Nabiximols

Approved indication: multiple sclerosis

Sativex (Emerge Health)
80 mg/mL pump metered dose spray
Australian Medicines Handbook section 16.5

Muscle spasticity occurs in more than two-thirds of patients with multiple sclerosis. Various drugs are used as muscle relaxants including baclofen and benzodiazepines. Nabiximols, a cannabinoid oromucosal spray, is indicated for moderate to severe spasticity that has not responded adequately to other treatments. The drug was approved in Australia in 2012, but only became available years later.

Nabiximols is derived from the *Cannabis sativa* plant. Each 100 microlitre spray contains delta-9-tetrahydrocannabinol (THC) 2.7 mg and cannabidiol 2.5 mg. It is thought that these cannabinoids act as agonists on the endocannabinoid system.

Trials have investigated the effect of self-titrated nabiximols spray as an add-on to other spasticity treatments in patients with multiple sclerosis (see Table).[1-3] The median daily dose in the studies was eight sprays. Response to treatment was scored by the patient each day using a numerical rating scale, ranging from zero (no spasticity symptoms) to 10 (worst possible symptoms).

Mean spasticity scores were decreased more with nabiximols than with placebo in a six-week[1] and a 15-week trial.[2] However, in the longer trial the difference between active treatment and placebo was not statistically significant (see Table).

In these trials, investigators observed that if a patient had not responded to nabiximols after four weeks, they were unlikely to respond at all.[1,2] A trial with an enriched design was therefore planned. Only patients who had at least a 20% improvement in their spasticity symptoms after a four-week single-blind period of nabiximols (241/572 patients) were randomised to receive nabiximols or placebo, double-blind, for a further 12 weeks.[3] In the single-blind period the spasticity score decreased from 6.91 to 3.9 points. During the 12-week treatment phase, the mean scores continued to drop slightly with nabiximols but increased with placebo. Half of the patients who were not eligible to enrol in the 12-week phase had less than a 5% improvement in their spasticity symptoms after four weeks of nabiximols.

The long-term safety and efficacy of nabiximols was assessed in a trial of 36 patients who had been taking nabiximols for 3–4 years. Participants were randomised to either continue nabiximols or take a placebo. After four weeks, those in the nabiximols group were less likely to withdraw from the trial than those in the placebo group (44% vs 94%).[4]

The most common adverse effects with nabiximols include dizziness and fatigue, particularly at the beginning of treatment. Driving or operating machinery should be avoided if this occurs. Altered appetite, nausea, dry mouth, vertigo and diarrhoea have also been reported.

Depression, disorientation, dissociation and euphoric mood occur in up to 10% of people and treatment may need to be reduced or stopped if psychiatric symptoms occur. Delusions, hallucinations and paranoia were also reported. Nabiximols is contraindicated in patients with a personal or family history of psychotic illness or other significant psychiatric disorders.

Decreased muscle tone and strength can occur with nabiximols and falls were common in the trials. Nabiximols may have an additive effect on any drug with sedating effects, including alcohol.

After an oral spray, nabiximols is rapidly absorbed. It is highly lipophilic and distributes to body fat. Nabiximols has an initial half-life of 1–2 hours and

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Table **Efficacy of self-titrated nabiximols for spasticity symptoms in multiple sclerosis**

	Number of patients	Duration of treatment	Baseline spasticity scores*		Change in spasticity scores*		
			Nabiximols	Placebo	Nabiximols	Placebo	P value
Trial A[1]	184	6 weeks	5.49	5.39	−1.18	−0.63	0.048
Trial B[2]	337	15 weeks	6.77	6.48	−1.05	−0.82	0.219
Trial C[3]	572	4 weeks single blind	6.91	–	−3.01	–	–
	241 eligible to continue	12 weeks double blind	3.87	3.92	−0.04	0.81	0.0002

* Spasticity score was based on a 0–10 numerical rating scale recorded by the patient each day (0 – no spasticity, 10 – worst possible symptoms).

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a terminal half-life of 24–36 hours due to its slow release from fatty tissue. Plasma concentrations reached after a dose of nabiximols are much less than levels reached after smoking cannabis.

Nabiximols is not recommended during pregnancy. In animal studies, it was secreted in breast milk so it is contraindicated during breastfeeding.

Nabiximols is extensively metabolised in the liver by cytochrome P450 (CYP) enzymes. Concomitant treatment with a CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin) or inducer (e.g. rifampicin, carbamazepine) may affect nabiximols exposure. If interacting drugs are started or stopped, the nabiximols dose may need to be re-titrated.

As there can be reactions at the site of application, the aerosol should be sprayed in the mouth at a different position each time (inside of cheek, under tongue). The dose should be titrated during the first two weeks, starting from one spray on day one, up to 12 sprays by day 14.

Nabiximols is the first cannabis-based medicine to be approved in Australia. It has been found to improve spasticity symptoms in less than half of patients. If improvements are not seen in the first four weeks, the patient is unlikely to benefit and treatment should be stopped.

T manufacturer provided the product information

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration.