PACKAGE LEAFLET: INFORMATION FOR THE USER

Orotral® 1mg/ml, oral solution
Risperidone

1. IDENTIFICATION OF THE MEDICINAL PRODUCT

1.1. Trade name

OROTRAL®

1.2. Composition

Active substance: Risperidone
Excipients: Tartaric acid, Benzoic acid, Sodium hydroxide, Purified water.

1.3. Pharmaceutical form

Oral solution.

1.4. Quantitative composition

Each ml of oral solution contains 1mg risperidone.

1.5. Nature and contents of the container

Oral solution 1mg/ml: Bottle of 100ml or 150ml and a pipet with ml indications

1.6. Pharmacotherapeutic category

Antipsychotic.

1.7. Marketing Authorization Holder

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1.8. Manufacturer

RAFARM AEBE.

2. WHAT SHOULD THE PATIENT KNOW ABOUT THIS MEDICINE

2.1. General information

Orotral® is an antipsychotic medicine that belongs to a new group of antipsychotic drugs derivatives of benzisoxazole.

2.2. Indications

Orotral® is indicated in the treatment of schizophrenia.

Orotral® is indicated in the treatment of manic episodes of moderate or severe severity in bipolar disorder.

Orotral® is indicated for the short term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer dementia, which do not correspond to non-pharmacological approaches and when there is a risk to harm to the patient or to others.

Orotral® is indicated for the short term treatment (up to 6 weeks) of persistent aggression in behavioral disorders in children aged 5 years and older and in adolescents with lower mental function or mental retardation diagnosed according to the DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviors require pharmacological treatment. Pharmacological therapy should be an integral part of a more general therapeutic program, including psychosocial and educational intervention. It is recommended that risperidone should be prescribed by a doctor specialized in child and adolescent neurology and psychiatryor by doctors who are experienced in the treatment of codnduct disorders in children and adolescents.

2.3. Contraindications
Hypersensitivity to the active substance or any of the excipients of the product.

2.4. Special warnings and precautions for use

2.4.1. General:
- During long-term treatment, **Orotral®** may cause involuntary movements on the face. If this happens, you should consult your doctor immediately.
- Very rarely may occur a situation of confusion, decreased level of consciousness, high fever or muscle stiffness. If this happens, immediately contact your doctor and tell him that you took **Orotral®**.
- If you experience decrease in your blood pressure, tell your doctor. He may reduce the dose of the medicine.
- Appropriate clinical monitoring is recommended in diabetic patients or in patients with risk factors for developing diabetes mellitus.
- Increase in body weight: Try to reduce your food intake as **Orotral®** can increase body weight.
- Cardiovascular diseases, Parkinson's disease, Lewy body dementia or epilepsy: If you have any of the mentioned conditions, tell your doctor. You may need medical attention while you take the medicine and the dosage may need to be adjusted appropriately (see section 2.6)
- Elderly people with impaired renal of hepatic function.

Always tell your doctor if you suffer from any of the above mentioned conditions (see section 2.6).

2.4.2. Elderly
Studies in elderly dementia patients have shown that administration alone or in combination with furosemide may be associated with increased mortality.
Tell your doctor if you are taking furosemide. Furosemide is a drug used for the treatment of high blood pressure or for the treatment of edema created in parts of the body due to the accumulation of fluid. Elderly patients and their caregivers should immediately report any symptoms such as a sudden change in mental status, sudden weakness or numbness in the face, hands or feet and disorders of speech or vision. These symptoms may indicate a possible stroke or a 'transient decrease in blood flow to the brain' (transient ischemic attack). If this happens, the doctor will re-evaluate the treatment and may need to stop using risperidone.
Elderly people should take less **Orotral®** than they would receive an adult (see section 2.6).

2.4.3. Pregnancy
If you are pregnant or planning to get pregnant, you should tell your doctor who will decide if you should take **Orotral®**.

2.4.4. Lactation
You should not breast-feed your baby if you are taking **Orotral®**, consult your doctor in this case.

2.4.5. Children
Orotral® is given to adults, adolescents and children as described in section 2.6.

2.4.6. Effect on the ability to drive and use machines
Orotral® may affect alertness or drivability, so do not drive or operate a machine until your doctor assesses your individual sensitivity to **Orotral®**.

2.5. Interactions with other medicines or substances
As with other antipsychotics, caution is advised when prescribing risperidone to medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g., quinidine, disopyramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressants (e.g., amitriptyline), tetracyclic antidepressants (e.g., maprotiline), certain antihistamines, other antipsychotics, certain antimalarials (eg quinine and mefloquine) and with drugs that cause electrolyte disturbances (hypokalaemia, hypomagnesaemia), bradycardia, or those that inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Possibility of **Orotral®** to affect other medicinal products
Risperidone should be used with caution in combination with other centrally acting substances, including in particular alcohol, opioids, antihistamines and benzodiazepines, due to an increased risk of sedation.
Orotral® may antagonize the action of levodopa and other dopamine agonists. If this combination is deemed necessary, especially in the final stages of Parkinson's disease, the lowest effective dose of each drug should be prescribed.
Post-marketing has been reported, clinically significant hypotension has been observed with concomitant use of risperidone and antihypertensive treatment.

Orotral® has no clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

Possibility other medicinal products to affect **Orotral®**
Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e. g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/ P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of **Orotral®**.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of **Orotral®**.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

2.6. Posology

Schizophrenia:

- Adults

Orotral® may be administered once or twice a day.

Patients should start with 2mg of **Orotral®** daily. The dose may be increased on the second day to 4 mg. Then, if necessary, the dosage may remain unchanged or further personalized. Most patients will benefit from daily doses between 4 and 6 mg. In some patients a slower titration phase and a lower initiation and maintenance dose may be appropriate.

Doses greater than 10mg per day have not shown better efficacy than lower doses and may cause an increase in the incidence of extrapyramidal symptoms. Safety of doses above 16 mg/ day has not been evaluated, and are therefore not recommended.

- Elderly

A starting dose of 0.5 mg twice a day is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

- Paediatric population

The use of risperidone in children under 18 years of age with schizophrenia is not recommended due to a lack of data on efficacy.

Manic episodes in bipolar disorder

- Adults

Orotral® should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient' s level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.

As with all symptomatic treatments, the continued use of **Orotral®** must be evaluated and justified on an ongoing basis.

- Elderly

A starting dose of 0.5 mg twice a day is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.

- Paediatric population

The use of risperidone in children under 18 years of age with bipolar mania is not recommended due to a lack of data on efficacy.

Persistent aggression in patients with moderate to severe Alzheimer' s dementia

A starting dose of 0.25 mg twice a day is recommended. This dosage can be individually adjusted by increments of 0.25 mg twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Orotral® should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.

Conduct disorders

- Children and adolescents aged 5 to 18 years

For subjects ≥ 50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit

from 0.5 mg once daily while others may need 1.5 mg once a day. For individuals <50kg, a starting dose of 0.25 mg once a day is recommended. This dosage can be individually adjusted by increments of 0.25 mg once daily not more frequently than every other day, if needed. The optimal dose for most patients is 0.5 mg once daily. Some patients, however, may benefit from 0.25 mg once a day, while others may take 0.75 mg once a day.

As with all symptomatic treatments, the continued use of **Orotral®** must be evaluated and justified on an ongoing basis.

Orotral® is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

Renal and liver dysfunction
Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Orotral® should be used with caution in these patient groups.

Method of administration

Orotral® is for oral use. Food intake does not affect the absorption of **Orotral®**.

Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines (see section 4.8). Recurrence of psychotic symptoms may aslo occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) have been reported.
Switch from other antipsychotics:
When medically appropriate, gradual discontinuation of the previous treatment while **Orotral®** therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipshychotics, initiate **Orotral®** in place of the next scheduled injection. The need to continue existing anti-Parkinson drugs should be re-evaluated periodically.

Orotral® oral solution instructions of use
Oral solution:
Opening the bottle and using the pipette.
Picture 1: Press the plastic cap down while rotating it counter clockwise.

- Remove the cap that is unscrewed.

Picture 2: Place the pipette into the bottle.

- While holding the lower ring of the pipette, pull the top ring to the point corresponding to the desired quantity in ml.

Picture 3: Holding the lower ring, remove the whole pipette from the bottle.

- Empty the pipe4tte in a non-alcoholic beverage, except for tea and cola drink by pressing the top ring down and drinking immediately. Close the bottle. Rinse the pipette with some water.

2.7. Overdose – Management:
Symptoms:
In general the reported signs and symptoms are due to the increase in the known pharmacological effects of risperidone. In overdose, prolongation of QT interval and convulsions have been reported.

Ventricular tachycardia – Torsade de pointes have been reported in combined overdose of **Orotral®** and paroxetine.

In the event of an acute overdose, the likelihood of multi-drug use should be considered.

Treatment:
It should be established and maintained a clear airway and ensure adequate oxygenation and ventilation. Gastric lavage should be considered (after intubation, if the patient is unconscious) and administration of activated charcoal with laxatives should be considered only if the drug was taken less than an hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote for **Orotral®**. Therefore, appropriate supportive measures should be implemented. Hypotension and circulatory collapse should be addressed by appropriate measures, such as intravenous fluids and/or sympathomimetic agents. In the event of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and control should continue until the patient recovers.
Poison Center Athens, Tel.: +30 210 77 93 777.

2.8. Possible side effects:
In general **Orotral®** is well tolerated and the side effects are difficult to differentiate from the disease symptoms.

- The most common side effects that may occur are: insomnia, agitation, anxiety and headache. Less common: listlessness, fatigue, poor concentration, blurred vision, dizziness, indigestion, nausea, vomiting, abdominal pain, δυσκολία στην κένωση, irregular sexual potency, mild urinary incompetence, nasal blockade, angioedema, skin rush. Sedation, usually moderate and for short duration occur more in children than in adults. Although these symptoms are generally not harmful, if you feel uncomfortable, talk to your doctor.
- In some cases, blood pressure may be slightly decreased in the initial stages of treatment, which may lead to dizziness. This usually subsides automatically. At later stages of the treatment increased blood pressure may occur, but this is very rare.
- A mild increase in body weight may be observed (see section 2.4.) during treatment and minor mobility abnormalities such as tremor, mild muscle stiffness and restlessness may occur. These later symptoms are not dangerous and will disappear when the doctor reduce the dose of **Orotral®** or administer an additional drug.
- In elderly patients with dementia have been reported side effects of the cerebral vessels (e.g. stroke, transient ischemic attacks) (see section 2.4.2. Elderly).
- Although it is rare and harmless, swelling in the ankles (ankle joint) may occur.
- In very rare cases increased blood sugar was reported. See your doctor if you have any symptoms such as increased thirst or increased urination.
- Hypersensitivity to **Orotral®** is rare. This may happen with a skin rush, itching, shorten of breathing, swollen face. If any of these symptoms appear to you should see your doctor.
- In very rare cases, confusion, low levels of consciousness, high fever or muscle stiffness may occur. If this happens to you, consult your doctor. Possibly you are not responding to **Orotral®** treatment.
- In very rare cases and as a result of several conditions combined, such as extreme heat or cold, significant changes in body temperature may occur. If this happens to you, you should contact your doctor immediately.
- During long term treatment, involuntary movements of the tongue face and mouth may occur. If this happens to you, contact your doctor immediately.
- In long term treatment, some people may have breast increase, breast discharge or disorders in the menstruation cycle. These signs are harmless.

It should be emphasized that the majority of the patients will not experience the problems mentioned above. However, do not hesitate to report any possible side effect to your doctor or pharmacist.

2.9. What should the patient know if forgets to take one dose

Initial period of treatment:
Take the missed dose as soon as possible to the time of next dose. Then continue taking your doses as instructed as described in section 2.6.

Other treatment periods:
Do not take the missed dose but take the next one as usual and continue your treatment normally.

2.10. What should the patient know about the expiration date

It is mentioned in inner and outer packaging.
Do not use this medicine after this date.

2.11. Special warnings about the storage of the product

Oral solution should not be kept at temperature above 30°C.
Protect from freezing. Keep out of reach of children.

2.12. Date of last revision of this leaflet

03/2016

3. INFORMATION FOR THE RATIONAL USE OF MEDICINES

- This pharmaceutical product was prescribed by your doctor to you, according to your medical history and condition. Do not pass the product to others or use it in any other condition even if the symptoms may appear the same and without receiving your doctor's or pharmacist's advice.
- If during treatment with this medicine you experience any problem or issue, contact immediately your doctor or pharmacist.
- If you have any questions regarding the information for this product, its use or about the medical condition that you suffer, you should ask your doctor or pharmacist.
- This product will be safe and effective if it is used exactly according to instructions provided.
- For your own safety it is highly recommended that you read carefully all information provided for the prescribed medicine.
- Do not store medicines in bathroom lockers, as the high temperature and the humidity may degrade the product which may be harmful to your health.
- Store the product in the original packaging.
- If your doctor instructed you to stop the use of this product, dispose the remaining product and do not use it.
- Do not keep the medicine you do not need any more or those that are expired.
- Keep all medicines in safe place out of reach and sight of children.

4. PRESCRIBING INFORMATION

This medicine is subjected to medicinal prescription.