REMLEAS ™

Valbenazine tosylate

1. NAME OF THE MEDICINAL PRODUCT

REMLEAS™ 40 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: valbenazine)

Each hard capsule contains valbenazine tosylate equivalent to 40 mg valbenazine.

3. PHARMACEUTICAL FORM

Hard capsule for oral use, with a white opaque body and purple cap, printed with 'VBZ' over '40' in black ink on body and cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REMLEAS is indicated for the treatment of adults with neuroleptic-induced tardive dyskinesia.

4.2 Posology and method of administration

Posology
The initial dosage for REMLEAS is 40 mg once daily. After one week, increase the dose to the recommended dosage of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients.
Administer REMLEAS orally with or without food *[see Pharmacokinetic properties (5.2)]*.

Special population
Pediatric Use
Safety and effectiveness of REMLEAS have not been established in pediatric patients.

Geriatric Use
No dose adjustment is required for elderly patients. In 3 randomized, placebo-controlled studies of REMLEAS, 16% were 65 years and older. The safety and effectiveness were similar in patients older than 65 years compared to younger patients.

CYP2D6 Poor Metabolizers
Dosage reduction of REMLEAS is recommended for known CYP2D6 poor metabolizers. The recommended dosage for known CYP2D6 poor metabolizers is REMLEAS 40 mg once daily. Increased exposure (C_{max} and AUC) to valbenazine's active metabolite is anticipated in CYP2D6 poor metabolizers. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions *[see Pharmacokinetic properties (5.2)]*.

Dose adjustments due to interactions
Coadministration with Strong CYP3A4 Inducers
Concomitant use of strong CYP3A4 inducers with REMLEAS is not recommended *[see Interactions with other medicinal products and other forms of interaction (4.5)]*.

Coadministration with Strong CYP3A4 Inhibitors
The recommended dosage for patients receiving strong CYP3A4 inhibitors is REMLEAS 40 mg once daily *[see Interactions with other medicinal products and other forms of interaction (4.5)]*.
Coadministration with Strong CYP2D6 Inhibitors
The recommended dosage for patients receiving strong CYP2D6 inhibitors is REMLEAS 40 mg once daily *[see Interactions with other medicinal products and other forms of interaction (4.5)]*.

Hepatic Impairment
The recommended dosage for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15) is REMLEAS 40 mg once daily. Patients with moderate to severe hepatic impairment had higher exposure of valbenazine and its active metabolite than patients with normal hepatic function *[see Pharmacokinetic properties (5.2)]*.

Renal Impairment
Dosage adjustment is not necessary for patients with mild, moderate, or severe renal impairment. REMLEAS does not undergo primary renal clearance *[see Pharmacokinetic properties (5.2)]*.

4.3 Contraindications

REMLEAS is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of REMLEAS. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported. *[see Undesirable effects (4.8.2)]*.

4.4 Special warnings and precautions for use

Somnolence
REMLEAS can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by REMLEAS *[see Undesirable effects (4.8)]*.

QT Prolongation
REMLEAS may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, REMLEAS concentrations may be higher and QT prolongation clinically significant *[see Pharmacodynamic properties (5.1)]*. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of REMLEAS to 40 mg once daily *[see Posology and method of administration (4.2)]*. REMLEAS should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Parkinsonism
REMLEAS may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with REMLEAS and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of REMLEAS. Associated symptoms have included falls, gait disturbances, tremor, drooling and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of REMLEAS therapy. Reduce the dose or discontinue REMLEAS treatment in patients who develop clinically significant parkinson-like signs or symptoms.

4.5 Interaction with other medicinal products and other forms of interactions

Drugs Having Clinically Important Interactions with REMLEAS

Table 1: Clinically Significant Drug Interactions with REMLEAS

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Implication:	Concomitant use of REMLEAS with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of REMLEAS.
Prevention or Management:	Avoid concomitant use of REMLEAS with MAOIs.
Examples:	isocarboxazid, phenelzine, selegiline
Strong CYP3A4 Inhibitors	
Clinical Implication:	Concomitant use of REMLEAS with strong CYP3A4 inhibitors increased the exposure (C_{max} and AUC) to valbenazine and its active metabolite compared with the use of REMLEAS alone *[see Pharmacokinetic properties (5.2)]*. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions *[see Special warnings and precautions for use (4.4)]*.
Prevention or Management:	Reduce REMLEAS dose when REMLEAS is coadministered with a strong CYP3A4 inhibitor *[see Posology and method of administration (4.2)]*.
Examples:	itraconazole, ketoconazole, clarithromycin
Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of REMLEAS with strong CYP2D6 inhibitors increased the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of REMLEAS alone *[see Pharmacokinetic properties (5.2)]*. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions *[see Special warnings and precautions for use (4.4)]*.
Prevention or Management:	Reduce REMLEAS dose when REMLEAS is coadministered with a strong CYP2D6 inhibitor *[see Posology and method of administration (4.2)]*.
Examples:	paroxetine, fluoxetine, quinidine
Strong CYP3A4 Inducers	
Clinical Implication:	Concomitant use of REMLEAS with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of REMLEAS alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy *[see Pharmacokinetic properties (5.2)]*.
Prevention or Management:	Concomitant use of strong CYP3A4 inducers with REMLEAS is not recommended *[see Posology and method of administration (4.2)]*.
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort[1]
Digoxin	
Clinical Implication:	Concomitant use of REMLEAS with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp) *[see Pharmacokinetic properties (5.2)]*.
Prevention or Management:	Digoxin concentrations should be monitored when co-administering REMLEAS with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.

[1] The induction potency of St. John's wort may vary widely based on preparation.

Drugs Having No Clinically Important Interactions with REMLEAS

Dosage adjustment for REMLEAS is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 based on *in vitro* study

results.

4.6 Pregnancy and lactation

Pregnancy

The limited available data on REMLEAS use in pregnant women are insufficient to inform a drug-associated risk. In animal reproductive studies, no malformations were observed when valbenazine was administered orally to rats and rabbits during the period of organogenesis at doses up to 1.8 or 24 times, respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on mg/m^2 body surface area. However, administration of valbenazine to pregnant rats during organogenesis through lactation produced an increase in the number of stillborn pups and postnatal pup mortalities at doses <1 times the MRHD based on mg/m^2 *[see Animal Data]*. Advise a pregnant woman of the potential risk to a fetus.

Animal Data

Valbenazine was administered orally to pregnant rats during the period of organogenesis at 1, 5, and 15 mg/kg/day, which are approximately 0.1, 0.6, and 2 times the MRHD of 80 mg/day based on mg/m^2 body surface area. Valbenazine produced a significant decrease in maternal body weight gain at 0.6 and 2 times the MRHD of 80 mg/day based on mg/m^2. No adverse embryo fetal effects were produced when valbenazine was administered at doses up to 2 times the MRHD of 80 mg/day based on mg/m^2.

Valbenazine was administered orally to pregnant rabbits during the period of organogenesis at 20, 50, and 100 mg/kg/day, which are approximately 5, 12, and 24 times the MRHD of 80 mg/day based on mg/m^2. No m.alformations were observed at doses up to 24 times the MRHD of 80 mg/day based on mg/m^2. However, valbenazine produced a delay in fetal development (decreased fetal weights and delayed ossification) at 24 times the MRHD of 80 mg/day based on mg/m^2, likely secondary to maternal toxicity (decreased food intake and loss in body weight).

Valbenazine was administered orally to pregnant rats during the period of organogenesis through lactation (day 7 of gestation through day 20 postpartum) at 1, 3, and 10 mg/kg/day, which are approximately 0.1, 0.4, and 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine produced an increase in the incidence of stillbirths and postnatal pup mortality at 0.4 and 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine did not affect neurobehavioral function including learning and memory and had no effect on sexual maturation at doses <1 times the MRHD of 80 mg/day based on mg/m^2 (because of death in the majority of the high dose group (1.2 times the MRHD), these parameters were not assessed in this group).

Lactation

There is no information regarding the presence of valbenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Valbenazine and its metabolites have been detected in rat milk at concentrations higher than in plasma following oral administration of valbenazine at doses 0.1 to 1.2 times the MRHD based on mg/m^2. Based on animal findings of increased perinatal mortality in exposed foetuses and pups, advise a woman not to breastfeed during treatment with REMLEAS and for 5 days after the final dose.

4.7 Effects on ability to drive and use machines

REMLEAS may impair patient's ability to drive or operate hazardous machinery *[see Special warnings and precautions for use (4.4)]*.

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in other sections of the labelling

- Hypersensitivity *[see Contraindications (4.3)]*
- Somnolence *[see Special warnings and precautions for use (4.4)]*
- QT Prolongation *[see Special warnings and precautions for use (4.4)]*
- Parkinsonism *[see Special warnings and precautions for use (4.4)]*

4.8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Variable and Fixed Dose Placebo-Controlled Trial Experience

In 3 randomized, placebo-controlled studies REMLEAS was administered once daily for up to 6 weeks at doses ranging from 25 mg to 100 mg (N=254) compared to placebo (N=178). In the controlled trial setting, the REMLEAS study population was approximately 59% male, 59% White and 37% Black or African American, and the mean age was 56 years at study entry. The study population was diagnosed with schizophrenia or schizoaffective disorder (72%) or mood disorder (28%). At study initiation, 83% of patients were taking concomitant antipsychotic medication; 64% of patients specified concomitant atypical antipsychotic use and 19% of patients specified concomitant use of typical or both typical and atypical antipsychotics.

Common Adverse Reactions (incidence ≥5% and at least twice the rate of placebo): somnolence.

Adverse Reactions Leading to Discontinuation of Treatment: During the 6-week placebo- controlled studies, 4% (10/254) of REMLEAS-treated patients (doses ranging from 25 mg to 100 mg) and 5% (8/178) of placebo treated patients discontinued because of adverse reactions.
No single adverse reaction leading to discontinuation occurred at a rate of ≥2% and at least twice the rate of placebo in REMLEAS-treated patients.

Adverse reactions of interest that occurred in the 3 placebo-controlled studies are presented in Table 2.

Table 2: Adverse Reactions of Interest in 3 Placebo-Controlled Studies of 6-week Treatment Duration

Adverse Reaction	**REMLEAS (n=262) (%)**	**Placebo (n=183) (%)**
Nervous System Disorders		
Somnolence	5.3%	2.2%
Headache	3.8%	2.2%
Akathisia	2.3%	0.5%
Sedation	1.1%	0.5%
Dizziness	0.8%	2.2%
Balance disorder	0.4%	0.0%
Disturbance in attention	0.4%	0.0%
Injury, Poisoning and Procedural Complications		
Fall	1.5%	0.0%
General Disorders		
Fatigue	3.8%	1.6%
Gait disturbance	1.1%	0.0%
Gastrointestinal Disorders		
Dry mouth	3.4%	1.6%
Vomiting	2.7%	0.5%
Nausea	1.9%	2.2%
Constipation	1.1%	2.7%
Musculoskeletal Disorders		
Arthralgia	2.3%	0.5%
Psychiatric Disorders		

Restlessness	0.4%	0.0%
Eye Disorders		
Vision blurred	0.4%	0.0%
Renal and Urinary Disorders		
Urinary retention	0.0%	0.5%

Other Adverse Reactions Observed During the Premarketing Evaluation of REMLEAS
Other adverse reactions of ≥1% incidence and greater than placebo are shown below.
The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.
General Disorders: weight increased
Infectious Disorders: respiratory infections
Neurologic Disorders: drooling, dyskinesia, extrapyramidal symptoms (non-akathisia) including dystonia, extrapyramidal disorder, muscle rigidity, tremor, muscle spasms, and cogwheel rigidity
Psychiatric Disorders: anxiety, insomnia
During controlled trials, there was a dose-related increase in prolactin.

4.8.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of REMLEAS that are not included in other sections of labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Immune System Disorders: hypersensitivity reactions (including allergic dermatitis, angioedema, pruritis, and urticaria)
Skin and Subcutaneous Tissue Disorders: rash

4.9 Overdose

The pre-marketing clinical trials involving REMLEAS in approximately 850 subjects do not provide information regarding symptoms with overdose.
No specific antidotes for REMLEAS are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX13

5.1.1 Mechanism of action
The mechanism of action of valbenazine in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of VMAT2, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

5.1.2 Pharmacodynamics
Valbenazine inhibits human VMAT2 (Ki ~ 150 nM) with no appreciable binding affinity for VMAT1 (Ki > 10 μM). Valbenazine is converted to the active metabolite [+]-α-dihydrotetrabenazine ([+]-α-HTBZ). [+]-α-HTBZ also binds with relatively high affinity to human VMAT2 (Ki ~ 3 nM).
Valbenazine and [+]-α- HTBZ have no appreciable binding affinity (Ki > 5000 nM) for dopaminergic (including D2), serotonergic (including 5HT2B), adrenergic, histaminergic or muscarinic receptors.

Cardiac Electrophysiology
REMLEAS may cause an increase in the corrected QT interval in patients who are CYP2D6 poor

metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from the healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. *[see Special warnings and precautions for use (4.4)]*.

5.1.3 Efficacy/Clinical studies

A randomized, double-blind, placebo-controlled trial of REMLEAS was conducted in patients with moderate to severe tardive dyskinesia as determined by clinical observation. Patients had underlying schizophrenia, schizoaffective disorder, or a mood disorder. Individuals at significant risk for suicidal or violent behavior and individuals with unstable psychiatric symptoms were excluded.

The Abnormal Involuntary Movement Scale (AIMS) was the primary efficacy measure for the assessment of tardive dyskinesia severity. The AIMS is a 12-item scale; items 1 to 7 assess the severity of involuntary movements across body regions and these items were used in this study. Each of the 7 items was scored on a 0 to 4 scale, rated as: 0=no dyskinesia; 1=low amplitude, present during some but not most of the exam; 2=low amplitude and present during most of the exam (or moderate amplitude and present during some of the exam); 3=moderate amplitude and present during most of exam; or 4=maximal amplitude and present during most of exam. The AIMS dyskinesia total score (sum of items 1 to 7) could thus range from 0 to 28, with a decrease in score indicating improvement. The AIMS was scored by central raters who interpreted the videos blinded to subject identification, treatment assignment, and visit number.

The primary efficacy endpoint was the mean change from baseline in the AIMS dyskinesia total score at the end of Week 6. The change from baseline for two fixed doses of REMLEAS (40 mg or 80 mg) was compared to placebo. At the end of Week 6, subjects initially assigned to placebo were re-randomized to receive REMLEAS 40 mg or 80 mg. Subjects originally randomized to REMLEAS continued REMLEAS at their randomized dose. Follow-up was continued through Week 48 on the assigned drug, followed by a 4-week period off-drug (subjects were not blind to withdrawal).

A total of 234 subjects were enrolled, with 29 (12%) discontinuing prior to completion of the placebo-controlled period. Mean age was 56 (range 26 to 84). Patients were 54% male and 46% female. Patients were 57% Caucasian, 38% African-American, and 5% other. Concurrent diagnoses included schizophrenia/schizoaffective disorder (66%) and mood disorder (34%). With respect to concurrent antipsychotic use, 70% of subjects were receiving atypical antipsychotics, 14% were receiving typical or combination antipsychotics, and 16% were not receiving antipsychotics.

Results are presented in Table 3, with the distribution of responses shown in Figure 1. The change from baseline in the AIMS total dyskinesia score in the 80 mg REMLEAS group was statistically significantly different from the change in the placebo group. Subgroup analyses by gender, age, racial subgroup, underlying psychiatric diagnostic category, and concomitant antipsychotic medication did not suggest any clear evidence of differential responsiveness.

The mean changes in the AIMS dyskinesia total score by visit are shown in Figure 2. Among subjects remaining in the study at the end of the 48-week treatment (N=123 [52.6%]), following discontinuation of REMLEAS, the mean AIMS dyskinesia total score appeared to return toward baseline (there was no formal hypothesis testing for the change following discontinuation).

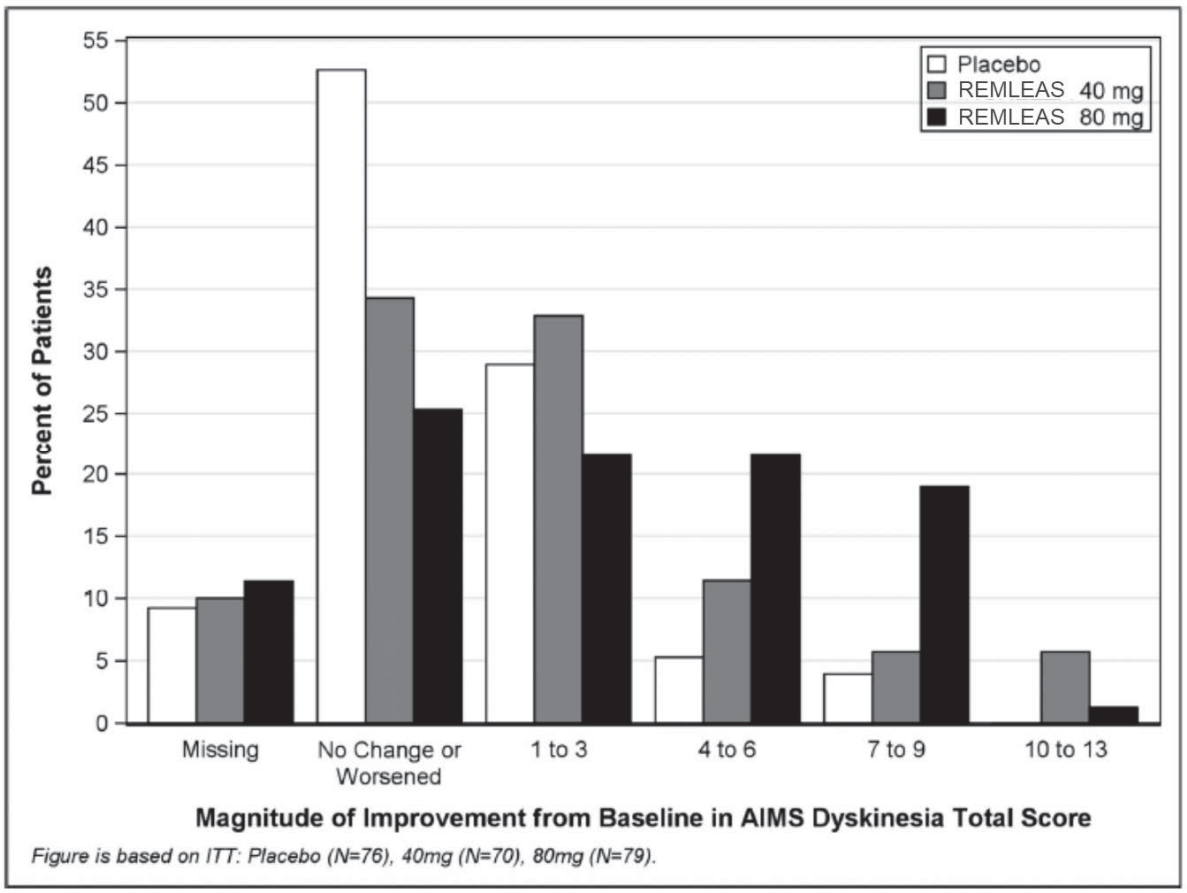
Table 3: Primary Efficacy Endpoint – Severity of Tardive Dyskinesia at Baseline and the End of Week 6

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SEM)**	Placebo-subtracted Difference (95% CI)
AIMS Dyskinesia Total Score	REMLEAS 40 mg	9.8 (4.1)	-1.9 (0.4)	-1.8 (-3.0, -0.7)
	REMLEAS 80 mg*	10.4 (3.6)	-3.2 (0.4)	-3.1 (-4.2, -2.0)
	Placebo	9.9 (4.3)	-0.1 (0.4)	

LS Mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean; CI=2-sided 95% confidence interval

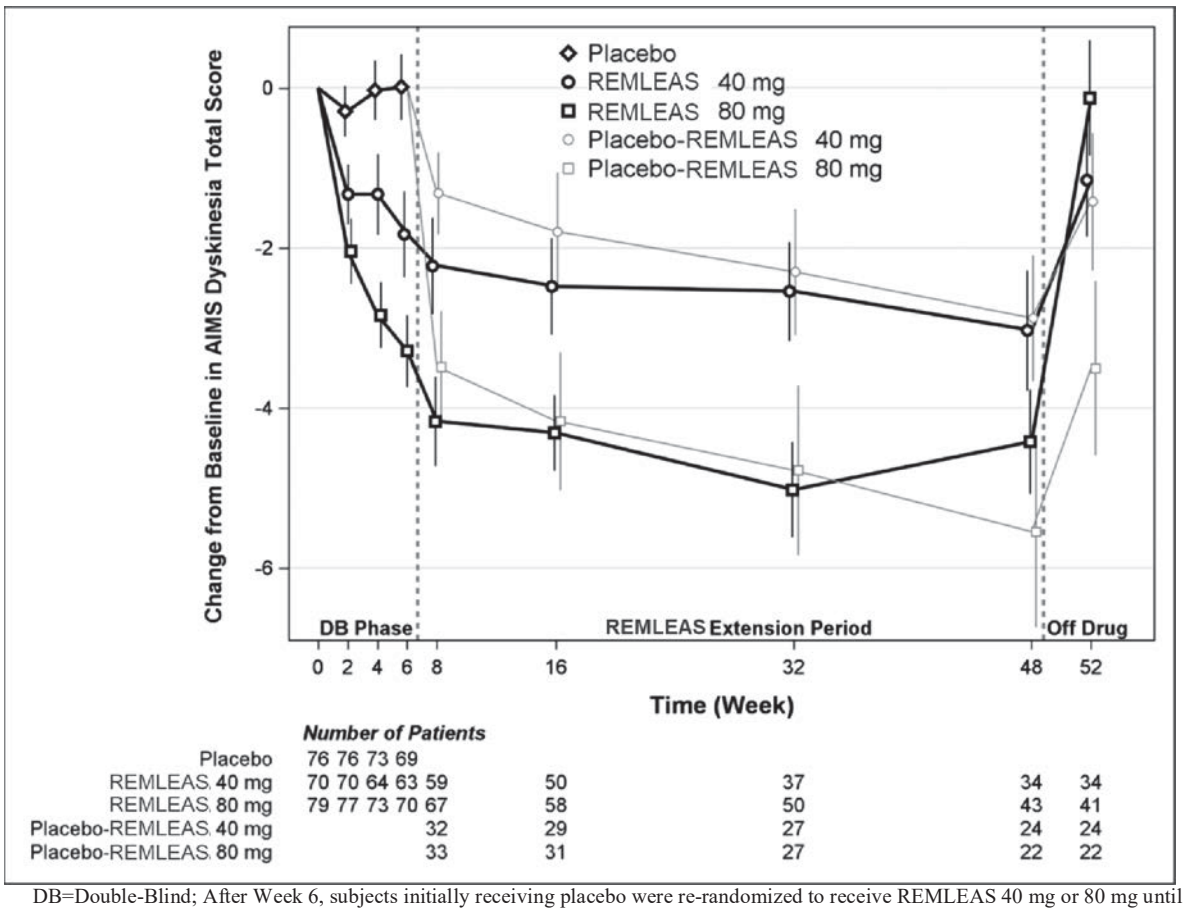
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.

**A negative change from baseline indicates improvement.



ITT=Intent to Treat; This analysis set includes all randomized patients who had a baseline and at least one post-baseline AIMS dyskinesia total score value reported.

Figure 1: Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at the End of Week 6



DB=Double-Blind; After Week 6, subjects initially receiving placebo were re-randomized to receive REMLEAS 40 mg or 80 mg until the end of Week 48. Error bars represent ±1 Standard Error of the Mean (SEM).

Figure 2: AIMS Dyskinesia Total Score Mean Change from Baseline – Entire Study Duration (Arithmetic Mean)

5.2 Pharmacokinetic properties

Valbenazine and its active metabolite ([+]-α-HTBZ) demonstrate approximate proportional increases for the area under the plasma concentration versus time curve (AUC) and maximum plasma concentration (C_{max}) after single oral doses from 40 mg to 300 mg (i.e., 50% to 375% of the recommended treatment dose).

Absorption

Following oral administration, the time to reach maximum valbenazine plasma concentration (t_{max}) ranges from 0.5 to 1.0 hours. Valbenazine reaches steady state plasma concentrations within 1 week. The absolute oral bioavailability of valbenazine is approximately 49%. [+]-α-HTBZ gradually forms and reaches C_{max} 4 to 8 hours after administration of REMLEAS.

Ingestion of a high-fat meal decreases valbenazine C_{max} by approximately 47% and AUC by approximately 13%. [+]-α-HTBZ C_{max} and AUC are unaffected.

Distribution

The plasma protein binding of valbenazine and [+]-α-HTBZ are greater than 99% and approximately 64%, respectively. The mean steady state volume of distribution of valbenazine is 92 L.

Nonclinical data in Long-Evans rats show that valbenazine can bind to melanin-containing structures of the eye such as the uveal tract. The relevance of this observation to clinical use of REMLEAS is unknown.

Elimination

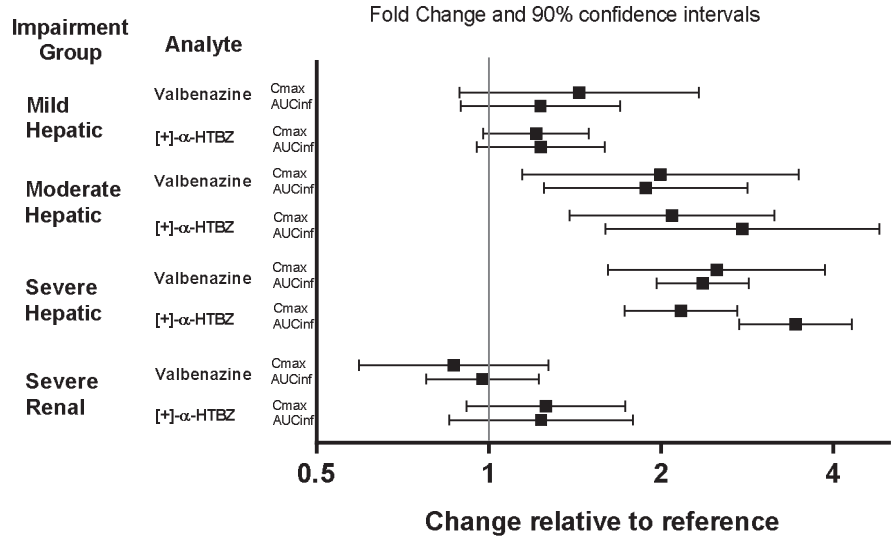
Valbenazine has a mean total plasma systemic clearance value of 7.2 L/hr. Valbenazine and [+]-α-

HTBZ have half-lives of 15 to 22 hours.

Metabolism
Valbenazine is extensively metabolized after oral administration by hydrolysis of the valine ester to form the active metabolite ([+]-α-HTBZ) and by oxidative metabolism, primarily by CYP3A4/5, to form mono-oxidized valbenazine and other minor metabolites. [+]-α-HTBZ appears to be further metabolized in part by CYP2D6.
The results of *in vitro* studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5, or induce CYP1A2, CYP2B6 or CYP3A4/5 at clinically relevant concentrations.
The results of *in vitro* studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit the transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at clinically relevant concentrations.

Excretion
Following the administration of a single 50-mg oral dose of radiolabeled C-valbenazine (i.e., ~63% of the recommended treatment dose), approximately 60% and 30% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 2% was excreted as unchanged valbenazine or [+]-α-HTBZ in either urine or feces.

Specific Populations
Exposures of valbenazine in patients with hepatic and severe renal impairment are summarized in Figure 3.

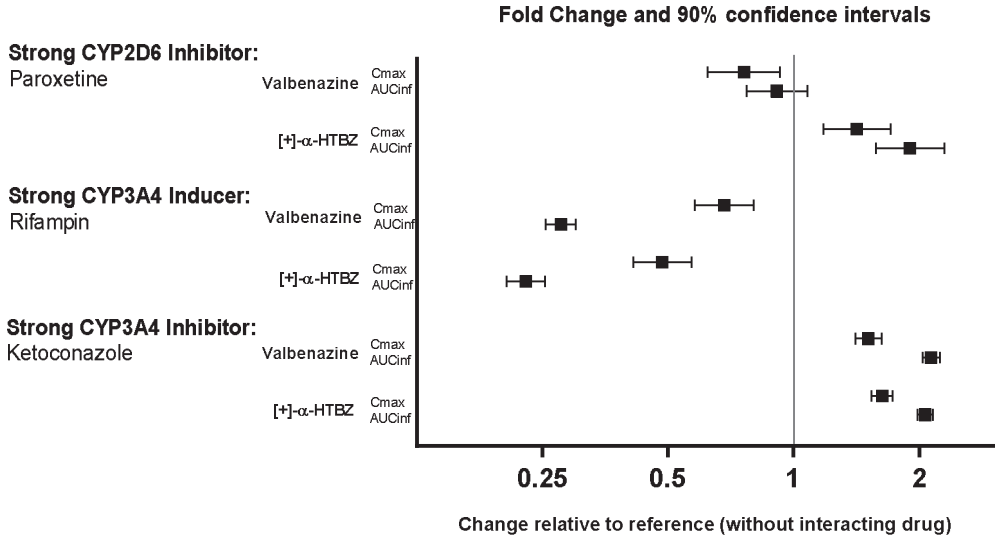


AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity
[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

Figure 3: Effects of Hepatic and Severe Renal Impairment on Valbenazine Pharmacokinetics

After administration of valbenazine 50 mg, subjects with mild hepatic impairment had little or no effect on C_{max} of valbenazine or NBI-98782 (Metabolite formed from hydrolysis of valbenazine). Administration in subjects with hepatic impairment resulted in valbenazine and NBI-98782 C_{max} and $AUC_{0-\infty}$ of approximately 2- to 3-fold greater in subjects with moderate and severe hepatic impairment than in subjects with normal hepatic function.
Administration of valbenazine 40 mg to subjects with severe renal impairment had little or no effect on C_{max} or $AUC_{0-\infty}$ of valbenazine or NBI-98782 compared to subjects with normal renal function.

Drug Interaction Studies
The effects of paroxetine, ketoconazole and rifampin on the exposure of valbenazine are summarized in Figure 4.



AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity
[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

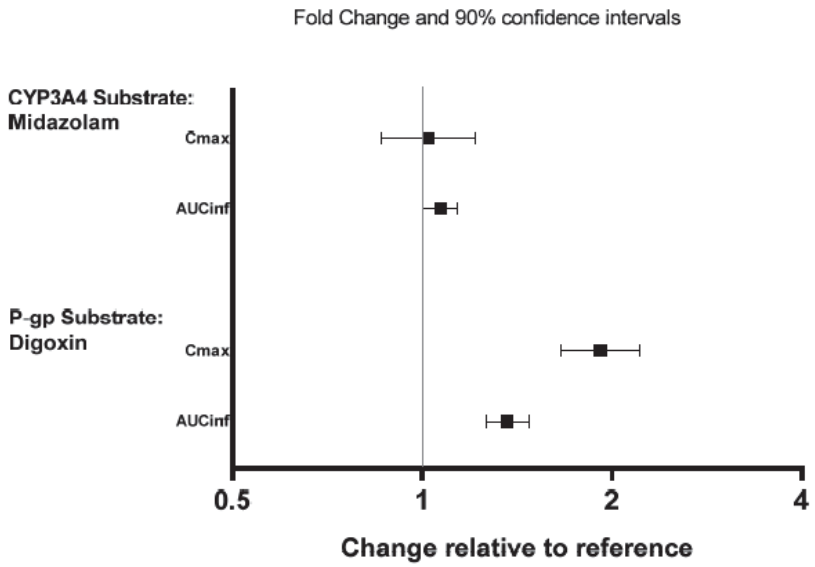
Figure 4: Effects of Strong CYP2D6 and CYP3A4 Inhibitors and CYP3A4 Inducers on Valbenazine Pharmacokinetics

Coadministration with rifampin (strong CYP3A4/5 inducer)
Coadministration of valbenazine and rifampin led to an approximate 30% decrease in C_{max} and an approximate 70% decrease in $AUC_{0-\infty}$ of valbenazine compared with administration of valbenazine alone. Concomitant administration of valbenazine and rifampin also led to an approximate 50% decrease in C_{max} and an approximate 80% decrease in $AUC_{0-\infty}$ of the active metabolite NBI-98782 compared with administration of valbenazine alone.

Coadministration with ketoconazole (strong CYP3A4/5 inhibitor)
Coadministration of valbenazine and ketoconazole led to a C_{max} and $AUC_{0-\infty}$ of valbenazine 1.5-fold and 2.1-fold, respectively, compared with administration of valbenazine alone. Administration of valbenazine plus ketoconazole also led to a C_{max} and $AUC_{0-\infty}$ of the active metabolite NBI-98782 1.6-fold and 2.1-fold, compared with administration of valbenazine alone.

Coadministration with paroxetine (strong CYP2D6 inhibitor)
Coadministration of valbenazine and paroxetine led to a 24% and 9% reduction in C_{max} and $AUC_{0-\infty}$, respectively, of valbenazine compared with administration of valbenazine alone. Coadministration of valbenazine and paroxetine led to a C_{max} and $AUC_{0-\infty}$ of the active metabolite NBI-98782 of 1.4-fold and 1.9-fold, respectively, compared with administration of valbenazine alone.

The effects of valbenazine on the exposure of other coadministered drugs are summarized in Figure 5.



AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity

Figure 5: Effects of Valbenazine on Pharmacokinetics of Other Drugs

Coadministration with digoxin (sensitive P-gp substrate)
Coadministration of valbenazine 80 mg and 0.5 mg digoxin resulted in an approximate 1.9-fold increase in the C_{max} of digoxin. The effect of valbenazine on digoxin $AUC_{0-\infty}$ was modest (1.4-fold increase) and the mean $t_{½}$ of digoxin was similar with and without valbenazine administration.

Coadministration with midazolam (CYP3A4 substrate)
Midazolam C_{max} and $AUC_{0-\infty}$ were similar with and without valbenazine administration. Median midazolam t_{max} was the same (0.50 hours) with and without valbenazine administration. The mean $t_{½}$ of midazolam was similar with and without valbenazine administration (4.7 and 4.5 hours, respectively).

5.3 Preclinical safety data

Carcinogenesis
Valbenazine did not increase tumors in rats treated orally for 91 weeks at 0.5, 1, and 2 mg/kg/day. These doses are <1 times (0.06, 0.1, and 0.24 times, respectively) the MRHD of 80 mg/day based on mg/m^2.
Valbenazine did not increase tumors in hemizygous Tg.rasH2 mice treated orally for 26 weeks at 10, 30 and 75 mg/kg/day, which are 0.6, 1.9 and 4.6 times the MRHD of 80 mg/day based on mg/m^2.

Mutagenesis
Valbenazine was not mutagenic in the *in vitro* bacterial reverse mutation test (Ames) or clastogenic in the *in vitro* mammalian chromosomal aberrations assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility
In a fertility study, rats were treated orally with valbenazine at 1, 3, and 10 mg/kg/day prior to mating and through mating, for a minimum of 10 weeks (males) or through Day 7 of gestation (females). These doses are 0.1, 0.4, and 1.2 times the MRHD of 80 mg/day based on mg/m^2, respectively. Valbenazine delayed mating in both sexes, which led to lower number of pregnancies and disrupted estrous cyclicity at the high dose, 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine had no effects on sperm parameters (motility, count, density) or on uterine parameters (corpora lutea, number of implants, viable implants, pre-implantation loss, early resorptions and post-implantation loss) at any dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, magnesium stearate, mannitol, and pregelatinized starch.
The capsule shells contain candurin silver fine, FD&C Blue#1, FD&C Red#40, and gelatin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

One filled, capped and sealed HDPE bottle contains 30 hard capsules and a desiccant canister. Bottle is packed in carton box.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder:

Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

Under license from:
Neurocrine Biosciences Inc.
San Diego, California, United States

Manufactured by:
Patheon France S.A.S,
Bourgoin Jallieu, France

8. Marketing authorization number

9. Date of authorization

10. Date of revision of the text[1]

[1] Apr 14, 2021