

דצמבר 2024

Reagila 1.5, 3, 4.5, 6 mg, Hard Capsules

צוות רפואי נכבד,

חברת דקסל בע"מ מבקשת להודיעכם על עדכון בהתוויה של התכשיר: ריאגילה 1.5, 3, 4.5, 6.

ההתוויה המאושרת:

Reagila is indicated for the:

- Treatment of schizophrenia in adult patients.
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adult.
- Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults.
- **Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults.**

בנוסף, ברצוננו להודיע על עדכון בעלון לרופא ובעלון לצרכן. בהודעה זו מפורטים העדכונים המהווים שינוי משמעותי או החמרה במידע הבטיחותי בלבד. למידע מלא, יש לעיין בעלונים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים ע"פנייה לבעל הרישום: דקסל בע"מ, רח' דקסל 1, אור עקיבא 3060000, ישראל, טל': 04-6364000.

הרכב התכשיר:

Each capsule contains cariprazine 1.5, 3, 4.5, or 6 mg respectively.

העלון לרופא עודכן בדצמבר 2024. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים באדום):

4. Clinical Particulars

4.2 Posology and method of administration

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Adjunctive Therapy to Antidepressants in Treatment of Major Depressive Disorder (MDD)

The starting dosage of Reagila is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. In clinical trials, dosage titration at intervals of less than 14 days resulted in a higher incidence of adverse reactions. Maximum recommended dosage is 3 mg once daily.

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4.8 Undesirable effects

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Adjunctive Therapy in Major Depressive Disorder (MDD)

The following findings are based on two placebo-controlled, fixed-dose 6-week trials with cariprazine doses of 1.5 and 3 mg once daily plus an antidepressant and one placebo-controlled, flexible-dose 8-week trial with cariprazine doses of (1 to 2 mg) and (2 to 4.5 mg) once daily plus an antidepressant for adjunctive therapy in MDD.

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of $\geq 2\%$ in cariprazine-treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 6% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 3% of placebo-treated patients in these trials.

Common Adverse Reactions ($\geq 5\%$ and at least twice the rate of placebo): Akathisia, nausea, and insomnia occurred in two 6-week, fixed-dose trials. Akathisia, restlessness, fatigue, constipation, nausea, increased appetite, dizziness, insomnia, and extrapyramidal symptoms occurred in one 8-week flexible-dose trial.

Adverse Reactions with an incidence of $\geq 2\%$ and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 4 below:

Table 4: Adverse Reactions Occurring in $\geq 2\%$ of cariprazine-Treated Patients and $>$ Placebo-Treated Adult Patients in Two Fixed-Dose 6-Week Placebo-Controlled Trials of Adjunctive Treatment of Major Depressive Disorder

System Organ Class / Preferred Term	Placebo+ADT (N=503) (%)	cariprazine	
		1.5 mg/day+ADT (N=502) (%)	3 mg/day +ADT (N=503) (%)
Eye Disorders			
Vision Blurred	<1	<1	2
Gastrointestinal Disorders			
Nausea	3	7	6
Dry mouth	2	3	3
Constipation	1	2	2
Vomiting	1	1	2
General Disorders			
Fatigue	2	3	3
Investigation			
Weight increased	1	2	2
Nervous System Disorders			
Akathisia ^a	2	7	10
Somnolence ^b	4	5	7
Extrapyramidal symptoms ^c	4	5	6
Psychiatric disorders			
Insomnia ^d	5	9	10
Restlessness	2	4	4
Anxiety	1	2	1
Skin and subcutaneous Tissue Disorder			
Hyperhidrosis	1	1	2

Note: Figures rounded to the nearest integer

^a**Akathisia terms:** akathisia, psychomotor hyperactivity, feeling jittery, nervousness, tension

^b**Somnolence terms:** hypersomnia, sedation, lethargy, somnolence

^c**Extrapyramidal symptoms terms:** drooling, dyskinesia, extrapyramidal disorder, hypotonia, muscle contractions involuntary, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, oromandibular dystonia, parkinsonism, resting tremor, restless legs syndrome, stiff leg syndrome, salivary hypersecretion, stiff tongue, tardive dyskinesia, tremor, trismus

^d**Insomnia terms:** initial insomnia, insomnia, middle insomnia, poor sleep quality, sleep disorder, terminal insomnia

Adverse Reactions with an incidence of $\geq 2\%$ and greater than placebo at 1 mg to 2 mg per day or 2 mg to 4.5 mg per day doses are shown in Table 5 below:

Table 5: Adverse Reactions Occurring in $\geq 2\%$ of cariprazine-Treated Patients and $>$ Placebo-Treated Adult Patients in a Flexible-dose 8-Week Placebo-Controlled Trial of Adjunctive Treatment of Major Depressive Disorder

System Organ Class / Preferred Term	Placebo+ADT (N= 266) (%)	Cariprazine 1 to 2 mg/day +ADT (N=273) (%)	Cariprazine 2 to 4.5 mg/day+ADT (N=273) (%)
Cardiac disorders			
Palpitations	1	2	<1
Eye Disorders			
Vision Blurred	1	1	4
Gastrointestinal Disorders			
Nausea	5	7	13
Constipation	2	2	5
Dry mouth	3	5	4
Vomiting	<1	1	3
General Disorders			
Fatigue	4	7	10
Edema	<1	2	1
Infections			
Nasopharyngitis	2	4	1
Investigations			
Increased appetite	2	2	5
Weight increased	1	2	3
Musculoskeletal and Connective Tissue disorders			
Back pain	1	2	3
Myalgia	0	1	2
Nervous System Disorders			
Akathisia ^a	3	8	23
Extrapyramidal Symptoms ^b	5	12	18
Somnolence ^c	6	10	11
Dizziness	2	4	5
Psychiatric disorders			
Insomnia ^d	8	14	16
Restlessness	3	8	8
Agitation	<1	<1	3
Anxiety	<1	1	3

^a**Akathisia terms:** akathisia, feeling jittery, nervousness, tension

^b**Extrapyramidal symptoms terms:** cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypertonia, jaw stiffness, muscle contractions involuntary, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, nuchal rigidity, parkinsonism, psychomotor retardation, reduced facial expression, resting tremor, restless legs syndrome, sensation of heaviness, salivary hypersecretion, tremor

^c**Somnolence terms:** hypersomnia, sedation, lethargy, somnolence

^d**Insomnia terms:** initial insomnia, insomnia, middle insomnia, terminal insomnia, sleep disorder, poor sleep quality

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Description of selected adverse reactions

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In the two 6-week adjunctive treatment of major depressive disorder trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 6% for cariprazine-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 0.3% of cariprazine-treated patients versus 0.6% of placebo-treated patients. The combined incidence of akathisia and restlessness was 12% for cariprazine-treated patients versus 4% for placebo-treated patients. These reactions led to discontinuation in 2% of cariprazine-treated patients versus 0.4% of placebo-treated patients.

In one 8-week adjunctive treatment of major depressive disorder trial, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 12% for cariprazine-treated patients versus 5% for placebo-treated patients. These reactions led to discontinuation in 1% of cariprazine-treated patients versus 0.4% of placebo-treated patients. The incidence of akathisia and restlessness was 22% for cariprazine-treated patients versus 6% for placebo-treated patients. These reactions led to discontinuation in 3% of cariprazine-treated patients versus 0.0% of placebo-treated patients.

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The proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in two 6-week adjunctive treatment of major depressive disorder trials ranged between 0% and 1% for cariprazine-treated patients depending on dose group administered and 0% for placebo-treated patients.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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Adjunctive Treatment of Major Depressive Disorder (MDD)

The efficacy of caiprazine as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) was evaluated in 2 trials in adult patients (mean age of 45 years, range 18 to 65 years; 72% were female; and 85% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to 1 to 3 courses of prior antidepressant (ADT) therapy. Inadequate response during antidepressant treatment was defined as less than 50% improvement to antidepressant treatment of adequate dose and adequate duration.

In each study, the primary endpoint was change from baseline to Week 6 (Study 10) or Week 8 (Study 11) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, a 10-item clinician-rated scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

Study 10: In a 6-week, placebo-controlled trial (N = 751) involving two fixed doses of caiprazine (1.5 mg per day or 3 mg per day) + ADT, caiprazine 1.5 mg + ADT was superior to placebo + ADT at end of Week 6 on the MADRS total score. The treatment effect in the caiprazine 3 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Study 11: An 8-week, placebo-controlled trial (N = 808) involved flexible doses of caiprazine 1 to 2 mg per day + ADT or 2 to 4.5 mg per day + ADT. Caiprazine 2 to 4.5 mg (mean dose was 2.6 mg) + ADT was superior to placebo + ADT at end of Week 8 on the MADRS total score. The treatment effect in the caiprazine 1 to 2 mg per day + ADT group (vs. placebo + ADT) was not statistically significant.

Results from the primary efficacy parameters for both trials (Studies 10 and 11) are shown in Table 10 below:

Table 10: Primary Analysis Results from Adjunctive Treatment of Major Depressive Disorder Trials

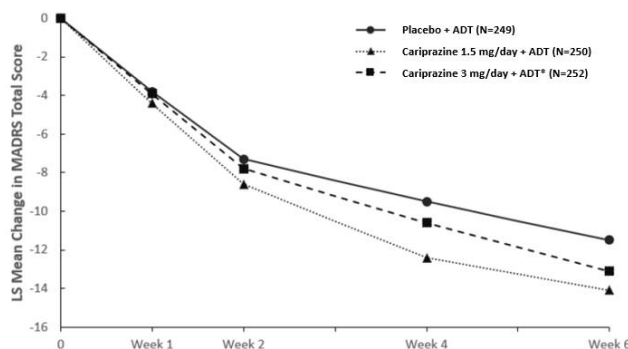
Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: MADRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference ^a (95% CI)
Study 10	Cariprazine (1.5 mg/day) + ADT* (n=250)	32.8 (5.0)	-14.1 (0.7)	-2.5 (-4.2, -0.9)
	Cariprazine (3 mg/day) + ADT (n=252)	32.7 (4.9)	-13.1 (0.7)	-1.5 (-3.2, 0.1)
	Placebo + ADT (n=249)	31.9 (5.7)	-11.5 (0.7)	
Study 11	Cariprazine (1 to 2 mg/day) + ADT (n=273)	29.0 (4.3)	-13.4 (0.5)	-0.9 (-2.4, 0.6)
	Cariprazine (2 to 4.5 mg/day) + ADT* (n=271)	29.3 (4.1)	-14.6 (0.6)	-2.2 (-3.7, -0.6)
	Placebo + ADT (n=264)	28.9 (4.3)	-12.5 (0.5)	

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
 *Dosages statistically significantly superior to placebo
^aDifference (drug minus placebo) in least-squares mean change from baseline

Examination of population subgroups based on age, sex, and race did not suggest any clear evidence of differential responsiveness.

The below figure shows the time course of response based on the primary efficacy measure (MADRS total score) in Study 10.

LS Mean[‡] Change from Baseline to Week 6 in MADRS Total Score in Adjunctive Treatment of Major Depressive Disorder (Study 10)



Placebo + ADT (N)	249	246	246	238	231
Cariprazine 1.5 mg/day+ADT (N)	250	250	242	237	231
Cariprazine 3 mg/day+ADT* (N)	252	252	245	235	223

[‡] LS Mean: least-squares mean
 * Dose was not statistically significant

העלון לצרכן עודכן בדצמבר 2024. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים באדום):

3. כיצד תשתמש בתרופה?

בטיפול במצב דיכאוני של הפרעה דו קוטבית ובמצב של דיכאון מג'ורי (MDD) המינון המרבי לא יעלה על 3 מ"ג פעם ביום.

4. תופעות לוואי

תופעות לוואי שכיחות (תופעות שמופיעות ב-10-1 משתמשים מתוך 100):

- הזעת יתר

תופעות לוואי שאינן שכיחות (תופעות שמופיעות ב-10-1 משתמשים מתוך 1,000):

- מודעות לפעימות לב (פלפיטציות)

- בצקת

- כאב שרירים

תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה):

- דלקת של האף והלוע