AtRest 12.5 25 Tablets

1. Composition

Tetrabenazine 12.5/25 mg

2. Dosage form and strength

AtRest tablets are available in blister pack of 10 Tablets.

3. Clinical particulars

3.1 Therapeutic indication

AtRest is indicated for the treatment of chorea associated with Huntington's disease.

3.2 Posology and method of administration

As directed by physician.

3.3 Contraindication

AtRest tablets are contraindicated in patients with:

- Active suicidal or who have depression which is untreated or undertreated
- Hepatic impairment
- Patient taking monoamine oxidase inhibitors (MAOIs) or reserpine.

3.4 Special warnings and precautions for use

- Periodically re-evaluate the benefit and potential for adverse effects such as worsening
- mood, cognition, rigidity, and functional capacity
- Do not exceed 50 mg/day and the maximum single dose should not exceed 25 mg if
- administered in conjunction with a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine)
- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs
- Restlessness, agitation, akathisia and parkinsonism: Reduce dose or discontinue if occurs
- Dysphagia and aspiration pneumonia: Monitor for dysphagia
- Sedation/Somnolence: May impair patient's ability to drive or operate complex machinery

- QTc prolongation: Not recommended in combination with other drugs that prolong QTc
- Exaggerates extrapyramidal disorders when used with drugs that reduce or antagonize dopamine. Discontinue ATREST if this occurs

3.5 Drug interactions

- Strong CYP2D6 Inhibitors

A reduction in ATREST dose may be necessary.

- Reserpine

Prescribers should wait for chorea to re-emerge before administering AtRest to avoid overdosage. At least 20 days should elapse after stopping reserpine before starting AtRest. ATREST and reserpine should not be used concomitantly.

- Monoamine Oxidase Inhibitors (MAOIs)

AtRest is contraindicated in patients taking MAOIs. AtRest should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.

- Alcohol

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

- Drugs that Cause QTc Prolongation

AtRest causes a small prolongation of QTc (about 8 msec), concomitant use with other drugs that are known to cause QTc prolongation should be avoided. AtRest should be avoided in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmias.

- Neuroleptic Drugs

The risk for Parkinsonism, NMS, and akathisia may be increased by concomitant use of AtRest and dopamine antagonists or antipsychotics.

3.6 Use in special population

- Paediatric: The safety and efficacy of AtRest in paediatric patients have not been established.
- Geriatric: The pharmacokinetics of AtRest and its primary metabolites have not been formally studied in geriatric subjects.
- Liver impairment: Because the safety and efficacy of the increased exposure to AtRest and other circulating metabolites are unknown, it is not possible to

adjust the dosage of AtRest in hepatic impairment to ensure safe use. The use of AtRest in patients with hepatic impairment is contraindicated.

- Renal failure: The effect of renal insufficiency on the pharmacokinetics of Tetrabenazine and its primary metabolites has not been studied.
- Pregnancy and lactation: There are no adequate and well-controlled studies in pregnant women. AtRest should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

3.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to AtRest is known.

3.8 Undesirable effects

- Most common adverse reactions:

Sedation and somnolence, fatigue, insomnia, depression, akathisia, anxiety and nausea.

- Other adverse reactions:

Hyperprolactinemia, dysphagia, QTc prolongation, hypotension and orthostatic hypotension and Tardive Dyskinesia (TD).

3.9 Overdose

Adverse reactions associated with AtRest overdose include acute dystonia, oculogyric crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, rubor, and tremor. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should be considered.

4. Pharmacological properties

4.1 Mechanism of action

The precise mechanism by which ATREST (Tetrabenazine) exerts its anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. Tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2) (Ki ≈ 100 nM), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Human VMAT2 is also inhibited by dihydrotetrabenazine (HTBZ), a mixture of α-HTBZ and β-HTBZ. α- and β-HTBZ, major circulating metabolites in humans, exhibit high in vitro binding affinity to bovine VMAT2.

Tetrabenazine exhibits weak in vitro binding affinity at the dopamine D2 receptor (Ki= 2100 nM)

4.2 Pharmacodynamics properties

Not available.

4.3 Pharmacokinetic properties

Absorption of tetrabenazine is poor and erratic after oral doses. It appears to be extensively metabolised by first-pass metabolism. Its major metabolite, hydroxytetrabenazine, which is formed by reduction, is reported to be as active as the parent compound. It is excreted in the urine mainly in the form of metabolites.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in cool and dry place. Protect from light. Keep away from children.