- **Dosage and administration:**

The starting and recommended dose of Vorasan is 10 mg vortioxetine once daily in adults less than 65 years of age.
Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily or decreased to a minimum of 5 mg vortioxetine once daily.
After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.
Treatment discontinuation
Patients treated with vortioxetine can abruptly stop taking the medicinal product without the need for a gradual reduction in dose.
Special populations
Elderly patients
The lowest effective dose of 5 mg vortioxetine once daily should always be used as the starting dose in patients ≥ 65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily for which data are limited . Cytochrome P450 inhibitors Depending on individual patient response, a lower dose of vortioxetine may be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to vortioxetine treatment.
Cytochrome P450 inducers
Depending on individual patient response, a dose adjustment of vortioxetine may be considered if a broad cytochrome P450 inducer (e.g., rifampicin, carbamazepine, phenytoin) is added to vortioxetine treatment . Paediatric population The safety and efficacy of Vorasan in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration
Vorasan is for oral use.
The film-coated tablets can be taken with or without food.

- **Precautions**:

Use in paediatric population
Vorasan is not recommended for the treatment of depression in patients aged less than 18 years since the safety and efficacy of vortioxetine have not been established in this age group .In clinical studies in children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, anger) were more frequently observed than in those treated with placebo.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical studies of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
Seizures
Seizures are a potential risk with antidepressants. Therefore, vortioxetine should be introduced cautiously in patients who have a history of seizures or in patients with unstable epilepsy . Treatment should be discontinued in any patient who develops seizures or for whom there is an increase in seizure frequency.
Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)
Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS), potentially life-threatening conditions, may occur with vortioxetine. The risk of SS or NMS is increased with concomitant use of serotonergic-active substances (including triptans), medicinal products that impair the metabolism of serotonin (including MAOIs), antipsychotics, and other dopamine antagonists. Patients should be monitored for the emergence of signs and symptoms of SS or NMS . Serotonin Syndrome symptoms include mental status changes (e.g., agitation,

hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, uncoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea). If this occurs, treatment with vortioxetine should be discontinued immediately and symptomatic treatment should be initiated.

Mania/hypomania

Vortioxetine should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase.

Haemorrhage

Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events, such as gastrointestinal or gynaecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effect, including vortioxetine. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA)] and in patients with known bleeding tendencies/disorders. Moreover, SSRIs/SNRIs may increase the risk of postpartum haemorrhage .

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of antidepressants with serotonergic effect (SSRIs, SNRIs). Caution should be exercised in patients at risk, such as the elderly, patients with cirrhosis of the liver or patients concomitantly treated with medicinal products known to cause hyponatraemia.

Discontinuation of vortioxetine should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted.

Elderly

Data on the use of Vorasan in elderly patients with major depressive episodes are limited. Therefore, caution should be exercised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine once .

Renal or hepatic impairment

Given that subjects with renal or hepatic impairment are vulnerable and given that the data on the use of Vorasan in these subpopulations are limited, caution should be exercised when treating these patients.

- **Contraindications:**

Hypersensitivity to the active substance or to any of the excipients .

Concomitant use with nonselective monoamine oxidase inhibitors (MAOIs) or selective MAO-A inhibitors.

- **Pregnancy and lactation:**

Pregnancy

There are limited data from the use of vortioxetine in pregnant women. Studies in animals have shown reproductive toxicity. The following symptoms may occur in the newborn after maternal use of a serotonergic medicinal product in the later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In the majority of instances, such complications began immediately or soon (<24 hours) after delivery. Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN with vortioxetine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth . Vorasan should only be administered to pregnant women if the expected benefits outweigh the potential risk to the foetus.

Breast-feeding

Available data in animals have shown excretion of vortioxetine/ vortioxetine metabolites in milk. It is expected that vortioxetine will be excreted into human milk . A risk to the breastfeeding child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Vorasan treatment taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

(This card focuses on major safety information for medicinal products in order to minimize possible side effects that arise from improper use of medicinal products).

Pharmacovigilance Department

CONTACT DETAILS OF THE QPPV:

Phone: (962)/ (6) 5233349/113

email: raghad@sana-pharma.com.

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