REAGILA®

CARIPRAZINE

Cariprazine (REAGILA®) is an EMA-approved medication that is indicated for the treatment of schizophrenia in adult patients.[1]

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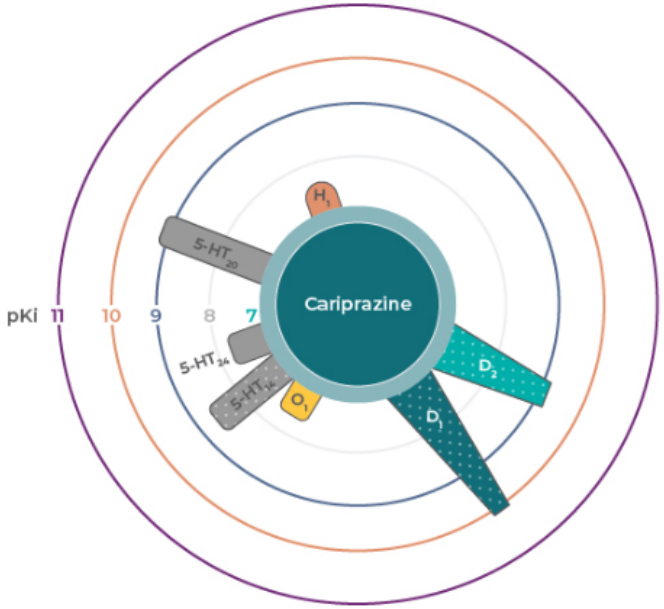
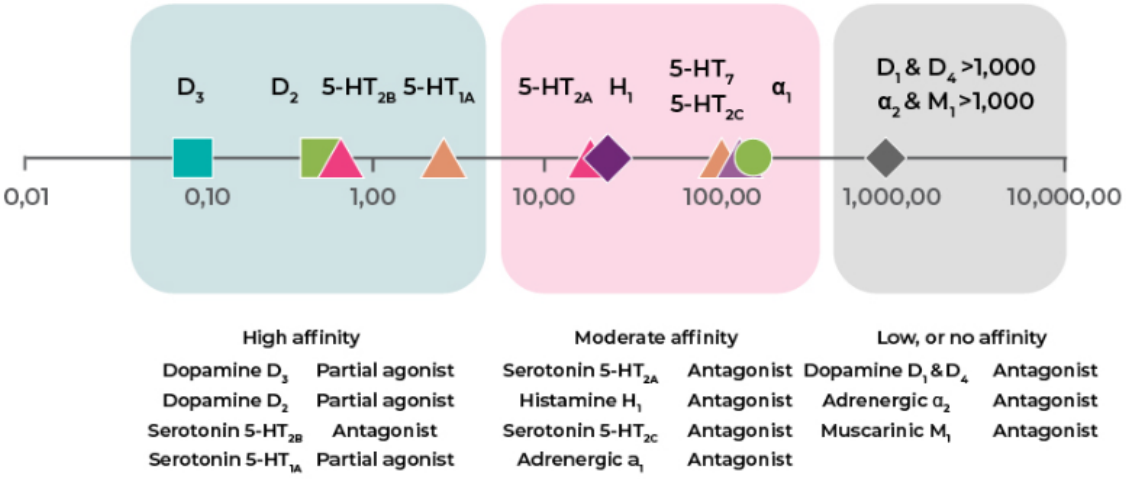
THE MECHANISM OF ACTION OF REAGILA

REAGILA® CARIPRAZINE

Click on these buttons to learn more!

THE RECEPTOR PROFILE OF CARIPRAZINE





High affinity		Moderate affinity		Low, or no affinity	
Dopamine D_3	Partial agonist	Serotonin 5-HT_{2A}	Antagonist	Dopamine D_1 & D_4	Antagonist
Dopamine D_2	Partial agonist	Histamine H_1	Antagonist	Adrenergic α_2	Antagonist
Serotonin 5-HT_{2B}	Antagonist	Serotonin 5-HT_{2C}	Antagonist	Muscarinic M_1	Antagonist
Serotonin 5-HT_{1A}	Partial agonist	Adrenergic a_1	Antagonist		

Adapted from Kiss, B. et al. *J. Pharmacol. Exp. Ther*. 333, 328–340 (2010).[2]

The mechanism of action of cariprazine is not fully known[1]. However, based on its receptor profile and numerous studies including in vivo preclinical studies and human PET studies, enough evidence exists to elucidate the key factors contributing to the mechanism of action of cariprazine.

At pharmacologically effective doses, cariprazine shows relatively similar occupancy at both D3 and D2 receptors, as demonstrated by in vivo nonclinical and human PET studies[3]. Effects attributed to D3 receptor blockade are not associated with any drug other than cariprazine, since in the living brain, in the presence of natural dopamine, D3 receptors are not blocked by any antipsychotic other than cariprazine[4,5].

D3 receptor antagonism is associated with pro-cognitive, antidepressant, and anti-negative symptom effects[3].

Watch a video about D3 receptors

from the
Neuroscience Education Institute

COD: 300020/R27 Submitted to AIFA on: 26.06.2020

THE MECHANISM OF ACTION OF REAGILA

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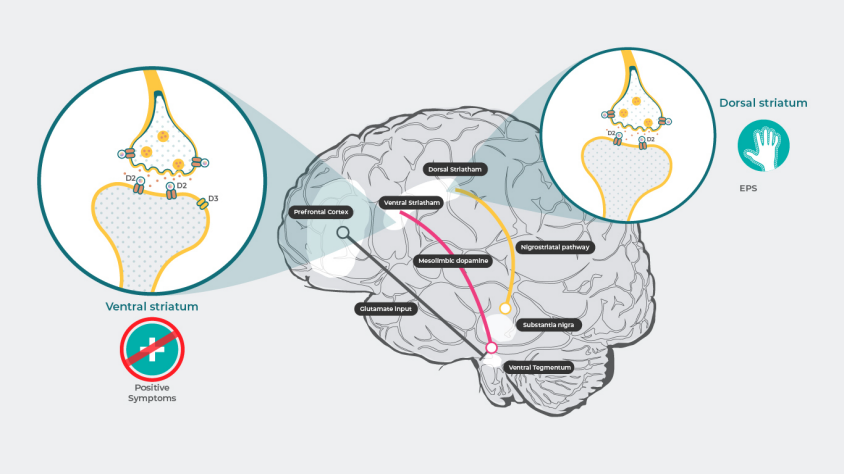
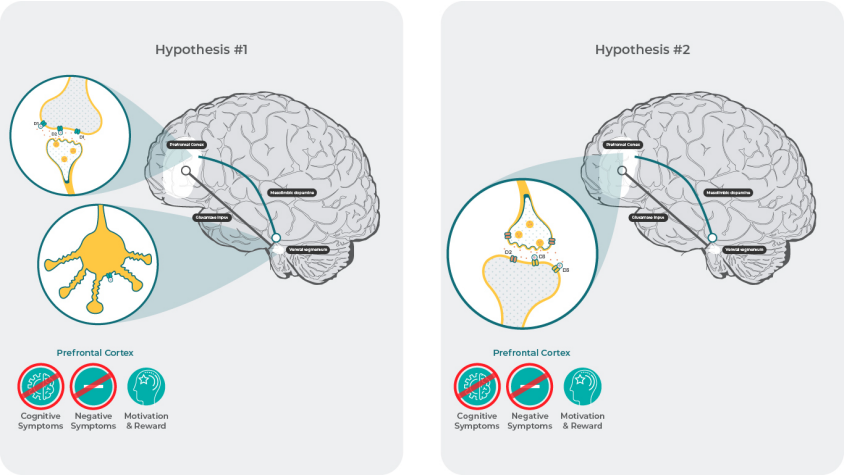
CARIPRAZINE



Adapted from Stahl SM.*CNS Spectrums*(2017),**22**, 375–384.3;[4] Howes J*Psychopharmacol*. 2015 February;**29**(2): 97–115[6]

For a clinical response, a minimum of 50% occupancy of dopamine D2 receptors by antipsychotics is generally required, while occupancy above 85% results in an increased risk of EPS and other undesirable side effects. This suggests that there is a therapeutic window between 60% and 80% for dopamine D2 receptor occupancy that balances a high likelihood of clinical response with low risk of EPS. Only clozapine and partial agonists at dopamine receptors have been shown to be exceptions to this generalization[7].

Prof Stahl explains the mechanism of action of cariprazine



Two hypothesis of how cariprazine normalizes hypodopaminergic states by D3 receptor blockade. Hypothesis 1: Adapted from Howes J Psychopharmacol 29(2): 97–115. (2015)[6]. Stahl SM. CNS Spectrums, 22, 375–384. (2017)[4] Hypothesis 2: Adapted from Bouthenet*et al. Brain research* **564**, 203-21928. (1991)[8]; Gurevich,*Neuropsychopharmacology* **20**, 60-80. (1999)[9]; Loiseau, *Eur Neuropsychopharmacol* **19**, 23-33.(2009)[10]; Watson, D.J. *Neuropsychopharmacology* **37**, 770-786 (2012)[11]; Clarkson,*J Neurosci* **37**, 5846-5860. (2017)[12]; Yang, S. Cell Rep **16**, 1518-1526. (2016)[13]; Neill, J.C.*Eur Neuropsychopharmacol* **26**, 3-14. (2016)[14]; Zimnisky, R.*Psychopharmacology*(Berl) **226**, 91-100. (2013)[15]

Most D3 receptors are localized in brain areas where hyperdopaminergia is present in schizophrenia (ie, in the mesolimbic dopaminergic system)[3,6], cariprazine acts as a functional antagonist on these receptors. D3 receptor antagonism is associated with pro-cognitive, antidepressant, and anti-negative symptom effects[4]. Confusingly, these same effects are also linked to cortical functions, where hypodopaminergia is present in schizophrenia[6].

Hypothesis #1: Increased Neurotransmission From VTA to PFC; Hypothesis #2: Postsynaptic D3 Receptor Binding in the PFC

WHY START WITH CARIPRAZINE?

REAGILA® CARIPRAZINE

The advantages of initiating treatment with Cariprazine include its **broad-spectrum efficacy** in short and long term[16], in negative symptoms[17]; its good cardimetabolic profile[18], low incidences of weight gain[18] and sedation[19], and convenient once-a-day dosing, with or without food[1].

SHORT-TERM EFFICACY

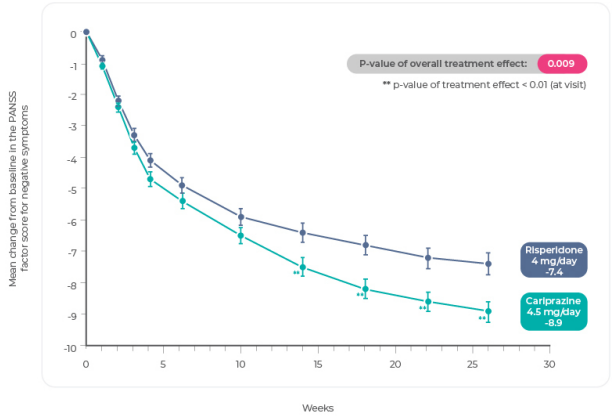
Across 3 short-term pivotal studies, Cariprazine demonstrated efficacy versus placebo in adult patients with acute exacerbation of schizophrenia[20-22].

LONG-TERM EFFICACY

Treatment with cariprazine doses (3–6 mg/d) was associated with a significantly delayed time to relapse compared with the corresponding placebo group P=0.026, HR [95% CI]=0.49 [0.25, 0.93])[1,23].

NEGATIVE SYMPTOMS

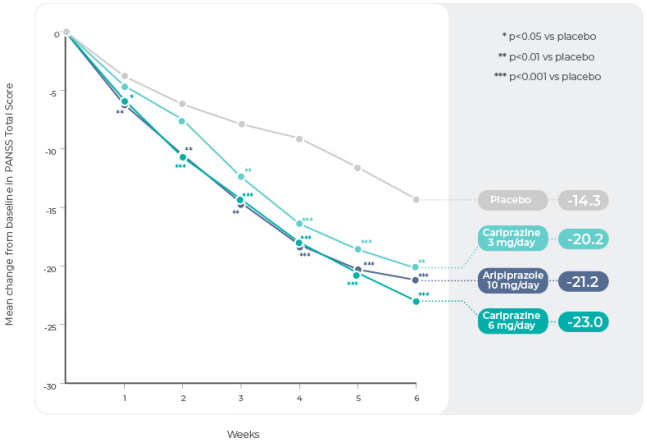
Cariprazine has the potential to change clinical practice by providing a treatment option for patient with predominant negative symptoms of schizophrenia[17].



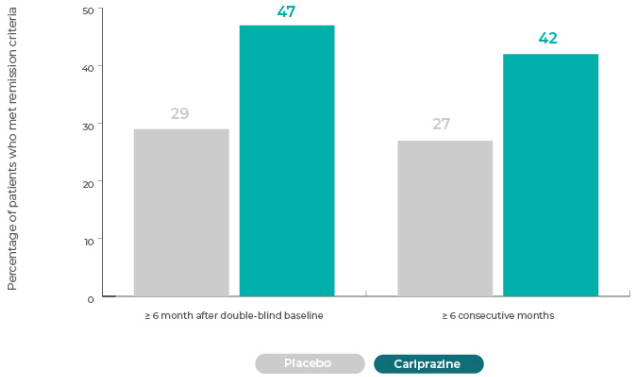
Adapted from Németh, G. et al. *Lancet* **389**, 1103–1113 (2017).[17]

STUDY 2

Sustained Remission Was Significantly Longer With Cariprazine Versus Placebo



Adapted from Durgam, S. et al. *J. Clin. Psychiatry* **76**, e1574-82 (2015).[22]



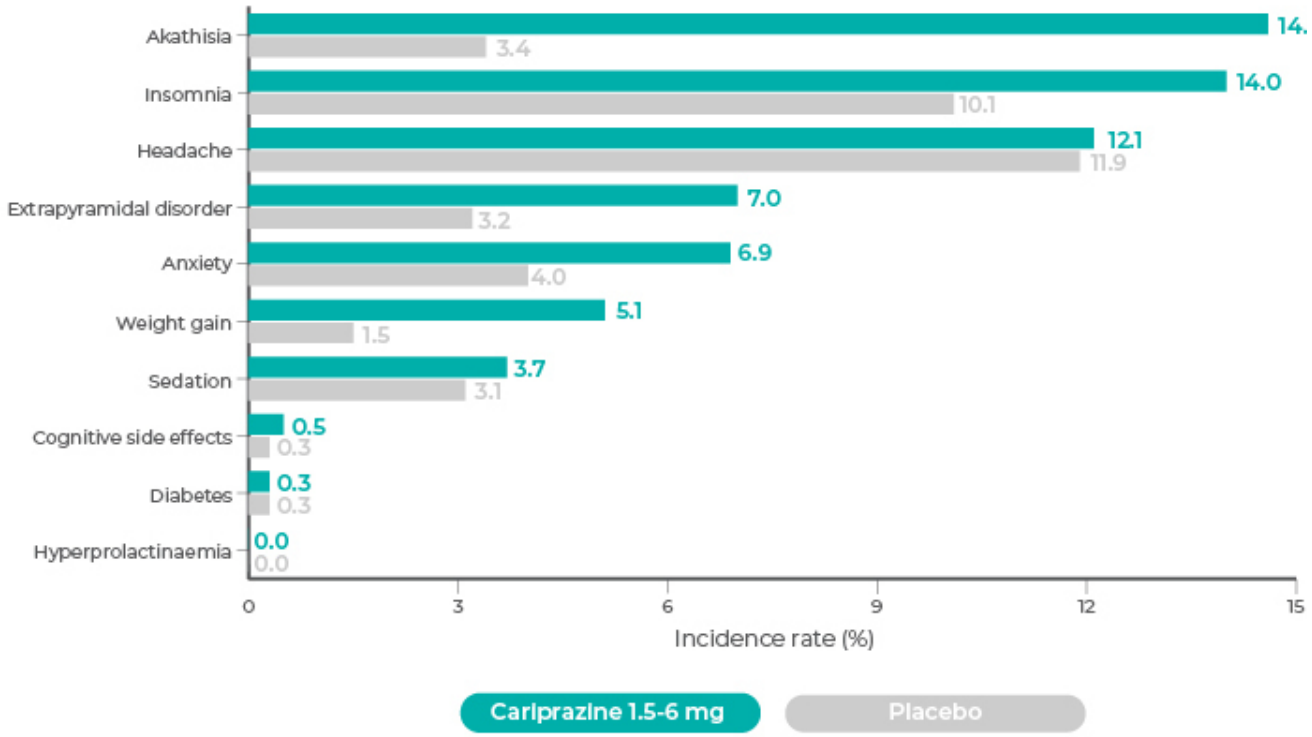
Adapted from Correll, C. U. et al. *J. Clin. Psychiatry* **80**, 18m12495 (2019).[24]

Patients who have shown improvement in positive symptoms but continue to have disabling negative symptoms while on an antipsychotic other than cariprazine, might benefit from treatment with cariprazine[1,17]. That is why in a recent publication cariprazine was suggested as the first step in the algorithm of negative symptom treatment[25].

SAFETY AND TOLERABILITY PROFILE OF REAGILA

REAGILA® CARIPRAZINE

The total number of cariprazine-treated patients who were included in the safety dataset was 2728; of these patients, 2048 patients were in the most relevant therapeutic dose range group of 1.5-6 mg/d[26].



Adapted from data in the Reagila Assessment Report EMA.*Reagila Assessment Report*5https://www.ema.europa.eu/en/documents/assessment-report/reagila-epar-public-assessment-report_en.pdf.[26]

The adverse event profile of cariprazine in the therapeutic 1.5-6 mg/d dose range shows that akathisia, insomnia, and headache occur at relatively high rates, but only the rate of akathisia is substantially higher with cariprazine than with placebo[26]. Most events of akathisia were considered mild or moderate in severity[1].

HIGHLIGHTS OF THE SAFETY PROFILE OF CARIPRAZINE

- Cariprazine does not cause hyperprolactinemia[26]; no TEAEs related to elevation of prolactin levels were reported in cariprazine-treated patients in the clinical studies[26].
- The incidence of sexual dysfunction was low in patients treated with cariprazine(1.0%)[26].
- Cariprazine is metabolically neutral: rates of hyperlipidemia, hyperglycemia, and diabetes mellitus were comparable to placebo[26].
- Frequencies of cognition-related adverse events were similar to placebo and uncommon[26]
- Cariprazine does not cause serious or severe QT prolongation[1].
- Sedation rates for cariprazine (3.8%) that are similar to placebo (3.1%)[26].
- Throughout the cariprazine development program, 6 deaths occurred due to completed suicide, but none were judged to be related to cariprazine[26].

MANAGEMENT OF AKATHISIA

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SHOULD WE BE CONCERNED?

Akathisia is a common side effect of antipsychotic treatment. It is usually considered a movement or extrapyramidal disorder, with motor signs and sensory disturbance (e.g., restlessness, the need to move) as the defining characteristics of the condition[27].

A COMMON ADVERSE EVENT

Akathisia is the most relevant adverse event associated with cariprazine treatment.[1]

In the pooled data set of 2048 cariprazine-treated patients (in the approved dose-range of 1.5-6 mg/d) and 683 placebo treated patients, the rate of akathisia was 14.6% for cariprazine and 3.4% for placebo[26].

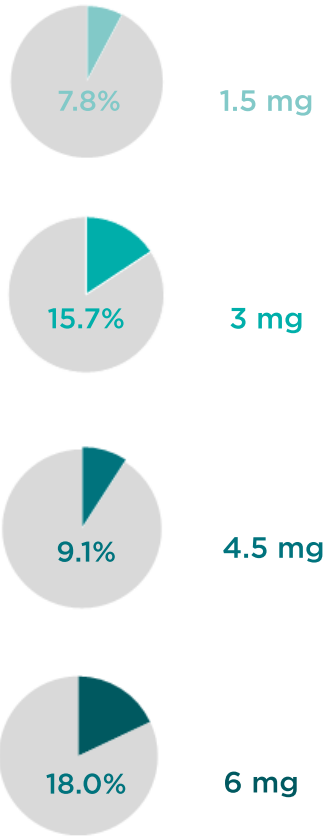
Most cases were mild to moderate in intensity, and rarely lead to study discontinuation[1].

The low discontinuation rates potentially mean that akathisia is an event that can be well managed in the clinic[28,29].

HOW WAS AKATHISIA MANAGED IN THE CARIPRAZINE STUDIES?

THE FIRST OCCURENCE OF AKATHISIA was generally reported within the first 6 weeks of treatment and showed a dose dependency[26], meaning that the likelihood of akathisia with low doses of cariprazine was less[26].

LIKELIHOOD OF AKATHISIA



ANTI EPS MEDICATION

The majority of patients used anti EPS medication to manage symptoms of akathisia/restlessness[28,29].

Propranolol along with diphenhydramine, benztropine or equivalent were used most[28,29].

DURATION OF AKATHISIA

The mean duration of akathisia was 24 days for cariprazine-treated and 29 days for placebo-treated patients in the short term studies[29].

Mean duration of akathisia

24 days

IS SUICIDE A CONCERN FOR CARIPRAZINE-TREATED PATIENTS WITH AKATHISIA ?

No relationship between akathisia and suicidal tendency was observed in the cariprazine schizophrenia program. The safe use of the product in the context of early detection and mitigation of treatment emergent akathisia /restlessness, and prevention of suicide should be assured by individualized dosing regimen with close monitoring during the initiation of the treatment and lowest effective maintenance doses[26].

COD: 300020/R27 Submitted to AIFA on: 26.06.2020

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ABBREVIATED SUMMARY OF PRODUCT CHARACTERISTICS REAGILA (CARIPRAZINE) 1.5 MG; 3 MG; 4.5 MG; 6 MG HARD CAPSULE

Name of the medicinal product :Reagila(cariprazine) 1,5 mg; 3 mg; 4,5 mg; 6 mg hard capsule, ATC code:N05AX15. Therapeutic indications:Reagilais indicated for the treatment of schizophrenia in adult patients. Posology: the recommended starting dose ofcariprazineis 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, ifneeded.Becauseof the long half-life ofcariprazineand its active metabolites, changes in dose will not be fully reflected in plasma for severalweeks.Whenswitching from another antipsychotic tocariprazinegradual cross-titration should be considered. When switching to another antipsychotic fromcariprazine, no gradual cross-titration is needed. Special populations: No dose adjustment is required in patients with mild to moderate renal impairment. No dose adjustment is required in patients with mild to moderate hepatic impairment. Use ofcariprazineis not recommended in patient with severe renal or hepatic impairment. Dose selection for an elderly patient should be more cautious. No data are available forpaediatricpopulation. Contraindications: Hypersensitivity to the active substance or to any of the excipients, concomitant administration of strong or moderate CYP3A4 inhibitors or inducers. Special warnings: Precautions for use in case of suicidal thoughts orbehaviour, close supervision for high risk patients is recommended. In thosewhoareprone to or already exhibit symptoms ofakathisiacariprazineshould be used cautiously.Akathisiadevelops early in treatment. Therefore close monitoring in the first phase of treatment is important. Prevention includes slow up-titration; treatment measures include slight down-titration ofcariprazineor anti-EPSmedication. The dose can be modified based on individual response andtolerability.Ifsigns and symptoms of tardive dyskinesia appear discontinuation should be considered. If prescribed to patients with Parkinson's disease, antipsychotic medicinal products may exacerbate the underlying disease and worsen symptoms ofParkinson?sdisease. Patients who would develop symptoms potentially related to cataract should be advised to ophthalmologicexamination.Drugdiscontinuation is recommended if signs and symptoms of neuroleptic malignant syndrome develops.Cariprazineshould be used cautiously in patients with history of seizures or with conditions that potentially lower the seizure threshold. Not recommended to treat elderly patients with dementia due to increased risk of overall mortality and should be used with caution in patients with risk factors for stroke. Cautious use is recommended in patient with known cardiovascular disease predisposing to blood pressure changes. Blood pressure should bemonitored.Cautioususe in patients with known cardiovascular disease or in patients with a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment withcariprazineand preventive measuresundertaken.Patientswith an established diagnosis of diabetes mellitus or patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should be monitored for serum glucoselevels.Womenof childbearing potential must use contraception while takingcariprazineand at least for 10 weeks after stopping treatment. Women using systemically acting hormonal contraceptives should add a second barrier method. Weight should be monitored regularly. Capsules of 3 mg, 4.5 mg and 6 mg containAlluraredACwhichcan cause allergic reactions. Adverse reactions: Very common:akathisia, parkinsonism.Common:bodyweight increase, increased or decreased appetite,dyslipidaemia, sleep disorders, anxiety, sedation, dizziness, dystonia, other extrapyramidal diseases and abnormal movement disorders, blurred vision, tachyarrhythmia, hypertension, nausea, constipation, vomiting, increased liver enzymes and creatinine phosphokinase in blood, fatigue. Uncommon:anaemia, eosinophilia, blood TSH decreased, blood sodium abnormal, blood glucose increased, diabetes mellitus, suicidalbehaviour, delirium, depression, libido decreased, libido increased, erectile dysfunction, lethargy,dysaesthesia, dyskinesia, tardive dyskinesia, eye irritation, intraocular pressure increased, accommodation disorder, visual acuity reduced, vertigo, cardiac conduction disorders,bradyarrhytmia, QT prolongation, abnormal T wave, hypotension, hiccups, GERD, blood bilirubin increased, pruritus, rash, dysuria,pollakisuria, thirst. Rare: neutropenia, hypersensitivity, hypothyroidism, seizures, amnesia, aphasia, photophobia, cataract, dysphagia,rhabdomyolysis. Not known frequency: NMS, toxic hepatitis, neonatal drug withdrawal syndrome. Not recommended during pregnancy or for fertile women not using reliablecontraception.Themedicinal product has minor or moderate influence on the ability to drive and use machines.

Before using t he medicinal product , please read t he det ailed Summary of Product Characteristics.

English SmPC | Italian SmPC

▼ 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. See section 4.8 of the SmPC for how to report adverse reactions

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COD: 300020/R27 Submitted to AIFA on: 26.06.2020