# Part VI: Summary of the risk management plan

**Summary of risk management plan for Reagila (cariprazine)**

This is a summary of the risk management plan (RMP) for Reagila. The RMP details important risks of Reagila, how these risks can be minimised, and how more information will be obtained about Reagila's risks and uncertainties (missing information).
Reagila's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Reagila should be used.
This summary of the RMP for Reagila should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Reagila's RMP.

## I. The medicine and what it is used for

Reagila is indicated for the treatment of schizophrenia in adult patients.
It contains cariprazine as the active substance and it is given orally once a day.

Further information about the evaluation of Reagila's benefits can be found in Reagila's EPAR, including its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/reagila).

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Reagila, together with measures to minimise such risks and the proposed studies for learning more about Reagila's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Reagila is not yet available, it is listed under 'missing information' below.

### *II.A List of important risks and missing information*

Important risks of Reagila are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Reagila. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

| **List of important risks and missing information** | |
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| Important identified risks | #1. Extrapyramidal symptoms including tardive dyskinesia |
| | #2. Weight gain |
| Important potential risks | #3. Neuroleptic Malignant Syndrome |
| | #4. Ocular changes (Lenticular changes and cataracts) |
| | #5. Suicidal ideation and behaviour |
| | #6. Interaction with CYP3A4 inhibitors and inducers |
| | #7. Developmental and reproductive toxicity |
| Missing information | #8. Use in patients > 65 years |

### *II.B Summary of important risks*

| **Safety Concern #1 - Important identified risk - Extrapyramidal symptoms including tardive dyskinesia** | |
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| Evidence for linking the risk to the medicine | Medical literature/Database |
| Risk factors and risk groups | Akathisia: Patient risk factors for akathisia have not been well established, but increasing age, female sex, negative symptoms, cognitive dysfunction, iron deficiency, prior akathisia, concomitant parkinsonism, and mood disorders may entail greater risk.<br>The risk of drug-induced parkinsonism has been associated with increasing age, female gender, dementia, HIV infection, and pre-existing extrapyramidal disease or family history of Parkinson's disease.<br>Patient risk factors for dystonia include age, male sex, race, previous dystonic reactions, family history of dystonia, cocaine use, mood disorders, hypocalcaemia, hypoparathyroidism, hyperthyroidism and dehydration. Children and young adults are highly vulnerable, whereas drug-induced dystonia is rare over 45 years of age.22 |

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| | Previous studies of TD risk have suggested an association with increasing age, female gender, psychiatric diagnosis, longer duration of antipsychotic treatment, higher cumulative drug doses, concomitant drug treatments, higher ratings of negative symptoms and thought disorder, greater cognitive impairments, presence of acute EPS, and diabetes.[22] |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.6; 4.8<br>PL sections 2; 4.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #2 - Important identified risk - Weight gain** | |
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| Evidence for linking the risk to the medicine | Medical literature/Database |
| Risk factors and risk groups | General risk for weight gain include a calorific diet and low physical activity. Risk of antipsychotic induced weight gain is associated with lower body weight (low/normal body mass index) at the beginning of antipsychotic treatment and the diagnosis of undifferentiated schizophrenia.[24] A systematic appraisal of the literature concluded that young non-overweight women with an acute psychotic episode were particularly high risk of antipsychotic-induced weight gain. |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.8.<br>PL sections 2; 4.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #3 - Important potential risk - Neuroleptic malignant syndrome** | |
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| Evidence for linking the risk to the medicine | Medical literature/Database |
| Risk factors and risk groups | Dehydration, exhaustion, agitation, catatonia, previous episodes, and high doses of high-potency drugs given parentally at a rapid rate. |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.8.<br>PL sections 2; 4.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #4 - Important potential risk - Ocular changes (Lenticular changes and cataracts)** |
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| Evidence for linking the risk to the medicine | Medical literature/Database |
| Risk factors and risk groups | Age is the most common cause. Lens proteins denature and degrade over time, and this process is accelerated by diseases such as diabetes mellitus and hypertension. Environmental factors, including toxins, radiation, and ultraviolet light, have cumulative effects, which are worsened by the loss of protective and restorative mechanisms due to alterations in gene expression and chemical processes within the eye. Risk factors for the development of cataract include poor general health, smoking, alcoholism, a high-fat diet and comorbidities such as diabetes and hypertension which are common in patients with schizophrenia |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.8.<br>PL sections 2; 4.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #5 - Important potential risk - Suicidal ideation and behaviour** | |
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| Evidence for linking the risk to the medicine | Medical literature/Database |
| Risk factors and risk groups | Risk factors with a strong association with later suicide included being young, male, and with a high level of education. Illness-related risk factors were important predictors, with number of prior suicide attempts, depressive symptoms, active hallucinations and delusions, and the presence of insight all having a strong evidential basis. A family history of suicide, and comorbid substance misuse were also positively associated with later suicide. The only consistent protective factor for suicide was delivery of and adherence to effective treatment. |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.8.<br>PL sections 2; 4.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #6 - Important potential risk - Interaction with CYP3A4 inhibitors and inducers** | |
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| Evidence for linking the risk to the medicine | Own study |
| Risk factors and risk groups | Patients who take strong or moderate CYP3A4 inhibitor (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, |

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| | posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, diltiazem, erythromycin, fluconazole verapamil) or inducer inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, nafcillin). |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.3; 4.5.<br>PL section 2.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• Clinical study to investigate the interaction between cariprazine and a moderate CYP3A4 inhibitor (erythromycin) in patients with different CYP2D6 genotypes. |

| **Safety Concern #7 - Important potential risk - Developmental and reproductive toxicity-** | |
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| Evidence for linking the risk to the medicine | Database |
| Risk factors and risk groups | Women of childbearing potential |
| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.4; 4.6; 4.5; 5.3.<br>PL section 2.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

| **Safety Concern #8 - Missing information – Use in patients > 65 years** | |
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| Risk minimisation measures | Routine risk minimisation measures:<br>SmPC sections 4.2; 4.4.<br>PL section 2.<br>Medicinal product subject to medical prescription.<br><br>Additional risk minimisation measures:<br>No additional risk minimisation measures are proposed. |

## *II.C Post-authorisation development plan*

### *II.C.1 Studies which are conditions of the marketing authorisation*

There are no studies which are conditions of the marketing authorisation or specific obligation of Reagila.

### *II.C.2 Other studies in post-authorisation development plan*

**Study short name: Clinical study to investigate the interaction between cariprazine and a moderate CYP3A4 inhibitor (erythromycin) in patients with different CYP2D6 genotypes.**

Purpose of the study: Provide dosing recommendations when cariprazine is used concomitantly with moderate CYP3A4 inhibitors. Investigate the effect of different genetics of CYP2D6 enzymes on the exposure of cariprazine.