Sativex (Cannabis based oromucosal spray)

Information sheet for health care professionals

Sativex is an oromucosal pain relief spray containing 2 of the active components of cannabis (∆9-THC and cannabidiol). It has a UK marketing authorization for adjunctive use in refractory muscle spasticity due to multiple sclerosis. However, NICE do not recommend it's use because the degree of benefit in research studies was not felt to be sufficient to justify the adverse effects and cost. In Canada (but not the UK) it is licensed for adjunctive use in refractory pain in advanced cancer.

It can still be prescribed in the UK for refractory pain but, like many medications used in palliative care, such use is 'off-licence'. Further, because of the high cost, special approval for funding (an individual funding request; 'IFR') is required.

This sheet is to provide background information about its use and what to look out for.

How does it work?

Cannabis based medicinal extracts potentially work in one or both of two ways:

- Some cannabis-based medicines attach to receptors on neurones (CB1) and have an inhibitory effect. In the case of pain pathways, this inhibition is analgesic. Other potential benefits being investigated include potential anti-epilepsy activity.
- Other cannabis-based medicines attach to receptors on white blood cells (CB2) and inhibit them resulting in an anti-inflammatory/immunosuppressive effect. Inflammation is thought to be one cause of neuropathic pain.

For more information, see PCF6 p229 and figure 1 p 230.

Who shouldn't receive it?

The main relevant contra-indications are:

- People with severe ischaemic heart disease, arrhythmias or severe heart failure
- People with a personal or family history of a significant psychiatric disorder (e.g. schizophrenia)

Others include pregnancy, those breast feeding or children
Additional care is also advised in hepatic or renal impairment, and in those with epilepsy.

Drug interactions

As with other central nervous system depressants used in combination, the central nervous system effects of Sativex are additive when used in combination with other drugs (i.e. more drowsiness, dizziness etc when used in combination).

Sativex potentially inhibits the breakdown of fentanyl and alfentanil (via CYP P450 inhibition) and so these may require dose reduction.

Metabolism of Sativex may be inhibited by CYP3A4 inhibitors (e.g. clarithromycin, itraconazole) and induced by CYP3A4 inhibitors (e.g. carbamazepine, rifampicin, St. John's Wort).

What are the potential adverse effects?

Adverse effects are generally related to the dose, and improve with dose reduction. Many resemble the effects of other analgesics acting on the nervous system (e.g. opioids, anti-epileptics drugs and ketamine)

Common effects

- Effects on the functioning of the nervous system:
    - Emotions: changes in mood, including euphoria and dysphoria
    - Thinking : altered perception (particularly altered time sense, but also auditory or visual hallucinations), confusion, paranoia, amnesia or even psychotic reactions
    - Mobility and balance: Unsteadiness, dizziness
    - Drowsiness, fatigue
    - Its unclear whether cannabis extracts have anti- or pro-seizure effects, or both
- Other effects noted in clinical trials include (for full list, see the SPC):
    - Cardiovascular: tachycardia and fluctuations in blood pressure (sometimes resulting in fainting spells or postural hypotension)

    - Buccal mucosal irritation.
- Dependence. As with many analgesics used in palliative care, Sativex has the potential to cause dependence and/or be abused.

The SPC lists the frequencies of these effects in clinical trials (see www.medicines.org.uk/emc/).

Action for staff:

Dose titration for pain[i]

- Treatment should be started at one spray as needed (minimum interval four hours; maximum dose of four sprays/24 hours).
- Subsequently gradually increase the total number of sprays as needed and tolerated.
- If unacceptable adverse reactions such as dizziness or other intoxication type reactions develop at any time, dosing should be suspended until they have resolved. Then discuss with the medical team
- Some patients may be able to continue therapy at the dose reached by increasing the interval between doses; others may require their subsequent doses reduced. Patients should then carefully re-titrate to a tolerated dosage regimen that gives acceptable pain relief.

What to look out for

1. Please check the oral mucosa for irritation, thrush etc. Sativex can cause mouth irritation. If irritation is a problem, omit the dose until discussed with the medical team
2. Please check pulse and blood pressure once a day during the initial titration phase. Discuss when to discontinue monitoring with the medical team (usually when clear they are stable)
3. Note the increased falls risk if completing a falls risk assessment
4. Be alert to the possibility of opioid toxicity if using a fentanyl patch or alfentanil spray (opioid dose may need to be reduced: their rate of breakdown may be reduced)
5. If hallucinations, agitation or other marked psychological adverse effects occur, give haloperidol (e.g. 0.5-1.5mg p.r.n. t.d.s. SCut or PO). If anxiety occurs give lorazepam (0.5mg SL p.r.n. t.d.s.) or midazolam (2.5-5mg p.r.n. SCut)

How is it used?

Priming *(only required on the 1st use of the spray)*

1. Shake the container gently before use.
2. Remove the protective cap.
3. Holding the container in an upright position, prime by pressing on the actuator two or three times firmly and quickly, directing into a tissue until a fine spray appears.
4. Important: Point the spray safely away when priming it into a tissue. Do not prime it near children, pets or an open flame.

Normal use

1. Shake the vial gently before use.
2. Remove the protective cap.
3. Hold the vial in the upright position and direct into the mouth. Press firmly and quickly towards the buccal surface in the following regions: below the tongue or towards the inside of the cheeks. The site should be varied each time it is used. Never aim at the throat, as SATIVEX® can cause irritation.
4. Replace the protective cap.
5. Keep away from sources of heat and direct sunlight.

Storage

1. Unopened vials must be kept in a **locked** refrigerator.
2. Once opened, Sativex vials are treated as Schedule 2 Controlled Drug[ii] and recorded in the Controlled Drug Register as normal (opened vials can be kept at room temperature for up to 6 weeks; they are then discarded).

[i] This titration regimen is based on the Canadian pain license rather than UK spasticity license

[ii] Although treated as a schedule 2, Sativex is classified as a schedule 4 (part 1) CD which is why it can be kept refrigerated until opened