Sativex (27 mg delta-9-tetrahydrocannabinol and 25 mg cannabidiol) AMBER 0

For the treatment adult patients with moderate to severe spasticity due to multiple sclerosis

Information for prescribers - to be read in conjunction with the SPC

Dosage and administration

A titration period is required to reach optimal dose. The number and timing of sprays will vary between patients. Local specialist have stated that a slow titration than that recommended in the SPC is often required as this is better tolerated by patients.

The number of sprays should be increased each day following the pattern given in the table below. The afternoon/evening dose should be taken at any time between 4 pm and bedtime. When the morning dose is introduced, it should be taken at any time between waking and midday. The patient may continue to gradually increase the dose by 1 spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays.

Day	**Number of sprays in the morning**	**Number of sprays in the evening**	(Total number of sprays per day)
1	**0**	**1**	1
2	**0**	**1**	1
3	**0**	**2**	2
4	**0**	**2**	2
5	**1**	**2**	3
6	**1**	**3**	4
7	**1**	**4**	5
8	**2**	**4**	6
9	**2**	**5**	7
10	**3**	**5**	8
11	**3**	**6**	9
12	**4**	**6**	10
13	**4**	**7**	11
14	**5**	**7**	12

Maintenance period

Following the titration period, patients are advised to maintain the optimum dose achieved. The median dose in clinical trials for patients with multiple sclerosis is eight sprays per day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses of greater than 12 sprays per day are not recommended.

The spray container should be shaken before use and the spray should be directed at different sites on the oromucosal surface changing the application site each time the product is used.

Monitoring

Manufacturer advises more frequent monitoring in significant renal impairment—possible risk of prolonged or enhanced effect.

Contraindications

Sativex is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients
- With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.
- Who are breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants).

Cautions

Mild or moderate dizziness is commonly reported. This most frequently occurs in the first few weeks of treatment.

Alterations in pulse rate and blood pressure have been observed following initial dose introduction so caution during initial dose titration is essential. Fainting episodes have been observed with use of Sativex. Use of Sativex is not recommended in patients with serious cardiovascular disease.

Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.

Psychiatric symptoms such as anxiety, illusions, changes in mood, and paranoid ideas have been reported during treatment with Sativex.

Disorientation (or confusion), hallucinations and delusional beliefs or transient psychotic reactions have also been reported and in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In any of these circumstances, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved.

No specific studies have been carried out in patients with significant hepatic or renal impairment. THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Thus, the systemic exposure and the effects of Sativex are dependent on both renal and hepatic function and in patients with significant impaired hepatic or renal function; the effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations.

Sativex contains approximately 50% v/v of ethanol. Each actuation contains up to 0.04g of ethanol.

There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of Sativex, particularly in elderly patients, could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

There is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls; patients should be warned of this possibility.

Women of childbearing potential

Sativex may reduce the effectiveness of hormonal contraceptives. Women using hormonal contraceptives should use an additional method of contraception for the duration of therapy and for three months after discontinuation of therapy.

Pregnancy

Sativex should not be used during pregnancy unless the potential risks to the fetus and/or embryo are considered to be outweighed by the benefit of treatment.

Withdrawal

The abrupt withdrawal of long-term Sativex treatment has not resulted in a consistent pattern or time-profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients.

Travel

Patients should be advised that if they travel to another country it may not be legal for them to take this medicine into some countries. They should be encouraged to check the legal status before travelling with Sativex.

Side effects [2]

Please refer to the SPC or BNF for full list.

The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued. When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced.

The frequency of adverse events:

MedDRa SOC	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100
Infections and infestations			pharyngitis
Metabolism and nutrition disorders		anorexia (including appetite decreased), appetite increased	
Psychiatric disorders		depression, disorientation, dissociation, euphoric mood,	hallucination (unspecified, auditory, visual), illusion, paranoia, suicidal ideation, delusional perception*
Nervous system disorders	dizziness	amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment somnolence	syncope
Eye disorders		vision blurred	
Ear and labyrinth disorders		vertigo	
Cardiac disorders			palpitations, tachycardia
Vascular disorders			hypertension
Respiratory, thoracic and			throat irritation

mediastinal disorders			
Gastrointestinal disorders		constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort, oral pain, vomiting	abdominal pain (upper), oral mucosal discolouration*, oral mucosal disorder, oral mucosal exfoliation*, stomatitis, tooth discolouration
General disorders and administration site conditions	fatigue	application site pain, asthenia, feeling abnormal, feeling drunk, malaise	application site irritation
Injury, poisoning and procedural complaints		fall	

* reported in long-term open-label studies

A single case of ventricular bigeminy has been reported though this was in the context of acute nut allergy.

Drug Interactions

Other drugs/medicines affecting Sativex

Co-administration of Sativex with other CYP3A4 substrates may result in an increase in plasma concentration of the concomitant drug.

Co-administration of Sativex with other drugs that are metabolised through cytochrome P-450 enzymes may accelerate the metabolism and reduce the activity of these other drugs such as coumarins, statins, beta-blockers and corticosteroids. When sensitive CYP substrates are co-administered with Sativex, review of their dosing regimen is advised.

Care should be taken when prescribing Sativex with concomitant medications which are metabolised by UGTs (e.g. Propofol and certain antivirals). Patients with genetic glucuronidation disorders (e.g. Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution when Sativex is co-administered.

Sativex affecting other drugs/medicines

If concomitant drug treatment with CYP3A4 inhibitors (e.g. itraconazole, ritonavir, clarithromycin) is started or stopped during treatment with Sativex, a new dose titration may be required.

Concomitant treatment of Sativex (4 sprays) with the CYP2C9 inhibitor fluconazole (200 mg capsule) resulted in an increased concentration of Sativex. Care should be taken when co-administering Sativex with potent CYP2C9 inhibitors as it may lead to an increase in exposure to THC, CBD and their metabolites.

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 is recommended, notably within the two weeks following the stop of the inducer.

General

Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects.

Sativex may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using Sativex,

especially at the beginning of treatment or when changing dose. Patients should be advised that if they do drink alcohol while using Sativex the additive CNS effects may impair their ability to drive or use machines, and increase the risk of falls.

Hormonal contraceptives

Sativex may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add an additional second barrier method.

References

GW Pharma Ltd, “Sativex Oromucosal Spray,” Electronic Medicines Compendium, 27 May 2020 [Online]. Available https://www.medicines.org.uk/emc/product/602 [Accessed 30th July 2021].

Royal Pharmaceutical Society, “British National Formulary,” Pharmaceutical Press. [Online]. Available: https://bnf.nice.org.uk/drug/cannabis-extract.html [Accessed 30th July 2021].