Public Summary Document

Product: Nabiximols, oral spray, 10 mL (90 actuations of 100 microlitres), Sativex®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought an Authority required listing for the treatment of moderate to severe spasticity due to multiple sclerosis in a patient who is intolerant to anti-spasticity medication and/or has not adequately responded to anti-spasticity medication.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Nabiximols was TGA registered on 26 November 2012 as treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis 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.

4. Listing Requested and PBAC's View

Authority required
Initial treatment
Initial treatment by a specialist with experience in the management of MS spasticity in subjects aged 18 years or older. Initial treatment for symptom improvement in subjects with moderate to severe spasticity (Numeric Rating Scale [NRS] Score ≥4) due to multiple sclerosis (MS) who are intolerant to anti-spasticity medication and/or have not adequately responded to anti-spasticity medication. A maximum of 4 weeks therapy will be supplied.

Continuing treatment
Continuing treatment by a specialist with experience in the management of MS spasticity in subjects aged 18 years or older. Continuing treatment for symptom improvement in subjects with moderate to severe spasticity due to multiple sclerosis where an adequate response to nabiximols therapy has been demonstrated. An adequate response to therapy is defined as a ≥20% improvement in spasticity severity over the initial treatment of 4 weeks using the NRS (as assessed by the treating specialist).

The PBAC noted that a 20% improvement required to continue treatment in the requested restriction was not consistent with a requirement of a change of 30% on the NRS for spasticity to be considered as clinically meaningful in presented trials.

5. Clinical Place for the Proposed Therapy

Spasticity is a common feature of many neurological conditions such as MS, stroke, spinal cord injury, traumatic brain injury, and cerebral palsy. The submission defined spasticity as disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of that muscles.

The submission stated based on a Delphi survey of 18 Australian clinicians, baclofen is used as first-line treatment for MS-related spasticity regardless of severity. Second-line therapy consists of oral baclofen dose escalation in combination with other therapies such as dantrolene or diazepam. Finally, third-line therapy consists of intrathecal baclofen in a small proportion of patients.

The submission proposed that nabiximols would likely be considered before intrathecal baclofen therapy as an important second-line treatment; and it would be expected to be used as 'add-on' therapy for patients taking other anti-spasticity medications (e.g. oral agents such as baclofen) or monotherapy for patients who are intolerant to anti-spasticity medication.

The PBAC noted the Product Information states that nabiximols is intended to be used in addition to the patient's current anti-spasticity medication.

6. Comparator

The submission nominated standard care (defined as multi-disciplinary involving physiotherapy and pharmacotherapy) as the comparator.

The PBAC noted that there are three potential groups of patients represented in the PBS restriction:

1. Patients in whom oral anti-spasticity agents (e.g. oral baclofen) have failed to produce adequate relief (i.e. partial responders);
2. Patients who are intolerant to anti-spasticity agents, and
3. Patients who have tried and failed anti-spasticity agents (i.e. non-responders).

The PBAC considered that the nominated comparator was not appropriate for all the patient groups represented in the PBS restriction, and that a comparison with the second-line therapy of oral baclofen dose escalation alone or in combination with dantrolene or diazepam, as identified in the Delphi survey, should have been included.

7. Clinical Trials

The submission presented one key trial GWSP0604 as the pivotal evidence for the safety and efficacy of nabiximols. The trial was considered by the submission to have most closely reflected the expected use of nabiximols in Australian clinical practice. The design of the trial included a 4 week 'trial of response' phase (see below) and this period was included in the proposed indication for nabiximols.

The key trial GWSP0604 was a two-phase, enrichment design trial: phase A (N=572, single-arm and single-blinded (only subjects were blinded), active treatment duration four weeks; 6.9 ± 1.8 sprays per day) and phase B (n=241, double-blinded, placebo-controlled, duration 12 weeks). During phase A, all subjects (N=572) received nabiximols treatment. At the end

of phase A, subjects who achieved at least a 20% improvement in spasticity as measured by the numeric rating scale (NRS) for spasticity moved into phase B (n=241, duration = 12 weeks) and were randomised between nabiximols (n=124; mean 8.3 ± 2.4 sprays per day) and placebo (n=117).

The submission also presented three supportive trials GWMS0001, GWMS0106 and GWCL0403.

Trial GWMS0001 (n=160) was a 6-week double-blind RCT followed by an open-label active medication for four weeks. The maximum permitted dose was eight sprays in any three hour period and 48 sprays in any 24-hour period, with an average of 14.1 ± 9.3 sprays per day used in the trial. The trial included patients with a variety of symptoms of MS, including, but not limited to spasticity.

Trial GWMS0106 (n=189) was an 8-week multicentre, double-blind RCT. The maximum number of sprays allowed in the trial was 48 per day, with an average of 9.4 ± 6.4 sprays per day used in the trial.

Trial GWCL0403 (n=337) was a 14-week double blind RCT. The maximum number of sprays allowed in the trial was 24 per day, with the mean dose of 8.5 ± 4.8 sprays per day.

The details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
GWMS0001 & GWMS0001ext	A double blind, randomised, parallel group, placebo controlled trial of a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in subjects with multiple sclerosis, followed by open label assessment and extension.	July 2003 July 2006
Wade D T. et al.	Do cannabis-based extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomised, placebo-controlled study on 160 subjects.	Multiple Sclerosis 2004; 10: 434-41.
Wade D T. et al.	Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis.	Multiple Sclerosis 2006; 12: 639-45.
GWMS0106	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.	July 2006
Collin C. et al.	Randomized controlled trial of cannabis-based medicine in	European Journal of Neurology 2007; 14: 290-

	spasticity cause by multiple sclerosis.	96.
GWCL0403 Collin C. et al.	A double blind, randomised, placebo controlled, parallel group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis.	21 July 2006 Neurological Research 2010; 32 (5): 451-59.
GWSP0604 Novotna A. et al.	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. 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.	02 January 2008 European Journal of Neurology 2011; 18(9): 1122-31
GWSP0702 Notcutt W. et al.	A placebo controlled, parallel group, randomised withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term GW-1000-02 (Sativex). A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols)	16 April 2009 *Multiple Sclerosis* 2012; 18(2): 219-228.
Meta-analyses of direct randomised trials		
Wade D T. et al.	Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis.	Multiple Sclerosis 2010; 16(6): 707-14.

8. Results of Trials

The submission presented change in the numeric rating scale (NRS) for spasticity as the primary outcome measure for key trial GWSP0604, and supportive trials GWMS0106 and GWCL0403; and change in primary symptom score as the primary outcome measure for trial GWMS0001.

The results of the analyses for all included trials are shown below.

Results of adjusted[a] mean change in spasticity severity, using NRS spasticity scale (0-10, where 10 is worst), across the direct randomised trials

Trial ID	Nabiximols	Placebo	Mean difference

					(95%CI)
	Baseline NRS	**Adjusted mean change**	**Baseline NRS**	**Adjusted mean change**	
Key trial					
GWSP0604 (phase A)[b]	6.8 (1.3)	-1.5 (1.8)	N/A	N/A	N/A
GWSP0604 (phase B)[c]	3.8	-0.0	3.9	0.8	**-0.8 (-1.3; -0.4)**
Supportive trials					
GWMS0001[d]	69.4	-23.3	68.7	-16.2	**-7.1 (-14.6; -0.4)**
GWMS0106	5.5	-1.2	5.4	-0.6	**-0.5 (-1.0; 0.0)**
GWCL0403	6.8	-1.1	6.5	-0.8	-0.2 (-0.6; 0.1)

A = not available; NRS = numeric rating scale; CI = confidence interval. **bold** = statistically significant.

[a] Results were adjusted for: baseline NRS, treatment group, country, ambulatory status and previous cannabis use (GWSP0604, GWMS0106, GWCL0403), and baseline primary impairment score (GWMS0001)

[b]Single arm trial period, value was not adjusted

[c]Only subjects who had a 20% response after the initial 4-week treatment were included in phase B of trial GWSP0604. The baseline NRS was measured when subjects were randomised in phase B.

[d]For subjects where spasticity is included as an impairment (N=140) using a subject self-report 100 mm VAS symptoms severity score (p20, CSR GWMS0001).

The PBAC noted that the submission referred to the results from Farrar et al. (2008) and claimed a strong correlation between the absolute change in NRS and the change in Patient Global Impression of Change Scale (PGIC) ($r=0.47$, $p<0.001$) and a strong correlation between the percentage change in NRS and the percentage change in PGIC ($r=0.51$, $p<0.001$). Using the definitions of 'much improvement' and 'minimally improved' from PGIC, the submission categorised that a change of -30% was most predictive of a patient's reporting 'much improved' while a change of -18% was most predictive of a patient's report 'minimally improved'. The submission then defined that a change of 30% on the NRS for spasticity was considered a clinically meaningful change.

The results of GWSP0604 showed an improvement in the average rating of spasticity severity in both treatment arms. However, the PBAC noted that in phase A of the trial, the average improvement in NRS spasticity was 1.5 (SD 1.8) and that for those patients who had a 20% response after phase A (i.e. patients who were randomised in phase B), no further improvement on the NRS score was observed when treated with nabiximols in phase B compared with a small increase in the NRS score in the group treated with placebo.

The results in trial GWMS0106 and trial GWSP0604 were also statistically significant. However the PBAC considered that the clinical relevance of the improvement in the group treated with nabiximols compared to placebo, 0.2 to 0.8 on the NRS for spasticity, was not clear. These values were less than the value in Farrar et al (2008) that was considered to be a minimally important difference (a change of -1.27 for the raw NRS most predictive of patients reported 'much improved' or better on the PGIC and a change of -0.9 for the raw NRS most predictive of patients who reported 'minimally improved' or better on the PGIC).

The submission also presented a responder analysis, with 'response' defined as greater than or equal to 30% improvement in spasticity severity, as shown in the table below.

Results of responder analysis (greater than or equal to 30% improvement in spasticity severity) across the direct randomised trials

Trial ID	Nabiximols n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95% CI)

Key trial					
GWSP0604 (phase B)[a]	92/124 (74.2%)	60/117(51.2%)	**1.4 (1.2; 1.8)**	**23% (11%; 35%)**	**4 (3; 9)**
Supportive trials					
GWMS0001[b]	39/72 (54.2%)	25/68 (36.8%)	**1.5 (1.0; 2.1)**	**17% (1%; 34%)**	**6 (3; 83)**
GWMS0106	48/120 (40.0%)	10/64 (21.9%)	**2.6 (1.4; 4.7)**	**24% (12%; 37%)**	**4 (3; 8)**
GWCL0403	51/166 (30.7%)	42/169 (24.9%)	1.2 (0.9; 1.8)	6% (-4%; 15%)	17 (NE)

RR = relative risk; RD = risk difference; NNT = number needed to treat; NE = not estimable.
Bold = statistically significant at 5%.
[a] In trial GWSP0604, the spasticity response was defined as an improvement of 30% or more in the primary endpoint at end of Phase B treatment compared to screening (i.e. beginning of phase A).
[b] For subjects where spasticity is included as an impairment (N=140).

The submission stated that the chance of responding to nabiximols was significantly higher than the chance of responding to placebo in the key trial GWSP0604 (phase B) and the supportive trials GWMS0001 and GWMS0106. However, the PBAC considered that given the enrichment design used in the trial GWSP0604 it was difficult to generalise the effect size for this response to patients likely to be treated if nabiximols was listed on the PBS.

Overall, the PBAC considered trial GWSP0604 to have a high risk of bias in favour of nabiximols, because of the following factors:

- The primary outcome measure of the change in the numeric rating scale (NRS) for spasticity was subjective.
- Missing data were analysed using last observation carried forward, likely to bias the effect in favour of nabiximols.
- There appeared to be a differential rate of discontinuation between the two treatment groups in Phase B treatment 12% for nabiximols v.s 2% in the placebo group and no explanation was provided for this discrepancy.

The PBAC considered that in addition to the risk of bias, there were problems in applying the results of the trial to the target PBS population because the enrichment design limited generalisability.

The PBAC also considered the supporting trials GWMS0001, GWMS0106 and GWCL0403 to have a high risk of bias because of the primary outcomes were subjective, there were differential discontinuation rates and there was inadequate information about the method of handling missing data in the analyses.

The submission presented a range of secondary outcomes. The PBAC noted the secondary outcomes showed inconsistent results for the spasm frequency score, sleep questionnaire, Barthel ADL, total Guy's neurological disability scale, subject global impression of change, carer global impression of change, physician global impression of change, while no effect was found for the Motricity Index, 10 metre walk, and the fatigue severity scale questionnaire.

The submission presented the results of the EQ-5D and SF-36 and stated that the trials were not powered to demonstrate a significant improvement in quality of life. The PBAC noted

none of the differences in the change in health outcomes between treatment arms reached statistical significance.

For all trials, 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%).

The PBAC noted that the submission provided additional data on potential safety concerns beyond those identified in the clinical trials. The reported adverse events were similar to those reported in the trials.

9. Clinical Claim

The submission described nabiximols as superior in terms of comparative effectiveness and did not make any explicit claim in terms of comparative safety over standard care.

The PBAC considered that the claim for superior efficacy over standard care was inadequately supported for the following reasons:

- The enrichment design of the key trial made it difficult to generalise the results to practice.
- The high risk of bias in the trials suggested that the effect size was likely to be overestimated.
- Even allowing for this likely overestimate, only small differences in outcomes were demonstrated that were of questionable clinical significance.

With respect to comparative safety, the PBAC considered that nabiximols appeared to be inferior to standard care.

10. Economic Analysis

The submission presented a cost-utility analysis. The economic model was a ten-state Markov model that compared nabiximols (added to standard care) to standard care alone. The model used data from trial GWSP0604 for the estimate of treatment effect for nabiximols and data from a retrospective observational Spanish Study (n=212 patients with MS and spasticity resistant to 1 or more previous standard therapies) (Arroyo et al. (2011)) to derive the estimate of progression of spasiticity for the standard care arm. The model was then extrapolated for five years.

The submission presented an ICER of $15,000 - $45,000 per QALY gained. The ICER was reduced, though in the same range, with the price reduction offered in the pre sub-committee response (p4) of 13.5%. Utility values were derived from the GWSP0604 trial.

The PBAC considered that the clinical data did not adequately support a claim of superior effectiveness, the basis for the cost-utility analysis was poorly supported. In addition, the

results of the economic analysis were biased in favour of nabiximols as the following key issues were not adequately addressed:

- Whether the effect size estimated from the patient population from the key trial GWSP0604 was representative of the likely effect in the proposed PBS population.
- Whether the population in the Arroyo et al. (2011) study was applicable to the PBS population. The populations had different mean age, duration of MS, and distribution of MS type, and therefore Arroyo (2011) may not be comparable to the GWSP0604 population and representative of the PBS population.
- The assumption that spasticity severity worsened for subjects receiving standard care and stabilised for subjects receiving nabiximols was inconsistent with the data in Arroyo (2011), where approximately 13% of standard care patients showed improvement. The assumption may not be appropriate as a proportion of the subjects with spasticity have relapsing remitting MS (MS Australia database, 36% of subjects). This assumption favoured nabiximols.
- The utility values used for the three health states were 0.61, 0.56 and 0.43 for mild, moderate and severe strata respectively. However, there was no statistically significant difference between mild and moderate strata.
- The distribution of NRS for spasticity score across the three health states was not consistent with the proposed PBS restriction and the inclusion criteria for the key clinical trial GWSP0604, where moderate and severe spasticity were defined with a NRS score greater than or equal to 4. The submission did not provide justification for the inconsistency.
- Adverse events were not included in the economic model. Nabiximols was noted to have associated with more adverse events than standard care so this was likely to favour nabiximols.

The PBAC noted the following key issues were not accounted for in the model:

- efficacy as observed in the supportive trials which compared nabiximols vs. placebo for the whole duration of the trial,
- relapsing and remitting MS is cyclic in nature and spasticity may improve over time in the standard care group.
- the costs and disutility of adverse events

The PBAC also noted that the sensitivity analyses showed that the ICER was only slightly sensitive to the utility values, based on the results of the key univariate sensitivity analysis presented by the submission and additional analyses conducted during the evaluation. updated to account for the price reduction, and based on the results of the sensitivity analysis where mild and moderate states were collapsed into one health state.

11. Estimated PBS Usage and Financial Implications

The net cost per year to the PBS was estimated in the submission to be between $10 million to $30 million in Year 5.

12. Recommendation and Reasons

The PBAC rejected the submission seeking listing of nabiximols for the treatment of moderate to severe spasticity due to multiple sclerosis in a patient who is intolerant to anti-spasticity medication and/or has not adequately responded to anti-spasticity medication, on the basis of insufficient evidence to establish comparative effectiveness and safety compared with standard care alone in patients who are intolerant to anti-spasticity medication; and no evidence of efficacy and safety provided in comparison with high dose baclofen alone, or in combination with dantrolene or diazepam as the second-line therapy.

The PBAC considered that the nominated comparator was not appropriate. The PBAC considered that the second-line therapy of oral baclofen dose escalation alone or in combination with dantrolene or diazepam should have been included at least as a secondary comparator.

The PBAC noted the although the results of the key trial showed an improvement in the average rating of spasticity, the design of the trial meant that it was difficult to extrapolate this benefit to patients likely to be treated in the PBS population. In addition, the clinical relevance of the benefit was not adequately substantiated.

The PBAC considered that the claim for superior efficacy over standard care was inadequately supported and that nabiximols appeared to be inferior over standard care in terms of comparative safety.

Given that the clinical data did not support the claim of comparative effectiveness and safety, the PBAC considered the validity of the economic analysis was not supported.

The PBAC considered that the estimated costs to the PBS were uncertain as potential wastage of nabiximols and potential costs for the treatment of adverse events of nabiximols and costs to other government health budgets were not accounted in the submission.

The PBAC noted the consumer comments received in relation to the submission.

Outcome:
Rejected

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no comment.