

רופא /ה, רוקח/ת נכבד/ה,  
חברת טבע מודיעה על העדכונים הבאים בעלון לרופא ובעלון לצרכן של התכשיר:

שם התכשיר	מספר רישום
AUSTEDO 6 MG	166.57.36154.00
AUSTEDO 9 MG	166.58.36155.00
AUSTEDO 12 MG	166.59.36156.00

**Contains:**

*Deutetrabenazine 6 mg, 9 mg, 12 mg*

**עדכונים בעלון לרופא**

**התוויה כפי שאושרה בתעודת הרישום:**

AUSTEDO is indicated in adults for the treatment of:

- Chorea associated with Huntington's disease
- Tardive dyskinesia

**ברצוננו להודיע שבפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):**

**עדכונים בעלון לרופא**

**12.3 Pharmacokinetics**

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Distribution

The median volume of distribution (V<sub>c</sub>/F) of the α-HTBZ, and the β-HTBZ metabolites of AUSTEDO are approximately 500 L and 730 L, respectively.

Results of PET-scan studies in humans show that following intravenous injection of <sup>11</sup>C-labeled tetrabenazine or α-HTBZ, radioactivity is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex.

The *in vitro* protein binding of deutetrabenazine and deuterated tetrabenazine α-HTBZ and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine at the concentration of 0.1 μM is 82%, 57%, and 49% respectively, with no preferential binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63% of drug-related total radioactivity to the cellular components of human blood.

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Drug Interaction Studies

Deutetrabenazine, α-HTBZ, and β-HTBZ have not been evaluated in *in vitro* studies for induction or inhibition of CYP enzymes or interaction with P-glycoprotein. The results of *in vitro* studies of tetrabenazine do not suggest that tetrabenazine or its α-HTBZ or β-HTBZ



metabolites are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. *In vitro* studies suggest that neither tetrabenazine nor its  $\alpha$ -HTBZ or  $\beta$ -HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19. Neither tetrabenazine nor its  $\alpha$ -HTBZ or  $\beta$ -HTBZ metabolites are likely to be a substrate or inhibitor of P-glycoprotein at clinically relevant concentrations *in vivo*.

### Effect of Other Drugs on AUSTEDO

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#### Digoxin

AUSTEDO was not evaluated for interaction with digoxin. Digoxin is a substrate for P-glycoprotein. A study in healthy subjects showed that tetrabenazine (25 mg twice daily for 3 days) did not affect the bioavailability of digoxin, suggesting that at this dose, tetrabenazine does not affect P-glycoprotein in the intestinal tract. *In vitro* studies also do not suggest that tetrabenazine or its metabolites are P-glycoprotein inhibitors.

#### Transporters

*In vitro* studies showed that at clinically relevant concentrations, deutetabenazine and its active metabolites are not substrates of P-glycoprotein (P-gp) and BCRP transporters. Deutetabenazine and its active metabolites are unlikely substrates of OATP1B1, OATP1B3, and OCT1.

### Effect of AUSTEDO on Other Drugs

#### CYP Enzymes

*In vitro* studies showed that at clinically relevant concentrations, deutetabenazine, and its active metabolites did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes, and did not induce CYP1A2, CYP2B6, and CYP3A4 enzymes.

#### Transporters

*In vitro* studies demonstrated that at clinically relevant concentrations, deutetabenazine and its active metabolites did not inhibit the following transporters: P-gp, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.

#### Minor Metabolites

The deutetabenazine metabolites, 2-methylpropanoic acid of  $\beta$ -HTBZ (M1) and monohydroxy tetrabenazine (M4), have been evaluated in a panel of *in vitro* drug-drug interaction studies; the results indicate that M1/M4 are not expected to cause clinically relevant drug interactions.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות  
<https://israeldrugs.health.gov.il> וניתן לקבלו מודפס ע"י פניה לחברת טבע.