

## **Sativex® Oromucosal Spray (Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD))**

### **Prescribing Information**

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

**Presentation:** 1mL contains: 38-44mg & 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. Each 100 microlitre spray also contains up to 0.04g ethanol. **Indication(s):** Symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (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. **Posology and method of administration:** Treatment must be initiated and supervised by a physician with specialist expertise in MS. Intended to be used in addition to patient's current anti-spasticity medication. Oromucosal use only. Shake before use. Direct spray at different sites on the oromucosal surface changing site each time product is used. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long-term treatment periodically. Standardise administration as far as possible in relation to food intake to minimise variability in bioavailability. Starting or stopping some concomitant medicinal products may require a new dose titration (see Interactions). **Adults:** titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. **Children and adolescents:** not recommended. **Elderly:** no specific studies but CNS side effects may be more likely (see Warnings and Precautions). **Significant hepatic or renal impairment:** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** Hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorders other than depression associated with MS. **Warnings and precautions:** Mild to moderate dizziness common mostly in first few weeks. Caution during initial titration essential since alterations in pulse rate and blood pressure observed following initial dosing. Fainting episodes observed. Not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. Psychiatric symptoms (anxiety, illusions, mood changes, paranoid ideas) reported. Disorientation (or confusion), hallucinations, delusional beliefs or transient psychotic reactions reported and causal association with suicidal ideation not ruled out in few cases: in any of these circumstances stop treatment immediately and monitor until symptom completely resolved. THC and CBD are metabolised in the liver and approx. one third (parent drug and metabolites) excreted in urine. Several THC metabolites may be psychoactive. Frequent clinical evaluation recommended if significant impaired hepatic or renal function exists due to possible exaggerated or prolonged effects. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects, particularly in elderly patients, could impact personal safety, e.g. hot food & drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception during treatment and for three months after discontinuation of therapy. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. Adverse reactions reported possibly associated with route of administration e.g. mild/moderate stinging at time of application and possible leukoplakia (unconfirmed or unrelated): prescribers should consult SmPC for further information. Vary site of application if discomfort or ulceration observed. Do not continue spraying onto sore or inflamed mucous membrane. Perform regular inspection of oral mucosa in long-term administration. In cases of lesions or persistent soreness, interrupt medication until complete resolution. Advise patient to check legal status of medicine before travelling to other countries. **Interactions:** THC and CBD metabolised by cytochrome P<sub>450</sub>: inhibitory effects seen *in vitro* on major CYP450 enzymes CYP3A4 and CYP2C19 occur at concentrations substantially higher than max. in clinical trials. No interaction with at risk-CYP3A4 substrates expected. Concomitant ketoconazole increases C<sub>max</sub> and AUC of THC & CBD. Starting or stopping concomitant treatment with CYP3A4 inhibitors (e.g. itraconazole, ritonavir, clarithromycin) may require new dose titration. Concomitant rifampicin reduces C<sub>max</sub> and AUC of THC & CBD. Concomitant treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) should be avoided whenever possible. If deemed necessary, careful titration required.

Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. Care when co-administering with anti-spasticity agents since reduction in muscle tone and power may occur, with greater risk of falls. Sativex may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. Recommend to avoid alcoholic beverages, especially at beginning of treatment or when changing dose. If alcohol is consumed, advise that additive CNS effects may impair ability to drive and use machines and increase risk of falls.

**Fertility, pregnancy and lactation:** Do not use in pregnancy unless benefit outweighs potential risks. Contra-indicated during breast feeding. Insufficient experience of effects on reproduction – see Warnings and precautions. In fertility studies in rodents, no effect on fertility was seen in treated males or females or on the offspring from treated mothers. **Effects on ability to drive and use machines:** Do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. Sativex can impair cognitive function and affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. Patients should be made aware of how Sativex may affect them. Further information is available in the SmPC. **Side effects:** *Very common* – dizziness, fatigue; *common* – anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/drunken, malaise, fall; *uncommon* – hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation. A single case of ventricular bigeminy has been reported although this was in the context of acute nut allergy. Prescribers should consult the SmPC for further information on side effects. **Overdose:** Symptomatic and supportive treatment required. **Special precautions for storage:** Refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. In-use stability after first opening (10ml): 42 days from date of opening. Discard unused product in accordance with local requirements. **Legal category:** POM. **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Sovereign House, Histon, Cambridge CB24 9BZ. **MA number(s):** PL 18024/0009. **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** April 2015. Sativex® is a registered trademark of GW Pharma Ltd.

Adverse events should be reported. Reporting forms and information can be found at <http://www.mhra.gov.uk/yellowcard>. Adverse events should also be reported to GW Pharma Ltd. Tel: 01223 233410, Fax: 01223 233319