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APPROVAL OF SATIVEX[®] WITH CONDITIONS

April 2005

Dear Health Care Professional,

GW Pharma Ltd. is pleased to announce that Health Canada has issued a conditional marketing authorisation under the Notice of Compliance with Conditions (NOC/c) policy for SATIVEX[®], a cannabis based medicine, as adjunctive treatment for the symptomatic relief of neuropathic pain in patients with multiple sclerosis in adults. This authorization reflects the promising nature of the clinical evidence and the need for confirmatory studies to verify the clinical benefit.

SATIVEX[®] contains Tetranabinex[®] and Nabidiolex[®], extracts of chemically and genetically characterised *Cannabis sativa* L. plants (hemp plants). SATIVEX[®] is provided as a buccal spray in a 5.5 ml vial, with each 100 microlitre spray providing 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD).

Conditional marketing approval was based on a four week clinical trial in patients with multiple sclerosis who had neuropathic pain of at least three months duration. There was a significant reduction in neuropathic pain as measured by both the Neuropathic Pain Scale and the Numerical Rating Scale (BS-11). Sleep disturbance was also significantly reduced.

Indication

SATIVEX[®] is indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults. SATIVEX[®] has two principal active components: THC and CBD that are scheduled under the Controlled Drugs and Substances Act and as such cannot be used or prescribed except for their recognized indication. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused

Geriatrics: There are limited data available on the use of SATIVEX[®] in elderly patients, therefore, the drug should be prescribed cautiously and carefully monitored in this patient population.

Paediatrics (<18 years of age): The safety and efficacy of SATIVEX[®] have not been established in adolescents or children under 18 years of age, therefore SATIVEX[®] should not be used in adolescents or children.

Contraindications

SATIVEX[®] is contra-indicated in patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil, patients with significant hepatic or renal impairment, patients with serious cardiovascular disease such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure, patients with a history of schizophrenia or any other psychotic disorder, children under 18 years of age; women of child-bearing potential not on a reliable contraceptive or men intending to start a family, and in pregnant or nursing women.

Dosage and Administration

This medication is administered as a self-titration regimen, with gradual increase in dose as needed and tolerated until satisfactory pain relief is achieved. During the initial self-titration period, patients may experience adverse effects of intoxication. These can be used to guide self-titration to establish a satisfactory dosage regime. Patients should be advised that it might take a week or more to find the optimal dosing level. The median daily dosage of SATIVEX[®] in the extension phase of the 4-week clinical trial was 5 sprays per day. There is limited experience with doses higher than 12 sprays per day. Some patients may require and may tolerate a higher number of sprays.

Warnings and Precautions

THC has complex effects on the central nervous system, some of which are called “intoxication type reactions”. These can result in changes of mood, decrease in cognitive performances and memory, decrease in ability to control drives and impulses, and alteration of the perception of reality, particularly altered time sense. Fainting episodes have been observed with use of SATIVEX[®]. “Intoxication type reactions” appear to be dose-related, increasing in frequency with higher dosages, and subject to great inter-patient variability. They usually remit on reduction of doses, increasing the interval between doses or interruption of SATIVEX[®]. Because of the potential of THC to alter the mental state, SATIVEX[®] should be used only as indicated and prescriptions should be limited to the amount necessary for the period between clinic visits.

Drug administration should be discontinued in patients experiencing a psychotic reaction and the patient should be closely observed in an appropriate setting until his/her mental state returns to normal. Patients should be warned not to drive or engage in activities requiring unimpaired judgment and coordination.

Cannabinoids have cardiovascular effects that include tachycardia, and transient changes in blood pressure, including episodes of postural hypotension, particularly during initial

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dose titration when caution is essential. Use of SATIVEX[®] is not recommended in patients with pre-existing cardiovascular disease, such as ischaemic heart disease, arrhythmias, poorly controlled hypertension or severe heart failure.

Published reports on cannabinoids are equivocal with regard to the effects of THC on seizure threshold. Until further information is available, caution should be used when treating patients with a history of epilepsy or recurrent seizures.

Pharmacology

SATIVEX[®] is thought to act via specific cannabinoid receptors, CB₁, CB₂ and possibly other uncharacterized cannabinoid receptors. Its precise mechanism of action is unknown. CB₁ is predominantly distributed in the central nervous system, while CB₂ is localised predominantly in immune cells. THC is a partial agonist at CB₁ receptors and can behave as either an agonist or antagonist at CB₂.

Adverse Events

SATIVEX[®] has been administered to over 424 patients during Phase III long-term open extension studies in various neurological conditions. A total of 207 patients have received more than six months treatment with SATIVEX[®], and 110 patients have received SATIVEX[®] for more than one year.

The incidence of adverse events is 89.2% in patients taking SATIVEX[®], compared with 71% in those taking placebo. Serious adverse events were observed in one patient (0.6%) taking SATIVEX[®]: upper respiratory tract infection and respiratory distress, whereas four patients (2.5%) taking placebo reported serious adverse events: lower respiratory tract infection, sepsis, urinary tract infection, appendicitis and arthritis.

The most common adverse events experienced were application site type reactions followed by intoxication type reactions.

Application site type reactions consisted of mainly mild to moderate stinging at the time of application. However, ulceration was rarely observed. Patients who complain of discomfort at the application site should be advised to vary the site of application within the mouth and should not continue spraying onto sore or inflamed mucus membrane. Regular inspection of the oral mucosa is essential in long-term administration. If lesions are observed or persistent soreness reported, treatment should be interrupted until complete resolution occurs.

The majority of patients (70.5%) experienced an adverse event classified as an “intoxication type reaction” compared with 22.8% of those taking placebo. “Intoxication type reactions” most commonly reported (in greater than 2% of patients) were: feeling drunk, disturbance in attention, dizziness, somnolence, disorientation, dissociation and euphoric mood. These generally resolve rapidly if further doses are withheld and can usually be avoided or minimised thereafter by careful reduction of dosing or by increasing the interval between doses.

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Small increases in pulse rate and transient hypotension have been observed following initial dose introduction. Episodes of feeling faint and occasional faints have been observed with use of SATIVEX[®].

In long term studies with SATIVEX[®], the terms “depressed mood”, “depression” and “depression aggravated” have been reported. One case of a causal relationship between SATIVEX[®] and suicidal ideation could not be ruled out. The incidence of these events is consistent with that observed in populations of multiple sclerosis patients followed for a prolonged period of time. Hallucinations, episodes of paranoia and other psychotic symptoms have been reported with SATIVEX[®].

Further information

The Product Monograph is available to health care professionals upon request. For medical enquiries regarding SATIVEX[®], please contact the medical information department of GW Pharma Ltd’s marketing partner in Canada, Bayer Inc at: 1-800-265-7382.

Original Signed by

Dr Geoffrey Guy,
Executive Chairman.

References:

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The medicinal use of cannabis and its constituents.
Phytother Res 1989;3:219-31.

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In: Marijuana and medicine: assessing the science base. Washington DC: National Academy Press; 1999.

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Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; 58(9):1404-7.

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Cannabinoids and multiple sclerosis.
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Whittle B.A, Guy GW, Robson P.
Prospects for New Cannabis-Based Medicines.
J Can Ther, 2001; 1(3/4):183-205.

Any suspected drug reactions can be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)

Health Product Safety Information Division

Marketed Health Products Directorate

HEALTH CANADA

Address Locator: 0701C

OTTAWA, Ontario, K1A 0K9

Tel: (613) 957-0337, Fax: (613) 957-0335

Toll free for consumers and health care professionals:

Tel: (866) 234-2345, Fax: (866) 678-6789

e-mail: cadrmpp@hc-sc.gc.ca

The ADR Reporting Form can be found in the Canadian Compendium of Pharmaceuticals and Specialties, or on the TPD website, along with the ADR Guidelines at:

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.html

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adr_guideline_e.html