AtRest 12.5/25 Tablets

1. **Generic Name**
   Tetrabenazine
2. **Qualitative and Quantitative Composition**

Tetrabenazine	12.5/25 mg

3. **Dosage form and strength**

AtRest tablets are available in blister pack of 10 Tablets.

4. **Clinical particulars**

4.1 Therapeutic indication

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

4.2 Posology and method of administration

As directed by physician.

4.3 Contraindication

AtRest tablets are contraindicated in patients with:

- Hypersensitivity to any ingredient of AtRest
- Active suicidal or who have depression which is untreated or undertreated
- Hepatic impairment
- Patient taking monoamine oxidase inhibitors (MAOIs) or reserpine**.**
- Hypokinetic disorder (Parkinson).

4.4 Special warnings and precautions for use

- **Risk of Depression and Suicidality**

Patients with Huntington's disease are at increased risk for depression and suicidal ideation and behavior (suicidality). Tetrabenazine increases these risks. All patients treated with tetrabenazine should be observed

- **Need for Careful Dosing of AtRest**

Proper dosing of ATREST involves careful titration of therapy to determine an individualized dose for each patient. When first prescribed, ATREST therapy should be

titrated slowly over several weeks to allow the identification of a dose that both reduces chorea and is well tolerated. Some adverse effects such as depression, fatigue, insomnia, sedation/ somnolence, parkinsonism and akathisia may be dose-dependent and may resolve or lessen with dosage adjustment or specific treatment. If the adverse effect does not resolve or decrease, consideration should be given to discontinuing tetrabenazine.

- 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

4.5 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.

4.6 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

4.7 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.

4.8 Undesirable effects

The adverse events are: Myocardial infarction, Dysphagia, Nausea, Vomiting, Death, Drug ineffective, Fatigue, Pneumonia, Weight decreased, Decreased appetite, Musculoskeletal stiffness, Somnolence, Tremor, Depression, Insomnia, Dyspnoea.

4.9 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.

5. Pharmacological properties

5.1 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)

5.2 Pharmacodynamics properties

The central effects of Tetrabenazine closely resemble those of reserpine, but it differs from the latter in having less peripheral activity and being much shorter acting. Animal studies have shown that tetrabenazine disturbs the metabolism of biogenic amines, for instance that of serotonin and noradrenaline, and that this activity is limited to the brain. The supposition is that this effect of tetrabenazine on amines in the brain explains the clinical effects in the brain. Tetrabenazine inhibits the re-uptake of monoamines in the neuroterminal of the presynaptic neurons of the central nervous system. This results in a depletion of monoamines, including dopamine. Dopamine depletion results in hypokinesis leading to a reduction in chorea severity. Tetrabenazine inhibits the re-uptake of monoamines in synaptic nerve terminals by a reversible and short-term binding to the vesicular monoamine transporter (VMAT). VMAT2 transports monoamines especially in peripheral and central neurons, while VMAT1 regulates the transport in peripheral chromaffine tissues. Tetrabenazine has a higher affinity for VMAT2 than for VMAT1. Thus, tetrabenazine has a short, hardly peripheral effect.

6. 5.2 Pharmacokinetic properties

6.1 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.

7. Nonclinical properties

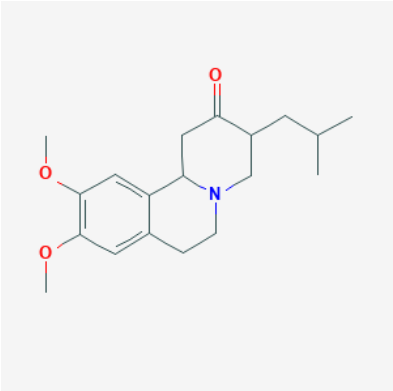
7.1 Animal Toxicology or Pharmacology

Not required.

8. Description

Tetrabenazine (TBZ) is a monoamine storage inhibitor that was first introduced in the 1970s for the management of hyperkinetic movement disorders. Despite acceptance and usage worldwide, TBZ was only recently approved in the United States for the treatment of Huntington chorea. A drug formerly used as an antipsychotic and treatment of various movement disorders. Tetrabenazine blocks neurotransmitter uptake into adrenergic storage vesicles and has been used as a high affinity label for the vesicle transport system.

The vesicular monoamine transporter type 2 (VMAT2) inhibitors are agents that cause a depletion of neuroactive peptides such as dopamine in nerve terminals and are used to treat chorea due to neurodegenerative diseases (such as Huntington chorea) or dyskinesias due to neuroleptic medications (tardive dyskinesia). The VMAT2 inihibitors have not been associated with serum enzyme elevations during therapy or linked to instances of clinically apparent liver injury, but they have had limited general clinical use.



Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

3 years.

8.3 Packaging Information

8.4 Storage and handling instructions

Protect from light. Keep away from children.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patients are advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

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11. Details of permission or license number with date

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