MINUTES OF THE 90TH MEETING OF THE MEDICINES ASSESSMENT ADVISORY COMMITTEE HELD VIA TELECONFERENCE ON WEDNESDAY 30 JUNE 2010 COMMENCING AT 9:30am

Associate Professor R Robson (Chair)
Dr R Acland
Professor N Anderson
Dr R DeBoyer
Dr M Harrison-Woolrych
Dr A Macleod
Dr D Pethica
Ms A Kerridge (Secretary)

5.1 Sativex oral spray (TT50-8053)
G W Pharma Limited (trading as G-Pharm Limited)

A new medicine application was submitted by G W Pharma Limited for Sativex oral spray to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) on 7 January 2008, initially under section 23 (provisional consent) of the Medicines Act 1981.

The proposed indications for Sativex (cannabis extracts 27 mg/ml delta-9-tetrahydrocannabinol and 25 mg/ml cannabidiol) oral spray were for the relief of spasticity in multiple sclerosis, the relief of neuropathic pain in multiple sclerosis and the relief of pain in cancer. Sativex is notable in that it is the first medicine containing the active components tetrahydrocannabinol and cannabidiol.

Initial evaluation of the administrative, chemical and pharmaceutical data commenced on 20 February 2008. A request for further information was sent to the applicant company on 8 April 2008. This request only related to the administrative section of the application. A satisfactory response to this request was received on 5 May 2008. There were no further outstanding issues in relation to the administrative, chemical and pharmaceutical data.

Initial evaluation of the clinical data, by two members of the Committee ([redacted] and [redacted]), commenced on 10 January 2008 and was discussed at the 85th Committee meeting on 18 March 2008. Following discussion at the 85th meeting the Committee concluded that there was insufficient data to recommend approval for Sativex at that time. The Committee requested the following further information in relation to the clinical data:

- more robust evidence of efficacy in spasticity and cancer pain
- data on the neuropsychiatric profile and cognitive function.

A response was received from the applicant company on 5 May 2008. The response contained very little information in support of two of the proposed indications, the relief of neuropathic pain in multiple sclerosis and the relief of pain in cancer. The response was evaluated by [redacted]. The reports from [redacted] and [redacted] were discussed at the 86th Committee meeting on 29 and 30 July 2008. Following discussion at the 86th meeting the Committee were unable to recommend approval at that time due to insufficient data. The Committee again requested further information:

- data from the ongoing studies into patients with multiple sclerosis and spasticity, when available
- a full transcript of [redacted] report (who assessed whether an occurrence of adverse events predicted efficacy in three phase III studies of Sativex in people with multiple sclerosis and spasticity).

A response was received from the applicant company on 1 December 2008. Additional data was also received on 27 May 2009. Due to the change in Committee procedures at the time, this data did not go directly back to the Committee for consideration. Rather, the primary and secondary evaluators [redacted] and [redacted] assessed the further data and made their recommendations

directly to Medsafe. [redacted] and [redacted] evaluated the additional data sent on 1 December 2008 and 27 May 2009 and produced two clinical assessment reports.

The peer review of these two clinical assessment reports concluded the following:

- the relief of spasticity in multiple sclerosis may be approvable under section 23, however, due to conflicting conclusions from the two assessors it was recommended that the application should be referred back to the Committee
- due to the lack of data, the risk-benefit balance was unclear and the indications of the relief of neuropathic pain in multiple sclerosis and relief of pain in cancer cannot be recommended for consent.

Following this peer review, Medsafe concluded that the recommendation to grant consent to distribute Sativex could not be made because of the absence of conclusive data on the efficacy of the product.

The application was therefore referred to the Minister of Health on 1 December 2009. Having reviewed the information supplied in the initial application and in the further responses, the Minister of Health was not satisfied that consent could be granted to the distribution of the product and referred the application to the Committee. On 7 December 2009 the applicant company was advised of the referral to the Committee.

Sativex was added to the agenda of the 89th meeting of the Committee held on 17 March 2010. However, two days prior to the meeting the applicant company requested that the item be deferred from that meeting and requested a teleconference with Medsafe.

The teleconference took place on 15 April 2010. The applicant company requested clarity of where Sativex was in the approval process because there was uncertainty as to whether section 20 (full consent) or section 23 (provisional consent) approval was being considered. The applicant company also advised that European approval would be granted over the following weeks for one indication, the relief of spasticity in multiple sclerosis. The European evaluator had reviewed new clinical data and concluded this supported the single indication. The other indications were not approved as there was a lack of efficacy data.

The conclusions from the teleconference were are follows:

- the Committee would be asked to consider section 20 approval, for the indication for the relief of spasticity in multiple sclerosis, as the first option
- the Committee would be asked to consider whether section 23 approval could be granted for all indications pending further clinical trial data, as the second option
- additional data would be accepted and provided to the Committee in the form of the European evaluation reports.

Medsafe evaluated the additional data that was received from the applicant company on 11 May 2010 and 20 May 2010.

The evaluator stated that a positive risk-benefit could be concluded in multiple sclerosis patients for a symptomatic indication. The indication statement approved by the Medicines and Healthcare products Regulatory Agency in the United Kingdom, and agreed by the applicant company, is as follows: "Sativex is indicated as add-on 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". The applicant company would need to commit to adopting the wording from the United Kingdom product license and summary of product characteristics into the New Zealand data sheet, and to provide and implement a risk management plan for post-market monitoring.

The Committee considered the following documentation:

a. Referral memo to the Deputy Director-General – 1 December 2009.
b. Referral letter to the company – 7 December 2009.
c. Medsafe internal memo from the evaluator – 27 October 2009.
d. Quality Review – 19 November 2009.
e. Evaluation Report – 27 May 2008.
f. MAAC Report – 29 July 2008 [redacted]
g. MAAC Report on Preclinical and Clinical Data [redacted]
h. MAAC Report on Preclinical and Clinical Data [redacted]
i. MAAC Report on Preclinical and Clinical Data [redacted]
j. MAAC Report on Preclinical and Clinical Data [redacted]
k. MAAC Report on Preclinical and Clinical Data [redacted]
l. MAAC Report on Preclinical and Clinical Data [redacted]
m. Medical Advisor's Report – October 2009.
n. Request for withdrawal from MAAC agenda – 5 March 2010.
o. Application deferred to the next meeting – 8 March 2010.
p. New Drugs Online Report – 6 April 2010.
q. G W Pharma regulatory update – 6 April 2010.
r. Minutes of the teleconference held on 15 April 2010.
s. Email following the teleconference – 11 May 2010.
t. United Kingdom email correspondence – 5 May 2010.
u. Decentralised procedure – RMS day 180 draft assessment report (assessment of the response) – 20 April 2010.
v. Decentralised procedure – RMS day 180 draft assessment report (overview and list of questions) – 20 April 2010.
w. Update from the United Kingdom on the decentralised procedure – 20 May 2010.
x. Decentralised procedure – RMS day 210 final assessment report (overview) – 18 April 2010.
y. Reference member state – day 210 end of procedure – 17 May 2010.
z. Medsafe internal memo summarising the European Union decentralised procedure – 31 May 2010.

On 21 June 2010, further documentation was received from the applicant company:
- Evidence of the product license from the Medicines and Healthcare products Regulatory Agency. The license is valid from 16 June 2010 and expires on 16 May 2015. Sativex is indicated as add-on 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.
- Summary of product characteristics for Sativex.

The Scrip articles presented to the Committee were:
- UK and Spanish approvals expected soon for Sativex in MS spasticity (20 May 2010)
- GW and Otsuka to take Sativex to Phase III for cancer pain (25 March 2010)
- EU approvals of GW's cannabinoid Sativex on track (18 March 2010).
- GW Pharmaceuticals to file Sativex in Europe for spasticity in MS (13 March 2009)
- Sativex disappoints in multiple sclerosis pain trial (16 April 2008).

Following summaries of the application from both [redacted] and [redacted], the Committee made the following comments:

a. A lot of effort from the Committee had gone into assessing the application, from the individual evaluations and assessments to discussions at a number of Committee meetings.

b. Although three indications were proposed in the original application (the relief of spasticity in multiple sclerosis, the relief of neuropathic pain in multiple sclerosis and the relief of pain in cancer), only one (the relief of spasticity in multiple sclerosis) had supporting data provided at this time. For example, only

GWSP0702 (a placebo-controlled, parallel group, randomised withdrawal study in subjects with spasticity due to multiple sclerosis who are receiving long-term Sativex) had provided evidence of efficacy.

c. All three indications have been conditionally approved in Canada. Sativex was approved in Canada for the relief of neuropathic pain in multiple sclerosis in April 2005 and for the relief of advanced cancer in August 2007.

d. The Numeric Rating Scale used in the clinical trials was considered by the Committee. Most members felt the scale was a good method for getting evidence from patients and were comfortable with the accuracy of the evidence provided. The [redacted] report had stated the Scale was not subjective.

e. One member commented that the benefit of Sativex seemed lower compared to its safety risk profile. There is also the potential for psychiatric issues or the potential to aggravate pre-existing psychiatric issues such as schizophrenia. However, contraindications are included in the datasheet to deal with such issues.

f. There is potential for abuse of Sativex as a cannabinoid. However, the dose form as an oral mucosal spray is not typical for abuse. Also, the proposed indications were such that widespread off-label use would be unlikely, especially with the controls under the Misuse of Drugs Act 1975.

g. Committee members considered there was now enough evidence to approve Sativex for the indication of relief of spasticity in multiple sclerosis in line with the United Kingdom. However, with section 20 approval there needed to be a robust risk management plan.

The Committee supported Medsafe's final conclusion and concluded that Sativex should be recommended for approval under section 20 for the indication of the relief of spasticity in multiple sclerosis with similar conditions as the United Kingdom, i.e. as an add-on 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. The Committee noted that there needed to be a robust risk management plan approved by Medsafe before approval of the application was finalised.

The Committee therefore recommended that the Minister of Health should grant consent to the distribution of the medicine Sativex for the relief of spasticity in multiple sclerosis under section 20 of the Medicines Act 1981. Also that the Minister of Health should refuse to grant consent to the distribution of the medicine Sativex for the relief of neuropathic pain in multiple sclerosis and the relief of pain in cancer.

Committee recommendations

That the Minister of Health should grant consent to the distribution of the medicine Sativex oral spray for the relief of spasticity in multiple sclerosis under section 20 of the Medicines Act 1981.

Consent is recommended to be granted for the indication of the relief of spasticity in multiple sclerosis as an add-on 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. Medsafe should be satisfied with a risk management plan before recommending final approval to the Minister.

That the Minister of Health should refuse to grant consent to the distribution of the medicine Sativex oral spray for the relief of neuropathic pain in multiple sclerosis and the relief of pain in cancer.