AUTHORIZATION WITH CONDITIONS OF ^{N}SATIVEX® (Tetranabinex® and Nabidiolex®)

SATIVEX® MAY BE USEFUL AS ADJUNCTIVE ANALGESIC TREATMENT IN ADULT PATIENTS WITH ADVANCED CANCER WHO EXPERIENCE MODERATE TO SEVERE PAIN DURING THE HIGHEST TOLERATED DOSE OF STRONG OPIOID THERAPY FOR PERSISTENT BACKGROUND PAIN

DEAR HEALTH CARE PROFESSIONAL LETTER

August 2007

Dear Health Professional,

GW Pharma Ltd. is pleased to announce that Health Canada has issued a marketing authorization with conditions under the Notice of Compliance with Conditions (NOC/c) policy for a further indication for SATIVEX® buccal spray, a cannabis based medicine. The further indication is "adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain". This authorization reflects the promising nature of the clinical efficacy and safety and the need for confirmatory studies to verify the clinical benefit.

SATIVEX® buccal spray 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).

Marketing approval with conditions was based on a two-week clinical trial in patients with pain in cancer who experienced moderate to severe pain during the highest tolerated dose of strong opioid therapy. There was a significant reduction in the Numerical Rating Scale pain scores on SATIVEX® compared with placebo.

Indication

SATIVEX® buccal spray is indicated as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain. SATIVEX® has two principal active components: THC and CBD that are scheduled under the Controlled Drugs and Substances Act. THC is a psychotropic agent which may produce physical and psychological dependence and has the potential to be abused.

Patients should be advised about the nature of the market authorization with conditions for SATIVEX® in this indication.

Geriatrics: There are limited data available on the use of SATIVEX® in elderly patients for any indication, therefore, the drug should be prescribed cautiously and carefully monitored in these patient populations.

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.

Other uses of SATIVEX®

SATIVEX® buccal spray has been issued marketing authorization with conditions, pending the result of studies to verify its clinical benefit for the following condition:

- as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

Contraindications

SATIVEX® is contra-indicated in patients with known or suspected allergy to cannabinoids, propylene glycol, ethanol or peppermint oil, 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.

Warnings and Precautions

THC has complex effects on the central nervous system (CNS). 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®. CNS effects 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 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.

No specific studies have been carried out in patients with hepatic and renal impairment, therefore if SATIVEX® is used in such patients, frequent review by the clinician is recommended.

Adverse Events

SATIVEX® has been administered to 662 patients during Phase 3 long-term open extension studies in various neurological conditions (excluding pain in cancer studies). More than 420 patients have received more than six months treatment with SATIVEX®, and over 310 patients have received SATIVEX® for more than one year.

The most common adverse events experienced were application site type reactions and CNS 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.

Certain AEs reported are recognised as CNS effects being associated with the use of SATIVEX®. CNS effects most commonly reported (in greater than 1% of patients) were: feeling abnormal, balance disorder, feeling drunk, disturbance in attention, dizziness, somnolence, disorientation, dissociation, dysarthria, lethargy, memory impairment, confusional state, depressed mood, 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.

Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with SATIVEX®. These are likely to be the result of CNS effects and are generally mild to moderate in severity. They often remit on reduction or interruption of SATIVEX® medication. Disorientation (or confusion), hallucinations and delusional beliefs have also been reported. In these circumstances, SATIVEX® should be stopped immediately and the subject monitored until the symptom has completely resolved.

Small increases in pulse rate and transient hypotension have been observed following initial dose introduction, so caution during initial dose titration is essential. Episodes of feeling faint and occasional faints have been observed with use of SATIVEX®.

Caution is advised in the urinary care of cancer patients who are using SATIVEX®.

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 CNS effects. 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. In patients with multiple sclerosis, the median daily dosage of SATIVEX® in the extension phase of the 4-week clinical trial was 5 sprays per day. The majority of patients required 12 sprays or less; dosage should be adjusted as needed and tolerated. There is limited experience with doses higher than 12 sprays per day. Some patients may require and may tolerate a higher number of sprays.

In patients with pain in cancer, the median daily dosage of SATIVEX® was 8 actuations (sprays).

Pharmacology

SATIVEX® is thought to act via specific cannabinoid receptors, CB_1, CB_2 and possibly other uncharacterized cannabinoid receptors. Its precise mechanism of action is unknown.

CB_1 is predominantly distributed in the central nervous system, while CB_2 is localised predominantly in immune cells. THC is a partial agonist at CB_1 receptors and can behave as either an agonist or antagonist at CB_2. CBD is an agonist of the TRPV-1 (vanilloid) receptor.

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 or www.bayerhealth.ca.

Original signed by

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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: cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties.*

For other inquiries related to this communication, please contact Health Canada at:
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