Internal Memo
Ministry Of Health

To: [redacted] MAAC Secretary, Medsafe

From: [redacted] Advisor – Science, Medsafe

Subject: **Referral to the Medicines Assessment Advisory Committee – Sativex oromucosal spray, TT50-8053**

Date: 31 May 2010

For Your: ACTION: √ DECISION: INFORMATION:

Background

Sativex is in the final stages of approval in the UK and Spain via the EU Decentralised Procedure. This approval is for the indication relating to symptom improvement in spasticity due to multiple sclerosis (MS). The company anticipates that Sativex will be marketed in the UK by late June 2010.

The applicant has supplied the MHRA Day 180 Clinical Assessment Report that outlines the MHRA's assessment of new pivotal clinical trials submitted in addition to the trials submitted in an earlier EU submission. The main aspects discussed in this report are summarised below.

Following assessment of additional pre-clinical data, the MHRA assessor concluded a low potential for genotoxicity, carcinogenicity and local toxicity, and that major organ toxicity at clinical doses is not expected. Preclinical data suggest Sativex should not be used during pregnancy or during breast-feeding.

The pharmacodynamic effects of the cannabinoids in Sativex are well documented in published literature. The report refers to literature confirming relief of motor dysfunction and spasticity in accepted animal models, and new published preclinical mechanistic data. Sativex dose-dependently inhibited spasticity in a validated mouse model of MS. Information is most lacking about effects on muscle tone or spasticity in humans. However, the MHRA assessor considers that preclinical data suffice in this instance as spasticity is not readily measurable in humans. Overall, the Phase I studies conducted by the company were considered adequate by the assessor.

The pharmacokinetics of Sativex were well described and discussed. The assessor mentioned that wording in the Summary of Product Characteristics justifies the lack of advice regarding hepatic or renal impairment. The therapeutic dose is highly variable among patients, indicating that individual dose titration is appropriate.

The Ashworth scale is the standard measure of spasticity in humans. However, there is highly persuasive information in the literature outlining how the Ashworth scale lacks the validity, reliability, and sensitivity necessary for an effective efficacy measure in clinical trials. Thus, the applicant employed the 0 - 10 point Numeric Rating Scale (NRS) which is a patient reported measure of spasticity symptoms. This scale can not detect a confirmed objective change in spasticity in response to treatment. However, the company demonstrated acceptable validity of the NRS as a measure of symptoms related to spasticity. The NRS is a symptomatic measure, and the proposed indication is fully symptomatic.

The first large study GWMS0001 was negative overall, but encouraging for spasticity as a secondary endpoint. The 6 week GWMS0106 pivotal trial showed a modest level of statistical significance in the difference from placebo. The 14 week study GWCL0403 was negative, although the majority of endpoints showed a favourable trend for Sativex. A meta-analysis of GWMS0106 and GWCL0403 showed a modest mean treatment effect of questionable clinical significance (-0.34 points on the 10 point NRS). The assessor commented that the clinical relevance of a difference in means observed on a scale can be assessed by comparing responder rates which were encouraging in this case. The responder rates were 35% for Sativex compared with 24% for placebo.

Based on this, the applicant adopted a 'therapeutic trial' approach to identify a sub-population of responders. Following post-hoc analyses comparing NRS scores, the applicant determined that a 4 week therapeutic trial may allow responders access to treatment without subjecting non-responders to long-term treatment. The new pivotal study GWSP0604 was designed to test the benefits of this approach. The assessor commented that although an enrichment study design was unusual, it reflects clinical practice in this setting. Patients who achieved a 20% response (according to the NRS) within 4 weeks gained benefit from continued treatment. Those who discontinued Sativex experienced a loss of efficacy. Highly significant superiority to placebo was detected in global impression of change for subjects, carers, physicians, and objective measures of spasticity or direct manifestations of spasticity. There was a statistically significant difference in spasm frequency, a significant treatment effect for sleep disruption, and borderline significant effects on barthel index and time 10 metre walk test.

Statistical significance was not seen for the modified Ashworth scale, although there was a strong trend favouring the Sativex group (95% CI -3.80, 0.30 and p-value 0.094). The assessor indicated that this is not indicative of a lack of efficacy, and the results for Sativex on the Ashworth scale are consistent with what is expected for other anti-spasticity agents in this patient population with advanced disease.

The new placebo controlled, parallel group, randomised withdrawal study GWSP0702 showed a highly statistically significant difference in primary efficacy endpoint of the time to treatment failure, with the risk of failure being reduced by around 65% in the Sativex group. The assessor concluded that the results of this trial give adequate evidence of a benefit of continued long-term treatment for responders.

The assessor concluded that taken as a whole, the data are considered sufficient to demonstrate an objective effect of cannabinoids in general, and Sativex in particular on the physiological phenomenon of spasticity.

The assessor commented that Sativex is very different from illicit cannabis in PK and CNS effect profiles. There is no evidence of CNS effects unrelated to spasticity confounding efficacy measures.

The adverse event rate was much higher in the Sativex groups compared to placebo groups, and the main safety and tolerability issues relate to CNS effects. The potential for oral mucosal lesions is a safety issue that in most cases can be managed by varying application site. The assessor indicated that psychiatric events are common in MS patients and the data is insufficient to establish a causal association with Sativex. This issue may be reasonably managed with post-market risk management and advice in patient information leaflets. The assessor concluded that the safety profile is acceptable and that the safety issues are outweighed by significant benefit in terms of efficacy. There are no safety issues that raise concern over the risk benefit of non-responders, and there is no evidence of long term sequelae following a 4 week therapeutic trial.

Conclusion

The assessor concluded that a positive risk-benefit is concluded in MS patients for a symptomatic indication. The indication statement approved by the MHRA, and agreed upon by the company is as follows:

"Sativex is indicated as add-on treatment for symptom improvement 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".

The applicant will need to commit to adopting the wording from the UK PL and SPC into the NZ data sheet, and to provide and implement a risk management plan for post-market monitoring.

Recommendations:
You are requested to accept the MHRA's decision, and recommend that Sativex be approved for the indication outlined in the conclusion above.

1	**Note** the attached MHRA Day 180 Assessment report	YES / NO
2	**Administer** the recommendation that the Minister's delegate refers this application to the Medicines Assessment Advisory Committee for approval based on the MHRA's assessment of additional clinical data.	YES / NO

[redacted]
Advisor – Science
Medsafe

Sarah Reader
Manager – Product Regulation
Medsafe

[redacted]
MAAC Secretary
Medsafe

Date: 03/06/2010