מאי 2022

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.

<u>ההתוויה המאושרת:</u>

- 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.

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"י פנייה לבעל הרישום: דקסל בע"מ, רח' דקסל 1, אור עקיבא 3060000, ישראל, טל': 04-6364000.

<u>הרכב התכשיר:</u>

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

העלון לרופא עודכן במאי 2022. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים באדום)**:**

4.2 Posology and method of administration

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Manic or Mixed Episodes Associated with Bipolar I Disorder

The recommended dosage range is 3 mg to 6 mg once daily. The starting dose of cariprazine is 1.5 mg and should be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily.

Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dose 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. Maximum recommended dosage is 3 mg once daily. Clinical trials have not demonstrated statistical efficacy in treatment of the higher dose of 3 mg once daily, hence the option of treatment with the maximum daily dose of 3 mg should be reserved only for patients resistant to the low dose of 1.5 mg once daily.

4.8 Undesirable effects

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<u>Patients with Bipolar Mania</u>

The following findings are based on three placebo-controlled, 3-week bipolar mania trials with cariprazine doses ranging from 3 to 12 mg once daily. The maximum recommended dosage is 6 mg daily**.**

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in cariprazine -treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 12% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 7% of placebo-treated patients in these trials

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness .

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at any dose are shown in Table below:

Adverse Reactions Occurring in ≥ 2% of cariprazine-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	**cariprazine***	
		3 -6 mg/day (N=263) (%)	9 -12 mg/day◦ (N=360) (%)
Cardiac Disorders			
Tachycardia[a]	1	2	1
Eye Disorders			
Vision blurred	1	4	4
Gastrointestinal Disorders			
Nausea	7	13	11
Constipation	5	6	11
Vomiting	4	10	8
Dry mouth	2	3	2
Dyspepsia	4	7	9
Abdominal pain[b]	5	6	8
Diarrhea[c]	5	5	6
Toothache	2	4	3
General Disorders/Administration Site Conditions			
Fatigue[d]	2	4	5
Pyrexia[e]	2	1	4
Investigations			
Blood creatine phosphokinase increased	2	2	3
Hepatic enzymes increased[f]	<1	1	3
Weight increased	2	2	3
Metabolism and Nutrition Disorders			
Decreased appetite	3	3	4
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	2	4	2
Back pain	1	1	3
Nervous System Disorders			
Akathisia	5	20	21
Extrapyramidal Symptoms[g]	12	26	29
Headache[h]	13	14	13
Dizziness	4	7	6
Somnolence[i]	4	7	8
Psychiatric Disorders			
Insomnia[j]	7	9	8
Restlessness	2	7	7
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	1	3
Vascular Disorders			

Hypertension[k]	1	5	4

Note: Figures rounded to the nearest integer
*Data shown by modal daily dose, defined as most frequently administered dose per patient
[a]**Tachycardia terms**: heart rate increased, sinus tachycardia, tachycardia
[b]**Abdominal pain terms**: abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness,
[c]**Diarrhea**: diarrhea, frequent bowel movements
[d]**Fatigue terms**: asthenia, fatigue
[e]**Pyrexia terms**: body temperature increased, pyrexia
[f]**Hepatic enzymes increased terms**: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased
[g]**Extrapyramidal Symptoms terms**: bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, tremor
[h]**Headache terms**: headache, tension headache
iSomnolence terms: hypersomnia, sedation, somnolence
[j]**Insomnia terms**: initial insomnia, insomnia, middle insomnia
[k]**Hypertension terms**: blood pressure diastolic increased, blood pressure increased, hypertension
[o]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Patients with Bipolar Depression

The following findings are based on three placebo-controlled, two 6-week and one 8-week bipolar depression trials with cariprazine doses of 1.5 mg and 3 mg once daily.

Adverse Reactions Associated with Discontinuation of Treatment: There were no adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in cariprazine -treated patients and at least twice the rate of placebo. Overall, 6% of the patients who received cariprazine discontinued treatment due to an adverse reaction, compared with 5% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): nausea, akathisia, restlessness, and extrapyramidal symptoms.

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

Adverse Reactions Occurring in ≥ 2% of cariprazine-treated Patients and > Placebo-treated Adult Patients in two 6-week trials and one 8-week trial

	Placebo (N=468) (%)	**cariprazine**	
		1.5 mg/day (N=470) (%)	3 mg/day (N=469) (%)
Restlessness	3	2	7
Akathisia	2	6	10
Extrapyramidal symptoms[a]	2	4	6
Dizziness	2	4	3
Somnolence[b]	4	7	6
Nausea	3	7	7
Increased appetite	1	3	3
Weight increase	<1	2	2

Fatigue[c]	2	4	3
Insomnia[d]	7	7	10

[a] **Extrapyramidal symptoms terms**: akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor

[b] **Somnolence terms**: hypersomnia, sedation, somnolence

[c] **Fatigue terms**: asthenia, fatigue, malaise

[d] **Insomnia terms**: initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder terminal insomnia

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In 3-week bipolar mania trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for cariprazine-treated patients versus 12% for placebo-treated patients. These events led to a discontinuation in 1% of cariprazine-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 20% for cariprazine-treated patients versus 5% for placebo-treated patients. These events led to discontinuation in 2% of cariprazine-treated patients versus 0% of placebo-treated patients. The incidence of EPS is provided in Table below.

Incidence of EPS Compared to Placebo in 3-Week Bipolar Mania Trials

Adverse Event Term	Placebo (N= 442) (%)	CARIPRAZINE	
		3 -6 mg/day (N=263) (%)	9 -12 mg/day° (N=360) (%)
All EPS events	18	41	45
All EPS events, excluding Akathisia/Restlessness	12	26	29
Akathisia	5	20	21
Dystonia**	1	5	3
Parkinsonism§	10	21	26
Restlessness	2	7	7
Musculoskeletal stiffness	1	2	2

Note: Figures rounded to the nearest integer

*Data shown by modal daily dose, defined as most frequently administered dose per patient

[*] **Dystonia includes adverse event terms:** dystonia, oromandibular dystonia

[§] **Parkinsonism includes adverse event terms:** bradykinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor

° The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, the incidence of reported events related to EPS, excluding akathisia and restlessness was 4% for cariprazine-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 0.4% of cariprazine-treated patients versus 0% of placebo-treated patients. The incidence of akathisia was 8% for cariprazine-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 1.5% of cariprazine-treated patients versus 0% of placebo-treated patients. The incidence of EPS is shown in Table below.

Incidence of EPS Compared to Placebo in two 6-Week and one 8-Week Bipolar Depression Trials

Adverse Event Term	Placebo (N= 468) (%)	CARIPRAZINE 1.5 mg/day (N=470) (%)	CARIPRAZINE 3 mg/day (N=469) (%)
All EPS events	7	10	19
All EPS events, excluding Akathisia/Restlessness	2	4	6
Akathisia	2	6	10
Dystonia*	<1	<1	<1
Parkinsonism§	2	3	4
Restlessness	3	2	7
Musculoskeletal stiffness	<1	<1	1
Tardive Dyskinesia	0	0	<1

Note: Figures rounded to the nearest integer

* **Dystonia includes adverse event terms:** dystonia, myoclonus, oculogyric crisis

§ **Parkinsonism includes adverse event terms:** akinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle tightness, salivary hypersecretion, and tremor.

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The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 3-week bipolar mania trials ranged between 2% and 4% for cariprazine-treated patients depending on dose group administered and 2% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week and 8-week bipolar depression trials ranged between 0% and 0.5% for cariprazine-treated patients depending on dose group administered and 0.4% for placebo-treated patients.

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העלון לצרכן עודכן במאי 2022. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים באדום):

3. כיצד תשתמש בתרופה?

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המינון ואופן הטיפול ייקבעו על ידי הרופא בלבד.

המינון ההתחלתי המומלץ הוא 1.5 מ"ג פעם ביום דרך הפה. לאחר מכן, ייתכן שהרופא יתאים לך את מינון התרופה בהדרגה, בעליות של 1.5 מ"ג, כתלות בתגובה שלך לטיפול. המינון המרבי בטיפול בסכיזופרניה ובמצב מאני של הפרעה דו קוטבית לא יעלה על 6 מ"ג פעם ביום; בטיפול במצב דיכאוני של הפרעה דו קוטבית המינון המרבי לא יעלה על 3 מ"ג פעם ביום.

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4. תופעות לוואי

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

- חרדה
- ישנוניות, קשיי שינה, חלומות חריגים, סיוטים, סהרוריות
- סחרחורת, כאב ראש
- תנועות התפתלות בלתי רצוניות, תנוחות חריגות

- חריקת שיניים מוגברת או הידוק הלסת, ריור, מצמוץ מתמיד בתגובה להקשה על המצח (רפלקס לא תקין), בעיות בתנועה, הפרעה בתנועת הלשון (אלה נקראים תסמינים חוץ פירמידליים)
- טשטוש ראייה
- לחץ דם גבוה
- דופק מהיר, סדיר או לא סדיר
- ירידה או עלייה בתיאבון
- בחילות, הקאות, עצירות, שלשול, קשיי עיכול, יובש בפה, כאבי בטן, כאב שיניים
- עלייה במשקל
- עייפות, חום
- כאב בגפיים, כאב גב
- כאב גרון
- תופעות שניתן לראות בבדיקות מעבדה:
  - עלייה ברמות אנזימי כבד
  - עלייה ברמות קראטין פוספוקינאז בדם
  - רמה לא תקינה של ליפידים (למשל כולסטרול ו/או שומן) בדם

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