EU RISK MANAGEMENT PLAN

Austedo® (deutetrabenazine)

RMP version to be assessed as part of this application	
RMP version number	1.0
Data lock point for this RMP	01 December 2023
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Summary of Significant Changes in This RMP Version	Not applicable.

QPPV Details	
QPPV name:	Iva Novak
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BID	Twice daily
CNS	Central Nervous System
CTD	Common Technical Document
DART	Developmental and Reproductive Toxicity
DDI	Drug-Drug Interaction
DRA	Dopamine Receptor Antagonists
DTBZ	Deutetrabenazine
e.g.	example given
EEA	European Economic Area
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
EMA	European Medicines Agency
EU	European Union
FGA	First Generation Antipsychotic
GLP	Good Laboratory Practice
hERG	Human Ether-à-go-go-Related Gene
HD	Huntington's Disease
HTBZ	α-dihydrotetrabenazine
i.e.	Id est (engl.: that means)
INN	International Non-proprietary Name
MAOI	Monoamine Oxidase Inhibitors
NMS	Neuroleptic Malignant Syndrome
PI	Product Information
PK	Pharmacokinetic
PL	Package Leaflet
PR	Prolonged release
PSUR	Periodic Safety Update Report

QD	Once daily
QPPV	Qualified Person for Pharmacovigilance
RBBB	Right Bundle Branch Block
RMP	Risk Management Plan
SGA	Second Generation Antipsychotic
SMQ	Standardised MedDRA Query
SP	Safety Population (In Clinical Trials)
SPC, SmPC	Summary Of Product Characteristics
TD	Tardive Dyskinesia
VMAT2	Vesicular Monoamine Transporter 2

Part I: Product(s) Overview

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	**Deutetrabenazine**
Pharmacotherapeutic group(s) (ATC Code)	Other nervous system drugs (N07XX16)
Marketing Authorisation Holder/Applicant	TEVA GmbH Graf-Arco-Str.3 89079 Ulm Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Austedo®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Deutetrabenazine (DTBZ) is deuterated hexahydro-dimethoxybenzoquinolizine.
	Summary of mode of action: DTBZ and its major circulating metabolites (deuterated α-dihydrotetrabenazine [HTBZ] and deuterated β-HTBZ) are reversible inhibitors of the vesicular monoamine transporter type 2 (VMAT2), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores in dopaminergic regions (e.g. striatum and cortex) of the brain. While the precise mechanism of action by which DTBZ exerts its effects in the treatment of tardive dyskinesia (TD) is unknown, it is believed to be related to its effect as a depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current**: Treatment of moderate to severe tardive dyskinesia in adults.
	Proposed (if applicable): Not applicable.

Dosage in the EEA	**Current**: Dosing should be determined individually for each patient, based on adequate reduction of tardive dyskinesia symptoms and tolerability. Therapy should be initiated at 12 mg once daily for one week. The dose should then be increased to 24 mg once daily for another week. After the second week, it is recommended that the dose be titrated at weekly intervals in increments of 6 mg once daily, based on reduction of tardive dyskinesia symptoms and tolerability. The efficacious dose range is considered to be 24 mg to 48 mg. The maximum recommended daily dose is 48 mg. In patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolisers, the daily dose should not exceed 36 mg.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: Prolonged-release tablets 12 mg, 24 mg, 30 mg, 36 mg, 42 mg, 48 mg
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication

Deutetrabenazine (DTBZ) is indicated for the treatment of moderate to severe tardive dyskinesia (TD) in adults.

Incidence:

TD is a disabling, potentially irreversible, delayed onset, hyperkinetic movement disorder in which predisposed patients experience abnormal involuntary movements resulting from chronic exposure to dopamine receptor antagonists (DRAs), such as antipsychotics and some anti-emetics (Caroff SN, 2020, Factor SA, 2020).

The risk of treatment-emergent TD with newer-generation antipsychotics is lower than with first-generation antipsychotics (FGA) which is in line with the observed global mean prevalence in adults of 30% for FGA exposure versus 21% for second-generation antipsychotics (SGA) exposure (Carbon et al , 2017). Despite the decreased use of FGA, the incidence of TD remains high in the antipsychotic treated population. The steady rise in patients treated with antipsychotics may contribute to the continued high incidence and impact of TD (Caroff SN, 2020).

Prevalence:

The global mean prevalence of TD in adults is estimated to be 21% in patients taking SGA versus 30% in those exposed to FGA, and 7% in those patients taking SGA that have never had previous treatment with FGA, although the prevalence is probably underestimated (Carbon et al , 2017).

Prevalence of TD in the United States in 2016 was estimated to be 573,000 patients (90% CI: 471,000–674,000, 234 per 100,000 US adults); this translates to 9% of the general antipsychotic user population. It is estimated that patients with severe TD consisted of approximately 32% of the prevalence pool in 2016 (Dhir et al, 2017).

Demographics of the population in the indication and risk factors for the disease:

Risk factors for TD can be divided into two categories: unmodifiable (patient-related and illness-related) and modifiable (comorbidity-related and treatment-related). Patient-related and illness-related risk factors for TD include older age, female sex, African descent, longer duration of severe psychiatric illness, intellectual disability and brain damage, negative symptoms in schizophrenia, mood disorders diagnosis, cognitive dysfunction in mood disorders, and gene polymorphisms involving antipsychotic drugs metabolism and dopamine functioning. Comorbidity-related and treatment-related factors include diabetes, smoking, alcohol and substance abuse, FGA vs SGA treatment, higher cumulative and current antipsychotic dose or

antipsychotic plasma levels, early parkinsonian side effects, anticholinergic co-treatment, akathisia, and emergent dyskinesia (Solmi et al, 2018).

The main existing treatment options:

The therapeutic goal for the treatment of TD is to reduce involuntary movements and improve quality of life. There are several treatment approaches for TD available in the European Union (EU). However, these options have inherent limitations, leaving a high unmet need in this patient population.

Cessation of the DRA, reduction of the DRA to the lowest efficacious dose for controlling the underlying condition, or switching to a different DRA (e.g., from first- to second-generation antipsychotic) is the first-line therapeutic approach in TD (Bhidayasiri et al, 2018). However, these actions do not guarantee resolution of TD and they risk stability of the underlying condition for which the DRA is being used, rendering this approach infeasible for many patients (Bhidayasiri et al, 2013; Factor SA, 2020).

Tiapride hydrochloride, a selective dopamine D2 and D3 receptor antagonist, is an approved treatment for TD in several European countries, although it has an undesirable side effect profile, including parkinsonism and hyperprolactinemia, only transient efficacy, a complicated dosing schedule, and a duration of use that is limited to only a few months (Greil et al, 1985; Pollak et al, 1985; Scatton et al, 2001). In addition, other therapies have been used off-label with varying degrees of success (Cloud et al, 2014, Factor SA, 2020).

Another therapeutic target for the treatment of TD is VMAT2 that mediates re-uptake of dopamine and other monoamines from the cytosol into presynaptic vesicles in the terminals of dopaminergic neurons, such as in the basal ganglia. The basal ganglia of the so-called extrapyramidal motor system are implicated in the regulation of voluntary movements. Dysregulation of dopamine in this system is associated with both hyperkinetic movement disorders, such as TD and chorea associated with Huntington's disease (HD-associated chorea; due to dopamine excess), and hypokinesia, postural changes, and tremor associated with Parkinson's disease (due to the degeneration of dopaminergic neurons). Treatments that inhibit VMAT2 decrease the presynaptic uptake and release of dopamine and other monoamines by vesicles at the synapse of dopaminergic neurons, thereby depleting vesicular and synaptic dopamine levels which, in turn, improves TD symptoms. Tetrabenazine (TBZ) is a reversible VMAT2 inhibitor that is widely approved in the EU for the treatment of HD-associated chorea. TBZ is also approved for the treatment of moderate to severe TD in only a small number of European countries. However, TBZ has poor tolerability and requires frequent dosing, which may impact treatment adherence and persistence. Poor tolerability may also lead to suboptimal efficacy of treatment (Jankovic and Beach, 1997). Additionally, the use of TBZ may be limited by its low-grade evidence for efficacy and tolerability per evidence-based treatment recommendations (Bhidayasiri et al, 2013, Bhidayasiri et al, 2018, American Psychiatric Association , 2021, Sławek et al, 2024).

Considering the limitations described above, there is a substantial unmet need for new efficacious treatment options for TD in the EU that have a favourable safety profile and that do

not compromise the stability or control of the underlying disorder. This need is fuelled by the high prevalence of TD in patients treated with antipsychotics (Carbon et al , 2017), the high disease burden on patients with TD (e.g., reduced quality of life, social stigma, and impact on employment) (Jackson et al, 2021) and the limited number of treatment options, which also have inconsistent availability across the EU, combined with the suboptimal nature of these treatment options.

Natural history of the indicated condition in the population, including mortality and morbidity:

The clinical manifestations of TD include chorea, athetosis, dystonia, akathisia, and stereotyped behaviours generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles). The involuntary movements typically persist beyond 4 to 8 weeks (American Psychiatric Association, 2013).

Symptoms of TD typically have an insidious onset, evolving to a full syndrome over days to weeks following onset. This is followed by a stabilisation of symptoms in a chronic, but sometimes waxing and waning course. TD can persist for years after discontinuation of the offending agent, although some patients can experience partial or complete remission of symptoms a few years after discontinuation of the causative agent (Savitt and Jankovic, 2018). Reported remission rates vary across studies depending on the definition of remission and duration of follow-up, but most studies report remission rates to be lower than 25% (Vinuela and Kang, 2014). The natural history of TD has not been well studied because patients often continue their therapy with DRAs chronically for symptomatic treatment of their underlying psychiatric illness or even to treat their TD, and prospective longitudinal, long-term follow-up is usually lacking (Savitt and Jankovic, 2018).

The symptoms of TD result in a high patient burden, as they are often persistent and disabling. The uncontrollable movements disrupt quality of life and adversely impact emotional, professional, and social well-being (Jackson et al, 2021, Jain et al, 2023).

Important co-morbidities:

Patients with TD have a higher risk of cardio-metabolic comorbidities, including diabetes, hypertension, and obesity, as well as higher odds of concurrent tobacco and drug abuse compared to those without TD. Additionally, patients with TD have higher odds of severe disability due to major loss of function compared to patients without TD (Patel et al, 2019).

Part II: Module SII - Non-Clinical Part of the Safety Specification

The non-clinical programme was comprised of targeted studies of DTBZ, its deuterated metabolites and impurities, often in comparison to TBZ, conducted to characterise the pharmacological action, pharmacokinetics, and toxicity of DTBZ.

Toxicity

The DTBZ toxicology programme was designed to characterise the safety profile of DTBZ, its deuterated metabolites and impurities. Some of the studies included TBZ as a comparator to

establish similarity in the non-clinical safety profile. Rat was selected as the rodent species for the in vivo studies because it has VMAT2 expression similar to humans, rats were the rodent species used in the TBZ non-clinical programme, to which DTBZ was compared, and the metabolic profile of DTBZ and TBZ was shown to be similar in this species. The oral route of administration was employed in all the toxicity studies as this is the route of administration in humans. A twice daily dosing regimen for DTBZ was employed in rats to maintain sufficient exposure relative to humans.

Key issues identified from acute or repeat-dose toxicity studies

DTBZ was compared with TBZ at 2 dose levels (2.5 and 15 mg/kg) in a non-GLP single oral dose toxicokinetic study in rats. Clinically adverse findings were limited to lethargy or hypoactivity in male and female rats in the 15 mg/kg group.

Repeat-dose oral toxicity studies for up to 3 months and juvenile toxicity studies were performed in rats with DTBZ and TBZ. There was no mortality and no DTBZ- or TBZ- related toxicologically significant changes in food consumption, clinical pathology parameters (haematology, clinical chemistry, coagulation time), or gross post-mortem examinations. Clinical observations were noted in a dose-related manner, primarily in males of the DTBZ 10 mg/kg/day, and in males and females of the DTBZ 30 mg/kg/day, and TBZ 30 mg/kg/day groups. After 4 weeks of dosing (interim necropsy) in the 3-month toxicology study deutetrabenazine in rats, observations of oestrus cycle arrest at the pro-oestrus (pre-ovulatory) phase and mammary hyperplasia in females at exposures similar to those expected in patients were likely physiological consequences of reduced central nervous system (CNS) dopamine with attendant disinhibition of prolactin. CNS-related clinical observations, comprised of intermittent tremors, partial eye closure, increased activity, and twitching of ears, that were observed at clinically relevant doses, with subclinical exposure to some major metabolites, were likely associated with perturbations of monoamine neurotransmitters. Male rats from the 3-month study, at DTBZ exposures slightly below clinical exposure levels, showed an adverse effect of decreased body weight gains.

Genotoxicity

Genotoxicity studies included in vitro AMES and chromosome aberration assays with DTBZ and its active metabolites, deuterated α-HTBZ and deuterated β-HTBZ, and in vivo micronucleus assay with DTBZ and TBZ in mice.

No genotoxic potential has been observed both in vitro and in vivo assays.

Developmental and reproductive toxicity (DART)

DART evaluations included an embryo-foetal developmental study with DTBZ and TBZ in rats, and assessment of reproductive performance parameters including fertility and early embryonic development in the 3-month rat toxicity study and juvenile toxicity study with DTBZ and TBZ.

No embryo-foetal toxicities were observed after twice daily administration of DTBZ or TBZ at the highest tested dose (30 mg/kg/day).

No embryo-foetal development studies in a non-rodent species or pre- and post-natal development studies in a rodent species with deutetrabenazine were conducted.

In an embryo-foetal development study with tetrabenazine in rabbits, the no observed effect level was the highest dose tested (60 mg/kg/day).

When tetrabenazine was orally administered to pregnant rats (5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. A no-effect dose for pre- and postnatal developmental toxicity in rats was not identified.

Fertility effects were similar to those reported for TBZ, with the main effects in rats being dose-related disruption of oestrus cyclicity.

Carcinogenicity

Carcinogenicity studies of DTBZ were not conducted. For carcinogenicity potential assessment, a weight of evidence approach was employed using data from binding and functional assays with DTBZ and its metabolites, genotoxicity studies with DTBZ and its metabolites, carcinogenicity studies with TBZ and with a major human metabolite, 9-desmethyl-β-DHTBZ, and from histopathology assessments in DTBZ and TBZ repeated-dose toxicity studies.

Given the lack of any signal in these assessments, it is considered that DTBZ is unlikely to present a carcinogenic risk.

Safety pharmacology

Central nervous system

The potential for DTBZ-related neurological effects was evaluated in a 3-month GLP-compliant toxicology study of DTBZ and TBZ and a GLP-compliant toxicity study in juvenile animals.

The catalepsy effects in the DTBZ 30 mg/kg/day and TBZ 30 mg/kg/day groups were comparable. Catalepsy is a known response to TBZ and other drugs which reduce concentrations of dopamine in the CNS (Fuenmayor and Vogt, 1979). There were no DTBZ-related effects on auditory startle response or learning and memory (Biel maze) assessments at any dosage level.

Cardiovascular

In vitro effects of deuterated α-HTBZ and deuterated β-HTBZ on the human ether-à-go-go-related gene (hERG) potassium channel current were evaluated in voltage-clamped human embryonic kidney cells (HEK-293).

Deuterated α-HTBZ and deuterated β-HTBZ inhibited hERG potassium channel current with IC50 values of 12.9 and 7.8 μM, respectively. These concentrations are approximately 144- and 116-fold higher than the calculated at steady state unbound C_{max} for α-HTBZ and β-HTBZ metabolites, respectively, after DTBZ administration of 22.5 mg twice daily (BID) in humans.

DTBZ may prolong the QT interval, but the degree of QT prolongation is not clinically significant when DTBZ is administered within the recommended dose range.

Photosafety

Both DTBZ and TBZ have been shown to distribute to melanin-containing tissues in rats in pharmacokinetic (PK) studies. Based on published data (Rhee et al, 2011), TBZ does not absorb light within the range of natural sun light 290-700 nm (ICH S10 2012) and is not considered to have a photoreactive potential. Although similar data has not been determined for DTBZ, in general, there should not be any significant isotopic shift in UV-absorbance spectra in the deuterated vs. the non-deuterated compound (TBZ), as electronic properties depend very weakly, if at all, on the relative change in the weight of the isotope atoms. DTBZ drug substance and drug product were tested in forced degradation studies being exposed to UV and visible light and for photostability per 'ICH Q1B Photostability Testing of New Drug Substances and Products' and no major degradants were observed.

Although DTBZ has been shown to distribute to melanin-containing tissues in rats, the absorbance outside the phototoxic range of TBZ, and likely that of DTBZ, demonstrated stability in light degradation and photostability studies. A retrospective analysis of general toxicity final reports to determine the incidence of ocular toxicity after oral dosing of DTBZ, deuterated β-HTBZ, or M1 in adult and/or juvenile rats do not suggest any phototoxic concern for DTBZ.

Pharmacokinetic Drug Interactions

DTBZ, deuterated α-HTBZ and deuterated β-HTBZ were evaluated in a series of drug interaction studies at clinically relevant concentrations, estimated for the maximal therapeutic dose of 48 mg using the exposures of 24 mg DTBZ osmotic prolonged release (PR) tablet once daily (QD), at steady state.

No induction of CYP1A2, CYP2B6 and CYP3A4 enzymes and no inhibition of the tested CYPs in human liver in vitro systems or substrate potential and inhibition of the human transporters at clinically relevant concentrations have been observed. DTBZ and the deuterated α-HTBZ and deuterated β-HTBZ seem not to have any drug-drug interaction (DDI) potential at the highest therapeutic exposures.

Overall conclusion

The non-clinical studies of DTBZ and its active metabolites, deuterated α-HTBZ and deuterated β-HTBZ, produced indistinguishable pharmacology and comparable rodent pharmacokinetics, general toxicity, genotoxicity and embryo-foetal development profiles relative to TBZ and its corresponding non-deuterated metabolites.

Based on non-clinical data, no important risks relevant for human use have been identified for DTBZ.

Part II: Module SIII - Clinical Trial Exposure

The DTBZ clinical safety programme in TD comprises 1 Phase 2/3 efficacy trial (flexible dose), 1 Phase 3 efficacy trial (fixed dose), and 1 long-term safety trial. All trials are completed.

A total of 514 participants with TD were treated with DTBZ or placebo (DTBZ=384; placebo=130) in Phase 3 programme. Demographic characteristics of participants with TD were generally well balanced across the treatment groups. The median age was approximately 58 years (ranging 21 to 81 years of age), and most of the participants were White. Distribution of participants according to the duration of DTBZ exposure in TD Phase 3 programme (Table 2), and DTBZ exposure by fixed and flexible dose group up to 12/15 weeks per sex (Table 3, Table 4) and per age group (Table 5, Table 6, Table 7) are presented below.

Additionally, the safety of DTBZ was evaluated also in 5 Phase 1 bioequivalence and PK trials in healthy adult participants (314 participants); and 1 Phase 3 efficacy trial and 1 Phase 3 long-term safety trial in adult participants with chorea associated with HD (121 participants).

Table 2: Duration of DTBZ exposure in TD Phase 3 programme

	DTBZ exposure						
	Any DTBZ exposure (N)	**≥ 6 weeks N (%)**	**≥ 15 weeks N (%)**	**≥ 28 weeks N (%)**	**≥ 54 weeks N (%)**	**≥ 106 weeks N (%)**	**≥ 158 weeks N (%)**
Total TD participants exposure to DTBZ	384 (100)	355 (92.4)	324 (84.4)	294 (76.6)	256 (66.7)	208 (54.2)	165 (43)
Patient-years of treatment	857.17	-	-	-	-	-	-

Table 3: Short-term DTBZ exposure by fixed dose and flexible dose groups for males

Duration of Exposure	**Variable**	**12 mg (N=31)**	**24 mg (N=32)**	**36 mg (N=31)**	**Titration[1] (N=78)**
< 1 month	n	3	4	2	3
	Patient-time (days)	49	77	22	47
1 to < 2 month	n	1	1	2	4
	Patient-time (days)	57	58	73	180
2 to < 3 months	n	27	27	27	26
	Patient-time (days)	2280	2284	2275	2148
3 to < 4 months	n	0	0	0	45

Duration of Exposure	Variable	12 mg (N=31)	24 mg (N=32)	36 mg (N=31)	Titration[1] (N=78)
	Patient-time (days)	0	0	0	4696
Total	**n**	**31**	**32**	**31**	**78**
	Patient-time (days)	**2386**	**2419**	**2370**	**7071**

[1] 12 mg, 24 mg, 36 mg=participants who received DTBZ in the fixed dose trial; Titration=participants who received DTBZ in the flexible dose trial and participants from the long-term safety trial who received placebo in the fixed dose trial or flexible dose trial.

Table 4: Short-term DTBZ exposure by fixed dose and flexible dose groups for females

Duration of Exposure	Variable	12 mg (N=41)	24 mg (N=40)	36 mg (N=41)	Titration[1] (N=90)
< 1 month	n	2	2	5	2
	Patient-time (days)	27	30	74	31
1 to < 2 month	n	1	2	1	3
	Patient-time (days)	39	83	55	117
2 to < 3 months	n	36	35	35	27
	Patient-time (days)	3016	2952	2944	2260
3 to < 4 months	n	2	1	0	58
	Patient-time (days)	214	90	0	6089
Total	**n**	**41**	**40**	**41**	**90**
	Patient-time (days)	**3296**	**3155**	**3073**	**8497**

[1] 12 mg, 24 mg, 36 mg=participants who received DTBZ in the fixed dose trial; Titration=participants who received DTBZ in the flexible dose trial and participants from the long-term safety trial who received placebo in the fixed dose trial or flexible dose trial.

Table 5: Short-term DTBZ exposure by fixed dose and flexible dose groups for age group: 18 to 64 years

Duration of Exposure	Variable	12 mg (N=55)	24 mg (N=54)	36 mg (N=48)	Titration[1] (N=140)
< 1 month	n	3	4	6	4
	Patient-time (days)	67	73	71	56
1 to < 2 month	n	2	2	3	5
	Patient-time (days)	96	107	128	197
2 to < 3 months	n	49	47	39	44
	Patient-time (days)	4130	3972	3282	3653
3 to < 4 months	n	1	1	0	87

Duration of Exposure	Variable	12 mg (N=55)	24 mg (N=54)	36 mg (N=48)	Titration[1] (N=140)
	Patient-time (days)	110	90	0	9106
Total	**n**	**55**	**54**	**48**	**140**
	Patient-time (days)	**4403**	**4242**	**3481**	**13012**

[1] 12 mg, 24 mg, 36 mg=participants who received DTBZ in the fixed dose trial; Titration=participants who received DTBZ in the flexible dose trial and participants from the long-term safety trial who received placebo in the fixed dose trial or flexible dose trial.

Table 6: Short-term DTBZ exposure by fixed dose and flexible dose groups for age group: 65 to 74 years

Duration of Exposure	Variable	12 mg (N=15)	24 mg (N=16)	36 mg (N=20)	Titration[1] (N=26)
< 1 month	n	2	1	1	1
	Patient-time (days)	9	28	25	22
1 to < 2 month	n	0	1	0	2
	Patient-time (days)	0	34	0	100
2 to < 3 months	n	12	14	19	8
	Patient-time (days)	996	1180	1601	673
3 to < 4 months	n	1	0	0	15
	Patient-time (days)	104	0	0	1574
Total	**n**	**15**	**16**	**20**	**26**
	Patient-time (days)	**1109**	**1242**	**1626**	**2369**

[1] 12 mg, 24 mg, 36 mg=participants who received DTBZ in the fixed dose trial; Titration=participants who received DTBZ in the flexible dose trial and participants from the long-term safety trial who received placebo in the fixed dose trial or flexible dose trial.

Table 7: Short-term DTBZ exposure by fixed dose and flexible dose groups for age group: 75 to 84 years

Duration of Exposure	Variable	12 mg (N=2)	24 mg (N=2)	36 mg (N=4)	Titration[1] (N=2)
< 1 month	n	0	1	0	0
	Patient-time (days)	0	6	0	0
1 to < 2 month	n	0	0	0	0
	Patient-time (days)	0	0	0	0
2 to < 3 months	n	2	1	4	1
	Patient-time (days)	170	84	336	82
3 to < 4 months	n	0	0	0	1

Duration of Exposure	Variable	12 mg (N=2)	24 mg (N=2)	36 mg (N=4)	Titration[1] (N=2)
	Patient-time (days)	0	0	0	105
Total	**n**	**2**	**2**	**4**	**2**
	Patient-time (days)	**170**	**90**	**336**	**187**

[1] 12 mg, 24 mg, 36 mg=participants who received DTBZ in the fixed dose trial; Titration=participants who received DTBZ in the flexible dose trial and participants from the long-term safety trial who received placebo in the fixed dose trial or flexible dose trial.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient received any of the following medications within 30 days of screening or baseline: TBZ (prohibited within 7 days of baseline for Long-term trial), reserpine, α-methyl-p-tyrosine, botulinum toxin (within 3 months of screening in Flexible-dose and Fixed-dose trials and within 3 months of baseline in Long term trial), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden).	These concomitant medications may confound the safety profile evaluation of DTBZ due to potential drug-drug interactions.	No	Concomitant treatment with other VMAT2 inhibitors and reserpine is contraindicated. Concomitant use of medications with strong anticholinergic activity may increase the risk of neuroleptic malignant syndrome (NMS).
Patient received any of the following medications within 30 days of screening or baseline: metoclopramide, promethazine, or prochlorperazine	These concomitant medications may confound the safety profile evaluation of DTBZ due to potential drug-drug interactions.	No	The risk of parkinsonism, NMS, and akathisia may be increased by concomitant use of medicinal products that reduce dopaminergic transmission (e.g. haloperidol, chlorpromazine, metoclopramide, ziprasidone, promazine), therefore caution is recommended.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient received any of the following medications within 30 days of screening or baseline: stimulants (i.e., methylphenidate, amphetamine/ dextroamphetamine, lisdexamphetamine, etc) or monoamine oxidase inhibitors (MAOI)	These concomitant medications may confound the safety profile evaluation of DTBZ due to potential drug-drug interactions.	No	The safety profile in patients taking stimulants is expected to be the same as in the populations studied in the clinical trials. DTBZ must not be used in combination with an MAOI. At least 14 days must elapse after stopping an MAOI before starting DTBZ.
Patient received any of the following medications within 30 days of screening or baseline: levodopa or dopamine agonists	These concomitant medications may confound the efficacy evaluation of DTBZ due to potential drug-drug interactions.	No	Dopaminergic medicinal products and levodopa may reduce the effect of DTBZ. Caution should be applied if DTBZ is used with levodopa or dopaminergic medicinal products.
The patient had a neurological condition other than TD that may interfere with assessing the severity of dyskinesias	Additional pre-existing neurological conditions may confound the study results.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
The patient had a serious untreated or undertreated psychiatric illness at screening or baseline	These pre-existing conditions may confound the safety profile evaluation of DTBZ.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
The patient had active suicidal ideation at baseline.	These pre-existing conditions may confound the safety profile evaluation of DTBZ.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
The patient had a score ≥11 on the Hospital Anxiety and Depression Scale - Depression Subscale (HADS-D) at screening or baseline.	The pre-existing condition may confound the safety profile evaluation of DTBZ.	No	DTBZ may cause depression or worsen pre-existing depression. Patients should be closely monitored for the emergence of such adverse events. Patients and their caregivers should be informed of the risks and instructed to report any concerns to their doctor immediately. If depression does not resolve, discontinuing treatment with DTBZ should be considered.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient was developmentally disabled or had evidence of dementia.	These pre-existing conditions may interfere with the patient's ability to participate in the study.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
Patient had an unstable or serious medical illness at baseline	These pre-existing conditions may confound the safety profile evaluation of DTBZ.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
Patient had a history (within 3 months of screening) or presence of violent behaviour.	This pre-existing condition may confound the safety profile evaluation of DTBZ.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
Patient had a QTcF value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block [RBBB]) on 12-lead electrocardiogram (ECG) at screening.	This pre-existing condition may confound the safety profile evaluation of DTBZ.	No	DTBZ may prolong the QT interval, but the degree of QT prolongation is not clinically significant when it is administered within the recommended dose range. DTBZ should be used with caution in combination with other medicinal products that prolong the QTc interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia, or hypomagnesaemia.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient had evidence of hepatic impairment at screening, as indicated by: • Aspartate transaminase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN). • Alkaline phosphatase (ALP) or total bilirubin (TBil) >2 times the ULN ○ Note: Patients with Gilbert's Syndrome were eligible to participate if approved by the Medical Monitor. ○ Note: Patients with abnormalities in 2 or more of these analytes (AST, ALT, ALP, TBil) must have been approved by the medical monitor in order to be enrolled • Prothrombin time >4 sec prolonged (Flexible-dose trial) or > 17seconds prolonged (exclusion criteria for Fixed-dose and Long-term trials) • Positive Hepatitis B surface antigen (HBsAg)	The major route of biotransformation for DTBZ and its deuterated active metabolites is hepatic. Hepatic impairment was listed as exclusion criterion due to potential concerns for increases in systemic exposure and greater risk for adverse events (AEs).	No	The use of DTBZ in patients with hepatic impairment is contraindicated.
Patient had evidence of significant renal impairment at screening, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockroft-Gault formula.	These pre-existing conditions may confound the safety profile evaluation of DTBZ.	No	As the major route of elimination of the active metabolites is non-renal and DTBZ is a titrated medicinal product, it is unlikely that patients with any degree of renal impairment will be exposed to excessive concentrations of DTBZ and its active metabolites. No dose adjustment is necessary in patient with renal impairment.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient was pregnant or breast-feeding at screening or baseline.	As a precaution, pregnant or breast-feeding patients were not included as the impact of DTBZ on growth and development of a foetus and newborn was not established.	No	DTBZ is not recommended during pregnancy and in women of childbearing potential not using contraception. It is unknown whether DTBZ or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from DTBZ therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Patient acknowledged present use of illicit drugs at screening.	This pre-existing condition may confound the safety profile evaluation of DTBZ.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
Patient had a history of alcohol or substance abuse in the previous 12 months, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), or patient was unable to refrain from substance abuse throughout the study.	This pre-existing condition may confound the safety profile evaluation of DTBZ.	No	Concomitant use of alcohol or other sedating products is not recommended, as these may have additive effects and worsen sedation and somnolence.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patient had a positive urine drug screen (for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, or opiates) at screening or baseline, except if patient was receiving a stable dose of a benzodiazepine (exclusion criteria for Fixed-dose and Long-term trials)	This pre-existing condition may confound the safety profile evaluation of DTBZ.	No	Concomitant use of other sedating products is not recommended, as these may have additive effects and worsen sedation and somnolence. Examples of sedating products include benzodiazepines (e.g. midazolam, diazepam, lorazepam), antidepressants (e.g. mirtazapine, amitriptyline, trazodone), antipsychotics (e.g. promethazine, chlorprothixene), opioids (e.g. oxycodone, buprenorphine), antihistamines (e.g. diphenhydramine, dimenhydrinate), and centrally acting antihypertensives (e.g. clonidine, moxonidine).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The DTBZ clinical development programme is unlikely to detect certain types of adverse reactions such as uncommon or rare adverse reactions.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the DTBZ TD trials. Even though female patients of childbearing potential had to agree to use one of the study acceptable methods of contraception from screening through study completion if sexually active, two pregnancies were reported in TD trials.
Breastfeeding women	Not included in the DTBZ TD trials.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Hepatic impairment was listed as exclusion criterion in the protocols of the DTBZ TD trials.
Patients with renal impairment	Patient with evidence of significant renal impairment at screening, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockroft-Gault formula, were excluded from DTBZ TD trials.
Patients with cardiovascular impairment	Not included in the DTBZ TD trials.
Immunocompromised patients	Not included in the DTBZ TD trials.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients had to have moderate or severe abnormal movements based on Item 8 of the Abnormal Involuntary Movement Scale (AIMS), and an AIMS total score of ≥6 (based on Items 1 through 7), as assessed by the investigator at screening or baseline. Patients with underlying psychiatric illness had to be psychiatrically stable. The screening AIMS examination was reviewed by a blinded central rater to confirm eligibility prior to randomisation; however, for logistical reasons, the baseline examinations could not be centrally reviewed prior to randomisation. As a result, 16 patients (14.1%) were randomised with baseline centrally-read AIMS total scores <6, indicating that the abnormal movements were less severe than specified by the protocol inclusion criteria.
Population with relevant different ethnic origin	Patients of African American race (N=110) and Hispanic or Latino (N=48) ethnicity have been included in TD trials.
Subpopulations carrying relevant genetic polymorphisms	Patients that were poor CYP2D6 metabolizers were included in TD trials (N=23).

Part II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Estimation of cumulative exposure from post-marketing (PM) sources was calculated based on sales data collected from Teva and acquired companies. This data is originated from the countries where DTBZ is registered for treatment of TD and HD, therefore cumulative information for both indications is presented until 01 December 2023 (DLP). Given that the dose of DTBZ is determined individually for each patient based on reduction of TD and HD-chorea and tolerability, an estimate of patients exposed to DTBZ was calculated in patient-years by assuming that one package per patient was used monthly.

SV.1.2 Exposure

Cumulatively, from FDA approval (03 April 2017) until DLP, 65,124,197 packages were sold corresponding to 94,806 patient-years of exposure outside of EU.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Given that increases in dopamine are associated with abuse potential and that DTBZ is a VMAT-2 inhibitor which reduces dopaminergic neurotransmission, abuse potential is not expected.

The studies in the DTBZ clinical trials did not reveal any tendency for drug-seeking behaviour, although these observations were not made in a systematic manner.

Cumulatively, until the DLP of the latest PSUR submitted in non-EU region (31 March 2023), none of the reported post-marketing cases were suggestive of abuse-potential of DTBZ in TD.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Potential risks that do not impact the risk-benefit profile:

- Hyperprolactinemia

Serum prolactin levels were not evaluated in the DTBZ TD trials. Elevated prolactin concentrations in humans have been reported for other VMAT2 inhibitors, however, the clinical significance of these elevations is unknown. Moreover, no clinical manifestations of elevated prolactin levels such as amenorrhea, galactorrhoea, gynecomastia, and impotence related to the use of DTBZ have been identified in TD trials or in the post-marketing period.

- Binding to Melanin-Containing Tissues

DTBZ or its metabolites bind to melanin-containing tissues and could therefore accumulate in these tissues over time. The photochemical properties of TBZ, with a light absorbance outside the natural sunlight range (Rhee et al, 2011), suggest that DTBZ (with no expected deuterium-related isotope shift in UV-absorbance spectra) is not photoreactive. Non-clinical data indicate that although DTBZ has been shown to distribute to melanin containing tissues in rats, it is unlikely that DTBZ presents a phototoxic concern. The clinical relevance of DTBZ binding to melanin-containing tissues in humans is unknown. Teva's proposed risk minimization measures include routine risk minimisation measures (RMMs) (description of the risk in the product information (PI) and prescription only medicine status).

- Neuroleptic malignant syndrome (NMS)

NMS is a potentially fatal condition characterized by mental changes, rigidity, hyperthermia, autonomic dysfunction and elevated creatinine phosphokinase levels. It has been reported in association with drugs that reduce dopaminergic transmission. While DTBZ acts as a depletor of monoamines such as dopamine from nerve terminals, NMS has not been observed in patients receiving DTBZ. Nevertheless, relevant wording has been included in PI. Teva's proposed risk minimization measures include routine RMMs (description of the risk in the PI and prescription only medicine status).

<u>Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the PI are adhered to by prescribers (e.g., actions being part of standard clinical practice)</u>:

- Depression

DTBZ may cause depression or worsen pre-existing depression. Reported adverse events and HADS-D data demonstrated a low risk of depression for participants with TD treated with DTBZ in double-blind placebo-controlled trials as well as in the long-term open label trial. While the risk of depression was low, related events were more common in TD participants treated with DTBZ compared to placebo. Therefore, patients should be closely monitored. If depression does not resolve, discontinuing treatment with DTBZ should be considered. Teva's proposed risk minimization measures include routine RMMs (description of the risk in the PI, prescription only medicine status).

- QTc prolongation

DTBZ may prolong the QT interval, but the degree of QT prolongation is not clinically significant when DTBZ is administered within the recommended dose range. Overall, no safety

signals were observed in ECG parameters in TD trials. Of the participants with normal QTcF at baseline, QTcF values >450 ms were observed in a similar proportion of placebo-treated participants and participants treated with DTBZ in TD trials. Two additional trials dedicated to evaluating QTc, showed that no QTcF prolongation was observed.

DTBZ should be used with caution in combination with other medicinal products that prolong the QTc interval and in patients with congenital long QT syndrome, a history of cardiac arrhythmias, bradycardia, hypokalaemia or hypomagnesaemia. Teva's proposed risk minimization measures include routine RMMs (description of the risk in the PI, prescription only medicine status).

- DDI with strong CYP2D6 inhibitors

Because DTBZ is titrated in a response-driven manner to a tolerable dose that controls TD, DTBZ can be titrated safely, independent of possible CYP2D6 phenotype or concomitant use of a strong CYP2D6 inhibitor. Nevertheless, patients who are concomitantly using a strong CYP2D6 inhibitors, as well as patients who are known CYP2D6 poor metabolizers, should not exceed a total daily dosage of 36 mg DTBZ as an increase of the systemic exposure to the active dihydro-metabolites of DTBZ has been observed. Teva's proposed risk minimization measures include routine RMMs (description of the risk in the PI, prescription only medicine status).

- Parkinsonism

The number of reported parkinsonism AEs was low for participants with TD treated with DTBZ in TD trials. Overall, less than 1% of participants with TD treated with DTBZ in a double-blind, placebo-controlled trial reported AEs related to parkinsonism. While review of the clinical data did not identify parkinsonism as an ADR, review of PM reports resulted in the classification of parkinsonism as an ADR and its inclusion in PI. Additionally, parkinsonism (and related conditions) are thoroughly monitored through routine PV activities. Teva's proposed risk minimization measures include routine RMMs (description of the risk in the PI, prescription only medicine status).

<u>Known risks that do not impact the risk-benefit profile:</u>

- Akathisia, Agitation, and Restlessness

Akathisia and restlessness were evaluated through monitoring of adverse events (AEs), including all preferred terms that could map to akathisia Standardised MedDRA Query (SMQ), and Barnes Akathisia Rating Scale (BARS) summary assessment scores. The occurrence of akathisia and restlessness events was sporadic; no trends could be observed regarding timing of the events. All akathisia (SMQ) AEs were considered mild or moderate, and none led to dose reduction or suspension. Only one participant experienced a serious AE of psychomotor hyperactivity resulting in a withdrawal from the trial, however it was considered moderate and unlikely to be related to trial drug. These risks have been assessed as identified and included in the PI as adverse drug reactions (ADRs).

- Somnolence

Somnolence was evaluated through monitoring of AEs and the Epworth Sleepiness Scale (ESS) in TD trials. The risk was found to be more frequent in the DTBZ titration group than in the placebo group (absolute risk difference 4.4%, relative risk 1.6). Somnolence and sedation generally occurred early during treatment, with most adverse events being reported during the first 2 to 3 weeks of treatment or during initiation/titration. Patients should therefore not perform activities requiring mental alertness to maintain the safety of themselves or others, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of DTBZ and know how the medicinal product affects them. Given the overall benign profile of the collected AEs, these events are considered as well tolerable not affecting benefit-risk balance of DTBZ. This risk has been assessed as identified and included in the PI as ADR.

Risk seen in psychiatric patient population:

- Suicidality

Suicidality is a known risk in the predominantly psychiatric population and was therefore systematically evaluated through monitoring of the C-SSRS and AE reporting in the TD trials. The frequency of suicidality was low based on both AE reporting and scale assessment. With long-term administration of DTBZ (≥158 weeks of treatment), no increased incidence was identified in comparison with the expected background of suicidality in this psychiatric patient population (Caldwell and Gottesman, 1992, Dean and Thuras, 2009). Review of the aggregated clinical data in the TD trial participants overall did not reveal any safety signal with DTBZ having a differential effect on causing or worsening suicidality compared to placebo.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 9: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concern.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

Routine minimisation activities are considered sufficient to minimise the risks associated with the use of DTBZ and no additional risk minimisation measures are deemed necessary.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of Risk Minimisation Measures

Not applicable.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Austedo® (deutetrabenazine)

This is a summary of the risk management plan (RMP) for Austedo® (deutetrabenazine) (herein after also referred to as deutetrabenazine). The RMP details important risks of deutetrabenazine, how these risks can be minimised, and how more information will be obtained about deutetrabenazine's risks and uncertainties (missing information).

Deutetrabenazine's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how deutetrabenazine should be used.

This summary of the RMP for deutetrabenazine should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of deutetrabenazine's RMP.

I. The Medicine and What It is used for

Austedo® (deutetrabenazine) is authorised for the treatment of moderate to severe tardive dyskinesia in adults (see SmPC for the full indication). It contains deutetrabenazine as the active substance and it is given orally.

Further information about the evaluation of Austedo® (deutetrabenazine)'s benefits can be found in Austedo® (deutetrabenazine)'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*link to the EPAR summary landing page*>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of deutetrabenazine, together with measures to minimise such risks and the proposed studies for learning more about deutetrabenazine's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of deutetrabenazine are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of deutetrabenazine. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 10: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Not applicable.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Austedo® (deutetrabenazine).

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Austedo® (deutetrabenazine).

Part VII: Annexes

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.