

## 5.06 DEUTETRABENAZINE, Tablet 6 mg, Tablet 9 mg, Tablet 12 mg, Austedo<sup>®</sup>, Teva Pharma Australia Pty Ltd

### 1 Purpose of submission

- 1.1 The submission requested a Section 85 (General Schedule), Authority Required PBS listing for deutetrabenazine for the treatment of chorea associated with Huntington’s disease in patients who have failed prior tetrabenazine treatment due to intolerance or inadequate response. The PBAC has not previously considered deutetrabenazine for any indication.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo (no active therapy). The requested listing against a placebo comparator was inconsistent with clinical practice as most patients continue to receive active therapy.

**Table 1: Key components of the clinical issue addressed in the submission**

Component	Description
Population	Huntington’s disease patients with chorea who have failed prior tetrabenazine treatment due to intolerance or inadequate response
Intervention	Oral deutetrabenazine tablets titrated to achieve a tolerated dose that reduces chorea (between 6-48 mg daily)
Comparator	Placebo
Outcomes	Reduction in chorea symptoms, improvements in quality of life
Clinical claim	Deutetrabenazine is superior in terms of efficacy and non-inferior in terms of safety compared to placebo

Source: Table 1-1 of the submission

- 1.3 The ESC advised the placement of deutetrabenazine in the submission as second or third line therapy was inappropriate and not supported by the available evidence. The ESC noted there was no evidence presented in the submission for the requested second or third line setting after failure (or inability to tolerate maximal dosing) of tetrabenazine. Furthermore, the ESC considered that as deutetrabenazine is a pharmacological analogue and isotopic isomer of tetrabenazine there was no clinical rationale to restrict deutetrabenazine to later line therapy.
- 1.4 On this basis, the ESC considered the most appropriate placement of deutetrabenazine is in first-line therapy as an alternative to tetrabenazine and that clinical and economic comparisons should be undertaken on that basis. Therefore, the ESC considered the clinical and economic comparisons presented in this submission were not informative for decision-making. Advice provided below on the technical components of the submission should not be interpreted as acceptance of the proposed PBS listing. The Pre-PBAC Response stated that a first-line listing would not be viable at a price similar to that for which tetrabenazine is currently PBS listed and

argued that it is not economical for a new treatment which offers advantages over the current alternative which is an old drug where the patient population is so small.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **2 Background**

### ***Registration status***

- 2.1 Deutetrabenazine was submitted under the TGA/PBAC parallel process with a proposed indication for the:
  - treatment of chorea associated with Huntington's disease; or
  - treatment of tardive dyskinesia in adults.
- 2.2 TGA Status at time of PBAC advice: The TGA clinical evaluation report, Delegate's Overview and draft product information for deutetrabenazine were available.

### ***Previous PBAC consideration***

- 2.3 The PBAC has not previously considered any therapy specifically for the treatment of chorea associated with Huntington's disease. Tetrabenazine is currently listed on the PBS for the treatment of hyperkinetic extrapyramidal disorders (which includes chorea). However, tetrabenazine has been available on the PBS since before cost-effectiveness criteria were introduced and therefore the cost-effectiveness of this therapy for the treatment of chorea had not previously been considered.

### 3 Requested listing

3.1 The proposed listing for deutetrabenazine is outlined below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DEUTETRABENAZINE, 6 mg, 60 tablets	2	120	5	\$ [REDACTED] (effective) \$ [REDACTED] (published)	Austedo® Teva
DEUTETRABENAZINE, 9 mg, 60 tablets	2	120	5	\$ [REDACTED] (effective) \$ [REDACTED] (published)	
DEUTETRABENAZINE, 12 mg, 60 tablets	2	120	5	\$ [REDACTED] (effective) \$ [REDACTED] (published)	

<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Mild, Moderate or Severe
<b>Condition:</b>	Chorea associated with Huntington’s disease
<b>PBS Indication:</b>	Mild, Moderate or Severe Chorea associated with Huntington’s disease
<b>Restriction:</b>	Authority Required
<b>Clinical criteria:</b>	For a patient without specified co-morbidities of psychoses, active depression, aggressive behaviours or compliance issues, AND Patient must have experienced an inadequate response, intolerance to tetrabenazine OR Patient was unable to achieve maximum effective dose with tetrabenazine due to adverse events.  For a patient with specified co-morbidities of psychoses, active depression, aggressive behaviours or compliance issues, AND Patient must have experienced an inadequate response, intolerance to a neuroleptic monotherapy or in combination with another treatment AND Patient must have experienced an inadequate response, intolerance to tetrabenazine monotherapy or in combination with another agent OR Patient was unable to achieve maximum effective dose with tetrabenazine due to adverse events.
<b>Population criteria:</b>	Patient must be aged 18 years or older.
<b>Administrative Advice:</b>	After initial script nurse practitioner prescribing should be permitted.
<b>Cautions:</b>	See PI

Source: Table 1-10, Table 1-13 of the submission

3.2 The submission proposed a Special Pricing Arrangement for deutetrabenazine consisting of a [REDACTED]-[REDACTED] % rebate on the published DPMQ per script.

3.3 The submission acknowledged that the proposed PBS restriction for subsequent-line treatment of chorea is narrower than the requested TGA indication which does not specify lines of therapy. The submission stated that the decision to limit PBS treatment to a subsequent-line setting was made due to economic reasons. The proposed

restriction was inconsistent with the clinical evidence provided in the submission which was primarily based on a first-line treatment setting.

- 3.4 It was unclear how deutetrabenazine use under the PBS could be effectively restricted to subsequent-line treatment given that the available data support first-line treatment and the proposed criteria are highly subjective with no well accepted definitions of response and intolerance to prior treatment. As a consequence, the risk of leakage outside the proposed listing is likely to be high. The ESC advised that substantial drift to first-line use would be expected in clinical practice.
- 3.5 The proposed restriction also included requirements for patients with concurrent behavioural conditions to have previously failed antipsychotic therapy. Additionally, the proposed restriction was agnostic regarding the potential use of deutetrabenazine in combination with antipsychotic therapy. However, neither of these indications was adequately supported in the submission.
- 3.6 The Pre-Sub-Committee Response (PSCR) argued there was an unmet need for new chorea-specific treatments for patients to transition to as their condition deteriorates and proposed amended restriction wording. The ESC agreed with the evaluation and considered the proposed placement of deutetrabenazine as second- or third-line therapy, and therefore the requested listing, was inappropriate. The Pre-PBAC Response proposed a further restricted PBS listing to only those who cannot tolerate or titrate a maximally effective to tetrabenazine, with more stringent requirements regarding TMC improvements for continuing treatment. The PBAC considered this proposal did not address the issue that the most appropriate clinical place of deutetrabenazine was as a first-line treatment option for chorea associated with HD.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Huntington's disease is an autosomal dominant genetic disorder caused by an expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat in the huntingtin gene. The exact pathophysiology associated with the mutation is unclear but the disease results in a gradual loss of neuronal cells.
- 4.2 Huntington's disease is a slowly progressive condition with symptom onset typically occurring between 30-50 years of age. The disease is associated with a broad range of symptoms affecting motor function, cognitive ability and behaviour. Symptoms of the disease gradually worsen over time with loss of independence and poor quality of life in the advanced stages of the disease. Huntington's disease is generally associated with reduced life expectancy due to progression of symptoms and a high risk of suicide in the patient population.
- 4.3 Chorea is one of the more prominent symptoms of Huntington's disease and is characterised by irregular involuntary movements with variable speed, timing, and direction that appear to "flow" between muscles. Mild cases of chorea may give the

appearance of fidgeting and/or restlessness while more severe symptoms may be associated with impairments to speech, swallowing, sleep, balance and functional capacity. The presence of chorea symptoms may also contribute to feelings of social stigma that are frequently associated with Huntington's disease. In general, chorea symptoms become less prominent with more advanced Huntington's disease as other symptoms become more severe.

- 4.4 In clinical practice, chorea symptoms are typically treated if the symptoms become troublesome to the patient and/or carer (patients may be unaware of the severity of their symptoms). The current standard of care involves the use of tetrabenazine and/or off-label antipsychotic medications (such as olanzapine, risperidone and haloperidol) with the preferred choice of therapy varying based on the presence of concurrent behavioural conditions. The mechanism of action for both tetrabenazine and antipsychotic medications is thought to be due to reduced dopamine transmission in the central nervous system.
- 4.5 Deutetrabenazine is a modified version (isotopic isomer) of tetrabenazine with deuterium ("heavy" hydrogen with one additional neutron) replacing hydrogen atoms in the molecule. It has the same mechanism of action as tetrabenazine with both molecules depleting dopamine and other monoamines in the central nervous system via inhibition of the presynaptic vesicular monoamine transporter 2 protein (VMAT-2).
- 4.6 The deuteration process results in changes to the pharmacokinetic profile of deutetrabenazine compared to tetrabenazine (prolonged half-life with smaller peak/trough fluctuations). The submission claimed that these differences potentially allow for less frequent dosing and improved tolerability.
- 4.7 In patients without concurrent behavioural conditions, the submission positioned deutetrabenazine as a second-line treatment option in patients who have failed prior therapy with tetrabenazine. In the current management algorithm, the most commonly used treatment in this line of therapy is tetrabenazine with antipsychotic combination therapy.
- 4.8 In patients with concurrent behavioural conditions, the submission positioned deutetrabenazine as a third-line treatment option in patients who have failed prior therapy with anti-psychotic medications and tetrabenazine. There was no clearly established treatment at this line of therapy in the current management algorithm but alternatives include cycling between anti-psychotic treatments, addition of anti-anxiety treatments and referral to rehabilitation specialists.
- 4.9 The submission stated that deutetrabenazine was positioned as a subsequent-line therapy after prior use of tetrabenazine due to economic considerations. However, the submission also argued that there was a clinical rationale for subsequent-line use, as patients failing to achieve a response at a tolerable dose of tetrabenazine may be able to achieve a response with deutetrabenazine due to a more favourable tolerability profile. No evidence was provided in the submission to support this claim.

Published indirect analyses of tetrabenazine and deutetrabenazine considered during the evaluation appeared to weakly support the claim of improved tolerability in the first-line treatment setting. However, there are no clinical data to inform efficacy and safety estimates in a subsequent-line treatment setting (given the shared mechanism of action between the two therapies it is unlikely that first-line treatment estimates would be representative of second-line use).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated placebo as the main comparator. The main arguments provided in support of this nomination were the lack of other registered treatment options for chorea in the subsequent-line setting and the limited evidence for the off-label use of other therapies.
- 5.2 The appropriate main comparator will depend on line of therapy.
- 5.3 In the subsequent-line setting, the nomination of a placebo comparator was inconsistent with the clinical advice provided with the submission which suggested that most patients continue to receive active therapy, primarily tetrabenazine with antipsychotic combination therapy. Additionally, the argument to exclude other off-label therapies due to lack of evidence was poorly supported given that there is no clear evidence for deutetrabenazine in the subsequent-line treatment setting.
- 5.4 In the first-line setting, the therapy most likely to be replaced in practice would be tetrabenazine, a pharmacological analogue of deutetrabenazine. The ESC and PBAC agreed that as listing in a first line setting was a more appropriate place for deutetrabenazine, tetrabenazine was the most appropriate comparator.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. In line with the submission's clinical positioning, the clinician noted there are limited therapeutic options for chorea in HD following failure with or an inability to tolerate tetrabenazine and argued deutetrabenazine represents a significant advance in treatment options for chorea symptoms that offers a better tolerability and adverse event profile than tetrabenazine.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from consumers (2) and the Coalition of Australian Huntington's Associations in support of the listing. The PBAC noted the individuals and organisations highlighted impact of HD on patients and families and

noted the improved tolerability and adverse event profile of deutetrabenazine makes it a useful treatment for chorea and that some patients will see improvements in quality of life while on treatment. The PBAC specifically noted the input of a patient being treated with deutetrabenazine who explained that deutetrabenazine has provided better symptom control and improved quality of life as the drug does not wear off in the same way as tetrabenazine, allowing for longer periods of consistent physical functioning and reduced social anxiety.

### **Clinical studies**

6.3 The submission was based on one head-to-head randomised trial comparing deutetrabenazine to placebo for the management of chorea associated with Huntington’s disease (FIRST-HD). The submission also presented an observational study of two population cohorts; patients continuing in an open-label extension of the FIRST-HD trial (ARC-HD-ROLLOVER) and stable patients switching from tetrabenazine to deutetrabenazine (ARC-HD-SWITCH).

6.4 Details of the included studies are provided in the table below.

**Table 2: Studies and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
SD-809-C-15 (FIRST-HD)	Auspex Pharmaceuticals (2015). A Randomized Double-Blind, Placebo-Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated With Huntington Disease	Internal study report
	Frank S et al (2016). Effect of deutetrabenazine on chorea among patients with Huntington disease: A randomized clinical trial.	JAMA 316: 40-50
SD-809-C-16 (ARC-HD)	Auspex Pharmaceuticals (2015). An Open-Label, Long Term Safety Study of SD-809 ER in Subjects With Chorea Associated With Huntington Disease	Internal study report [interim]
	Teva Pharmaceuticals (2018). An Open-Label, Long Term Safety Study of SD-809 ER in Subjects With Chorea Associated With Huntington Disease	Internal study report [final]
	Frank S et al (2017). Safety of converting from tetrabenazine to deutetrabenazine for the treatment of chorea.	JAMA Neurology 74: 977-982

Source: Table 2-5 of the submission

Note: Abstracts of studies with full publications are not presented

6.5 The key features of the included studies are summarised in the table below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
FIRST-HD	90	Double-blind, placebo-controlled RCT 12 weeks duration	Low	Patients who have chorea associated with Huntington's disease	Chorea and motor symptoms, quality of life and adverse events	Treatment responders (based on chorea symptoms), adverse events, population and treatment characteristics
ARC-HD-ROLLOVER	82	Open label extension of FIRST-HD 2.2 year mean duration	High	Patients previously enrolled in FIRST-HD	Adverse events, chorea and motor symptoms	Treatment discontinuation rate
ARC-HD-SWITCH	37	Prospective longitudinal study 2.4 year mean duration	High	Patients receiving a stable dose of tetrabenazine for chorea associated with Huntington's disease	Adverse events, chorea and motor symptoms	Not used

Source: Section 2.3, Section 2.4 of the submission  
Abbreviations: RCT, randomised controlled trial

- 6.6 None of the included studies assessed the use of deutetrabenazine in patients who had already failed prior therapy with tetrabenazine. Therefore, there are no reliable estimates to quantify the effectiveness and safety of deutetrabenazine in this population. The PSCR argued the data from the FIRST-HD trial was generalisable to the Australian HD population with chorea requiring therapy and allowed patients who had previously received tetrabenazine (>6 months prior) to participate and was therefore applicable to the requested population. The ESC agreed with the commentary and considered the clinical evidence did not examine the efficacy of deutetrabenazine after failing tetrabenazine. The switch or prior treatment populations in the FIRST-HD or ARC-HD-SWITCH studies also did not require patients to have failed treatment with tetrabenazine and cannot be used to inform the proposed positioning in second or third line treatment.
- 6.7 In the economic analysis and financial implications, the submission noted observational data suggesting that dosing of deutetrabenazine may be lower in clinical practice (Ayyagari 2020; available as poster presentation only) compared to the included clinical studies (FIRST-HD, ARC-HD patient cohorts).
- 6.8 The Ayyagari 2020 analysis indicated that the average stable dose of deutetrabenazine in patients with Huntington's disease was 28.5 mg per day compared to 39.7 mg per day in the FIRST-HD trial and 42.6 mg per day in the ARC-HD-ROLLOVER cohort. The analysis also suggested a much higher rate of treatment discontinuation (4.1% per 4-week period) compared to long-term study data from the ARC-HD-ROLLOVER cohort (1.1% per 4-week period). Therefore, response rates reported in the clinical studies may not be representative of the real-world effectiveness of deutetrabenazine.
- 6.9 The PSCR argued the mean dose in the FIRST-HD and ARC-HD studies were generally similar and noted the variable in the ARC-HD trial measured whether patients ever

received a dose greater than 48mg and was not representative of the number or proportion of patients who were stable on a dose higher than the maximum in the draft product information. The ESC considered it was unclear what doses of deutetrabenazine may be used in the real-world setting and this added additional uncertainty for the clinical, economic and financial comparisons.

### Comparative effectiveness

6.10 The change in Unified Huntington Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score with deutetrabenazine and placebo in the FIRST-HD trial (primary outcome) is summarised in the table below.

**Table 4: Change in UHDRS TMC score from baseline to maintenance period (average of Week 9 and Week 12 values) in the FIRST-HD trial**

Outcome	Baseline Mean (SD)	Endpoint Mean (SD)	Least Squares Mean (SD) change from baseline	Least Squares Mean (95% CI) difference in change from baseline	P-value
<b>UHDRS Total Maximal Chorea score (0-28 scale, with higher scores indicating more severe chorea)</b>					
Deutetrabenazine (N = 45)	12.07 (2.727)	7.70 (3.868)	-4.42 (2.953)	-2.49 (-3.69, -1.29)	<0.0001
Placebo (N = 45)	13.24 (3.488)	11.26 (4.075)	-1.93 (2.666)		

Source: Table 2-29 of the submission

Abbreviations: CI, confidence interval; SD, standard deviation; UHDRS, Unified Huntington Disease Rating Scale, TMC, Total Maximal Chorea

6.11 Treatment with deutetrabenazine was associated with a statistically significant reduction in UHDRS Total Maximal Chorea score compared to placebo over 12 weeks (LSM difference -2.49; 95% CI -3.69, -1.29).

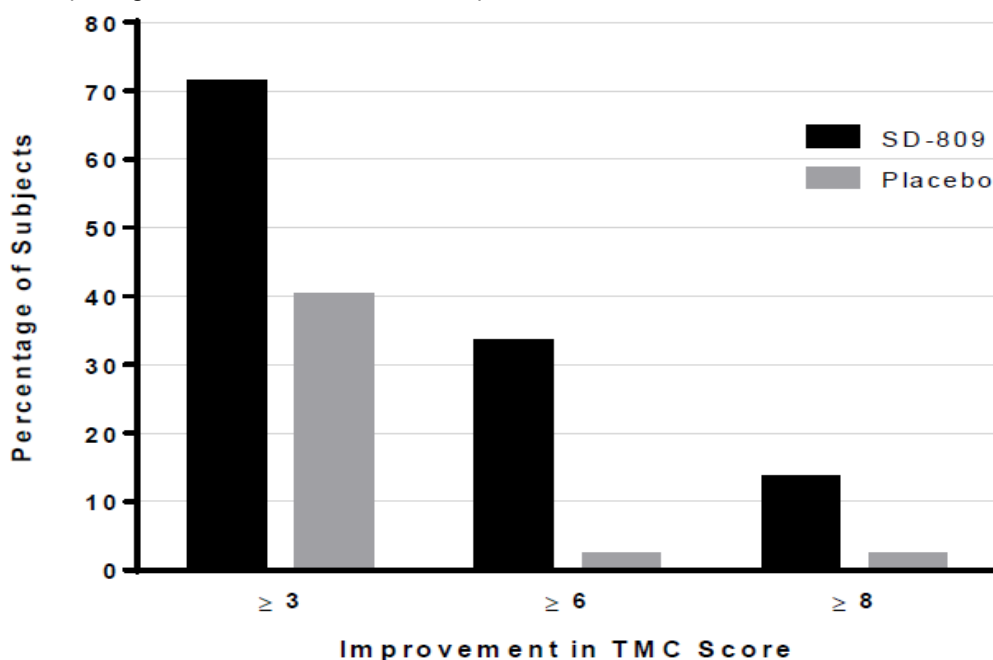
6.12 The submission nominated a minimal clinically important difference of 2-3 points for the change in Total Maximal Chorea (TMC) score. This nomination was based on the American Academy of Neurology 2011 guidelines on the treatment of chorea which indicated that a difference of 1 point was modestly important, 2 points was moderately important and 3 points was very important for the broader Total Motor Score (TMS). The submission argued that given the differences in scales between the two scores (TMS: 0-124; TMC 0-28) it is likely that a 2-3 point difference in Total Maximal Chorea score is clinically important.

6.13 The most recent publication of the FIRST-HD trial (Frank 2016) noted that the trial was powered to detect a 2.7 point difference in TMC score similar to that observed with tetrabenazine versus placebo. However, the study authors noted that the clinical importance of this difference was unclear. Additionally, there appeared to be poor correlation between the proportion of patients reporting a > 2 point reduction (67%; 60/90) or > 3 point reduction (56%; 50/90) in TMC score from baseline compared to proportion of patients with treatment success based on patient global impression (36%; 32/90) or physician global impression (28%; 25/90). These results suggest that for some patients a 2-3 point reduction in TMC score may not be clinically important. The ESC considered that the outcome of change in TMC score was a subjective measure that varies based on a range of factors, however agreed that overall the

results support a conclusion that deutetrabenazine is more effective than placebo for reducing chorea in HD, in the first-line setting.

- 6.14 Feedback from the sponsor-commissioned physician survey indicated that TMC scores are not used in clinical practice with physicians relying on a more global impression of symptoms. The physicians also noted that chorea symptoms can vary from one consultation to the next, depending on how the patient is feeling on any given day. Overall, the nominated minimal clinically important difference used in submission does not appear to be well supported.
- 6.15 Additional analyses of chorea scores using different definitions of response consistently favoured deutetrabenazine treatment compared to placebo (shown in Figure 1). The proportion of patients achieving a  $\geq 3$  point reduction from baseline (71.1% deutetrabenazine, 40% placebo) was the key efficacy outcome used in the economic analysis.

Figure 1: Responder analyses of change in UHDRS Total Maximal Chorea score from baseline to maintenance period (average of Week 9 and Week 12 values) in the FIRST-HD trial



Source: Figure 2-2 of the submission  
 Abbreviations: SD-809, deutetrabenazine; TMC, Total Maximal Chorea

- 6.16 The proportion of patients with treatment success based on patient or physician global impression is summarised in the table below.

**Table 5: Proportion of patients with treatment success in the FIRST-HD trial**

Outcome	Responders n (%)	Difference in the proportion of responders (95% CI)	P-value
<b>Patient global impression of change responses (patients with treatment success at Week 12, based on “much improved” or “very much improved”)</b>			
Deutetrabenazine (N = 45)	23 (51.1%)	31.1% (12.4%, 49.8%)	0.0020
Placebo (N = 45)	9 (20.0%)		
<b>Physician global impression of change responses (patients with treatment success at Week 12, based on “much improved” or “very much improved”)</b>			
Deutetrabenazine (N = 45)	19 (42.2%)	28.9% (11.4%, 46.4%)	0.0022
Placebo (N = 45)	6 (13.3%)		

Source: Table 2-32, Table 2-33 of the submission

Abbreviations: CI, confidence interval

6.17 A higher proportion of patients achieved treatment success at 12 weeks with deutetrabenazine compared to placebo based on global impressions of change.

6.18 The change in other relevant symptoms scores and quality of life measures with deutetrabenazine and placebo treatment in the FIRST-HD trial is summarised in the table below.

**Table 6: Change in functional/symptom scores from baseline in the FIRST-HD trial**

Outcome	Baseline Mean (SD)	Endpoint Mean (SD)	Least Squares Mean (SD) change from baseline	Least Squares Mean (95% CI) difference in change from baseline	p-value
<b>SF-36 Physical Functioning score (0-100 scale, with higher scores indicating higher physical function)</b>					
Deutetrabenazine (N = 45)	47.54 (10.755)	47.40 (10.305)	0.74 (9.773)	4.34 (0.41, 8.27)	0.0308
Placebo (N = 45)	43.24 (10.247)	39.90 (11.972)	-3.61 (9.669)		
<b>Berg Balance test (0-56 scale, with higher scores indicating better balance)</b>					
Deutetrabenazine (N = 45)	51.3 (4.5)	53.0 (3.1)	2.2 (3.47)	1.0 (-0.3, 2.3)	0.1415
Placebo (N = 45)	48.4 (7.0)	50.3 (5.8)	1.3 (4.04)		
<b>UHDRS TMS (0-124 scale, with higher scores indicating worse motor function)</b>					
Deutetrabenazine (N = 45)	34.06 (13.174)	26.77 (15.161)	-7.35 (6.344)	-3.99 (-6.52, -1.46)	0.0023
Placebo (N = 45)	38.82 (15.162)	35.40 (14.921)	-3.36 (5.469)		

Source: Table 2-31, Table 2-34 of the submission; Frank (2016) publication

Abbreviations: CI, confidence interval; SD, standard deviation, TMS, Total Motor Score, UHDRS, Unified Huntington Disease Rating Scale

6.19 Treatment with deutetrabenazine was associated with a statistically significant improvement in SF-36 Physical Functioning score and UHDRS TMS (primarily driven by differences in Total Maximal Chorea and Maximal Dystonia scores) compared to placebo. There were no statistically significant differences in other motor symptoms (rigidity/bradykinesia, hand movements, eye movements and gait/balance; or quality of life measures between treatment arms. There was no statistically significant difference in Berg Balance test scores between treatment arms.

6.20 Longer-term data from the ARC-HD patient cohorts indicated that treatment with deutetrabenazine was associated with a reduction in UHDRS Total Maximal Chorea score compared to baseline, with the treatment effect maintained through to Week 145 in the ARC patient cohorts. However, the longer term data also suggested that while deutetrabenazine was associated with an initial corresponding improvement in UHDRS Total Motor Score this improvement quickly deteriorated over time with the progression of other motor symptoms of Huntington’s disease.

- 6.21 A substantial proportion of patients in the ARC-HD cohorts (43%) received doses exceeding the maximum recommended dose of deutetrabenazine (> 48 mg per day; Frank 2020). As a consequence, it is unclear whether the treatment effect on chorea symptoms can be maintained over time without further dose escalation.
- 6.22 One published indirect analysis comparing the efficacy of deutetrabenazine and tetrabenazine for the treatment of chorea was identified during the evaluation (Rodrigues 2017). This analysis was based on a comparison of the FIRST-HD trial with the pivotal trial for tetrabenazine (TETRA-HD). The indirect analyses indicated that there were no statistically significant differences in chorea symptoms or broader motor symptoms between deutetrabenazine and tetrabenazine in the first-line setting. The Pre-PBAC Response argued that a formal indirect comparison was not undertaken as the sponsor could not, for economic reasons, accept a listing where the price of tetrabenazine was used as a basis for considering the cost-effectiveness of deutetrabenazine.

### Comparative harms

- 6.23 An overall summary of the adverse events reported in the FIRST-HD trial and the ARC-HD patient cohorts is presented in the table below.

**Table 7: Overall summary of adverse events in the included studies**

Adverse event	FIRST-HD (12 weeks)		ARC-HD-ROLLOVER (mean: 2.2 years)	ARC-HD-SWITCH (mean: 2.4 years)
	Placebo N = 45	Deutetrabenazine N = 45	Deutetrabenazine N = 82	Deutetrabenazine N = 37
Any adverse event	27 (60.0)	27 (60.0)	77 (93.9)	35 (94.6)
Treatment-related adverse event	12 (26.7)	19 (42.2)	55 (67.1)	26 (70.3)
Severe adverse event	1 (2.2)	2 (4.4)	17 (20.7)	7 (18.9)
Serious adverse event	1 (2.2)	1 (2.2)	21 (25.6)	11 (29.7)
Adverse events leading to dose reduction	3 (6.7)	3 (6.7)	20 (24.4)	10 (27.0)
Adverse events leading to dose suspension	1 (2.2)	1 (2.2)	8 (9.8)	3 (8.1)
Adverse events leading to discontinuation	1 (2.2)	1 (2.2)	5 (6.1)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

Source: Table 2-35, Table 2-40 of the submission; Table 21 of the final ARC-HD trial report  
Abbreviations: CI, confidence interval; SD, standard deviation

- 6.24 Treatment with deutetrabenazine in the FIRST-HD trial was associated with a higher incidence of treatment-related events compared to placebo (predominantly somnolence, dry mouth and fatigue). The submission claimed that the incidence of adverse events of special interest were broadly comparable between treatment arms (depression, suicidal ideation, anxiety, irritability, agitation, akathisia/restlessness, Parkinsonism and balance difficulty). There was no difference between treatment arms in the incidence of serious/severe events or events requiring dose modification.

- 6.25 The submission also noted that the safety data indicated that mean body weight remained relatively stable in the placebo arm but increased over time in the deutetrabenazine arm (mean 1.78 kg increase from baseline). The submission suggested that this difference may be explained by an improvement in chorea symptoms and swallowing function in patients treated with deutetrabenazine.
- 6.26 The incidence of adverse events over time in the ARC-HD patient cohorts was generally comparable to the FIRST-HD trial (after accounting for the differences in exposure periods) but treatment-related adverse events continued to occur throughout the long-term follow-up period.
- 6.27 Two published indirect analyses comparing the safety of deutetrabenazine and tetrabenazine for the treatment of chorea were identified during the evaluation (Claassen 2017, Rodrigues 2017). Both of these analyses were based on a comparison of the FIRST-HD and TETRA-HD trials and suggested an improved tolerability profile with deutetrabenazine compared to tetrabenazine although the statistical significance of the result varied by methodology (i.e. using relative or absolute risk measures). The results of these indirect comparisons are included in the table below.

**Table 8: Indirect comparison of safety outcomes with deutetrabenazine and tetrabenazine**

Adverse event	Rodrigues 2017 Odds ratio (95% CI)	Rodrigues 2017 Risk difference (95% CI)	Claassen 2017 Unmatched Risk difference (95% CI)	Claassen 2017 Matched Risk difference (95% CI)
Any adverse event	-	-	-0.21 (-0.48, 0.06)	-0.35 (-0.72, 0.02)
Serious adverse event	5.44 (0.09, 322.08)	-0.07 (-0.17, 0.03)	-0.07 (-0.17, 0.02)	-0.08 (-0.17, 0.01)
Adverse events leading to dose reduction	-	-	<b>-0.41 (-0.59, -0.23)</b>	<b>-0.41 (-0.62, -0.19)</b>
Adverse events leading to discontinuation	-	-	-0.09 (-0.19, 0.01)	<b>-0.10 (-0.20, 0.00)</b>
<b>Individual adverse events</b>				
Agitation	-	-	<b>-0.13 (-0.23, -0.02)</b>	<b>-0.14 (-0.25, -0.04)</b>
Akathisia	-	-	<b>-0.19 (-0.31, -0.07)</b>	<b>-0.19 (-0.32, -0.06)</b>
Anxiety	-	-	-0.12 (-0.24, 0.02)	-0.12 (-0.25, 0.01)
Coughing	-	-	0.03 (-0.10, 0.15)	0.03 (-0.10, 0.15)
Depression	17.15 (0.55, 531.90)	<b>-0.17 (-0.31, -0.28)</b>	<b>-0.19 (-0.32, -0.07)</b>	<b>-0.21 (-0.34, -0.08)</b>
Depression/agitated depression	-	-	<b>-0.17 (-0.30, -0.04)</b>	<b>-0.20 (-0.34, -0.07)</b>
Diarrhoea	0.07 (0.03, 2.06)	0.12 (-0.03, 0.27)	0.12 (-0.04, 0.27)	0.10 (-0.09, 0.29)
Somnolence	4.95 (0.34, 72.37)	<b>-0.21 (-0.39, -0.03)</b>	<b>-0.22 (-0.39, -0.04)</b>	<b>-0.23 (-0.45, -0.01)</b>
Fall	2.71 (0.31, 23.98)	-0.07 (-0.26, 0.12)	-0.08 (-0.27, 0.11)	-0.11 (-0.32, 0.11)
Fatigue	1.21 (0.31, 11.14)	-0.07 (-0.26, 0.12)	-0.07 (-0.26, 0.12)	-0.08 (-0.28, 0.12)
Insomnia	14.18 (0.47, 426.77)	<b>-0.24 (-0.40, -0.04)</b>	<b>-0.24 (-0.39, -0.09)</b>	<b>-0.24 (-0.41, -0.08)</b>
Nausea	-	-	-0.09 (-0.23, 0.06)	-0.10 (-0.25, 0.05)
Parkinsonism	-	-	<b>-0.15 (-0.24, -0.05)</b>	<b>-0.15 (-0.24, -0.05)</b>
Vomiting	-	-	-0.09 (-0.20, 0.03)	-0.09 (-0.21, 0.04)

Source: Rodrigues 2017 publication; Claassen 2017 publication with accompanying Rodrigues letter

Abbreviations: CI, confidence interval

Note: Odds ratios > 1 and risk difference < 0 favour deutetrabenazine

Note: Bolded values indicate results with p < 0.05

- 6.28 Treatment with deutetrabenazine was consistently associated with reduced adverse events compared to tetrabenazine in both the Rodrigues 2017 and Claassen 2017 indirect analyses but the statistical significance of the results varied by use of relative or absolute risk measures. Overall, deutetrabenazine may have a tolerability advantage compared to tetrabenazine in the first-line setting although the robustness of this result is uncertain. The PSCR argued the evidence presented demonstrated tetrabenazine has a worse safety profile compared to deutetrabenazine. The ESC considered that it may be reasonable to conclude that deutetrabenazine has a tolerability advantage over tetrabenazine (noting no evidence of greater effectiveness was presented), however the robustness of the results was uncertain.
- 6.29 The extended assessment of harms did not adequately address the safety concerns associated with tetrabenazine (a pharmacological analogue of deutetrabenazine) and the broader class of VMAT-2 inhibitors.

### ***Benefits/harms***

- 6.30 On the basis of direct evidence presented in the submission, as a first-line treatment, for every 100 patients treated with deutetrabenazine in comparison with placebo (no treatment) over 12 weeks:
- There would be 30 additional patients who experience a reduction in chorea symptoms (based on patient global impression and physician global impression).
  - There would be 15 additional patients who experience treatment-related adverse events (predominantly somnolence, dry mouth and fatigue).

### ***Clinical claim***

- 6.31 The submission described deutetrabenazine as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo. Based on the clinical trial evidence presented, this claim was reasonable in terms of comparative effectiveness in the first-line setting, although comparative effectiveness for the proposed PBS setting was not established. The safety claim was not adequately supported. The evaluation considered the following issues should be considered:
- Whether the evidence from the first-line treatment setting (FIRST-HD) is applicable to the subsequent-line setting after prior failure of tetrabenazine particularly given that both treatments share the same mechanism of action (i.e. pharmacological analogues).
  - Whether the evidence comparing deutetrabenazine to placebo is relevant to the Australian setting given that most patients failing first-line treatment continue to receive subsequent lines of active treatment.
  - Whether the deutetrabenazine dosing regimen used in the clinical trial is representative of dosing used in the clinical practice (observational claims data suggest much lower doses in clinical practice).

- Whether the treatment effect of deutetrabenazine can be maintained long-term without the need to escalate dosing over time (long-term results included 43% of patients using doses exceeding the proposed maximum dose).
  - The long-term benefit of managing chorea symptoms given the progressive worsening of a wide range of symptoms associated with Huntington’s disease (initial improvements in TMS quickly deteriorated over time with the progression of other motor symptoms).
  - Deutetrabenazine is associated with a higher risk of adverse events compared to placebo and belongs to a drug class (VMAT-2 inhibitors) that is known to be associated with the development or exacerbation of behavioural conditions.
- 6.32 As mentioned at numerous points above, the ESC agreed that whilst a clinical claim of superior comparative effectiveness over placebo (as first line therapy or in patients who have perhaps been previously treated with and not failed tetrabenazine) may be reasonable, such a claim was neither applicable to the requested PBS population nor relevant to the clinical place it considered to be appropriate, as a first line alternative to tetrabenazine. The ESC maintained that the most appropriate clinical place for deutetrabenazine was as a first line treatment option with tetrabenazine as the primary comparator and a clinical claim should be based on that comparison.
- 6.33 The ESC agreed with the commentary and considered while there was substantial uncertainty in terms of the comparative safety claim in the requested PBS population versus placebo in tetrabenazine failure patients, it may be reasonable to conclude that deutetrabenazine has a tolerability advantage over tetrabenazine.
- 6.34 The PBAC considered that the claim of superior comparative effectiveness to placebo was likely reasonable in the first-line setting, however considered the claim in the requested population as a subsequent line of therapy after tetrabenazine was not adequately supported.
- 6.35 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported.

### ***Economic analysis***

- 6.36 The submission presented a modelled economic evaluation of deutetrabenazine compared to placebo for the treatment of chorea associated with Huntington’s disease. The economic evaluation was based on a direct randomised trial (FIRST-HD) with additional modelled data and was presented as a cost-utility analysis.
- 6.37 The ESC advised the cost utility analysis was uninformative for decision-making, as the requested clinical place of deutetrabenazine was inappropriate and the benefit in that population was not supported by the clinical evidence (which is in largely tetrabenazine naïve patients). The ESC noted the requested price was substantially higher than that of tetrabenazine and considered any future economic analysis should be based on use in a first line setting comparing deutetrabenazine to tetrabenazine

either on a cost minimisation basis or a modelled cost utility basis, if the clinical evidence supports such an approach. Comments from the ESC on the economic model, as presented, are provided at the end of this section.

**Table 9: Key components of the economic evaluation**

<b>Component</b>	<b>Description</b>
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years
Time horizon	10 years
Methods used to generate results	Decision tree (first 12 weeks) linked with a Markov cohort model
Treatments	Deutetrabenazine; placebo
Health states	Three health states: improved chorea, chorea, dead
Cycle length	12 weeks first cycle, 4 weeks subsequent cycles
Patient characteristics	Age and gender distribution were based on the FIRST-HD trial. The submission assumed that patient and treatment characteristics from the FIRST-HD trial would be broadly representative of the target PBS population.
Transition probabilities	<p>Transition probabilities for improved chorea and chorea were based on the proportion of responders in each treatment arm from the FIRST-HD trial. It was assumed that all non-responders in the deutetrabenazine arm cease treatment after 12 weeks while all responders maintain treatment benefits for up to 10 years while on treatment. All patients in the placebo arm were assumed to be non-responders after 12 weeks. It was also assumed that results from the first-line setting are generalisable to all treatment settings.</p> <p>The probability of treatment discontinuation (1.1% every 4 weeks) was derived from the ARC-HD-ROLLOVER cohort.</p> <p>Transition probabilities for death were based on Australian life tables adjusted using a standardised mortality ratio for Huntington's disease (Hille 1999).</p>
Utility values	<p>Utility values for the improved chorea and chorea health states were based on a sponsor-commission TTO study in the US general population using health state vignettes with varying chorea severity (Attachment 7 of the submission).</p> <p>The estimated TTO utility values were mapped to the improved chorea health state based on the relative proportion of responders achieving a 3-6 point reduction (assumed to have mild-to-moderate symptoms) or &gt; 6 point reduction (assumed to have mild symptoms) in TMC scores from baseline for each treatment arm in the FIRST-HD trial. Estimated TTO utility values were mapped to the chorea health state assuming that patients have moderate to severe chorea symptoms.</p> <p>Deutetrabenazine improved chorea health state: 0.555                      Placebo improved chorea health state: 0.489                      Chorea health state: 0.257</p> <p>The disutility associated with the progression of disease over time (-0.0023 per year) was estimated based on a published study of SF-6D utility values in Huntington's disease patients (Hawton 2019).</p> <p>Adverse event disutility values (-0.05 per event) were based on an assumption. Adverse event disutilities were applied as a once-off decrement in the first 12 weeks of treatment to the combined incidence of the most frequent events in the FIRST-HD trial.</p>

Component	Description
Costs	<p>Drug costs were estimated based on the titration algorithm and average daily dose from the FIRST-HD trial. The distribution of use across dose strengths was back-calculated to achieve the average daily dose from the FIRST-HD trial. Drug utilisation was valued using the proposed effective prices.</p> <p>Adverse event costs were based on the combined incidence of the most frequent events in the FIRST-HD trial. Adverse events were valued using AR-DRG and non-admitted care items. Adverse event costs were assumed to only occur once in the model.</p> <p>Disease management costs were based on resource use estimates from a clinical survey of specialists and nurses as well as an audit of treating physicians in Australia (Attachments 1, 2 and 4 of the submission). Health resource use was valued using various MBS items, URG/AR-DRG items and reported service fees.</p> <p>Estimated disease management costs were mapped to the improved chorea/chorea disease states assuming that all patients with improved chorea are controlled and all patients with chorea are uncontrolled.</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3-1 of the submission

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; DPMQ, dispensed price per maximum quantity; MBS, Medicare Benefits Schedule; TMC, Total Maximal Chorea; TTO, time-trade-off; URG, urgency-related group; US, United States

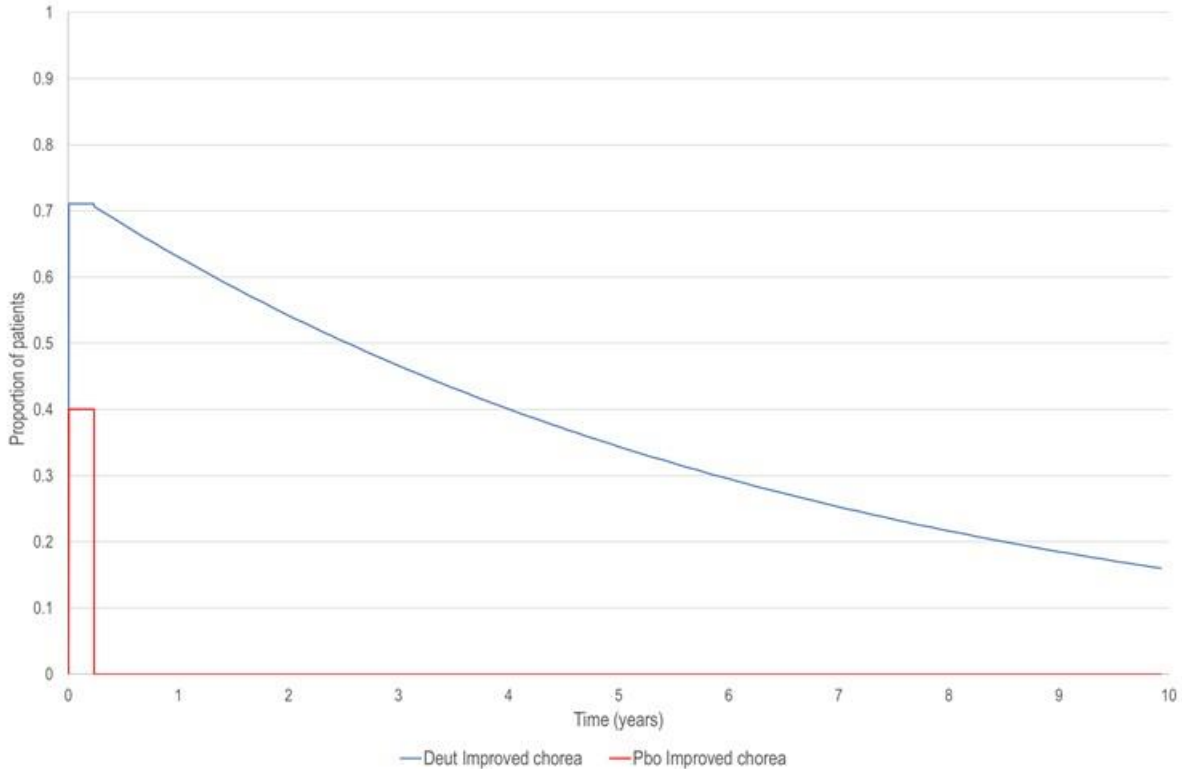
6.38 All patients were assumed to begin the model with chorea associated with Huntington's disease. During the first 12 week decision-analysis period, patients were assigned to the improved chorea and chorea states based on the reported response rates from the FIRST-HD trial. Patients were then transferred to the long-term Markov model assuming that:

- Non-responders in the deutetrabenazine arm for the initial period would discontinue treatment. This was inconsistent with the expert advice provided with the submission that indicates that patients are likely to add-on to their underlying therapy rather than cease treatment.
- Responders in the deutetrabenazine arm for the initial period would maintain response while on treatment in the long-term period. This assumption may be reasonable but appears to require further up-titration of deutetrabenazine dose over time.
- All patients in the placebo arm (responders and non-responders in the initial period) would be non-responders in the long-term period. The persistence of non-specific treatment effects (i.e. placebo effects) is unknown however the assumption that all of these effects cease in the placebo arm but not the treatment arm after 12 weeks was not adequately justified. Additionally, the assumption that placebo patients would remain untreated was inappropriate as the majority of patients would move onto subsequent lines of therapy.

6.39 During each cycle of the Markov model, patients could remain in their current health state, discontinue treatment (and switch to being a non-responder) or die.

6.40 The modelled proportion of patients with improved chorea over time is presented below.

Figure 2: Modelled proportion of patients with improved chorea over time



Source: constructed during the evaluation using Austedo - Section 3 - CEA - 2 Nov 2020 (Final) model provided with the submission  
 Abbreviations: Deut, deutetrabenazine; Pbo, placebo

6.41 The model trace shows the initial 12-week response rates from the FIRST-HD trial followed by a gradual decrease in number of responders over time in the deutetrabenazine arm due to treatment discontinuation. The trace also shows the impact of the assumed loss of effect in the placebo arm at 12 weeks.

6.42 The vast majority of incremental QALYs (97.0%) and incremental costs (90.8%) are accrued in the extrapolated period beyond 12 weeks.

6.43 Key drivers of the economic model are summarised in the table below.

Table 10: Key drivers of the model

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Description	Method/Value	Impact
Structural assumptions	<p>The initial 12-week decision-analysis period was linked to the long-term Markov cohort model based on the following assumptions:</p> <ul style="list-style-type: none"> <li>- Non-responders in the deutetrabenazine arm for the initial period would discontinue treatment. However, patients are likely to add-on to their underlying therapy rather than cease treatment in clinical practice.</li> <li>- Responders in the deutetrabenazine arm for the initial period would maintain response while on treatment in the long-term period. This assumption may be reasonable but the dose of deutetrabenazine may need to be increased over time.</li> <li>- All patients in the placebo arm (responders and non-responders in the initial period) would be non-responders in the long-term period. The assumption that all non-specific effects (i.e. placebo effects) cease in the placebo arm but not the treatment arm after 12 weeks was not adequately justified. Additionally, the assumption that patients would remain untreated was inappropriate as the majority would move onto subsequent lines of therapy.</li> </ul>	High, favours deutetrabenazine
Health state utility values	<p>The submission argued that the generic SF-36 quality of life instrument used in the FIRST-HD trial was not sensitive enough to capture changes in motor function and there is no established method for mapping these scores to SF-6D utility values specifically for chorea symptoms. Instead the submission presented utility values for the improved chorea and chorea health states based on a sponsor-commissioned TTO study in the US general population using health state vignettes with varying chorea severity.</p> <p>The definitions of chorea severity levels were problematic as they overlap with other movement-related disorders (e.g. dystonia) experienced by patients with Huntington's disease. Additionally, the vignettes did not vary other Huntington's disease symptoms and therefore do not adequately address the importance of chorea symptoms relative to other symptoms (e.g. the utility impairment associated with chorea is likely to vary based on the patient's other behavioural/cognitive/motor symptoms and functional capacity). The magnitude of the utility difference between chorea severity levels was implausibly large (severe: 0.07, moderate-to-severe: 0.26, mild-to-moderate: 0.48, mild: 0.64) given the claim that generic instruments were not sensitive enough to capture these differences.</p> <p>The estimated TTO utility values were mapped to the improved chorea health state based on the relative proportion of responders achieving a 3-6 point reduction (assumed to have mild-to-moderate symptoms) or &gt; 6 point reduction (assumed to have mild symptoms) in TMC scores from baseline for each treatment arm in the FIRST-HD trial. Estimated TTO utility values were mapped to the chorea health state assuming that patients have moderate to severe chorea symptoms.</p> <p>The assumption that all responders have mild or mild-to-moderate symptoms and all non-responders have moderate-to-severe symptoms was inappropriate as it does not account for the distribution of chorea symptoms at baseline and during treatment.</p> <p>Overall, the estimation of health state utility values for chorea appeared unreliable and inconsistent with other data sources which suggest that the main drivers of utility loss in Huntington's disease patients are behavioural symptoms and overall functional capacity, with motor symptoms having a negligible direct impact (Hawton 2019). Additionally, data from the FIRST-HD trial showed that while deutetrabenazine was associated with a modest improvement in physical functioning compared to placebo it was not associated with any statistically significant differences in other physical or mental components of quality of life.</p>	High, favours deutetrabenazine

Description	Method/Value	Impact
Disease management costs	Disease management costs were based on resource use estimates from a clinical survey of specialists and nurses as well as an audit of treating physicians in Australia. There was inadequate documentation to adequately assess the validity of health resource use estimates. There were substantial differences in health resource use between data sources with the nurse survey results (which generally favoured deutetrabenazine) being highly discordant with other estimates. The heterogeneity of responses was not addressed in the submission and therefore the validity of the average results was uncertain.	High, favours deutetrabenazine
	Health resource use was valued using various MBS items, URG/AR-DRG items and reported service fees. The submission did not adequately justify the choice of item codes for health care resources particularly in regards to: attendance durations, use of items for specific populations (telehealth eligible patients, patients aged > 65 years), use of temporary items for COVID-19, use of items with frequencies that exceed MBS caps, and levels of complexity for emergency room and hospitalisation visits.	
	Estimated disease management costs were mapped to the improved chorea/chorea disease states assuming that all patients with improved chorea are controlled and all patients with chorea are uncontrolled. This assumption was not appropriate as survey respondents stated that the determination of whether patients were adequately managed was based on a global impression rather than the TMC response criteria used to define health states. Additionally, even if TMC response criteria were used it would be inappropriate to assume that all responders have controlled disease and all non-responders have uncontrolled disease as it does not account for the distribution of chorea symptoms at baseline and during treatment.	

Source: Constructed during the evaluation

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; MBS, Medicare Benefits Schedule; TMC, Total Maximal Chorea; TTO, time-trade-off; URG, urgency-related group; US, United States.

6.44 The results of the modelled economic evaluation are summarised below.

**Table 11: Results of the modelled economic evaluation**

Component	Deutetrabenazine	Placebo	Increment
Costs	\$ [redacted]	\$215,928	\$ [redacted]
QALYs	2.8201	1.8949	0.9252
<b>Incremental cost per QALY gained</b>			<b>\$ [redacted]<sup>1</sup></b>

Source: Table 3-25 of the submission

Abbreviations: QALY, quality adjusted life years

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000/QALY gained

6.45 Based on the economic model, treatment with deutetrabenazine was associated with an incremental cost per QALY gained of \$55,000 to < \$75,000 compared to placebo for the treatment of chorea associated with Huntington’s disease. The cost-effectiveness estimate should not be considered reliable given poorly justified assumptions linking the decision tree and Markov cohort models, the implausibly large differences in health state utility values, and highly discordant estimates of disease management costs (see Table 9).

6.46 The cost effectiveness estimate was based on clinical inputs from the first-line treatment setting which are unlikely to be generalisable to the subsequent-line setting.

6.47 The results of the sensitivity analyses indicated that the model was most sensitive to the assumptions linking the decision tree and Markov cohort models, health state utility values and disease management costs.

Table 12: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case</b>	\$ [redacted]	0.9252	\$ [redacted] <sup>1</sup>
<b>Assumptions linking decision analysis and Markov cohort model (base case: deutetrabenazine non-responders discontinue therapy, deutetrabenazine responders maintain benefit while on treatment while placebo responders/non-responders discontinue therapy)</b>			
Deutetrabenazine non-responders continue therapy	\$ [redacted]	0.9252	\$ [redacted] <sup>2</sup>
Deutetrabenazine responders lose benefit after 5 years	\$ [redacted]	0.6719	\$ [redacted] <sup>2</sup>
Deutetrabenazine responders lose benefit after 3 years	\$ [redacted]	0.4732	\$ [redacted] <sup>3</sup>
Placebo responders maintain benefit for 1 year	\$ [redacted]	0.8529	\$ [redacted] <sup>4</sup>
Placebo responders maintain benefit for 5 years	\$ [redacted]	0.5398	\$ [redacted] <sup>3</sup>
Placebo responders maintain benefit for 10 years	\$ [redacted]	0.2420	\$ [redacted] <sup>5</sup>
<b>Health state utility values (base case: improved chorea with deutetrabenazine 0.555, improved chorea with placebo 0.489, chorea 0.257 based on sponsor commission TTO study)</b>			
Same utility in the improved chorea health state for both treatment arms based on deutetrabenazine value (0.555)	\$ [redacted]	0.9191	\$ [redacted] <sup>1</sup>
Same utility in the improved chorea health state for both treatment arms based on placebo value (0.489)	\$ [redacted]	0.7150	\$ [redacted] <sup>4</sup>
Reduce improved chorea utility benefits by 50% (deutetrabenazine 0.406, placebo 0.373) compared to chorea health state	\$ [redacted]	0.4625	\$ [redacted] <sup>6</sup>
Reduce improved chorea utility benefits by 75% (deutetrabenazine 0.332, placebo 0.315) compared to chorea health state	\$ [redacted]	0.2312	\$ [redacted] <sup>7</sup>
Reduce improved chorea utility benefits by 90% (deutetrabenazine 0.287, placebo 0.280) compared to chorea health state	\$ [redacted]	0.0924	\$ [redacted] <sup>8</sup>
Utility gain associated with improved chorea state estimated based on Hawton 2019 assuming a 28 point difference in total motor score (equivalent to the whole TMC scale; $0.0002756 \times 28 = 0.0077$ ) Improved chorea: 0.2648, chorea: 0.2571	\$ [redacted]	0.0235	\$ [redacted] <sup>9</sup>
<b>Disease management and fracture costs (base case: resource utilisation based on weighted average results from sponsor-commission clinical survey and audit, valuation based on various MBS items, URG/AR-DRG items and reported service fees, no separate estimation of fracture costs)</b>			
Resource use based on physician responses from survey	\$ [redacted]	0.9252	\$ [redacted] <sup>6</sup>
Resource use based on nurse responses from survey	\$ [redacted]	0.9252	\$ [redacted] <sup>10</sup>
Resource use based on physician audit	\$ [redacted]	0.9252	\$ [redacted] <sup>6</sup>
Resource item costs doubled	-\$ [redacted]	0.9252	Dominant
Resource item costs halved	\$ [redacted]	0.9252	\$ [redacted] <sup>2</sup>
Include additional weekly costs of fracture	\$ [redacted]	0.9252	\$ [redacted] <sup>1</sup>

Source: 3-28 of the submission

The redacted values correspond to the following ranges:

- <sup>1</sup> \$55,000 to < \$75,000
- <sup>2</sup> \$95,000 to < \$115,000
- <sup>3</sup> \$155,000 to < \$255,000
- <sup>4</sup> \$75,000 to < \$95,000
- <sup>5</sup> \$455,000 to < \$555,000
- <sup>6</sup> \$115,000 to < \$135,000
- <sup>7</sup> \$255,000 to < \$355,000

<sup>8</sup> \$555,000 to < \$655,000

<sup>9</sup> > \$1,055,000

<sup>10</sup> \$45,000 to < \$55,000

6.48 The ESC considered there were numerous issues with the structure and inputs of the economic model, including:

- The available evidence (primarily tetrabenazine-naïve patients) models a different population to the requested PBS listing. The ESC considered it was unreasonable to expect that the proposed PBS population would achieve the same outcomes as the modelled population.
- The assumption that all patients receiving deutetrabenazine will benefit was implausible and the model should have included a proportion of patients who switch to deutetrabenazine and receive no extra benefit.
- For the utility values, the submission only reported on the physical component scores from the SF-36 instrument used in the trial and did not include the overall utilities. The ESC noted the argument in the PSCR that the SF-36 instrument is not sensitive to chorea-specific quality of life impacts and considered this may be plausible but this raised the question of how important chorea aspects of HD are relative to other aspects of the disease, which was not explored in the submission. The ESC considered the decrements between increasing chorea severity states to be implausibly large and agreed the importance of this symptom relative to other QoL aspects of HD needed to be explored further.
- The costs used in the model were overly simplistic. The ESC noted the submission assumed no differences in concomitant medication costs and did not model these, however the ESC noted the submission assumed patients would continue other medications (such as antipsychotics) and therefore the assumption of no benefit in the placebo arm is likely implausible. The ESC also considered the health state management costs in the model to be highly uncertain as the mental health aspects varied greatly between the chorea improved and unimproved states and the magnitude of impact of deutetrabenazine treatment on mental health was not well defined in the submission.
- The Markov trace appears to implausibly apply a benefit at baseline (t=0) and did not include any half-cycle adjustment. Further, the ESC considered the assumption that the effect of placebo would reduce to 0 at 12 weeks was unjustified and implausible.
- The time horizon maybe be problematic as the ICER appeared to plateau at 3–4 years in the model.
- The ESC noted the model was highly sensitive to changes in assumptions relating to placebo response rate, utility score inputs and health resource usage and specifically noted that sensitivity analyses increasing the placebo response to time to 5 or 10 years increased the ICER to ~\$155,000 to < \$255,000/QALY and almost \$455,000 to < \$555,000 per QALY respectively; and further analyses using alternative utility scores based on Hawton 2019 increased the ICER to more than > \$1,055,000 per QALY.

- 6.49 Given the uncertainty of many of the model assumptions and inputs and sensitivity to these factors, the ESC considered the model lacked face validity.
- 6.50 The ESC advised that as the requested clinical place was inappropriate, any future resubmission should be for listing in a first line setting with new clinical and economic analyses.

**Drug cost/patient/month**

6.51 The estimated drug cost per patient per month is summarised in the table below.

**Table 13: Deutetrabenazine drug cost per patient**

	FIRST-HD	ARC-HD-ROLLOVER	Economic model	Financial estimates
Dose titration included	Yes	Yes	Yes	No
Mean daily dose	39.7 mg	42.6 mg	39.7 mg	39.7 mg
Distribution of dosing	NR	NR	5% 6 mg tab (39.7 mg/day) 25% 9 mg tab (39.7 mg/day) 70% 12 mg tab (39.7 mg/day)	5% 6 mg tab (24 mg/day) 25% 9 mg tab (36 mg/day) 34% 12 mg tab (36 mg/day) 36% 12 mg tab (48 mg/day)
Adherence estimate (%)	93.99 (8.055)	92.28 (13.524)	-	93.99
Treatment discontinuation	0.70%/4 weeks	1.09%/4 weeks	1.09%/4 weeks	-
Cost per 30 days	-	-	\$ [REDACTED] <sup>1</sup>	\$ [REDACTED] <sup>2</sup>

Source: Constructed during the evaluation using Austedo – Section 3 – CEA – 2 Nov 2020 (Final) and Austedo – Section 4 -v106 – 2 Nov 2020 (final) – Base case spreadsheets provided with the submission

<sup>1</sup> (5% × \$ [REDACTED] [cost per mg of 6 mg strength=\$ [REDACTED]/720 mg] × 39.7 mg/day × 30 days)+(25% × \$ [REDACTED] [cost per mg of 9 mg strength=\$ [REDACTED]/1080 mg] × 39.7 mg/day × 30 days)+(70% × \$ [REDACTED] [cost per mg of 12 mg strength=\$ [REDACTED]/1,440 mg] × 39.7 mg/day × 30 days); does not incorporate dose titration or treatment discontinuation

<sup>2</sup> (5% × \$ [REDACTED] [cost per tablet of 6 mg strength=\$ [REDACTED]/120] × 120 tablets per 30 days [4 tablets per day])+(25% × \$ [REDACTED] [cost per tablet of 9 mg strength=\$ [REDACTED]/120] × 120 tablets per 30 days [4 tablets per day])+(34% × \$ [REDACTED] [cost per tablet of 12 mg strength=\$ [REDACTED]/120] × 90 tablets per 30 days [3 tablets per day])+(36% × \$ [REDACTED] [cost per tablet of 12 mg strength=\$ [REDACTED]/120] × 120 tablets per 30 days [4 tablets per day]); weighted cost per 30 day period of \$ [REDACTED] × 93.99% adherence

6.52 For comparison, the drug cost for tetrabenazine ranges from \$81 (25 mg total daily dose) to \$645 (200 mg total daily dose) per month.

**Estimated PBS usage & financial implications**

6.53 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of deutetrabenazine. Key inputs are summarised in the table below.

Table 14: Key inputs for financial estimates

Data	Value	Source	Comment
<b>Eligible population</b>			
Prevalence of Huntington's disease	8 cases per 100,000 individuals	Prevalence estimate for 1999 based on the Huntington Disease Register of Victoria and additional case ascertainment through genetic testing (Tassicker 2009)	This appeared reasonable for the base case value however plausible estimates of disease prevalence in Australia range from 6-12 cases per 100,000 individuals.
Proportion with troublesome symptoms requiring treatment	90%	Assumption based expert advice from sponsor's advisory board (█%), weighted average response from a sponsor commissioned clinical survey of specialists and nurses (█%); and published estimates from an international survey of Huntington's disease physicians (85%; Burgunder 2011)	<p>The estimates from the clinical survey and international survey could not be validated. The average proportion of patients treated was █% from specialists and █% from nurses based on the clinical survey. The international survey reported the proportion of physicians who would not nominate a first-line choice; it did not report the proportion of patients treated for chorea.</p> <p>The estimate was also inconsistent with the results of the sponsor-commissioned physician audit which indicated that approximately 63% of patients were treated with chorea symptoms.</p> <p>Other publications provided with the submission also suggested lower estimates:</p> <ul style="list-style-type: none"> <li>- 39% of European Huntington's disease patients (not limited to patients with chorea symptoms) used dyskinctic medications (Orth 2010)</li> <li>- 75% of American Huntington's disease patients with chorea used dyskinctic medications (Simpson 2016)</li> </ul>
Distribution of first-line treatments for chorea symptoms	Tetrabenazine: █% Antipsychotic: █% Other: █%	Based on sponsor commissioned survey of specialists and nurses (results from specialists only).	<p>The estimates used in the base case were uncertain given the discordant results between physicians and nurses (tetrabenazine: █%, antipsychotics: █%, anticonvulsants: █%, antidepressants █%, anxiolytics: █%).</p> <p>Additionally the estimated number of patients using tetrabenazine for chorea (500 to &lt; 5000 first-line, &lt; 500 second-line) is substantially higher than expected based on PBS scripts for tetrabenazine (500 to &lt; 5000 annual scripts) particularly given that the PBS listing of tetrabenazine includes a broader population with other diseases including tardive dyskinesia (likely to be a relatively large proportion of use).</p>

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Data	Value	Source	Comment
Proportion of patients failing first-line therapies	Tetrabenazine: █% Antipsychotic: █% Other: █%	Based on expert advice from sponsor's advisory board	Estimated first-line treatment failures were widely different between data sources: - Clinical survey: █% (all treatments) - Physician audit: █% (all treatments) - Advisory board: █% (weighted estimate for tetrabenazine, antipsychotic and other treatment failure)
Proportion of antipsychotic/ other treatment patients receiving second-line treatment with tetrabenazine	100%	Assumption	This assumption was inconsistent with estimates from all data sources which indicated that patients receive a variety of monotherapies, combinations therapies or no therapy.
Proportion of patients failing second-line tetrabenazine	█%	Based on expert advice from sponsor's advisory board for second-line treatment failure	Second-line treatment failure rates were not specific to tetrabenazine.
Proportion of patients with chorea symptoms who have suboptimal control	10%	Assumption	No justification was provided for the numerical value.  Applying this assumption to the broader population of patients with chorea symptoms was not appropriate as patients still require prior exposure to tetrabenazine
<b>Treatment utilisation</b>			
Deutetrabenazine uptake rate	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4: █% Yr 5: █% Yr 6: █%	Based on projections by the Sponsor	The data informing the projections were not provided in the submission. The uptake of deutetrabenazine in clinical practice is unclear particularly given the uncertainty associated with the proposed place in therapy.

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Data	Value	Source	Comment
Distribution of patients across dose strengths	4 x 6mg tabs: 5% 4 x 9mg tabs: 25% 3 x 12mg tabs: 34% 4 x 12mg tabs: 36%	Back-calculation based on the average total daily dose reported during the maintenance period of the FIRST-HD trial	<p>The utilisation estimates do not account for use (and wastage) during the initial titration period.</p> <p>The back-calculation results in an average dose that was the same as the FIRST-HD trial (39.7 mg per day). However, many different combinations may achieve this same dose with different costs. The median dose of 36 mg per day from the model was lower than the median dose of 42 mg per day reported in the FIRST-HD trial.</p> <p>The utilisation estimates assume no patients will use doses &gt; 48 mg per day which was inconsistent with available long-term data which suggest maintenance of treatment effect may require dose escalation (43% of ARC-HD patients exceeded the proposed maximum dose).</p> <p>Conversely, the submission noted observational data suggesting that dosing of deutetrabenazine may be lower in clinical practice (Ayyagari 2020). However, this data was only available as a poster presentation and there was insufficient information (regarding treatment rules, co-payments, patient characteristics and other factors) to assess the applicability of this data source.</p>
<b>Other impacts</b>			
Reduction in ED/hospitalisation visits	Yr 1: -452 Yr 2: -579 Yr 3: -712 Yr 4: -790 Yr 5: -810 Yr 6: -830	Based on sponsor commissioned survey of specialists and nurses (results from nurses only). Resource use based on the difference between controlled and uncontrolled chorea symptoms assuming that all patients treated with deutetrabenazine achieve control	<p>There was inadequate documentation to adequately assess the validity of health resource use estimates.</p> <p>Additionally, the assumption that all patients treated with deutetrabenazine achieve control and all other patients fail was inconsistent with the available clinical data.</p> <p>Health resource use is discussed further in Section 3.6 of the commentary.</p>

Source: Table 1-5, Table 4-4, Table 4-5, Table 4-6, Table 4-8, Table 4-12, Table 4-13, Table 4-14 of the submission  
Abbreviations: DPMQ, dispensed price per maximum quantity; ED, emergency department

6.54 The table below presents the estimated use and financial implications of deutetrabenazine over 6 years of listing based on the proposed effective prices.

**Table 15: Estimated utilisation and cost of deutetrabenazine**

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Eligible population	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Deutetrabenazine uptake rate	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %	█ <sup>1</sup> %
Patients treated with deutetrabenazine	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Scripts per year for 6 mg tablets	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Cost of 6 mg dose strength (effective DPMQ less co-pay)	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
Scripts per year for 9 mg tablets	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost of 9 mg dose strength (effective DPMQ less co-pay)	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
Scripts per year for 12mg tablets	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost of 12 mg dose strength (effective DPMQ less co-pay)	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>	\$█ <sup>4</sup>
<b>Net cost to the PBS/RPBS</b>	<b>\$█<sup>3</sup></b>	<b>\$█<sup>4</sup></b>	<b>\$█<sup>4</sup></b>	<b>\$█<sup>4</sup></b>	<b>\$█<sup>4</sup></b>	<b>\$█<sup>4</sup></b>
<b>Other budget impacts</b>						
Reduction in ED/hospitalisation visits	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>2</sup>
Cost savings of ED/hospitalisation visits	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>

Source: Table 4-4, Table 4-5, Table 4-6, Table 4-8, Table 4-12, Table 4-13, Table 4-14 of the submission

Abbreviations: DPMQ, dispensed price per maximum quantity; ED, emergency department

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500<sup>3</sup> \$0 to < \$10 million

<sup>4</sup> \$10 million to < \$20 million

- 6.55 The net cost of listing deutetrabenazine on the PBS/RPBS was estimated to be up to \$10 million to < \$20 million in the sixth year of listing, with a cumulative total cost of \$80 million to < \$90 million over six years.
- 6.56 The submission also estimated a cost saving to State/Territory governments over six years due to reduced emergency room visits and hospitalisations.
- 6.57 The utilisation/financial estimates for deutetrabenazine are highly uncertain given the unknown size of the eligible population, unsupported uptake predictions, unknown dosing in clinical practice and inadequately justified estimates of emergency room visits and hospitalisations for the management of chorea (see key inputs table above).
- 6.58 Additionally, the submission did not adequately address the potential for leakage into the first-line treatment setting given that the available data support first-line treatment and the proposed criteria are highly subjective with no well accepted definitions of response and intolerance.
- 6.59 Sensitivity analyses presented in the submission indicated that budget impact estimates were highly sensitive to prevalence estimates, uptake rates and deutetrabenazine doses.

- 6.60 DUSC considered the estimates presented in the submission to be unreliable due to likely use in first line. The main issues were:
- The utilisation and financial estimates for deutetrabenazine are highly uncertain given the unknown size of the eligible population, unsupported uptake predictions, unknown dosing in clinical practice and inadequately justified estimates of emergency room visits and hospitalisations for the management of chorea.
  - The submission’s placement of deutetrabenazine as second and third line therapy likely will not match its use in practice.
  - The estimate of prevalence should be applied to the estimated Australian population rather than multiplying the eligible population by 102.5% each year.
  - The proportion of patients with troublesome symptoms requiring treatment was likely overestimated.
  - The estimate of patients that would meet the proposed PBS restrictions or are currently receiving sub-optimal chorea control was problematic and included substantial uncertainty. However, this step should be removed or altered to account for first line therapy.

### **Quality Use of Medicines**

- 6.61 The submission stated the sponsor’s intent to conduct quality use of medicines activities to support the listing of deutetrabenazine for the treatment of chorea associated with Huntington’s disease.

### **Financial Management – Risk Sharing Arrangements**

- 6.62 In its Pre-PBAC Response, the sponsor indicated it was amenable to a Risk Sharing Arrangement.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of deutetrabenazine for the treatment of chorea associated with Huntington’s Disease (HD) in patients who have failed prior tetrabenazine treatment due to intolerance or inadequate response. The PBAC considered the proposed clinical place of deutetrabenazine as second line treatment was inappropriate and considered that the most appropriate clinical place for deutetrabenazine was first-line treatment as an alternative to tetrabenazine (irrespective of prior or co-therapy with an antipsychotic). The PBAC further noted the evidence base was primarily as a first-line treatment option and there was no evidence provided to support use in the requested place in therapy. The PBAC also considered the economic model constructed for the proposed place in therapy was unreliable for decision-making.
- 7.2 The PBAC acknowledged the devastating impact HD has on patients and their families and considered there was a high clinical need for new therapies to assist patients with

the wide range of debilitating physical and mental impacts of this disease and improve quality of life. The Committee considered that whilst deutetrabenazine likely represents an effective treatment option for the treatment of chorea symptoms in people with HD, the most appropriate approach for considering its comparative efficacy, safety and cost-effectiveness was to compare it to tetrabenazine, its non-deuterated analogue.

- 7.3 The PBAC did not accept the arguments in the submission that the placement of deutetrabenazine as a subsequent line of therapy following failure, intolerance or inability to titrate to an effective dose of tetrabenazine was appropriate and noted the sponsor acknowledged the requested placement was primarily for commercial reasons so as to not be compared to tetrabenazine. While acknowledging it can be challenging for sponsors to be expected to price a new drug based on a comparison to old drugs for commercial reasons, the PBAC considered that the submission should be considered on its merits and a commercial imperative was not a valid reason to consider deutetrabenazine differently to other applications. The PBAC noted the pre-PBAC response proposed revisions to the restriction and an RSA to support the positioning as subsequent-line to tetrabenazine, however it was not considered these adjustments were a reasonable way forward.
- 7.4 The PBAC considered the requested restriction also inappropriately restricted treatment to require prior treatment with antipsychotics for patients with co-morbid conditions and considered that any potential listing for deutetrabenazine should not restrict the population on this basis; rather that a listing should reflect how tetrabenazine (irrespective of antipsychotic treatment) is used in practice and should not dictate how clinicians manage other co-morbid conditions. Further, the PBAC was concerned that a second line listing would result in substantial use of deutetrabenazine as a first-line therapy, given the tolerability profiles of tetrabenazine and deutetrabenazine.
- 7.5 The PBAC noted very limited evidence was presented to support sequential use of tetrabenazine and deutetrabenazine (the ARC-SWITCH study) and no clinical trial evidence to support sequential use in patients who had failed or could not tolerate tetrabenazine. The PBAC noted the pre-PBAC response included expert advice on how the pharmacokinetic differences between tetrabenazine and deutetrabenazine can provide a rationale for circumstances where deutetrabenazine may be useful in subsequent-line settings after the prior failure of tetrabenazine. The PBAC acknowledged the expert opinions provided in the pre-PBAC response but did not consider it was sufficient evidence to value the use in subsequent lines of therapy.
- 7.6 Based on its consideration of the most appropriate clinical place for deutetrabenazine, the PBAC considered the nominated comparator of placebo was not appropriate and considered tetrabenazine was the most appropriate comparator.
- 7.7 The PBAC noted the clinical trials presented were not reflective of the requested populations. In particular, the PBAC noted the key randomised controlled trial, FIRST-

HD, and the open-label extension, ARC-HD, studies were predominantly in the first-line setting. Also, the limited number of patients who switched from tetrabenazine in the ARC-HD-SWITCH prospective longitudinal study were also not reflective of the requested listing as these patients were stable on current treatment, whereas the requested listing was for patients who had failed or were intolerant to or unable to titrate to an effective dose of tetrabenazine. Therefore, the PBAC agreed with the ESC that the clinical evidence was uninformative for the requested population.

- 7.8 The PBAC considered based on the evidence presented, deutetrabenazine was likely effective at reducing chorea symptoms in patients with HD in a first-line setting, compared to placebo; although the nominated minimum clinically important difference (MCID) of a change in total maximum chorea (TMC) score of 2-3 points was not well supported and TMC was not used in clinical practice.
- 7.9 The PBAC noted the indirect comparison (Rodrigues 2017) identified during the evaluation did not find any significant differences in terms of chorea or broader motor symptoms between deutetrabenazine and tetrabenazine in the first-line setting.
- 7.10 The PBAC considered the claim of non-inferior safety compared to placebo was not adequately supported in the FIRST-HD trial and ARC-HD patient cohorts given the higher rates of treatment-related adverse events with deutetrabenazine (predominantly somnolence, dry mouth and fatigue).
- 7.11 The PBAC noted the indirect comparisons of deutetrabenazine and tetrabenazine presented in the evaluation, from Rodriguez 2017 and Claassen 2017, found deutetrabenazine appeared to have a tolerability advantage over tetrabenazine.
- 7.12 The PBAC agreed with the ESC and considered the economic model presented was not informative for decision-making. The PBAC noted the issues with the model structure and inputs raised by the ESC (paragraph 6.48) created significant uncertainties and therefore considered it could not be relied upon for considering the cost-effectiveness of deutetrabenazine.
- 7.13 The PBAC agreed with the DUSC advice (paragraph 6.60) and considered the utilisation estimates were complex and highly uncertain. The PBAC considered there was a substantial risk of use outside of the proposed restriction as first-line treatment. The PBAC also considered the overall financial impact was very high and poorly justified given deutetrabenazine will be used to replace tetrabenazine.
- 7.14 The PBAC agreed with the ESC and DUSC that the requested clinical place was inappropriate, and any future resubmission should be for listing in a first line setting with new clinical, economic and financial analyses.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

The Sponsor will continue to work with the PBAC and the Department to make deutetrabenazine (Austedo) available to Australian patients.