. Brexpiprazole acts as a partial agonist at the 5-HT_{1A}, D_2, and D_3 receptors and as an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors. Brexpiprazole also exhibits affinity for histamine H_1 receptor (19 nM) and for muscarinic M_1 receptor (67% inhibition at 10 μM).

Cardiac Electrophysiology

At a dose 3-times the MRHD for the treatment of schizophrenia and 4-times the MRHD for adjunctive therapy to antidepressants for the treatment of MDD, ZETAZOLEX does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

After single dose administration of ZETAZOLEX tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration; and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10-12 days of dosing.

ZETAZOLEX can be administered with or without food. Administration of a 4 mg ZETAZOLEX tablet with a standard high fat meal did not significantly affect the C_{max} or AUC of brexpiprazole. After single and multiple once daily dose administration, brexpiprazole exposure (C_{max} and AUC) increased in proportion to the dose administered.

In vitro studies of brexpiprazole did not indicate that brexpiprazole is a substrate of efflux transporters such as MDRI (P-gp) and BCRP.

Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56±0.42 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99%) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of *in vitro* studies, brexpiprazole protein binding is not affected by warfarin, diazepam, or digitoxin.

Elimination

Metabolism

Based on *in vitro* metabolism studies of brexpiprazole using recombinant human cytochrome P450 (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6.

In vivo brexpirazole is metabolized primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple-dose administrations, brexpiprazole and its major metabolite, DM-3411, were the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represented 23% to 48% of brexpiprazole exposure (AUC) in plasma. DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

Based on *in vitro* data, brexpiprazole showed little to no inhibition of CYP450 isozymes.

Excretion

Following a single oral dose of [^{14}C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged in the feces. Apparent oral clearance of a brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of ZETAZOLEX, the terminal elimination half-lives of brexpiprazole and its major metabolite, DM-3411, were 91 hours and 86 hours, respectively.

- Shelf life : 2 years داخلي

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

داخلي 1,2,3

Carton box containing (Al/ transparent colorless PVC) strip of 10 tablets + inner leaflet.

16.2 Storage

Store at temperature not exceeding 30°C, in dry place.

Manufactured by AL Esraa Pharmaceutical Optimer.

~~Manufactured by~~ ***Zeta Pharma for Pharmaceutical Industries.***

for

داخلي