

**7.04 NABIXIMOLS,  
Oromucosal spray, 8 mg per dose, 90 doses,  
Sativex<sup>®</sup>,  
Emerge Health Pty Ltd**

**1 Purpose of submission**

- 1.1 The resubmission requested a Section 100 Highly Specialised Drugs Program (Community Access), Authority Required (STREAMLINED) listing of nabiximols for the adjunctive treatment of moderate to severe spasticity in patients with multiple sclerosis (MS) who have not adequately responded to oral anti-spasticity agents.
- 1.2 Listing was requested on the basis of a cost-effectiveness and cost-utility analysis versus standard care (SC) (i.e. oral anti-spasticity treatment) alone.
- 1.3 Nabiximols is a spray containing a combination of 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD) and lesser amounts of other cannabinoids (56mg total cannabinoids). Together these cannabinoids exert different effects on many systems including the GABAergic, glutaminergic, dopaminergic, cholinergic, serotonergic and opioid systems. Key components of the clinical issue addressed by the resubmission are shown in Table 1.

**Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)**

Component	Description
Population	Patients with moderate to severe spasticity <sup>1</sup> due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy <sup>2</sup>
Intervention	Nabiximols 80mg/mL oral spray <u>as adjunctive therapy to standard care, which includes oral anti-spasticity medication</u> , titrated up to a maximum of 12 sprays per day until optimum symptom relief is achieved
Comparator	Standard care; that being oral anti-spasticity medication
Outcomes	Primary: Percentage of patients who responded after 12 weeks of randomised treatment (a Numerical Rating Scale (NRS) score of 30% or more). (Patients who entered the randomised treatment period of the trial were required to have displayed an improvement in the NRS score of 20% or more in the preliminary 4-week treatment phase) Secondary: Percentage of patients who achieved improvement of 20% on the NRS spasticity scale; and percentage of patients who responded after 4 and 8 weeks of randomised treatment, change from baseline in spasticity NRS scores after 4 and 8 weeks of randomised treatment. Change from baseline in various parameters including spasm, sleep disruption, pain, SF-36 and EQ-5D scores
Clinical claim	Nabiximols, as adjunctive therapy, is superior in terms of efficacy and <u>inferior in terms of safety</u> compared to standard care (anti-spasticity medication alone) in patients with moderate to severe spasticity due to MS who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy

<sup>1</sup> Moderate to severe spasticity is defined by Numeric Rating Scale (NRS) Score  $\geq 4$ .

<sup>2</sup> Clinically significant improvement in spasticity related symptoms is defined as a  $\geq 20\%$  improvement in spasticity severity over the initial treatment of 4 weeks using the Numerical Rating Scale (NRS).

Underlining refers to differences from previous submission

Source: Table 9, p3 of the resubmission.

## 2 Background

### **Registration status**

2.1 Nabiximols was approved for registration by the TGA in November 2012 for symptomatic treatment of spasticity in patients with moderate to severe spasticity due to MS who have not adequately responded to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

### **Previous PBAC consideration**

2.2 Nabiximols was previously considered for this indication by the PBAC at its July 2013 meeting.

2.3 Key issues of outstanding concern and how the resubmission addressed these are detailed in Table 2.

**Table 2: Summary of key matters of concern**

Component	Matter of concern	How the resubmission addresses it
Clinical effectiveness	The clinical data did not support a claim of superior effectiveness (Section 9). The submission relied on clinical data from Novotna 2011 with supportive data from Collin 2007, Collin 2010 and Wade 2004.	In addition to Novotna 2011, Collin 2007 and Collin 2010, two new relevant trials (Markovà 2019 and Vachovà 2014) were identified.
	The enrichment design of the key Novotna 2011 trial made it difficult to generalise results (Section 9).	Partially addressed. Markovà 2019 also had an enrichment design, however Vachovà 2014 supported the claim of superior effectiveness, and it did not have an enrichment design.
	There was a high risk of bias in the trials suggesting that the effect size was likely to be overestimated (Section 9).	Additional trials still considered to have a high risk of bias, particularly Markovà 2019.
	Small differences in outcomes were demonstrated that were of questionable clinical significance (Section 9).	Markovà 2019 demonstrated a higher magnitude of benefit compared to Novotna 2011. Markovà 2019 enrolled fewer patients (106 in Phase B versus 241 in Novotna Phase B) and had a different trial design that may contribute to the difference in benefit observed.
Economic analysis	Was biased in favour of nabiximols since it was not clear if the effect size from Novotna 2011 was representative of the likely effect in the proposed population (Section 10).	Markovà 2019 still had an enrichment design and further bias was evident based on the requirement for Phase A patients to have demonstrated a 20% improvement, and then enter a washout phase of up to 4 weeks. Only those patients whose improvement in NRS score had reduced by $\geq 80\%$ during the washout phase were then randomised into Phase B.
	Extrapolation of effect was biased in favour of nabiximols by the assumption that standard care patient's spasticity worsens and stabilises for nabiximols treated patients (Section 10).	No change in spasticity over time was assumed in resubmission for both treatment arms.
	Efficacy in the supportive trials was not accounted for in the model (Section 10).	Not addressed.
	Adverse events were not included and disutilities from adverse events were not included (Section 10).	Adverse events and disutilities were costed and included, albeit from a separate meta-analysis by Wang 2008.
Financial analysis	Potential for wastage was not accounted for (Section 12).	Not addressed.

Section references refer to the 5-15 Nabiximols Public Summary Document (PSD) at the July 2013 PBAC Meeting  
Source: Nabiximols PSD, July 2013, PBAC Meeting and sections 1-4 of the resubmission.

### 3 Requested listing

3.1 The proposed listing with Secretariat additions in italics and deletions in strikethrough is presented below.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
NABIXIMOLS 80 mg/mL spray, 3 x 10 mL	NEW	1	3	0	Sativex®	Emerge Health Pty Ltd

Public Summary Document – March 2020 PBAC Meeting

<b>Category / Program:</b> General Schedule Section 100 – Highly Specialised Drugs Program (Community Access)
<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>Restriction Level / Method:</b> <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
<b>Severity:</b> Moderate to severe
<b>Condition:</b> <del>Multiple sclerosis related spasticity</del> spasticity
<b>Indication:</b> <del>Multiple sclerosis related spasticity</del> Moderate to severe spasticity
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> <del>Patient must not have adequately responded to oral anti-spasticity agents</del> AND The treatment must be adjunctive treatment <del>Patient must have spasticity due to multiple sclerosis</del> AND Patient must have moderate to severe spasticity, as defined by a numeric rating scale score of 4 or greater AND The treatment must be as adjunctive therapy following an inadequate response to prior anti-spasticity treatment AND <b>Treatment criteria:</b> Must be treated by a neurologist or rehabilitation physician. AND <b>Population criteria:</b> Patient must be experiencing moderate to severe spasticity <b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. <b>Caution:</b> <del>Maximum recommended dose of nabiximols should not be exceeded.</del> The risk of drug dependency is high. Care must be taken to comply with the provisions of State/ and Territory law when prescribing and administering this drug.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
NABIXIMOLS 80 mg/mL spray, 3 x 10 mL	NEW	12	3	53	Sativex® Emerge Health Pty Ltd

<b>Category / Program:</b> General Schedule Section 100 – Highly Specialised Drugs Program (Community Access)
<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>Restriction Level / Method:</b>
<input type="checkbox"/> Unrestricted benefit
<input type="checkbox"/> Restricted benefit
<input type="checkbox"/> Authority Required – In Writing
<input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
<input checked="" type="checkbox"/> Authority Required – Streamlined
<b>Severity:</b> <del>Moderate to severe</del>
<b>Condition:</b> <del>Multiple sclerosis related spasticity</del> spasticity
<b>Indication:</b> <del>Multiple sclerosis related spasticity</del> Moderate to severe spasticity
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
<del>Patient must not have adequately responded to oral anti-spasticity agents</del>
<b>AND</b>
The treatment must be adjunctive treatment
<b>AND</b>
<del>Patient must have spasticity due to multiple sclerosis</del>
<b>AND</b>
<del>Patient must have previously received PBS-subsidised treatment with this drug for this condition</del>
<b>AND</b>
<del>Patient must have demonstrated or maintained an adequate response to PBS subsidised therapy as defined by a 20% or greater improvement in Numeric Rating Scale score from baseline</del>
<b>AND</b>
<del>The treatment must be as adjunctive therapy following an inadequate response to prior anti-spasticity treatment</del>
<b>Treatment criteria:</b>
Must be treated by a neurologist or rehabilitation physician.
<b>AND</b>
<b>Population criteria:</b>
<del>Patient must be experiencing moderate to severe spasticity</del>
<del>No increase in the maximum number of repeats may be authorised.</del>
<b>Caution:</b> <del>Maximum recommended dose of nabiximols should not be exceeded.</del>
<del>The risk of drug dependency is high.</del>
<del>Care must be taken to comply with the provisions of State and Territory law when prescribing and administering this drug.</del>
<b>Definitions:</b> <del>Moderate to severe spasticity is defined by Numeric Rating Scale Score <math>\geq 4</math></del>

3.2 The submission requested a Section 100 Highly Specialised Drugs Program (Community Access), Authority Required (STREAMLINED) listing. A General Schedule listing may be more appropriate for nabiximols, given its administration does not require an institutional setting. Further, an Authority Required (telephone/electronic) listing may be more appropriate for nabiximols due to the risk of use in other indications. The Pre-PBAC Response indicated the Sponsor was amenable to a General Schedule, Authority Required (telephone/electronic) listing.

3.3 Based on the mean trial doses used in Markovà 2019 at Week 12 (7.3 doses/day) and the doses reported in observational studies, the requested number of units of two packs of three would provide more than the quantity required for 2 months of treatment for continuing treatment. The ESC considered the requested maximum

quantities may be too high and require consideration given the requested streamlined authority listing and the potential for diversion.

- 3.4 The requested listing did not include criteria for re-trialling nabiximols after a treatment failure. The ESC considered that it would be appropriate to allow patients to re-trial therapy at a later time as patients may become responders to nabiximols as their condition progresses. The Pre-PBAC Response stated there was no clinical trial evidence to support the re-trial of patients following a treatment failure and that the Sponsor would accept the decision of the PBAC as to whether patients should be allowed to re-trial nabiximols.
- 3.5 The requested restriction differed from the previous submission in that it required patients to use nabiximols as adjunctive therapy, the option for patients to be intolerant to oral anti-spasticity medication has been removed, and the patient population has been broadened from 'severe', to 'moderate to severe' spasticity.

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

## **4 Population and disease**

- 4.1 Multiple sclerosis is an inflammatory, neurodegenerative autoimmune disease of the central nervous system (CNS) where the patient's own immune system attacks the nerve's protective sheath formed by myelin, resulting in the demyelisation and then transection of neurons' axons in the brain, spinal cord, and optic nerves, delaying or blocking the propagation of electrical potentials through the neuronal pathways. Spasticity has been reported by more than 80% of patients with MS. It reduces mobility and is associated with continuous muscle rigidity and often painful muscular spasms and weakness. In older patients and as MS progresses, the severity of spasticity tends to increase.
- 4.2 The resubmission sought listing in patients with MS-related moderate to severe spasticity (defined as a baseline Numerical Rating Scale for spasticity (NRS)  $\geq 4$ ) that have not responded adequately to oral anti-spasticity agents.
- 4.3 The ESC noted local and international guidelines and position statements suggest the use of cannabinoids in refractory spasticity may be useful in some patients.<sup>1, 2</sup>

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

## **5 Comparator**

- 5.1 The nominated comparator of standard care (SC) alone is the same as for the previous submission. Standard care was defined as oral anti-spasticity medication, which

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<sup>1</sup> <https://www.racgp.org.au/advocacy/position-statements/view-all-position-statements/clinical-and-practice-management/medical-cannabis#ref-num-7>

<sup>2</sup> <https://www.nice.org.uk/guidance/ng144/chapter/Recommendations#spasticity>

includes baclofen, tizanidine (not registered in Australia), diazepam, clonazepam, gabapentin and dantrolene. The July 2013 submission defined standard care as multi-disciplinary involving physiotherapy and pharmacotherapy (including oral anti-spasticity agents, botulinum toxin and intrathecal baclofen). The PBAC previously considered that “the nominated comparator was not appropriate for all the patient groups represented in the PBS restriction [(i) anti-spasticity agents have failed to produce adequate relief (partial responders), (ii) intolerant to anti-spasticity agents and (iii) tried and failed anti-spasticity agents (non-responders)]...and that a comparison with the second-line therapy of oral baclofen dose escalation alone or in combination with dantrolene or diazepam..., should have been included” (section 6, nabiximols PSD, July 2013). The ESC considered the nominated comparator in the resubmission was appropriate, given that the requested restriction for nabiximols was adjunctive to anti-spasticity medications (rather than replacing anti-spasticity medications as proposed in the previous submission).

- 5.2 The ESC noted other medicinal cannabis products, available via the TGA Special Access Scheme (Category B) or Authorised Prescriber programs, may substitute for nabiximols in practice. The ESC noted there is a wide variation in cost amongst the medicinal cannabis products (which also varies depending on the condition treated), and some treatments may be less costly than nabiximols.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (HCP) (1) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted comments from individuals and organisations discussed the debilitating effects of muscle spasticity in MS and the potential benefits of symptomatic improvement and improvements in quality of life. The consumer input also highlighted cost as a barrier preventing patients from accessing treatment. The PBAC noted the HCP input supported the listing of nabiximols for patients who fail to adequately respond to first line agents.

### ***Clinical trials***

- 6.3 The resubmission was based on two head-to-head randomised trials comparing nabiximols to placebo (Markovà 2019, n=197 enrolled (Phase A) and n=106 randomised (Phase B) and Novotna 2011, n=572 (Phase A) and n=241 (Phase B)) and four supplementary randomised trials comparing nabiximols to placebo (Collin 2010,

n=337, Collin 2007, n=189, Vachovà 2014, n=121, Leocani 2015, n=44). The Markovà 2019, Vachovà 2014 and Leocani 2015 trials were new to this resubmission.

- 6.4 All trials allowed patients to receive anti-spasticity medication, and all trials apart from Collin 2007 excluded use of cannabis based medications. These medicines (defined as SC) could be used in the trials in addition to treatment with nabiximols or placebo. All references to placebo herein assume that placebo was given in addition to the patient's usual anti-spasticity medications and therefore the term 'placebo' is interchangeable with the term 'placebo and SC'.
- 6.5 While the resubmission categorised trials as 'primary' and 'supplementary', the evaluation considered that the Markovà 2019, Novotna 2011, Vachovà 2014, Collin 2007 and Collin 2010 trials each provided relevant information for the requested listing. Each of these trials had limitations including an enrichment trial design (Markovà 2019, Novotna 2011), use of non-TGA-approved dosing schedules (Collin 2007, Collin 2010, however mean doses were within those recommended in the approved TGA Product Information) or did not report outcomes that are relevant to the continuation criteria (i.e. NRS) specified by the resubmission (Vachovà 2014). Leocani 2015 was excluded given its cross-over design, small sample size (n=34 analysed), 20/44 enrolled patients were not taking concomitant anti-spasticity medications, and its short duration of 4 weeks.
- 6.6 Details of the trials presented in the resubmission are provided in Table 3.

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
Marková 2019	Sativex® as Add-on therapy Vs. further optimized first-line ANTispastic: the SAVANT trial  Marková J, Essner U, Akmaz B, et al. Sativex® as Add-on therapy Vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial	January 2018  <i>International Journal of Neuroscience</i> 2019;129(2): 119-128
Novotna 2011 (GWSP0604)	A two-phase, phase 3 study of the safety and efficacy of Sativex, in the symptomatic relief of spasticity in subjects with spasticity due to multiple sclerosis: Phase A – Single-blind response assessment; Phase B – Double-blind randomised, placebo controlled, parallel group study.  Novotna A, Mares J, Ratcliffe S, Novakova I et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis	January 2008  <i>European Journal of Neurology</i> 2011; 18(9): 1122-31
Vachová 2014 (GWMS1137)	A multicentre, double-blind, randomised, parallel group, placebo-controlled study of the effect of long-term treatment with Sativex on cognitive function and mood of patients with spasticity due to multiple sclerosis.  Vachová M, Novotna A, Mares J et al. A multicentre, double-blind, randomised, parallel-group, placebo-controlled study of effect of long-term Sativex® treatment on cognition and mood of patients with spasticity due to multiple sclerosis	October 2013  <i>J Mult Scler</i> 2014; 1(2); 10000122
Collin 2010 (GWCL0403)	A double blind, randomised, placebo controlled, parallel group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis.  Collin C, Ehler G, Wabertzinek Z, Alsindi P et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis	July 2006  <i>Neurological Research</i> 2010; 32 (5); 451-59
Collin 2007 (GSMS0106)	A double blind, randomised, parallel group study to assess the efficacy, safety and tolerability of Cannabis Based Medicine 1:1 THC:CBD compared with placebo for the treatment of spasticity in subjects with multiple sclerosis.  Collin C, Davies P, Mutiboko IK & Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity cause by multiple sclerosis	July 2006  <i>European Journal of Neurology</i> 2007; 14: 290-96
Leocani 2015	Leocani L, Nuara A, Houdayer E et al. Sativex® and clinical neurophysiological measures of spasticity in progressive multiple sclerosis	<i>Journal of Neurology</i> 2015; 262(11): 2520-27

Blue shading indicates trials considered in the previous submission. Collin 2007 and Collin 2010 were considered supportive trials in the previous submission.

The previous July 2013 submission also included Wade et al 2004 as a supportive trial, with Wade et al 2006 and the 2010 meta-analysis of these two trials, as well as Notcutt et al, 2012 being referred to in the previous submission but not used as supportive trials in relation to efficacy.

Source: Table 25, pp48-49 of the resubmission and constructed during the evaluation.

## 6.7 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Nabiximols plus standard care versus placebo and standard care</b>						
Markovà 2019	191 Phase A 106 Phase B	SB nabiximols in Phase A, R, DB in Phase B versus placebo 4 weeks Phase A, 4 weeks washout, 12 weeks Phase B	Phase A: High <sup>a</sup> Phase B: Moderate <sup>a</sup>	Moderate to severe MS spasticity, patients taking oral anti-spasticity medication, with spasticity not adequately relieved. Phase B required patients to have 20% or more response in phase A and to have had their improvement reduced by $\geq 80\%$ during washout	Proportion of 30% or more responders in Phase B  Other outcomes of change in spasticity severity from baseline, PGIC and pharmacoeconomic outcomes, QOL	Used to inform proportion of responders
Novotna 2011	571 in Phase A 241 in Phase B	SB nabiximols in Phase A – 4 weeks, and R, DB in Phase B versus placebo – 12 weeks plus 2 weeks of follow-up	Phase A: High <sup>b</sup> Phase B: Moderate <sup>b</sup>	At least moderate MS spasticity not wholly relieved with current anti-spasticity medication: phase B patients had to have had at least a 20% improvement on the NRS	Proportion of 30% or more responders in Phase B, change in spasticity severity from baseline, PGIC, QOL, other secondary outcomes	Not used
Vachovà 2014	121	Versus placebo. R, DB, 48 weeks of treatment and 2 weeks of follow-up	Moderate <sup>c</sup>	MS with at least moderate spasticity, tried and failed anti-spasticity medication	Subject's (Patient's), Carer's and Physician's global impression of change as secondary outcome, visits to healthcare professionals, other secondary outcomes: Key outcome mood	Not used
Collin 2010	337	Versus placebo. R, DB, 1 week of baseline and 14 weeks treatment	Moderate <sup>d</sup>	MS spasticity not wholly relieved with current medication	Change in spasticity severity on NRS from baseline	Not used
Collin 2007	189	Versus placebo. R, DB, 2 weeks of baseline and 14 weeks of treatment	Moderate <sup>d</sup>	MS spasticity not wholly relieved with current medication	Change in spasticity severity on NRS from baseline, PGIC, other secondary outcomes	Not used

<sup>a</sup> Subjective assessment on the Numerical Rating Scale may bias outcomes. In Phase A there may have been some unblinding due to effects of nabiximols on mood and pain. Phase B excluded patients who responded to initial therapy but whose spasticity NRS score had not reduced by  $\geq 80\%$  in the 4-week washout phase.

<sup>b</sup> Subjective assessment on the Numerical Rating Scale in both phases may impact validity of outcomes. In Phase A there may have been some unblinding due to effects of nabiximols on mood and pain. Patients who discontinued due to adverse events in phase A were not randomised to phase B. The discontinuation rate in the treatment arm in phase B was higher than the control arm.

<sup>c</sup> Use of a per protocol analysis for efficacy, subjectivity of global impression of change outcomes.

<sup>d</sup> Subjective assessment on the Numerical Rating Scale may bias outcomes.

Source: compiled from Section 2 of the resubmission.

SB = single blind; DB = double blind; MC = multi-centre; MS = multiple sclerosis; NRS = numerical rating scale; PGIC = patient's global impression of change; QOL = quality of life; R = randomised:

Blue shading indicates information considered in previous submission.

6.8 Markovà 2019 consisted of a single-blinded 4-week Phase A treatment period to determine those whose drug-resistant MS spasticity responded to nabiximols at the minimal threshold (defined as a  $\geq 20\%$  improvement in NRS score) followed by 12 weeks of double-blinded placebo-controlled Phase B where a higher clinically

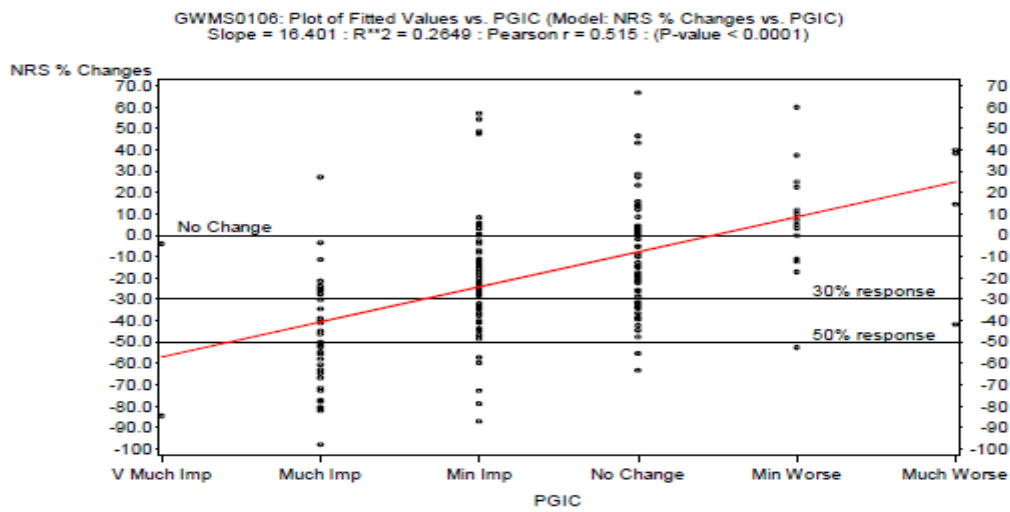
important response threshold was set ( $\geq 30\%$  improvement from baseline NRS). Only patients whose improvement in NRS score had reduced by  $\geq 80\%$  in the 4 week washout period were then randomised in Phase B.

- 6.9 Novotna 2011 consisted of a single-blinded 4-week Phase A treatment period followed by 12 weeks of double-blinded placebo-controlled Phase B. Novotna used the same response thresholds in Phase A and Phase B as those used in Markovà (20% and 30% respectively). In contrast to the Markovà study, non-responders in Phase A were discontinued from the trial and responders were immediately randomised into Phase B of the study without a washout period.
- 6.10 Selection of patients for the randomised phase of the trials on the basis of response in a lead-in phase (i.e. an enriched population) added complexity to the interpretation of the evidence.
- 6.11 Vachovà 2014, Collin 2007 and Collin 2010 were all 'standard' trials where patients were randomised at baseline to nabiximols or placebo. However, Collin 2007 and Collin 2010 both allowed higher maximum doses (48 and 24 doses daily, respectively although mean doses were within maximum doses) than the approved product information (12 doses daily) and Vachovà 2014 did not include any discontinuation based on clinical response (i.e. NRS not reported).
- 6.12 A proportion of patients in all five trials were not taking anti-spasticity medication, although the Collin 2007 trial had the highest proportion of patients not taking anti-spasticity medication during the trial (25% and 35% of nabiximols treated and placebo treated patients respectively).
- 6.13 While a range of evidence was available and presented by the resubmission, only the results from Markovà 2019 were used in the economic evaluation. This may not have been reasonable as it was unclear why Markovà 2019 should be preferred over Novotna 2011 given they had similar trial designs and Novotna 2011 enrolled three times as many patients as Markovà 2019 at the beginning of the trial. The ESC considered it was reasonable to also include the results of the Novotna 2011 trial in the economic analysis, as its design (which enrolled an enriched population but did not include a washout period) may be more reflective of clinical practice than the Markovà 2019 trial.
- 6.14 For all trials there was potential for unblinding given that cannabinoids can have positive effects on mood and pain, and a well-recognised side effect profile. The ESC considered there was also often a placebo effect in trials for outcomes such as mood and pain which may reduce the likelihood of unblinding. The Pre-PBAC Response (p2) argued the enriched study designs of Markovà 2019 and Novotna 2011 reflected the intended use of nabiximols in the target population, and that the use of subjective outcomes was unlikely to bias the results as the studies were blinded. Further discussion on the impact of the trial designs and risk of bias are discussed in paragraphs 6.42-6.43.

### **Comparative effectiveness**

- 6.15 The key outcomes for the resubmission were:
- Proportion achieving at least a 30% reduction in spasticity on the NRS from baseline;
  - Change in spasticity severity using NRS from baseline;
  - Patient global impression of change (PGIC) relating to spasticity (referred to as ‘Subject Global Impression of Change’ in Markovà 2019; where ‘Physician Global Impression of Change’ is used herein this is noted throughout); and
  - Quality of life.
- 6.16 The NRS is a subjective measure with a scale, similar to a visual analogue scale, asking patients to rate their level of spasticity over the previous 24 hours from 0 to 10. In PGIC, patients were asked a single question relating to improvement in their spasticity since the start of the study: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.
- 6.17 The ESC considered NRS and PGIC to be reasonable measures of patient spasticity in MS, as a clinical judgment for continuing treatment will be made on the basis of any perceived improvement in spasticity by patient and clinician.
- 6.18 The resubmission considered a  $\geq 20\%$  improvement from baseline NRS (e.g. response criteria at end of Phase A for Markovà 2019 and Novotna 2011) was considered to be a minimally clinically important difference (MCID) and a  $\geq 30\%$  improvement from baseline NRS (e.g. response criteria at end of Phase B for Markovà 2019 and Novotna 2011) to be a clinically important difference (CID).
- 6.19 The margins of  $\geq 20\%$  and  $\geq 30\%$  change from baseline in NRS were based on the association between PGIC and NRS as reported in Farrar 2008, a post hoc analysis of the Collin 2007 trial (Figure 1). The degree of correlation between the PGIC and the NRS scores was only moderately strong ( $r = 0.51$ ,  $p < 0.001$ ). Despite this, based on the results of this analysis, the use of NRS as an outcome measure has been adopted in preference to PGIC and it formed the primary outcome measure in the key Markovà 2019 trial used in the resubmission.
- 6.20 The Pre-PBAC Response argued that as the Collin 2007 trial was supplementary, consideration of those trial results should not have a bearing on the pivotal trials (Markovà 2019 and Novotna 2011) in the resubmission.

Figure 1: Association between percent improvement in NRS spasticity score and PGIC



Source: Figure 8, Collin 2007 CSR

- 6.21 The PBAC previously noted that “(u)sing the definitions of ‘much improvement’ and ‘minimally improved’ from PGIC, the submission categorised that a change of -30% [on the NRS] was most predictive of a patient’s reporting ‘much improved’ [on the PGIC] while a change of -18% [on the NRS] was most predictive of a patient’s report ‘minimally improved’ [on the PGIC]. The submission then defined that a change of 30% on the NRS for spasticity was considered a clinically meaningful change.” (Section 8, nabiximols PSD, July 2013 PBAC Meeting).
- 6.22 Therefore, even though the resubmission nominated the proportion of patients who achieve  $\geq 30\%$  improvement in NRS as the primary outcome, this can be considered equivalent to the proportion of patients who report “much improved” or “very much improved” on the PGIC, and that PGIC is also a valid efficacy outcome. This is important as the results in relation to the outcomes of NRS and PGIC in Markovà 2019 differ quite significantly, as shown in Table 5 and Table 7, with odds ratios of 7.24 versus 1.85 respectively. (Refer to paragraph 6.32 for further discussion of this issue.)
- 6.23 Results for the proportion of patients achieving  $\geq 30\%$  improvement from baseline NRS for spasticity are shown in Table 5. This outcome was not reported in Vachovà 2014.

**Table 5: Results of proportion of 30% or more responders on the NRS for spasticity across the trials**

Trial ID	Nabiximols n/N (%)	Placebo n/N (%)	Odds ratio (95% CI) ^	Relative risk (95% CI)	Risk difference (95% CI)
Markovà 2019 <sup>a</sup>	41/53 (77%)	17/53 (32%)	<b>7.24 (2.82, 18.9)</b>	2.4 (1.6, 3.6)	45% (28, 62)
Novotna 2011 <sup>a</sup>	92/124 (74.2%)	60/117 (51.2%)	<b>2.73 (1.54, 4.88)</b>	1.4 (1.2, 1.8)	23% (11, 35)
Collin 2007 <sup>b</sup>	48/120 (40.0%)	14/64 (21.9%)	<b>2.38 (1.21, 4.91)</b>	1.83 (1.10, 3.05)	18% (5, 32)
Collin 2010 (ITT) <sup>c</sup>	51/166 (30.7%)	42/169 (24.9%)	1.34 (0.81, 2.23)	1.2 (0.9, 1.8)	6% (-4, 15)
Collin 2010 (PP) <sup>c</sup>	44/121 (36.4%)	35/144 (24.3%)	<b>1.74 (1.02, 2.96)</b>	<b>1.50 (1.03, 2.17)</b>	<b>12% (1, 23)</b>

Source: Table 52, p89 of the resubmission, previous commentary Table B.6.2, Markovà 2019 CSR, p103.

<sup>a</sup> results at end of Phase B (4+12 weeks)

<sup>b</sup> results reported at 6 weeks

<sup>c</sup> results reported at 14 weeks

<sup>^</sup> For patients with spasticity as an impairment N=140

CI = confidence interval; n = number of patients with event; N = total patients in group. ITT = intent to treat, PP = per protocol

Bold indicates statistically significant results.

Text in italics indicate values added during evaluation calculated with StatsDirect.

Grey shaded trial indicate values used in economic evaluation. Blue shading indicates results previously considered by the PBAC

6.24 Results of the mean change in spasticity 0-10 on the NRS from baseline to the end of treatment are shown in Table 6.

**Table 6: Results of mean change in spasticity 0-10 NRS from baseline to end of treatment**

	Nabiximols			Placebo			Mean difference (95% CI)	P value (95% CI)
	Mean baseline (SD)	Mean end point (SD)	Mean change (SD)	Mean baseline (SD)	Mean end point (SD)	Mean change (SD)		
Markovà 2019: n=53 in each group – responders from Phase A whose NRS improvement reduced by least 80% NRS: Endpoint 12 weeks in Phase B: ITT analysis								
Phase B	6.89 (NR)	3.40 (NR)	-3.49 (NR)	6.92 (NR)	5.32 (NR)	-1.60 (NR)	-1.89 (NR)	<b>P&lt;0.0001</b> <b>(-2.73, -1.06)</b>
Novotna 2011: n=241 for patients enrolled at start of Phase A who responded and went into Phase B: n=124 nabiximols and n=117 placebo for start of Phase B: End point 4 weeks for Phase A and another 12 weeks in Phase B: ITT analysis								
From start of Phase A*	6.91 (1.25)	3.90 (1.38)	-3.01 (NR)	(NR)	(NR)	(NR)	(NR)	(NR)
From start of Phase B	3.87 (NR)	3.83 (NR)	-0.04 (NR)	3.92 (NR)	4.73 (NR)	0.81 (NR)	-0.84 (NR)	<b>P=0.0002</b> <b>(-1.29, -0.40)</b>
Collin 2007: n=120 on nabiximols and 64 on placebo.								
ITT	5.49 (NR)	4.31 (NR)	-1.18 (NR)	5.39 (NR)	4.76 (NR)	-0.63 (NR)	-0.52 (NR)	<b>P=0.048</b> <b>(-1.029, -0.004)</b>
Collin 2010: n=167 on nabiximols and 170 on placebo for ITT, n=121 on nabiximols and 144 on placebo for PP:								
ITT	6.77 (NR)	5.72 (NR)	-1.05 (NR)	6.48 (NR)	5.26 (NR)	-0.82 (NR)	-0.23 (NR)	P=0.219 (-0.59, 0.14)
PP	6.84 (NR)	5.54 (NR)	-1.30 (NR)	6.49 (NR)	5.65 (NR)	-0.84 (NR)	-0.46 (NR)	P=0.035 (NR)

Source: Table 52, p89 of the resubmission, Novotna CSR p91.

NRS = Numerical Rating Scale; CI = confidence interval; SD = standard deviation. NR = not reported

Bold indicates statistically significant results. Italics indicate values calculated during evaluation

Note: The previous commentary reported adjusted mean change in spasticity severity. These results were on a page of the CSRs that were not provided at the time of the evaluation and could not be verified. Therefore unadjusted results were provided

\* The CSR for Novotna 2011 noted that patients who received nabiximols for the full 16 weeks had a 48% improvement in their spasticity.

6.25 Markovà 2019, Novotna 2011, and Collin 2007 reported that more patients treated with nabiximols + SC compared to placebo + SC had a clinically significant change in spasticity (defined by the submission as at least a 30% change) on the NRS spasticity scale, while the Collin 2010 trial did not report a statistically significant difference in the ITT population.

- 6.26 The PBAC previously considered the benefits observed from Novotna 2011 were small, likely to be overestimated (due to high risk of bias) and to have questionable clinical significance (section 9, nabiximols PSD, July 2013 PBAC Meeting).
- 6.27 Overall, there was evidence that a greater proportion of patients treated with nabiximols had a clinically significant improvement in spasticity as measured by proportion of patients achieving  $\geq 30\%$  improvement in baseline NRS, though the magnitude is uncertain given that all trials had risk of bias and the large variation in both nabiximols and placebo response rates across trials. The evaluation noted the magnitude of benefit was variable between trials, with varying rates for both nabiximols response (from 30.7% in Collin 2010 to 77% in Markovà 2019) and SC response (from 21.9% in Collin 2007 to 51.2% in Novotna 2011).
- 6.28 Response to nabiximols appeared to decrease over time towards the end of the trials, and placebo response in some cases increased. In Markovà 2019, the proportion of patients treated with nabiximols who experienced improvement of  $\geq 30\%$  improvement from baseline NRS decreased from 71.7% at Week 8 to 67.9% at Week 12 in the General Linear Mixed Model sensitivity analysis, with the proportion of responders treated with placebo increasing from 28.3% to 30.2% for the same period.
- 6.29 Subject's (Patient's), Carer's and Physician's Global Impression of Change across the trials (where measured) are presented in Table 7.

Table 7: Results of changes in Subject's (Patient's), Carer's and Physician's global impression of change from baseline to end of treatment

Trial	Nabiximols + SC n/N (%)	Placebo + SC n/N (%)	Odds Ratio (95%CI)	Relative risk (95% CI)	Risk difference (95% CI)
<b>Patient's Global Impression of Change</b>					
Marková 2019 (Phase B)	23/51 (43%)	14/46 (26%)	1.85 (0.79, 4.35) <sup>a</sup>	1.48 (0.87, 2.52)	15% (-4.4%, 34%)
Novotna 2011 (Phase B)	NR/NR (77%)	NR/NR (61%)	<b>1.70 (1.08, 2.70)</b>	NR	NR
Vachová 2014	NR/NR (72%)	NR/NR (38%)	<b>4.02 (1.96; 8.22)</b>	NR	NR
Collin 2007	66/116 (57%)	31/64 (48%)	1.36 (0.78; 2.37)	1.17 (0.88, 1.61)	8% (-7%, 23%)
Collin 2010	NR/NR (51%)	NR/NR (39%)	NR	NR	NR
<b>Carer's Global Impression of Change</b>					
Novotna 2011 (Phase B)					
On functional status	NR/NR (68%)	NR/NR (44%)	<b>2.40 (1.30; 4.44)</b>	NR	NR
Ease of transfer	NR/NR (52%)	NR/NR (33%)	1.97 (0.97; 3.30)	NR	NR
Vachová 2014	NR/NR (65%)	NR/NR (40%)	<b>2.79 (1.23; 6.31)</b>	NR	NR
Collin 2010	NR/NR (35%)	NR/NR (24%)	1.25 (0.84; 1.85)	NR	NR
<b>Physician's Global Impression of Change</b>					
Marková 2019 (Phase B)	25/51 (47%)	14/46 (26%)	2.18 (0.93, 5.12) <sup>a</sup>	1.61 (0.96, 2.7)	19% (-0.5%, 38%)
Novotna 2011 (Phase B)	NR/NR (78%)	NR/NR (54%)	<b>1.96 (1.23; 3.11)</b>	NR	NR
Vachová 2014	NR/NR (71%)	NR/NR (40%)	<b>3.07 (1.51; 6.21)</b>	NR	NR

Source: Vachová CSR, pp76-77, Marková 2019 CSR Table 59 and 60, Previous commentary Table B.6.3 (provided as an attachment to the submission)

<sup>a</sup> adjusted odds ratio

<sup>b</sup> calculated from logistic regression of data

NR = not reported

A patient was considered to have a positive change in global impression of change if the patient, carer or physician assessed the change as "Minimally better", "Much better" or "Very much better" (from visit 2 in phase A of Novotna, visit 2 in Vachová, from visit 4 in Marková and from baseline in Collin 2007 and Collin 2010)

Bold indicates statistically significant results.

Text in italics indicate values calculated during evaluation using StatsDirect

- 6.30 All trials reported an improvement in global impression of change in patients treated with nabiximols compared to patients treated with placebo though statistically significant differences were not reported in some of the trials.
- 6.31 The correlation between improvement from baseline NRS and PGIC was not supported by the results of Marková 2019. If the correlation between PGIC and NRS improvement from baseline was accurate, it would be reasonable to expect there would be more patients reporting any improvement in PGIC (roughly equivalent to  $\geq 18\%$  improvement from baseline NRS) than patients reporting a  $\geq 30\%$  improvement from baseline NRS. However, there were almost twice as many patients treated with nabiximols who reported  $\geq 30\%$  improvement from baseline NRS (41/53, 77%) than those who reported any improvement in PGIC (23/51, 44%). At 12 weeks, there was no statistically significant difference between treatment groups in the proportion of patients who reported improvement in PGIC in Marková 2019, but a statistically significantly greater proportion of patients treated with nabiximols reported a  $\geq 30\%$  improvement from baseline NRS. The ESC noted the inconsistency across the NRS and

PGIC outcomes and considered this increased the uncertainty regarding the interpretation of incremental benefit of nabiximols.

- 6.32 The difference in the proportion of patients who reported improvement in PGIC between the two treatment arms in Markovà 2019 also declined over time. At Week 4, 55% of nabiximols treated patients and 17% of placebo treated patients reported improvements in PGIC, with a difference of 38% between the two treatment arms. By Week 8 the proportions were 49% and 23% for patients treated with nabiximols and placebo, respectively; and at Week 12 the proportions were 43% and 26% for nabiximols and placebo treated patients, respectively.
- 6.33 Data on quality of life was collected in Markovà 2019 and the results showed significant differences only for bodily pain at Weeks 4, 8 and 12. There was no statistically significant difference in overall health related quality of life as measured using the SF-36. The ESC considered it may have been informative to convert the SF-36 data collected in Markovà 2019 to SF6D values for use in the economic model.
- 6.34 Outcomes from the EQ-5D and SF-36 were collected in the Novotna 2011 and Collin 2010 trials, with the PBAC previously noting that none of the differences in the change in health outcomes between treatment arms reached statistical significance (section 8, nabiximols PSD, July 2013 PBAC Meeting). While the trials were not powered to show a statistically significant difference in relation to quality of life, the resubmission assumed that there was an incremental difference in quality of life depending on severity of disease as measured by NRS in the economic model.
- 6.35 The Pre-PBAC Response argued that SF-36 scores for at least bodily pain and sleep disruption were improved in both the Markovà 2019 and Novotna 2011 trials, which supported a conclusion of improved quality of life from treatment with nabiximols.
- 6.36 In relation to healthcare resource use data collected in Markovà 2019, there was no statistically significant difference in the hours per day of caregiver support required for nabiximols or placebo treated patients, with low numbers of hours per day required at the start and the end of treatment. Physiotherapy hours per week increased in the placebo group and decreased by 0.4 hours in the nabiximols group with a difference of 1.7 hours per week. However additional care is a key driver of the economic evaluation (see paragraphs 6.69 - 6.73). There was insufficient data to draw any conclusions regarding the change in number of medical consultations.

### ***Comparative harms***

- 6.37 The most common treatment-related adverse events in Markovà 2019 and Vachovà 2014, were vertigo, fatigue and dizziness as summarised in Table 8 below.

**Table 8: Most common treatment related adverse events in new trials for this resubmission**

	Vertigo		Dizziness		Somnolence		Fatigue	
	Nabiximols n/N (%)	Placebo n/N (%)	Nabiximols n/N (%)	Placebo n/N (%)	Nabiximols n/N (%)	Placebo n/N (%)	Nabiximols n/N (%)	Placebo n/N (%)
Vachová 2014	6/62 (9.7%)	0/59 (0%)	5/62 (8.1%)	2/59 (3.4%)	1/59 (1.7%)	0/59 (0%)	5/62 (8.1%)	1/59 (1.7%)
Marková 2019 Phase A	14/191 (7.3%)	-	4/191 (2.1%)	-	3/191 (1.6%)	-	3/191 (1.6%)	-
Marková 2019 Phase B	1/53 (1.9%)	0/53 (0%)			2/53 (3.8%)	0/53 (0%)		

Source: Table 72-7, pp196-203 Marková 2019 CSR, p114 Vachová 2014 CSR

- 6.38 In Vachová 2014, 40.3% of patients on nabiximols reported treatment emergent adverse events compared to 8.5% in the placebo group. This led to withdrawal in 9 patients (14.5%) on nabiximols and 2 patients (3.4%) on placebo.
- 6.39 In Marková 2019, there were 4 patients who withdrew due to treatment emergent adverse events during Phase A and 1 patient withdrew during the washout phase (approximately 2.6%).
- 6.40 No new adverse event signals were identified in the Marková 2019 and Vachová 2014 trials.
- 6.41 In the consideration of the July 2013 submission, the PBAC considered that “[f]or all trials (Novotna 2011, Collin 2007 and Collin 2010), patients treated with nabiximols had more adverse events than placebo-treated subjects. The most common adverse events were gastrointestinal disorders (e.g. nausea or dry mouth), general disorders, nervous system disorders and psychiatric disorders. The submission stated that the majority of adverse events resolved within the trial period. The most common treatment-related adverse events in the supportive trials were nervous system disorders (48% to 69% of subjects treated with nabiximols vs. 26%-34% of placebo treatment subjects), followed by gastrointestinal disorders (32%-39% vs. 20%-29%), general disorders (27%-46% vs. 12%-28%) and psychiatric disorders (17%-23% vs. 4%-11%)” (Section 8, nabiximols PSD, July 2013 PBAC Meeting). It remains reasonable to conclude that patients treated with nabiximols are more likely to experience adverse events than patients treated with placebo based on the results from clinical trials.
- 6.42 Differences in the reported rates of the number of treatment-emergent adverse events (TEAEs) and nervous system disorder adverse events (NAEs) between Phase A and Phase B of the Marková 2019 and Novotna 2011 trials are presented in Table 9.

**Table 9: Treatment-emergent adverse events (number of patients) and neurological adverse events in Phase A and B of Markovà 2019 and Novotna 2011**

Trial	Phase A*			n/N continued to Phase B (%)	Phase B			
	N	N (%) exp. TEAEs	N (%) exp. NAE		n/N (%) exp. TEAEs		n/N (%) exp. NAEs	
					Nabiximols	Placebo	Nabiximols	Placebo
Markovà 2019	191	46 (24.1%)	16 (8.4%)	106/191 (55%)	12/53 (22.6%)	7/53 (13.2%)	4/53 (7.5%)	1/53 (1.9%)
Novotna 2011	571	268 (46.9%)	148 (25.9%)	241/571 (42%)	66/124 (53.2%)	57/117 (48.7%)	19/124 (15%)	15/117 (13%)

\*Does not include adverse events observed during the washout phase. Section 2.5.2 of the submission notes 12 patients with TEAEs and 4 patients with NAEs during the washout phase of Markovà 2019. Novotna 2011 did not have a washout phase.

NAEs included dizziness, somnolence, headache, muscle spasticity, disturbance in attention, paraesthesias and dysaesthesias, MS relapse  
Source: Markovà 2019: Section 2.5.2.1 and Table 59 of the submission; Novotna 2011: Section 2.5.2.2 and Tables 60 and 61 of the submission.

Abbreviations: TEAE = treatment-emergent adverse event; NAE = nervous system disorder adverse event

- 6.43 The PBAC noted the risk difference (RD) between nabiximols and placebo for TEAEs and NAEs in Phase B was higher in Markovà 2019 than in Novotna 2011 (9.4% vs 4.5% for TEAEs and 5.6% vs 2% for NAEs). The PBAC considered the higher RD in Markovà 2019 may be partly due to the washout period after Phase A resulting in patients being aware of their treatment (i.e. unblinding) in Phase B. Novotna 2011 did not have a washout period and therefore patients were less likely to be aware of their re-randomisation to nabiximols or placebo in Phase B. The PBAC considered the differences in trial design may have contributed to the observed difference in the relative risk of achieving a 30% or more reduction in NRS between Markovà 2019 and Novotna 2011 (2.4 vs 1.4, respectively) (Table 5) as the higher risk of unblinding in Markovà 2019 may have resulted in an overestimate of nabiximols benefit and underestimate of placebo benefit, given the subjective nature of the outcome.

### **Benefits/harms**

- 6.44 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with nabiximols plus standard care in comparison with standard care alone:
- Approximately 6 to 45 additional patients would achieve  $\geq 30\%$  improvement from baseline NRS at up to 16 weeks of treatment for treatment naïve patients (Collin 2010) and Phase A responders (Markovà 2019, see paragraph 6.8), respectively.
- 6.45 Based on the results from Vachová (2014), the trial with the longest duration:
- Approximately 10 additional patients would experience vertigo at up to 48 weeks of treatment.
  - Approximately 5 additional patients would experience dizziness at up to 48 weeks of treatment.
  - Approximately 6 additional patients would experience fatigue at up to 48 weeks of treatment.
- 6.46 Based on the evidence in the supportive trials presented in the previous submission (paragraph 6.42):

- Approximately 14 to 43 additional patients would experience nervous system disorders at up to 16 weeks of treatment.
- Approximately 3 to 19 additional patients would experience gastrointestinal disorders at up to 16 weeks of treatment.
- Approximately 6 to 19 additional patients would experience psychiatric disorders at up to 16 weeks of treatment.

### ***Clinical claim***

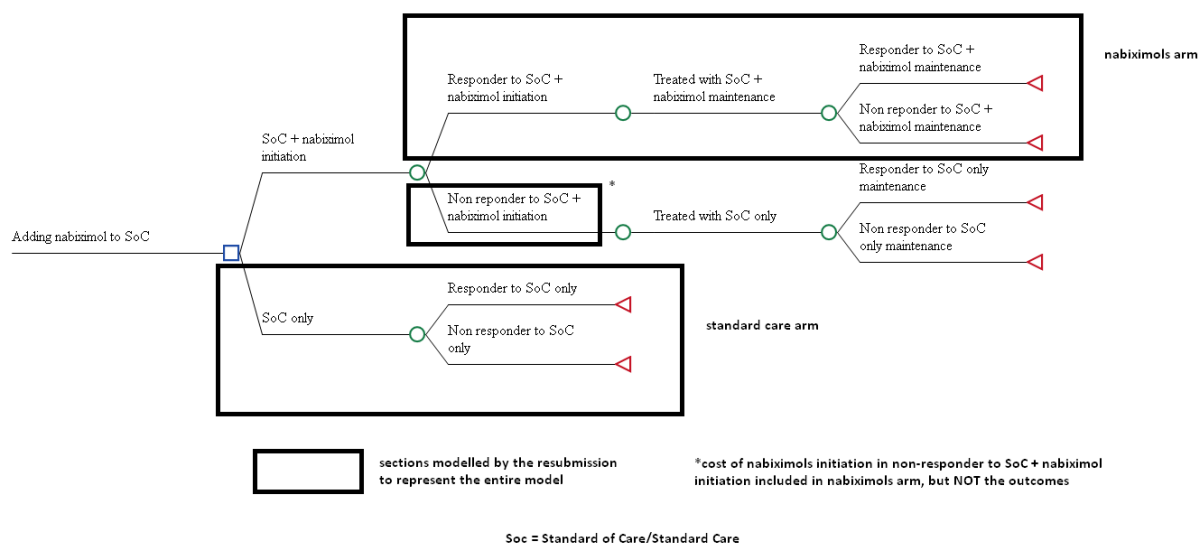
- 6.47 The resubmission described nabiximols, as adjunctive therapy, as superior in terms of effectiveness compared with oral anti-spasticity medication alone and inferior in terms of safety in patients with moderate to severe spasticity due to MS who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.
- 6.48 The PBAC had previously considered that a claim of superior efficacy over standard care was inadequately supported (section 12, nabiximols PSD, July 2013 PBAC meeting).
- 6.49 When considering the entire body of evidence presented, while the evidence appeared to support the conclusion that nabiximols plus SC is superior in efficacy to SC alone, the magnitude and clinical significance of any difference was difficult to determine as:
- The efficacy outcome measures (both  $\geq 30\%$  improvement from baseline NRS and PGIC) were subjective;
  - The trial design in the primary trials (Markovà 2019 and Novotna 2011) had significant applicability issues as they used an enrichment trial design;
  - At 12 weeks in Markovà 2019 (which was used to inform the economic model), there was no statistically significant difference between treatment groups in the proportion of patients who reported any improvement in PGIC, but a statistically significantly greater proportion of patients treated with nabiximols reported a  $\geq 30\%$  improvement from baseline NRS. Therefore it is possible to both conclude that nabiximols + SC is more effective than SC alone AND that it is no more effective than SC alone with results from the same trial, depending on which outcome is to be relied upon;
  - There was a large variation in results between trials, making the extent of any incremental benefit difficult to determine. The divergent trial designs and durations also precluded a meaningful meta-analysis;
  - There is little information on the persistence of efficacy (as measured by  $\geq 30\%$  improvement from baseline NRS) beyond 16 weeks of total treatment, with some evidence that it might decline over time; and

- There was no evidence of any improvement in quality of life and little evidence of clinically relevant differences in resource utilisation associated with management of spasticity when patients were treated with nabiximols + SC.
- 6.50 The PSCR argued the outcomes demonstrated to be improved in the key clinical evidence would lead to improvements in patient quality of life (QoL), as demonstrated by the Svensson 2011 study which demonstrated improvements in NRS resulted in differences in QoL/utilities.
- 6.51 The ESC considered that the use of subjective outcomes (NRS and PGIC) in the studies was reasonable and considered nabiximols was likely to have an effect for some patients, however key factors outlined above (refer to paragraph 6.48) resulted in substantial uncertainties. As such, the ESC considered there was insufficient evidence available to estimate the magnitude of any benefit, and noted this had significant implications for the economic analysis.
- 6.52 The PBAC considered that the claim of superior comparative effectiveness was reasonable, however the effect size was uncertain and likely to be modest.
- 6.53 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.54 The resubmission presented a stepped economic evaluation based on Markovà 2019 and implemented a modelled cost-effectiveness and a cost-utility analysis.
- 6.55 The ESC agreed with the evaluation that the structure of the economic model did not reflect the proposed treatment algorithm as it excluded modelling costs and outcomes for non-responders to initial therapy. Figure 2 presents a diagram of what the model structure should have been (the model in its entirety) with the boxes representing what was modelled in the resubmission and suggested to represent the entire model.

Figure 2: Comparison of decision tree of requested PBS population and model presented by resubmission



Source: Constructed during the evaluation.

- 6.56 In the economic evaluation presented in the resubmission, patients with moderate to severe MS-related spasticity were assumed to be treated with either nabiximols + SC or SC only. Patients treated with nabiximols + SC were assigned costs related to the supply of nabiximols and cost of adverse events, and patients treated with SC only were only assigned costs associated with adverse events. The initiation costs for nabiximols were multiplied by 1.8 (191/106) to represent the number of patients who were treated in Phase A but did not progress to Phase B in Markovà 2019.
- 6.57 A proportion of patients in both treatment groups were assumed to achieve a  $\geq 30\%$  improvement from baseline NRS, based on the results of Phase B at Week 12 of Markovà 2019, and the health state of responder or non-responder was assumed to persist for the entire duration of the model (12 months). Responders were assumed to have lower costs of treating spasticity (beyond drug costs) and higher utility than non-responders. Response was assumed to occur at the beginning of the model.
- 6.58 The evaluation considered the model structure used in the resubmission was overly simplistic and problematic as:
- The model did not capture the ongoing costs and response rates for patients who were non-responders to nabiximols after the initiation period and who would go on to receive SC alone. This is a significant proportion of the entire patient population, with 85/191 (44.5%) patients in Markovà 2019 not progressing to Phase B;
  - It did not adequately capture transitions from response to the non-response state for patients treated with nabiximols or SC over time;
  - It did not allow for discontinuation of therapy or variations in dosage;

- Responder utilities were inappropriately assumed to be applied immediately from the start of the model;
  - A 12 month time horizon was likely too short for a treatment which is likely to be lifelong, and therefore the incremental cost-effectiveness ratio (ICER) for the presented 12 month model was unlikely to be representative of the ICER in subsequent years;
  - The structure did not include costs for consultation to assess treatment response and there was no consideration of patients discontinuing treatment due to adverse events or for lack of response after the first 4 weeks; and
  - Drug costs were not appropriately applied (30 days of initiation + 360 days of continuation applied to nabiximols responders, rather than 30 days of initiation + 335 days of continuation).
- 6.59 There were substantial changes from the previous submission. Key changes included the model structure, inputs for comparative effectiveness from Markovà 2019 (instead of Novotna 2011), a reduced timeframe of 1 year compared to 5 years, incorporation of different utility values, and incorporation of cost offsets from treating spasticity. Key differences between the model in the resubmission and the previous submission are presented in Table 10.
- 6.60 The PSCR presented a revised economic model which extended the time horizon to ten years and included a decline in response of 1% per annum in the absence of long-term data to model outcomes over a longer duration, as well as adding the cost of treatment for initial non-responders. The ESC considered the extended base case model was uninformative as there were other fundamental issues with the model that were not resolved by merely extending the model duration and adding an arbitrary decline in response.

**Table 10: Summary of model structure, key inputs and rationale**

Component	Summary of resubmission	Key changes from previous submission
Treatments	Nabiximols + SC versus SC alone	Nabiximols ( $\pm$ SC) versus SC alone
Time horizon	1 year in the model base case versus 12 weeks in the Markovà trial (Phase B)	5 years in the model base case versus 16 weeks in Novotna 2011
Outcomes	Quality-adjusted life years and responders on the spasticity NRS scale defined as a 30% or more improvement	No change
Methods used to generate results	Simple decision tree model based on initial and continuing response or non-response to nabiximols	A 10-state Markov model
Cycle length	1 year	Unknown
Transition probabilities	Entry into the initial and continuing response and non-response states were based on results from phase B of Markovà 2019 only	Based on phase B in Novotna 2011
Extrapolation method	Response and non-response rates were assumed to remain the same as at 12 weeks in Markovà 2019.  Approximately █% of QALYs and costs occur in the extrapolated period.	Probability of improvement in SC arm expected to worsen, based on Arroyo 2011
Health related quality of life	Responders 0.679 and non-responders 0.574, based on mapping mean baseline NRS (6.91) and responder NRS (4.84) from Markovà 2019 to EQ-5D using algorithm by Svensson 2014  Disutilities were assigned to adverse events (AE) based on Wang 2008 with values of 0.02 for dizziness, dry mouth, fatigue and 0.04 for headache, 0.06 for nausea and 0.10 for serious AE	Based on Novotna 2011, 0.58 for moderate spasticity and 0.43 for severe as requested by ESC No disutilities applied to AE
Costs of treating spasticity	Based on utilisation reported in Stevenson 2015 for patients with various NRS levels mapped to Australian unit costs, and fitted exponential curve to costs to read off overall costs for patients with NRS of 4.84 and 6.91 in the model	Unknown

SC = standard care

Source: Section 3 of the resubmission and previous PBAC minutes (provided as an attachment to the submission)

- 6.61 The NRS at baseline in Phase B of the Markovà 2019 trial was 6.91. Therefore, the resubmission estimated that patients who had  $\geq 30\%$  improvement from baseline NRS would have had an NRS of 4.84 or lower at week 12. The resubmission also assumed that non-responders would have had no change to their baseline NRS, with this remaining at 6.91. The estimated NRS is important as it determines both the utility of the patient as well as the ‘cost of treating spasticity’ as assumed by the resubmission.
- 6.62 The utility values for each health state were mapped from the mean NRS reported in Markovà 2019 to EQ-5D using an algorithm developed by Svensson 2014. The resubmission estimated that responders with an NRS of 4.84 will have a utility of 0.679 and non-responders with an NRS of 6.91 will have a utility of 0.574. Other utility values have been used in published economic evaluations and health technology assessments but were not explored in the resubmission. The utilities in the previous submission were based on Novotna 2011, with 0.58 for moderate spasticity and 0.43 for severe (as requested by ESC). In the NICE evidence review for spasticity 2019 (for cannabis-based medicinal products), adjusted values of 0.537 and 0.352 for moderate and severe spasticity, respectively, were used in their analysis.

- 6.63 The ESC considered the approach used to model NRS responders and non-responders to utilities was highly uncertain, as patient EDSS score was an important component of the linear regression model in Svensson 2014. The ESC noted the regression was significant for EDSS states  $\geq 7.5$  and considered the utilities for responders and non-responders calculated according to EDSS states may have been informative.
- 6.64 Furthermore, the ESC noted the clinical trials included in the resubmission reported no difference in health related quality of life (HRQoL) between patients treated with nabiximols + SC compared to SC alone.
- 6.65 The resubmission estimated health care resource use based on data from a published UK study by Stevenson 2015 and applied Australian unit costs. Stevenson 2015 was a study based on a survey of health care professionals in the UK. It was unclear whether the resource use as depicted by Stevenson 2015 would be applicable to patients in Australia. The cost in Stevenson 2015 for a patient with an NRS score of 9-10 was a total of \$70,330 (including outpatient treatment, A&E attendance, hospital admissions, district nurses and home care) when using Australian unit costs. This was significantly higher than the costs reported in Ahmad 2018<sup>3</sup> where it was reported that the direct and indirect costs of management for a patient with MS with severe disability in Australia in 2017 was \$14,000 (health professionals, nursing services, community and private services and hospital stay<sup>4</sup>) and \$15,000 (informal care costs<sup>5</sup>), respectively. It is unlikely informal care costs would be a cost attributable to the health budget.
- 6.66 In its consideration of resource use associated with spasticity, the NICE evidence review for spasticity 2019 stated that advanced spasticity is highly associated with advanced MS more generally. As such, moving an average patient who is experiencing NRS spasticity of 10, for example, to NRS of 6-8 would be unlikely to reduce resource use by the total difference between the two categories, since some of the resource use would likely not be spasticity-specific. Accordingly, the NICE evidence review for spasticity 2019 considered that only a portion (25%) of the resource use and 49.65% of the home care visits could be attributable to changes in NRS spasticity alone. However, these proportions were also considered by NICE to be highly uncertain.
- 6.67 The PSCR argued the resource use and costs used in the economic model were reasonable and relevant to Australia and were supported by the results of an evaluation of the economic impact of MS in Australia using the Australian MS Longitudinal Study (AMSL) in 2017. The PSCR argued this approach of modelling Australian health system use, based on adjusted UK values, may be substantially underestimating costs in Australia. The PSCR further argued it was inappropriate and

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<sup>3</sup> Ahmad H et al. 'Health Economic Impact of Multiple Sclerosis in Australia in 2017: An analysis of MS Research Australia's platform—the Australian MS Longitudinal Study' (2018).

<sup>4</sup> Estimated from Figure 3.10, Panel B, p36, Ahmad 2018

<sup>5</sup> Estimated from Figure 3.2, Panel B, p30, Ahmad 2018

arbitrary to propose that only 25% of the resource use costs were reasonable and attributable to MS-related spasticity.

- 6.68 The ESC considered the health care resource costs used in the economic model were high and not likely to be reflective of actual costs. The ESC noted the direct and indirect costs of management of MS for a patient with severe disability published in Ahmad 2018 were substantially lower, and considered that it was likely that only a portion of health system costs were attributable specifically to the management of spasticity in MS, and a substantial amount of care would still take place for the overall management of MS, particularly for patients with greater disability. The ESC noted that the proposed portion of the resource use costs attributable to MS-related spasticity (25%) was generated from the NICE evidence review for spasticity 2019 and considered that this was reasonable.
- 6.69 The resubmission estimated the cost for managing spasticity in patients with NRS levels of 4.84 for responders to be \$20,000 per annum and with an NRS level of 6.91 for non-responders to be \$38,000 per annum. The ESC considered the estimated costs for managing spasticity based on NRS in the resubmission’s economic model were overestimated.
- 6.70 The key drivers of the model are summarised in Table 11.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact Adjusted base case: Dominant.
Cost offsets for treating spasticity	High cost offsets for treating spasticity taken from Stevenson 2015	High, favours nabiximols. Use of 25% of Stevenson 2015 costs and also reducing home care visit costs to 49.65% increases the ICER to \$75,000 - \$105,000/QALY gained.
Response rate for treating spasticity	Use of estimates for 30% or greater responders based on NRS from Phase B in Markovà 2019	High, favours nabiximols. Use of pooled estimate from NICE evidence review for spasticity 2019 increases ICER to \$105,000 - \$200,000/QALY gained.

- 6.71 The results of the stepped economic evaluation are presented in Table 12. Assuming a total treatment of 360 days (30 day initiation plus 11 × 30 days of continuing treatment) the cost per patient treated with nabiximols becomes \$ [REDACTED].

**Table 12: Results of the stepped economic evaluation**

Step and component	Nabiximols plus standard care	Standard care alone	Increment
<b>Step 1: Initiation of therapy 4-week trial of nabiximols: costs and outcomes for 4 months</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
30% or more responders on NRS	0.77	0.32	0.45
Incremental cost/extra 30% responder at 2 months			\$ [REDACTED]
<b>Step 2: cost per responder with time horizon extended to 1 year – drug costs only</b>			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
30% or more responder on NRS	0.77	0.32	0.45
Incremental cost/extra 30% responder			\$ [REDACTED]
<b>Step 3: cost per responder with time horizon extended to 1 year – drug costs and incorporation of medical resource costs</b>			
Costs	\$ [REDACTED]	\$32,728	-\$ [REDACTED]
30% or more responders on NRS	0.77	0.32	0.45
Incremental cost/30% responder with all costs for 12 months			-\$ [REDACTED]
<b>Step 4: utility weights applied</b>			
Costs	\$ [REDACTED]	\$32,728	-\$ [REDACTED]
QALYs	0.6519	0.6055	0.0464
<b>Incremental cost/extra QALY gained (base case)</b>			<b>-\$ [REDACTED]</b>

NRS = Numeric Rating Scale

Costs and ICERs in steps 2, 3 and 4 indicate values corrected during evaluation to correct for 12 months treatment duration

Source: Table 87, pp137-138 of the resubmission.

6.72 The resubmission considered that over 12 months, treatment with nabiximols plus SC would be dominant compared to SC alone, with a lower cost (cost-saving of \$ [REDACTED] per patient) and higher QALY (incremental gain of 0.0464). The ICER in the previous submission was \$15,000 - \$45,000.

6.73 The ESC considered the conclusion that nabiximols + SC is dominant compared to SC only was likely to be highly optimistic and unreliable as:

- The model did not include the outcome of patients who fail nabiximols initiation, therefore was not a complete representation of the proposed PBS population;
- The use of data from Markovà 2019 only may not be reasonable, as it has issues with high risk of bias, trial design not being generalisable to the proposed PBS population (an enrichment study design with a washout period) and provided the most optimistic estimate for efficacy of nabiximols + SC compared to SC alone relative to other, larger trials (e.g. Novotna 2011, which enrolled three times as many patients as Markovà 2019 at the beginning of Phase A). The ESC also noted the issues raised above regarding the magnitude and clinical significance of the benefit (paragraphs 6.48, 6.50);
- The calculation of costs for managing spasticity based on Stevenson 2015 was likely to be significantly overestimated. The ESC considered the cost offsets for reduction of disease management were implausible, as the estimated cost of disease management is high and the proportion of these costs that can be attributed to spasticity in MS is only a portion of overall MS disease management costs;
- The assumption that patients will respond from Day 1 and have an improved

quality of life from the very start of the model was unrealistic;

- The assumption that patients will maintain their response beyond 12 weeks was unsupported;
- The incremental QALY gain from achieving  $\geq 30\%$  improvement from baseline NRS may be overestimated. The utility estimates derived using NRS responder and non-responder states may not be appropriate as EDSS states were not considered which was a key component of the Svensson regression model;
- There was no statistically significant difference in hours per day of caregiver support required for nabiximols or placebo treated patients, with low numbers required at the start and end of the trial, however differences in additional care costs are a key driver of the model;
- A model duration of 1 year was too short for a treatment that is ongoing; however the ESC noted the lack of long-term data to inform a longer model and residual fundamental issues with the model that would not be resolved by simply extending its duration.

6.74 The ESC agreed in principle with the argument in the PSCR that health economic literature advocates selecting the simplest model that addresses the objectives of the study and structure of the disease and treatment processes. However, in this case the ESC considered the model did not adequately address the objectives of the study or structure of the disease and treatment process.

6.75 The results of key univariate and multivariate sensitivity analyses around the economic evaluation are summarised in Table 13.

**Table 13: Key sensitivity analyses compared to the resubmission's base case**

<b>Analyses</b>	<b>Incremental cost</b>	<b>Incremental QALY</b>	<b>ICER</b>
Base case (nabiximols cost corrected)	-\$██████	0.0464	Dominant
<b>Univariate sensitivity analyses</b>			
Assume 50% of management of spasticity costs reported in Stevenson (2015) (base case 100%)	\$██████	0.046	\$██████
Assume only 25% of costs reported in Stevenson (2015) and also reduced home care visits cost to 49.65% (Base case 100%)**	\$██████	0.046	\$██████
Use of pooled estimate from NICE review (50% response for nabiximols and 32.9% for placebo****, base case 77.4% and 32.7% respectively)*	\$██████	0.017	\$██████
Assume 44.5% of patients fail to respond after 4 weeks of nabiximols initiation as per Markovà 2019 (Base case: omitted)	-\$██████	0.026	Dominant
<b>Multivariate analyses</b>			
Use of NICE review values for proportion of 30% responders* and utility values (0.537 and 0.352 for responder and non-responder, respectively)***	\$██████	0.031	\$██████
Use of NICE review values for proportion of 30% responders*, assume only 25% of costs reported in Stevenson (2015) and also reduced home care visits cost to 49.65%**	\$██████	0.017	\$██████
Use of NICE review values for proportion of 30% responders, utility values*** and reduction in Stevenson costs	\$██████	0.031	\$██████

Text in italics indicate Sensitivity analyses conducted during evaluation

\*Change values in response rate worksheet B15 and C15 to 50% and 32.9% and B16 and C16 to 50% and 67.1% respectively

\*\*Multiply cells C64:F69 by 25 % in costs worksheet, and cells B69 to F68 by an additional 49.65%

\*\*\*Change utilities worksheet Cells B37 and B38 to 0.537 and 0.352, respectively. In relation to the NICE values, NICE also acknowledged that their approach may have overestimated the utility gain with nabiximols

\*\*\*\* In its evaluation of nabiximols, the NICE model in the NICE evidence review for spasticity 2019 pooled estimates on the proportion of patients with ≥30% improvement from baseline NRS from Collin 2007, Collin 2010, Marková 2019 and Novotna 2011.

Source: Table 91, pp140-141 of the resubmission.

6.76 Based on the results of the sensitivity analyses, the key drivers of the model were the assumed proportion of responders in each treatment arm, the cost of managing spasticity for responders and non-responders and the assumed utility gain from a ≥30% improvement from baseline NRS.

6.77 The ESC considered the multivariate analyses incorporating the NICE values for responders, reduced costs and different utility values provided more reasonable ICERs (\$105,000 - \$200,000 and more than \$200,000), notwithstanding the significant issues identified with the model (paragraph 6.72).

6.78 The ESC considered the modelled analysis presented in the resubmission was uninformative for decision making.

**Drug cost/patient/year: \$ [REDACTED]**

6.79 The drug cost per patient per year for nabiximols is shown in Table 14.

**Table 14: Drug cost per patient for nabiximols as an adjunct to standard care**

	Marková 2019 dose and duration	Model	Financial estimates
Mean dose for initially treated patients	6.18 (phase A) to 6.25 (phase B) sprays/day <sup>a</sup>	6.5 sprays/day	0.92 packs of three spray bottles = 9.64 sprays/day*
Mean dose for continuing patients	7.33 sprays/day <sup>c</sup>	7.3/day <sup>b</sup>	7.3 sprays/day <sup>b</sup>
Mean duration	12 weeks	360 days	365 days
Cost/initially treated patient	\$ [REDACTED] for 4 weeks or \$ [REDACTED] for 30 days <sup>f</sup>	\$ [REDACTED] for 30 days	\$ [REDACTED] for 30 days <sup>d</sup>
Cost/continuing patient/month		\$ [REDACTED]	
Cost/patient/year as presented in the resubmission		\$ [REDACTED]	\$ [REDACTED]
Cost/ patient/year revised to 1 month initial therapy and 11 months continuing therapy	*	\$ [REDACTED] <sup>e</sup>	\$ [REDACTED]

Source: Table 86, p136 of the resubmission, Section 3 workbook. Italicised values have been calculated.

<sup>a</sup> Mean dose for the first 4 weeks in phase A was 6.18 sprays/day, mean dose for first 4 weeks in phase B was 6.25 sprays/day

<sup>b</sup> Mean sprays per day in Marková 2019 at Week 12 was 7.3, and this was used and assumed to be the ongoing dose with no reduction in dose for continuing patients

<sup>c</sup> Based on average of doses from Weeks 5 to 12 in Marková 2019. Dose patients were taking during Week 12 was 7.3 sprays per day

<sup>d</sup> 0.92 x \$ [REDACTED]

<sup>e</sup> A revised estimate was conducted during the evaluation to limit costs to one month of initial treatment and 11 months of continuing treatment

<sup>f</sup> Based on 6.18 sprays per day in Phase A of Marková 2019

No discontinuations were assumed. Wastage was not accounted for patients not continuing from initial therapy

\* The financial estimates equated that to 4.93 x two units of three spray bottles, sufficient quantity for 12 months, which was an overestimate given that patients would have received initial treatment for 4 weeks – assuming that the 12 months represents the first 12 months of therapy with nabiximols and not therapy in subsequent years

6.80 There were slight differences in drug costs between the estimate in the economic and financial models, predominantly relating to higher costs of initiating therapy assumed in the financial estimates. The trial-based costs were lower, since patients received a

lower overall mean dose in the first 4 weeks of the trial compared to that assumed in the model or the financial estimates.

***Estimated PBS usage & financial implications***

- 6.81 This resubmission was not considered by DUSC.
- 6.82 Key inputs for the financial estimates are presented in Table 15.

**Table 15: Key inputs for financial estimates**

Parameter	Value applied and source		Comment
Prevalent population	Prevalence of 103.7 per 100,000 with 1.23% growth rate based on Ahmad 2018.		Considered uncertain and other methods of estimation were not explored
% with moderate to severe spasticity	34% based on Rizzo 2014.		Rizzo 2014 did not use NRS to define severity of spasticity. Flachenecker 2013, which used NRS to define severity of MS associated spasticity, reported that 47.3% of all MS patients would have moderate to severe spasticity.
% taking oral anti-spasticity medication	80% based on survey of two neurologists		Uncertain based on method of estimation and low survey number
Uptake rate	15% in Year 1 and 2, 5% in Year 3 and 1% thereafter based on predictions by Sponsor and historical uptake rates in the UK.		Likely underestimated because restriction does not preclude patients from re-trialling therapy, and appears low for a group considered treatment refractory
Proportion of patients meeting criteria for continuation	55.5% based on proportion entering Phase B of Marková 2019, based on having at least a 20% improvement in NRS in Phase A and having reverted back to at least 80% of their baseline NRS		May be underestimated since patients also discontinued for reasons other than non-response in Marková 2019, and real-world data indicates a higher rate of continuation.
Grandfathered patients	None included.		It is uncertain if the estimated 56 patients currently being treated with nabiximols will qualify under the proposed PBS criteria.
Dose	0.92 scripts of three spray bottles for initial patients and 4.93 scripts for two units of three spray bottles		Inconsistent with the economic evaluation (which estimated lower use for initial patients).
Change in comparator/ subsequent therapies	None included.		May be unreasonable, given that patients need to be taking oral anti-spasticity medication to access nabiximols under the proposed restriction. Therefore there may be an increase in use of other therapies associated with initiation of nabiximols.
Cost of adverse events	None included.		These should have been included.
Treatment costs for responders and non-responders on nabiximols and standard care	\$1,400 Treatment for drug disorders for serious adverse event	AR-DRG Public Sector V66Z	While the sources look appropriate, for the costs per episode or hour, it wasn't clear where the value of \$38.78 per hour for home care was in the reported reference source. Rates for NDIS self-care for example appeared to be at least 10% higher.
	\$185 outpatient treatment per episode	AMA: List of medical services and fees	
	\$666 A&E per episode	National hospital cost data round 21 2016-17	
	\$2,087 per hospital admission	As above (cost weight table)	
	\$91.83 per hour district nurse	Pbs.gov.au. December 2016 manual of resources	
	\$38.78 per hour home care	Arts.unsw.edu.au NDIS pricing report	
Cost offsets for medical services (per continuing patient treated with nabiximols per annum)	-\$6,362.29	Resource utilisation from Stevenson 2015 and MBS fee	The ESC considered the cost offset for reduced health care resource utilisation was high and not likely to be reflective of actual costs. The ESC noted most of the cost offset (85%) was due to a reduction in home care costs.

Source: Section 4 of the resubmission.

6.83 The resubmission used an epidemiological approach to estimate the impact of listing nabiximols on the PBS. The number of patients treated, script numbers and overall financial impact of listing nabiximols as adjunctive treatment of moderate to severe spasticity in patients with MS who have not adequately responded to oral anti-spasticity agents is summarised in Table 16.

**Table 16: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients who trial therapy	■	■	■	■	■	■
Number of patients who continue therapy	■	■	■	■	■	■
Number of scripts dispensed for initial patients <sup>a</sup>	■	■	■	■	■	■
Number of scripts dispensed for continuing patients <sup>b</sup>	■	■	■	■	■	■
<b>Net financial implications</b>						
Net cost to PBS/RPBS of nabiximols <sup>c</sup>	\$■	\$■	\$■	\$■	\$■	\$■
Net cost of medical services	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■
<b>Net cost to the health budget</b>	<b>-\$■</b>	<b>-\$■</b>	<b>-\$■</b>	<b>-\$■</b>	<b>-\$■</b>	<b>-\$■</b>
Revised net cost to the health budget based on resource use of only 25% of that estimated in Stevenson 2015	\$■	\$■	\$■	\$■	\$■	\$■
<b>Previous submission July, 2013</b>						
Patients initiated on therapy	■	■	■	■	■	
Patients continuing on therapy		■	■	■	■	
Net cost to PBS/RPBS using DPMQ of \$413.30	\$■	\$■	\$■	\$■	\$■	

Source: Section 4 Workbook provided with the resubmission, Table 103, p151 of the resubmission, Paragraph 6.31 and 6.34 5-15 Nabiximols Minutes July 2013 PBAC Meeting (provided as an attachment to the submission)

<sup>a</sup> Assuming 0.92 scripts per year as estimated by the resubmission.

<sup>b</sup> Assuming 4.93 scripts per year as estimated by the resubmission.

<sup>c</sup> There were no financial implications included for other medicines and no copayments assumed.

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.*

6.84 The total cost to the PBS/RPBS of listing nabiximols was estimated to be less than \$10 million in Year 6, and a total of \$20 - \$30 million over the first 6 years of listing. There was an estimated saving to the health budget of less than \$10 million over the first 6 years of listing. The estimated savings were optimistic and unlikely to be realised, as it was based on overestimated costs for managing spasticity (see paragraphs 6.67 to 6.68). Assuming reduction in cost to 25% for managing spasticity, an overall net cost to the health budget of \$10 - \$20 million over the first six years of listing was estimated.

- 6.85 The PSCR argued the cost offsets were not overestimated, as the treatment costs were taken from the Stevenson 2015 study and furthermore, the cost offsets are more likely to be underestimated as the cost of care in Australia is 38% higher than the UK, based on figures in the AMSLS study (see paragraph 6.66).
- 6.86 The ESC agreed with the evaluation, and considered the estimated savings were implausible and agreed with the NICE conclusion that many of the costs for disease management will be incurred regardless of changes in spasticity, so are not likely to be offset.
- 6.87 Additionally, the estimated cost to the PBS/RPBS was likely to be underestimated due to an underestimation of the number of MS patients with moderate to severe spasticity, no inclusion of grandfathered patients or patients who might retrial nabiximols, underestimation of the uptake rate, and underestimation of the proportion of patients likely to continue on nabiximols after an initial 4-week trial of treatment.
- 6.88 There may also be patients who need to reinitiate therapy with oral anti-spasticity medication in order to be able to access nabiximols under the proposed restriction. The financial estimates made no allowance for increased costs associated with increased use of concomitant medications.

### **Quality Use of Medicines**

- 6.89 The Sponsor proposed a prescriber education program to cover safety aspects, dosing and titration schedule and treatment criteria, in order to ensure that health practitioners receive the appropriate education before prescribing nabiximols.

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

- 6.90 The Sponsor indicated they were willing to negotiate a Risk Sharing Arrangement as part of negotiations for a ‘reasonable price for listing, which is competitive by international listing standards’ (Pre-PBAC Response).

*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 nabiximols as an adjunctive treatment for moderate to severe spasticity due to multiple sclerosis (MS). In deciding not to recommend the listing of nabiximols, the PBAC considered the treatment effect was likely overestimated in the resubmission due to the design of the key clinical trial and that there were substantial structural issues and unrealistic assumptions in the economic model. On that basis, the PBAC considered the ICER was very uncertain and unacceptably high at the proposed price.
- 7.2 The PBAC noted there were treatment options currently available for MS-related moderate to severe spasticity, including intrathecal baclofen and botulinum toxin;

however, acknowledged there was a clinical need for additional effective and safe treatment options.

- 7.3 The PBAC considered the proposed patient population for nabiximols of patients with moderate to severe spasticity, defined as a numeric rating scale (NRS) score of 4 or greater, associated with MS, following an inadequate response to prior anti-spasticity treatment was appropriate. The PBAC considered the proposed threshold for continuing treatment of at least a 20% improvement in NRS after 4 weeks of treatment was reasonable and consistent with the clinical trial data presented in the resubmission.
- 7.4 The PBAC considered the nominated comparator of standard care, defined as oral anti-spasticity medication, was reasonable.
- 7.5 The PBAC noted clinical data from five studies was provided in the resubmission and the results generally supported a conclusion that nabiximols is effective at reducing MS-related spasticity. Three of the five studies (Vachová 2014, Collin 2007 and Collin 2010) were inconsistent with the requested population and listing as Vachová 2014 did not include criteria for discontinuation and the Collin 2007 and 2010 studies permitted maximum doses of nabiximols higher than that approved for use in the Product Information. The PBAC considered the Marková 2019 and Novotna 2011 studies to be the most reflective of the requested place in therapy for nabiximols.
- 7.6 The PBAC noted the key clinical trial (Marková 2019) presented in the resubmission used an enriched population design, which included a response testing phase (Phase A), and a washout period for responders prior to the randomised controlled phase (Phase B), while non-responders were excluded from further participation in the study. The PBAC considered that, while the trial design was reasonable, it was likely to result in an overestimate of the clinical benefit and an underestimate of the adverse events for nabiximols because:
- The inclusion of a washout period in the Marková 2019 study was likely to have led to some patients becoming aware of their treatment allocation (i.e. unblinding) in Phase B given they had been exposed to nabiximols in Phase A of the study followed by treatment withdrawal. Unblinding may lead to an overestimate of nabiximols benefit and underestimate of placebo benefit, given the subjective nature of the outcome.
  - The Novotna 2011 study used an enrichment design without a washout period and its participants were unaware of the potential change of drug/placebo allocation between Phases A and B. These study design features would reduce the risk of unblinding, and accordingly, the PBAC noted the incremental benefit of nabiximols versus placebo in the Novotna 2011 study, was lower than observed in Markova 2019 (paragraph 7.7).
  - The enriched population design may limit the generalisability of the trial to the broader population as non-responders were excluded from the randomised

controlled phase.

- Adverse events in Phase B may be underestimated as patients experiencing tolerability issues may withdraw from treatment in Phase A or the washout period
- 7.7 The PBAC noted the risk difference (RD) for the proportion of patients treated with nabiximols achieving a 30% or more reduction in NRS over 12 weeks of treatment compared to placebo was 45% and 23% in Markova 2019 and Novotna 2011, respectively. The PBAC noted the nabiximols treatment response rates were similar in the Markova 2019 and Novotna 2011 studies (77% and 74%, respectively) and the observed differences in RD was attributable to the observed differences in placebo response rates (32% and 51% in Markova 2019 and Novotna 2011, respectively). Due to the design of the Markovà 2019 trial (see paragraph 7.6), the PBAC considered the difference in placebo response rates was likely due to potential unblinding of participants in Markovà 2019. Further, the PBAC considered the impact of unblinding was likely to be exacerbated as the primary outcome of improvement in NRS score was a subjective measure.
- 7.8 The PBAC considered that based on the available evidence, it was likely that nabiximols was of modest benefit in the requested population; however, the magnitude and durability of the benefit was uncertain.
- 7.9 The PBAC considered the claim that nabiximols was of inferior safety to standard care was reasonable, however further considered the comparative safety may be less favourable than reported for nabiximols due to the likely underestimate of adverse events in Phase B of the Markovà 2019 trial (paragraph 7.6).
- 7.10 The PBAC had substantial concerns with the structure and inputs to the economic model and considered the submission base case to be uninformative for decision making because:
- The model structure was overly simplistic and did not capture the complexity of MS-related spasticity, inappropriately assumed responders would respond from day 1 of treatment, excluded initial non-responders to nabiximols (and associated costs) and nominated a time horizon of 12 months, which was too short for a chronic condition where treatment would likely be long-term in patients who received a benefit. The PBAC noted the PSCR provided an updated model extended to 10 years and applied an arbitrary decline in response of 1% per year. However, the PBAC noted the model was informed by only 12 weeks of data which created substantial uncertainty in a longer model duration and extending the model duration in isolation of other changes did not provide more certainty or better inform the cost effectiveness of nabiximols;
  - Given the issues with the design of the Markovà 2019 trial (see paragraph 7.6) and as the only study used in the economic model, the clinical data that informs the model is highly uncertain. The PBAC considered the effect size included in the economic model was likely to be an overestimate and the rate of adverse events

were likely to be an underestimate;

- The method used to determine the utility gain from achieving  $\geq 30\%$  improvement from baseline NRS was uncertain;
- The cost offsets in the model were substantially overestimated, as the model inappropriately assumed all MS-related treatment costs would be offset. The PBAC considered this was inappropriate and agreed with ESC that health system costs for the management of MS would continue, and that only a proportion of costs which could be attributed to spasticity may be offset. The PBAC noted there was no observed significant difference in healthcare use between the nabiximols and standard care arms in Markovà 2019. The PBAC noted the economic model was highly sensitive to healthcare cost assumptions and applying the NICE review values of 25% of costs reported in Stevenson 2015 and 49.65% of home care visits increased the ICER substantially.

7.11 Noting the substantial issues with the economic model the PBAC considered the cost-effectiveness of nabiximols to be very uncertain and unacceptably high at the proposed price.

7.12 The PBAC considered the base case financial estimates of total cost to the health system to be underestimated, as the cost offsets for other health system costs avoided were not realistic. As for the economic model, the PBAC noted the submission assumed large proportions of MS-related health system costs would be avoided and considered this was an unreasonable assumption, as only a portion of those costs were attributable to MS-related spasticity. Furthermore, the PBAC considered the assumption of reduced health system costs to be uncertain as changes in health resource use were not observed in the Markovà 2019 trial.

7.13 The PBAC considered any potential resubmission would require a major submission with a re-specified economic model addressing the issues raised in paragraph 7.10 and revised financial estimates noting the issues raised in paragraphs 6.87 and 7.12. The PBAC considered that while the economic model presented in the resubmission was unreliable, it was likely to have substantially underestimated the ICER and considered a reasonable re-specified economic model would likely require the price of nabiximols to be reduced substantially to achieve a reasonable ICER.

7.14 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**

Emerge Health is disappointed with the PBAC outcome but will continue to work collaboratively with the PBAC, the Department of Health and Federal Government to ensure patients with MS related spasticity receive access to Sativex through the Pharmaceutical Benefits Scheme.