Summary Report of Benefit-Risk Assessment

REMLEAS HARD CAPSULES 40MG

NEW DRUG APPLICATION

Active Ingredient(s)	Valbenazine ditosylate 73mg equivalent to valbenazine 40mg
Product Registrant	Mitsubishi Tanabe Pharma Singapore Pte. Ltd.
Product Registration Number	SIN16198P
Application Route	Abridged evaluation
Date of Approval	19 May 2021

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A INTRODUCTION

Remleas is indicated for the treatment of adults with tardive dyskinesia (TD).

The active substance, valbenazine, is a vesicular monoamine transporter 2 (VMAT2) inhibitor that inhibits the transporter protein VMAT2 which mediates presynaptic dopamine release and regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. This leads to a selective, reversible decrease in dopamine release at presynaptic nerve terminals.

Remleas is available as hard capsules containing 40mg of valbenazine. Other ingredients in the capsule include mannitol, pregelatinized maize starch, colloidal silicon dioxide and magnesium stearate. The components of the hard capsule shell include candurin silver fine, gelatin, FD&C Blue #1 and FD&C Red #40, and those of the printing ink comprise black iron oxide, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, valbenazine, is manufactured at Fabbrica Italiana Sintetici S.p.A., Vicenza, Italy. The drug product, Remleas hard capsules 40mg, is manufactured at Patheon France S.A.S, Bourgoin Jallieu, France.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented is adequate to support the approved retest period of 36 months when stored at or below 30°C. The drug substance is packed in a translucent low-density polyethylene (LDPE) bag and placed within a black LDPE bag, and subsequently placed in a high density polyethylene (HDPE) container.

Drug product:

The drug substance is mixed with the excipients, and subsequently filled into the gelatin capsules. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines.

Information on the reference standards used for identity, assay and impurities testing was adequately presented.

The stability data presented is adequate to support the approved shelf-life of 48 months when stored at or below 30 ºC. The container closure system is a HDPE bottle containing 30 hard capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of valbenazine in the treatment of TD was based primarily on a pivotal Phase III study, Study 1304. This was a randomised, double-blind, placebo-controlled, parallel, fixed dose study of valbenazine in medically stable patients with schizophrenia or schizoaffective disorder with TD, or mood disorder with TD.

A total of 234 subjects were randomised in a 1:1:1 ratio to receive valbenazine 40mg, 80mg or placebo once daily during a 6-week double-blind period. There were 70 subjects in the 40mg group, 79 in the 80mg group and 76 in the placebo group. Patients randomised to the valbenazine 80mg group received 40mg for the first week and 80mg thereafter. At the end of week 6, patients initially assigned to placebo were re-randomised to receive valbenazine 40mg or 80mg. Patients originally assigned to valbenazine continued the same treatment at their randomised dose. Follow-up was continued through week 48 during a subject and investigator-blinded extension phase, followed by a 4-week treatment-free period.

The primary efficacy endpoint was the mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score (total score ranges from 0 to 28) at week 6. The AIMS was scored by central raters who interpreted the videos blinded to subject identification, treatment assignment and visit number. A 2-3 point reduction from baseline in the AIMS mean score compared to placebo represents a clinically meaningful improvement. The key secondary endpoint was the Clinical Global Impression of TD (CGI-TD).

The majority of patients were male (53.8%), Caucasian (56.4%), with a mean age of 56.1 years (range 26 to 84 years). 65.8% of patients had schizophrenia/schizoaffective disorder and 34.2% had mood disorder. More than 80% were taking antipsychotic medications during the double-blind period. At baseline, the mean (SD) AIMS dyskinesia total scores as assessed by the central AIMS video raters were 9.8 (0.5) and 10.4 (0.4) in the valbenazine 40 mg and 80 mg treatment groups respectively, and 9.9 (0.5) in the placebo group.

The statistical testing employed a fixed-sequence procedure for adjusting multiplicity to control the family-wise error rate for the primary and key secondary endpoints. Each endpoint was performed at the nominal $\alpha=0.05$ level of significance. The first hypothesis was to test if there was a significant difference between valbenazine 80mg and placebo for the AIMS score (primary efficacy endpoint). If a significant result ($p<0.05$) was achieved, the next step was to test to significance of valbenazine 80mg vs placebo for the CGI-TD mean score (key secondary

endpoint). Subsequently, the same endpoints would be evaluated in the same order for valbenazine 40mg vs placebo.

The primary analysis for the mean change from baseline in AIMS score demonstrated a statistically significant improvement for patients in the valbenazine 80mg arm compared to placebo [LS mean change of -3.1(95% CI -4.2, -2.0), p<0.0001]. Statistical significance was not met in the second test for CGI-TD mean score (valbenazine 80mg vs placebo), hence the sequential testing could not proceed for valbenazine 40mg vs placebo for the AIMS score and a statistical significance could not be concluded [LS mean change of -1.8 (95% CI -3.0 -0,7) nominal p value =0.0021]. Nonetheless, numerical improvement vs placebo was observed and the results demonstrate a dose-dependent improvement in the AIMS score between valbenazine 40mg and 80mg.

Although the results for the key secondary endpoint CGI-TD were not statistically significant (p=0.0560 and p=0.0742 for valbenazine 80mg and 40mg respectively), numerical improvement was demonstrated for both valbenazine 40mg and 80mg compared to placebo (-0.3 for both valbenazine 40mg and 80mg vs placebo).

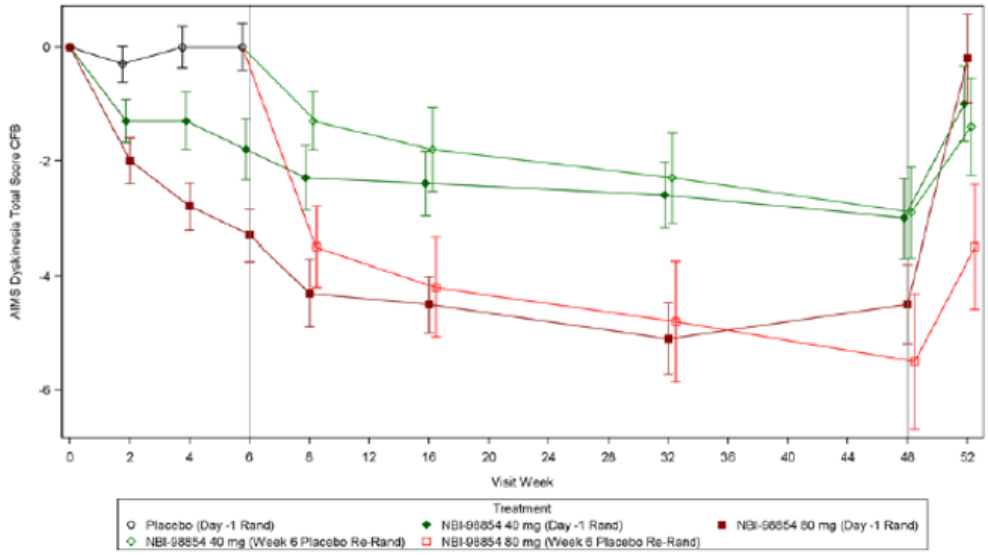
Summary of key efficacy results (Study 1304)

Primary endpoint: Change from baseline in AIMS score (week 6)			
	Placebo (n=76)	Valbenazine 40mg (n=70)	Valbenazine 80mg (n=79)
Mean baseline score (SD)	9.9 (4.3)	9.8 (4.1)	10.4 (3.6)
LS mean change from baseline (SEM)	-0.1 (0.4)	-1.9 (0.4)	-3.2 (0.4)
LS Mean difference (SEM) vs placebo		-1.8 (0.6)	-3.1 (0.6)
95% CI		(-3.0, -0.7)	(-4.2, -2.0)
p value		0.0021*	<0.0001
Key secondary endpoint: CGI-TD mean score (week 6)			
LS mean (SEM)	3.2 (0.1)	2.9 (0.1)	2.9 (0.1)
LS Mean difference (SEM) vs placebo		-0.3 (0.1)	-0.3 (0.1)
95% CI		(-0.5, 0.0)	(-0.5, -0.0)
p value		0.0742	0.0560

*Nominal p value for valbenazine 40mg
LS: Least-squares mean

The long-term efficacy of valbenazine 40mg and 80mg of up to 48 weeks was supported by data from the extension period of Study 1304. At week 48, the mean change from baseline in AIMS score was -3.0 and -4.8 for valbenazine 40mg and 80mg respectively. The improvements in AIMS score were attenuated with a return towards baseline at week 52 after valbenazine treatment was ceased at week 48. This suggests that TD symptoms may recur in patients during the 4-week period following treatment discontinuation. This finding has been included in the Clinical Studies section of the package insert.

AIMS score mean change from baseline by Visit Week



NBI-98854: valbenazine

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of valbenazine was based primarily on safety data pooled from Phase 2/3 controlled studies, comprising 254 patients on valbenazine (doses ranging from 25mg to 100mg) compared with 178 patients on placebo. The mean duration of treatment during the 6-week placebo-controlled period was 39 days (range, 1 to 56 days) for patients who received valbenazine and 40 days for patients who received placebo (range, 1 to 52 days). The long-term safety for up to 48 weeks was based on a total of 427 patients exposed to valbenazine with a mean duration of 172 days (range 1 to 349 days).

Overview of safety profile

AE	Valbenazine 40mg (n=110)	Valbenazine 80mg (n=112)	Placebo (n=178)
At least 1 AE	48 (43.6%)	53 (47.3%)	71 (39.9%)
Treatment-related AE	24 (21.8%)	26 (23.2%)	27 (15.2%)
At least 1 SAE	3 (2.7%)	4 (3.6%)	5 (2.8%)
Treatment-related SAE	0	1 (0.9%)	0
Discontinuations due to AE	4 (3.6%)	5 (4.5%)	8 (4.5%)
Deaths due to AE	0	1 (0.9%)	1 (0.6%)

AE: adverse event; SAE: serious adverse event

The most commonly reported AEs in the pooled Phase 2/3 studies which occurred at an incidence of ≥2% and higher than placebo included somnolence (5.5% valbenazine vs 2.2% placebo), fatigue (3.9% vs 1.7%), headache (3.9% vs 2.2%), dry mouth (3.1% vs 1.7%), akathisia (2.4% vs 0.6%), arthralgia (2.4% vs 0.6%) and vomiting (2.4% vs 0.6%). Most AEs

were mild to moderate in intensity and the safety profile was comparable between the valbenazine 40mg and 80mg doses. The AEs reported during the long-term extension period were consistent with those observed during the 6-week double-blind phase.

The incidences of SAEs in valbenazine and placebo patients were 5% vs 3% during the 6-weeks double-blind phase. A numerically greater incidences of SAEs were reported for the higher 80mg dose group compared to 40mg dose group in Study 1304 (8% vs 6%). There was 1 SAE of acute hepatitis in the valbenazine 80mg arm which was assessed as possibly treatment related. During the long-term extension period, SAEs were reported in 15% of patients in the valbenazine 40mg group and 20% in the 80mg group. The most common SAEs were schizophrenia and suicidal ideation (1% each).

The incidences of AEs leading to discontinuation in the valbenazine and placebo patients were 4% vs 5% during the 6-weeks double-blind phase. During the long-term extension period, the most common AEs leading to discontinuation was suicidal ideation (2%), schizophrenia, fatigue, somnolence, syncope and tremor (<1% each).

There were 3 deaths reported in the valbenazine arm compared to 1 death in the placebo arm in the overall clinical program. The AEs leading to death in the valbenazine arm were 1 case each of sudden death, breast cancer and cardiac failure. All deaths were assessed as to be not related or unlikely related to study treatment.

The AEs of special interest (AESI) included QT prolongation and parkinsonism. These safety concerns have been adequately described as warnings and precautions in the package insert. During the 6-week double blind period, similar incidences of QTcF intervals > 450 msec and QTcF interval increased > 30msec were observed between patients who received valbenazine and placebo patients. In the long-term extension period, 5 valbenazine patients had a QTcF interval >480 msec, and 1 subject had a QTcF interval of >500msec. Slightly higher incidences of QTcF intervals >450 msec (13.9% vs 11.2%) and QTcF interval increases >30 msec (13.9% vs 10.7%) were observed between patients who received valbenazine 80 mg than those who received 40 mg. The package insert includes warnings against the use of valbenzine in patients with congenital long QT syndrome or with arrhythmias associated with prolonged QT interval. Patients at increased risk of prolonged QT interval should also be assessed before any dose increment.

The incidences of Parkinson-like AEs were higher among patients treated with valbenazine (3%) compared to patients on placebo (<1%), and appeared to increase with duration of valbenazine treatment. Dose reduction or discontinuation of valbenazine in patients who develop clinically significant parkinson-like signs or symptoms is recommended.

Overall, valbenazine presented an acceptable safety profile for the intended population given the disease setting. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

TD is a distressing and disabling movement disorder that affects patients with schizophrenia or mood disorders on long-term antipsychotic therapy. Given the limited treatment options available, there is an unmet medical need for patients with TD who are unable to discontinue or reduce their dose of antipsychotic treatment.

The efficacy of valbenazine was demonstrated in pivotal Study 1304 where a clinically meaningful improvement in the AIMS score was achieved by valbenazine 80mg (-3.1) and 40mg (-1.8) compared to placebo during the 6-weeks double-blind period. The efficacy of both doses relative to placebo was maintained up to 48 weeks. While the recommended dose for TD in adults is 80mg following an initial 1-week treatment with 40mg, the lower 40mg dose is recommended as an alternative dose for patients who may not require or unable to tolerate the higher 80 mg dose based on clinical judgement.

The safety profile of valbenazine was considered acceptable relative to the benefits. Most AEs were mild to moderate and generally manageable. Notable safety concerns such as somnolence, QT prolongation and parkinsonism have been addressed in the package insert.

Overall, the benefit-risk profile of valbenazine in the treatment of TD in adults was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Remleas for the treatment of TD in adults was deemed favourable and approval of the product registration was granted on 19 May 2021.

REMLEAS TM

Valbenazine tosylate

Mitsubishi Tanabe Pharma

1. NAME OF THE MEDICINAL PRODUCT

REMLEAS^{TM} hard capsules 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: valbenazine)

Each hard capsule contains valbenazine tosylate corresponding to 40 mg valbenazine.
For the full list of excipients, see section 6.1.

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 a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with 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 interaction

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 malformations 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 unclear, 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).

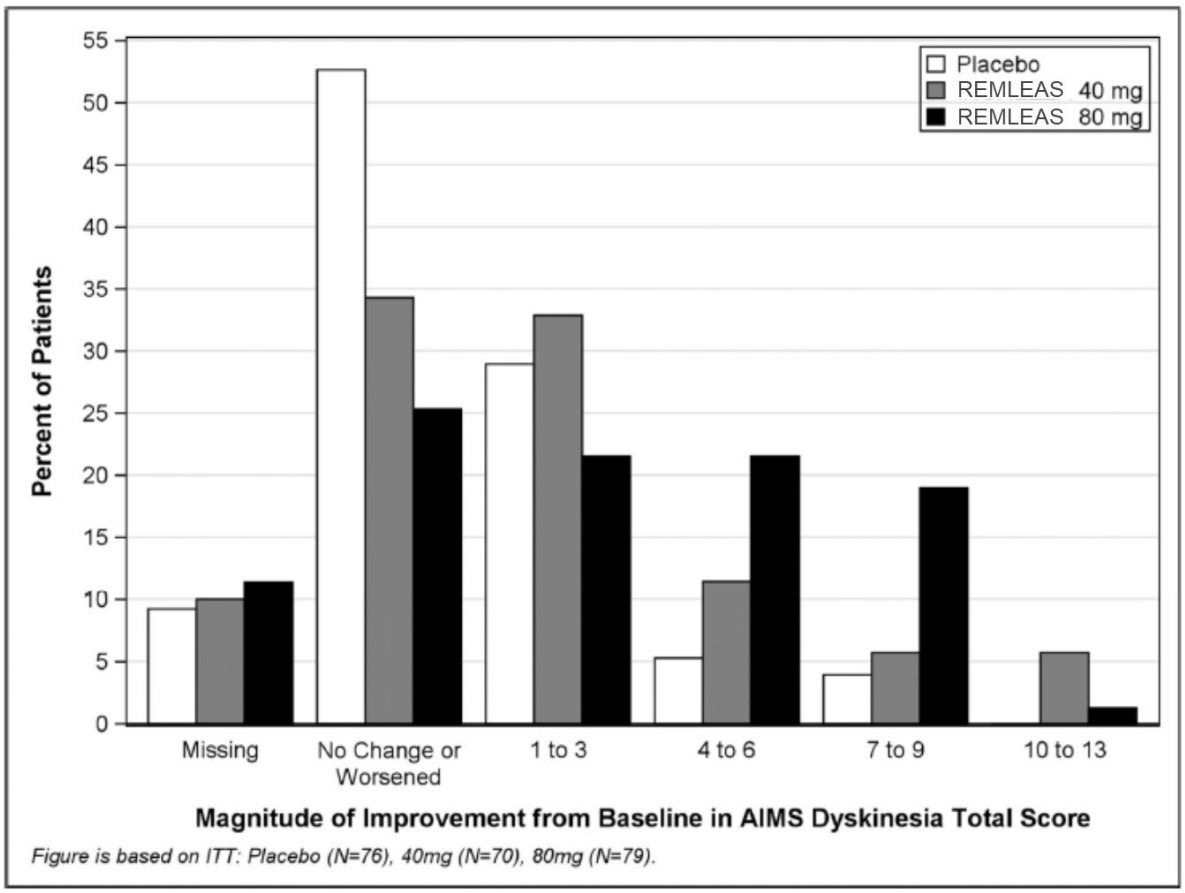
Table 3: Primary Efficacy Endpoint – Severity of Tardive Dyskinesia at Baseline and the End of Week 6

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

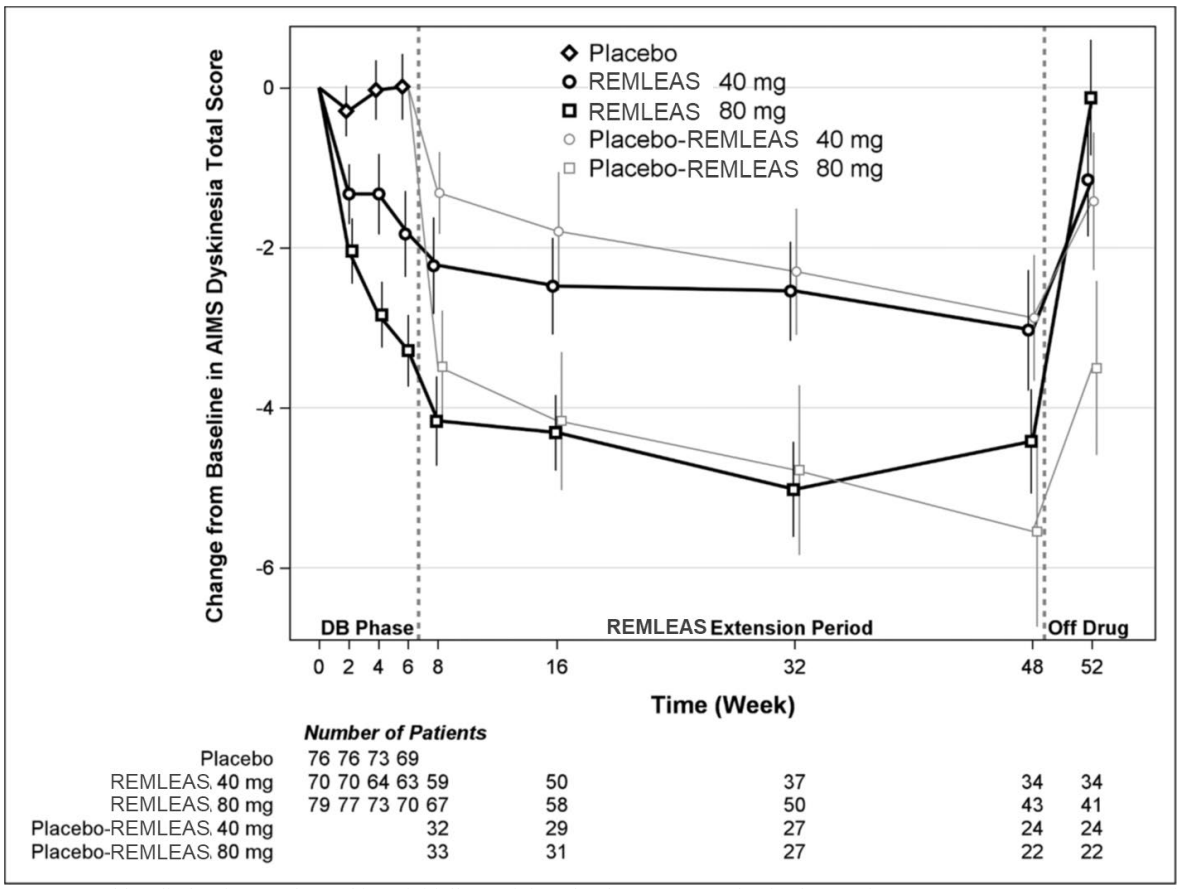
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.

**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.

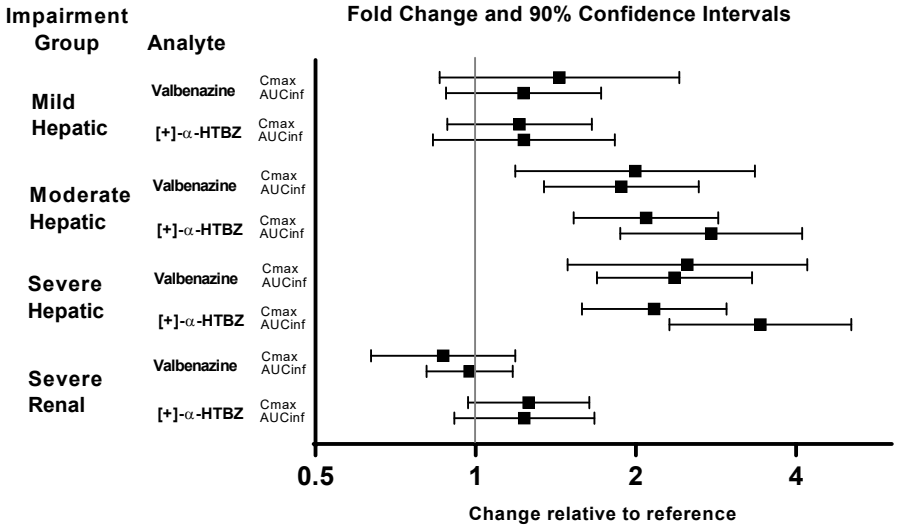
Elimination

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.

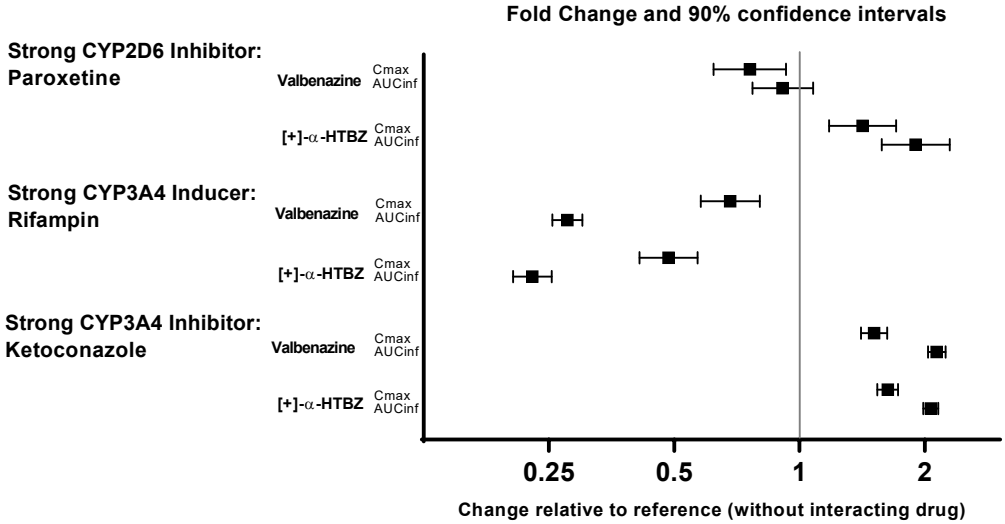


AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity
[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

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)

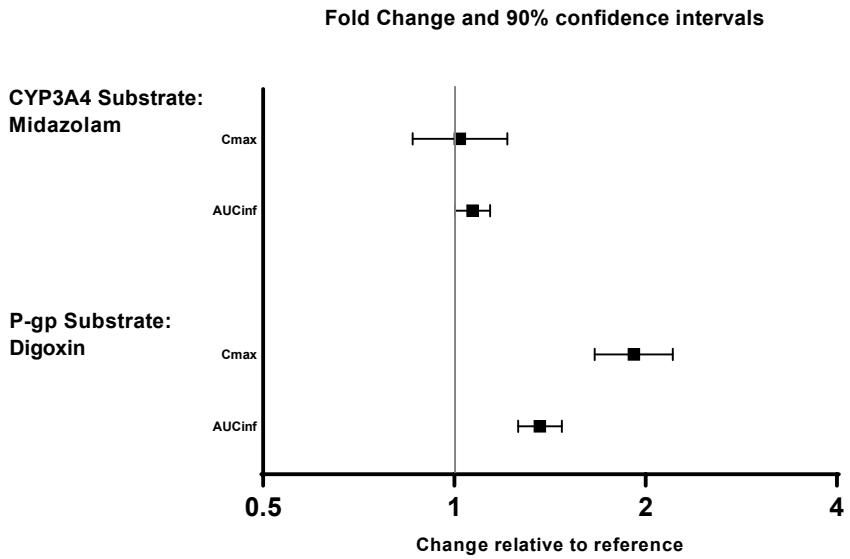
Figure 4: Effects of Strong CYP2D6 and CYP3A4 Inhibitors and CYP3A4 Inducers on Valbenazine Pharmacokinetics

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.
The black printing ink contains black iron oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Nature and contents of container

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

6.5 Special precautions for disposal

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

Product Owner:
Neurocrine Biosciences Inc.
San Diego, California, United States

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

Product Registrant:
Mitsubishi Tanabe Pharma Singapore Pte. Ltd.
Singapore

Date of Package Insert
10 May, 2021 (version 1.0)