ATREST® Tablets

Each Tablet Contains

Tetrabenazine 12.5/25 mg

PHARMACEUTICAL INFORMATION –

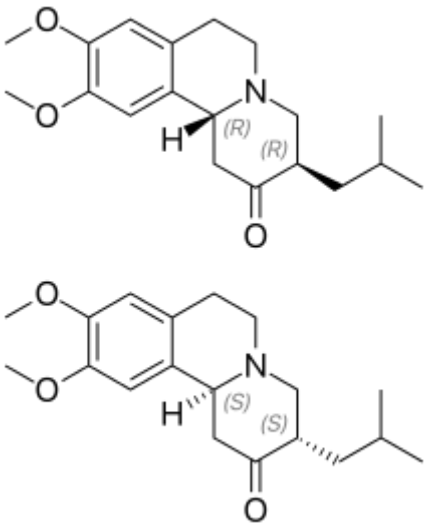
TENTRABENAZINE

Generic name: Tetrabenazine

Chemical name: (*SS*,*RR*)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-pyrido[2,1-*a*]isoquinolin-2-one

Molecular mass: 317.427 g/mol

Structural formula:



Empirical formula – $C_{19}H_{27}NO_3$

Storage and Stability:

Empirical Formula: $C_{19}H_{27}NO_3$

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)

(K_i ≈ 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 (K_i= 2100 nM).

Pharmacokinetics and Pharmacodynamics

Following oral administration of ATREST, the extent of absorption is 75%. Food has no effect on doses (12.5 mg to 50 mg). The protein binding of ATREST is 82 % to 85 %. Peak plasma concentrations (C_{max}) of α-HTBZ and β-HTBZ are reached within 1 to 1½ hours post-dosing. After oral administration, ATREST is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. α-HTBZ, β-HTBZ and 9-desmethyl-β-DHTBZ have half-lives of 7 hours, 5 hours and 12 hours respectively. At 50 mg, ATREST can cause approx. 8 msec mean increase in QTc. ATREST (Tetrabenazine or its metabolites) may bind to melanin-containing tissues. Accumulation in these tissues over time raises the possibility that ATREST may cause toxicity in these tissues after extended use.

Indications

ATREST is a vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington's disease.

Dosage and Administration
General Dosing Considerations
The chronic daily dose of ATREST used to treat chorea associated with Huntington's disease (HD) is determined individually for each patient.
Individualization of Dose
The dose of ATREST should be individualized.

Dosing Recommendations Up to 50 mg per day
The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. ATREST should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If the adverse reaction does not resolve, consideration should be given to withdrawing ATREST treatment or initiating other specific treatment (e.g., antidepressants).

Contraindications

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

Warnings and Precautions

- Periodically reevaluate 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

Adverse 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).

Drug Interactions
Strong CYP2D6 Inhibitors
A reduction in ATREST dose may be necessary.
Reserpine
Prescribers should wait for chorea to reemerge 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.

Use in specific populations

(a) Pregnancy category C: 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 fetus.

(b) Pediatric Use: The safety and efficacy of ATREST in pediatric patients have not been established.

(c) Geriatric Use: The pharmacokinetics of ATREST and its primary metabolites have not been formally studied in geriatric subjects.

(d) Hepatic 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.

(e) Poor or Extensive CYP2D6 Metabolizers: Patients who require doses of ATREST greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of ATREST should then be individualized accordingly to their status as either poor (PMs) or extensive metabolizers.

OVERDOSAGE

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.

SHELF-LIFE -

PACKAGING INFORMATION -