1. Generic Name

Tetrabenazine

2. Qualitative and Quantitative composition

Tetrabenazine 12.5/25 mg

3. Dosage form and strength

AtRest tablets contain 12.5/25 mg of Tetrabenazine.

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

Proper dosing of tetrabenazine involves careful titration of therapy to determine an individualised dose for each patient. When first prescribed, tetrabenazine therapy should be titrated slowly over several weeks to allow the identification of a dose for chronic use that reduces chorea and is well tolerated.

Dosage and administration are variable and only a guide is given.
Starting doses should be 12.5 mg to 25 mg per day and should be titrated up slowly every 4 to 7 days to allow identification of a dose that is efficacious and well tolerated.
After titration is initiated, the total daily dose should be given in two to three divided doses.
Titration can be up to 200 mg per day or dose-limiting adverse events, whichever happens first.
If the adverse event does not resolve, after dose reduction, consideration should be given to withdrawing tetrabenazine treatment.

Discontinuation of Treatment with Tetrabenazine

Discontinuation of tetrabenazine is associated with the return of chorea (without significant worsening compared to baseline).

Other adverse reactions to sudden treatment withdrawal are possible but unlikely and generally mild.

Resumption of Treatment

Following treatment interruption of greater than 5 days or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications, tetrabenazine therapy should be retitrated when resumed. The dose should be initiated at 12.5 mg twice a day, wait 7

days then titrate up by 12.5 mg per day. For short-term treatment interruption of less than 5 days, treatment can be resumed at the previous maintenance dose without titration.

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 closely monitored.

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.

Anger and Aggression

There is a potential risk of anger and aggressive behaviour occurring or worsening in patients taking tetrabenazine with a history of depression or other psychiatric illnesses.

Parkinsonism

Tetrabenazine can induce parkinsonism and exacerbate pre-existing symptoms of Parkinson's disease. The tetrabenazine dose should be adjusted as clinically indicated to minimise this side effect.

Dysphagia

Dysphagia is a component of Huntington's disease. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in patients treated with tetrabenazine and other drugs that reduce dopaminergic

transmission. This may occur soon after initiation of therapy, following changes in dosage or after prolonged treatment.

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

Tetrabenazine may cause drowsiness & therefore may impair ability to drive & use machines.

4.8 Undesirable effects

System/organ categories	**Reactions**					
	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to ≤1/100)	Rare (≥ 1/10,000 to ≤1/1,000)	Very rare (≤1/10,000)	Not Known (cannot be estimated from the available data)
Blood & lymphatic system disorders					Leukopaenia, Neutropenia	
Immune system disorders					Hypersensitivity	
Metabolism and nutrition disorders		Decreased appetite			Dehydration	Increased appetite

Psychiatric disorders	Depression, Anxiety, Restlessness, Confusion	Irritability, Obsessive compulsive disorder, Agitation			Aggression, Anger, Suicidal ideation, Suicide attempt, Nervousness, Sleep disorder	
Nervous system disorders	Sedation/ Somnolence/ Drowsiness, Extrapyramidal event, Insomnia, Akathisia	Parkinsonism (may include balancing problems), Gait imbalance/balance difficulty, Bradykinesia, Dystonia, Lethargy, Dizziness, Dysarthria, Headache			Neuroleptic malignant syndrome, Ataxia, Tremor, Excess salivation	Memory loss
Eye disorders	Blepharospasm				Oculogyric crisis, Photophobia	
Cardiac disorders					Palpitations	
Vascular disorders					Hypertension	Postural hypotension, Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection	Pneumonia, Dyspnoea, Bronchitis			Cough, Pneumonia aspiration	
Gastro-intestinal disorders	Nausea	Diarrhoea, Vomiting, Constipation		Dysphagia	Dry mouth	
Heptaobiliarydisorders						Increased ALT, Increased AST
Skin & subcutaneous tissue disorders					Hyperhidrosis, Rash, Pruritus, Urticaria	
Renal and urinary disorders		Dysuria			Urinary tract infection	
Reproductive system and breast disorders					Irregular menstrual cycle/ amenorrhea/ menstrual disorders	
General disorders and administration site conditions	Fatigue	Ecchymosis			Malaise, Pyrexia, Drug interaction	Weakness
Investigations					Weight decreased	Weight increased
Injury, poisoning and procedural complications	Fall	Laceration, Inflicted injury		Drug administration error	Overdose	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued
monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms associated with overdoses of tetrabenazine may include acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypotension, confusion, hallucinations, hypothermia, sedation, rubor and tremor.

Treatment should consist of those general measures employed in the management of overdosage with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control centre on the treatment of any overdose.

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.

6.1 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, hydroxy tetrabenazine, 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

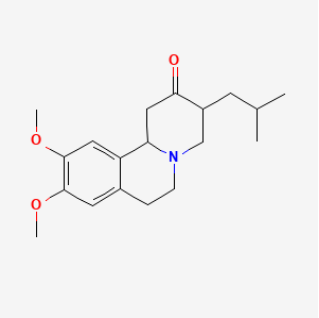
Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

8. Description

Tetrabenazine is a vesicular monoamine transporter 2 (VMAT 2) inhibitor used for the management of chorea associated with Huntington's Disease. VMAT2 inhibitors are agents that cause a depletion of neuroactive peptides such as dopamine in nerve terminals.

The IUPAC chemical name of Tetrabenazine is 9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7,11*b*-hexahydrobenzo[a]quinolizin-2-one. The empirical formula is $C_{19}H_{27}NO_3$ and its molecular weight is approximately 317.4 g/mol.

The chemical structure of Tetrabenazine is as follows:



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

3 years

8.3 Packaging Information

2 X 5 pack of 10 tablets.

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

10. Manufactured by

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11. Details of permission or license number with date

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