NHS
Vale of York
Clinical Commissioning Group

COMMISSIONING POLICY RECOMMENDATION
TREATMENT ADVISORY GROUP
Policy agreed by (Vale of York CCG/date)

Drug, Treatment, Device name		
Delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex▼, Bayer)		
Licensed indication		
Sativex is indicated as treatment for 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.		
Cost per patient (at recommended dose)		
Sativex	6 to 12 sprays a day	£2798 to £5596 a year (£345 for 270 dose pack)
Gabapentin	2400mg daily (800mg tab)	£398 a year
Diazepam	15mg daily	£34 a year
Dantrolene sodium	225mg daily (25mg cap)	£554 a year
Baclofen	60mg daily	£49 a year
Tizanidine	24mg daily (4mg tabs)	£428 a year
Resource impact on population		
It is estimated 9 per 100,000 population would be treated with sativex of which 4 would continue after 1 month. This would equate to £11,192 - £22,384 per 100,000 population per year.		
Recommendation to Routinely Commission ☐ **OR** **Not Routinely Commission** ☒ **OR** **Commission under criteria** ☐		
When is funding appropriate?		
Sativex is not recommended to be funded for patients with multiple sclerosis. The medicine should not be withdrawn from patients already established on treatment but other treatment options should be considered at routine review.		
Clinical and cost effectiveness evidence		

Background

Multiple sclerosis is an autoimmune disease of the central nervous system in which inflammation destroys the protective sheath surrounding nerve cells. Estimates of the percentage of patients with MS who experience symptoms of spasticity vary from 21% to 84%. This loss of muscle control can lead to pain, spasms, reduced mobility, limited range of movement and contractures.

The NICE clinical guideline on multiple sclerosis, published in 2003, recommends physiotherapy as a first-line option for patients with persistent spasticity or spasms. Specific measures such as drug treatment should be considered only if the spasms or spasticity are causing pain or distress. Recommended options for initial drug treatment are baclofen or gabapentin [unlicensed indication]. If these treatments are unsuccessful or not well tolerated, then tizanidine, diazepam, clonazepam or dantrolene are further options.

Sativex is a mixture of two extracts of the Cannabis sativa L. plant: delta-nine tetrahydrocannabinol (THC, 27 mg/ml) and cannabidiol (CBD, 25 mg/ml) delivered as a 100

microlitre dose via an oromucosal spray. It acts on cannabinoid receptors in the central nervous system; this activity has been shown in animal models to ameliorate limb stiffness and improve motor function.1 It is licensed for use as add-on treatment for symptom improvement in patients with moderate to severe spasticity due to 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.

NICE Clinical guideline 8: Multiple sclerosis. November 2003 (under review, publication expected October 2014).
Sativex was not considered at the time this guidelines was published.
Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. If these are unsuccessful or the patient is unable to tolerate it then consider tizanidine, diazepam, clonazepam or dantrolene can be used.
http://www.nice.org.uk/nicemedia/live/10930/29199/29199.pdf

Yorkshire and Humber SCG policy: Sativex; March 2010
Sativex is not routinely funded for patients with multiple sclerosis. The medicine should not be withdrawn from patients already established on treatment but other treatment options should be considered at routine review.
Following appraisal of the available evidence and anticipated costs, the Yorkshire and the Humber Expert Panel for disease modifying therapies in multiple sclerosis recommend that Sativex should not be routinely funded. The Panel advised that, on the available evidence, Sativex lacked compelling evidence of benefit for the target population and was unlikely to be cost-effective.
http://www.yhscg.nhs.uk/commissioning/non-cancer-drug-policy.htm

Scottish Medicines Consortium
Statement of Advice
Cannabinoid oromucosal spray (Sativex ®) (No: 703/11) Bayer plc.
4 March 2011
ADVICE: in the absence of a submission from the holder of the marketing authorisation **cannabinoid oromucosal spray (Sativex ®)** is not recommended for use within NHS Scotland.
Indication under review: as an add-on treatment for symptom improvement in 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.
The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result we cannot recommend its use within NHS Scotland.
http://www.scottishmedicines.org.uk/SMC_Advice/Advice/703_11_cannabinoid_Sativex/cannabinoid_Sativex

MTRAC February 2011
COMMISSIONING GUIDANCE Cannabis extract *(Sativex®▼)*

Prescribing guidance: Category D *(cannot be recommended for prescribing because of inadequate*

evidence for efficacy and/or safety)
Sativex cannot be recommended for prescribing because the current evidence for its efficacy and safety is considered to be inadequate to support its use. Results from published comparisons of Sativex with placebo for the treatment of spasticity in patients with multiple sclerosis were inconsistent. Limitations of the trials included definitions of disease severity and outcome measures not commonly used in clinical practice, and small effect sizes. No published trials have compared Sativex with an active comparator.
www.mtrac.co.uk
http://www.keele.ac.uk/media/keeleuniversity/fachealth/fachealthsop/mtrac/documents/summary/Sativex.pdf

Three published, double-blind RCTs compared Sativex with placebo in a total of 767 patients with MS and symptoms of spasticity that had not responded to current therapy. The trials were of six to fifteen weeks' duration. One of the trials used a two-phase
'enriched' design. In this trial, 572 patients were first enrolled in a four-week single-blind screening phase where all patients were given Sativex and only those showing a response to treatment (≥ 20% improvement in NRS spasticity score) were randomised to the double-blind treatment phase.

In all three trials, the mean number of sprays taken per day reported by patients was 8 to 9, although maximum daily doses of up to 12, 24, or 48 sprays were permitted. Patients also continued existing medications, including anti-spasticity treatment. The primary outcome was a patient-rated measure of spasticity severity on a numerical rating scale (NRS) from 0 (no spasticity or stiffness) to 10 (total spasticity or stiffness). A response to treatment was defined as a ≥ 30% improvement in score on the scale compared with baseline. Secondary outcomes included changes in scores on the Ashworth Scale and Motricity index, NRS scores for other MS-related symptoms e.g. spasm or sleep quality, Barthel Activities of Daily Living and quality-of-life measures.

In the six-week trial, the difference in improvement in spasticity-symptom scores between Sativex treatment and placebo treatment was statistically significant (difference between groups 0.52 points, 95% CI -1.029 to -0.004, p = 0.048), and significantly more Sativex-treated patients responded to treatment (40% vs. 22% for placebo, p = 0.014). There were no significant differences between treatment groups for any of the secondary outcomes.
In the 15-week trial,7 there were no significant differences between Sativex and placebo for improvements in symptoms, or numbers of patients responding to treatment. There were also no significant differences between groups for any of the other secondary outcomes.

In the two-phase trial, 272 patients (48%) showed a response to treatment during the first four-week, single-blind screening phase, of whom 241 were randomised to the double-blind phase. During the screening phase there was a mean improvement in NRS-spasticity score of 3 points. After 12 weeks' double-blind treatment, spasticity-symptom scores in Sativex-treated patients showed slight improvement (-0.04 points) whilst placebo-treated patients showed slight deterioration (+ 0.81 points). The difference between treatments was statistically significant (difference 0.84 points, 95% CI -1.29 to -0.40, p = 0.0002). Responder analysis showed that 74% of Sativex-treated patients responded to treatment vs. 51% of placebo-treated patients (p = 0.0003).

Some secondary outcomes showed significant differences between treatment groups. Compared

with placebo, Sativex treatment resulted in greater improvements in spasm frequency and sleep disruption scores ($p \leq 0.005$), Barthel Activities of Daily Living ($p = 0.0067$) and the physicians', patients' and carers' impression of change ratings ($p \leq 0.05$).
There were no published trials that compared Sativex with other anti-spasticity medication.

London New Drugs Group Briefing Document: Sativex. June 2010
http://www.medicinesresources.nhs.uk/upload/Sativex_June_2010.pdf

NETAG appraisal of Sativex; October 2010
Sativex® is not recommended for use within NHS North East for the treatment of spasticity due to multiple sclerosis.
Clinical evidence for the efficacy of Sativex® was considered to be of low quality and demonstrated a modest but clinically unclear benefit. Combined with a high acquisition cost, Sativex® was considered unlikely to meet conventional cost-effectiveness criteria.
http://www.netag.nhs.uk/files/appraisal-reports/Sativex%20appraisal%20report%20-%20NETAG%20-Oct2010.pdf

Place in therapy relative to available treatments

It is not recommended for prescribing on the NHS.

Health gains

N/A

Patient monitoring / impact

N/A

Patient safety / pharmacovigilance

The most common adverse effects are dizziness, fatigue, somnolence, nausea and dry mouth. Common application-site reactions are oral pain and discomfort, dysgeusia (taste distortion), mouth ulceration and glossodynia (burning sensation in tongue). Regular inspection of the oral mucosa is advised during long term administration.

When to stop treatment

N/A

Who prescribes?

Not routinely commissioned

Stakeholder views

Equity of access

SPECIFICATION DATE, REVIEW DATE, AND LEAD NAME/JOB TITLE

Origin Date: November 2013	Originator: Stuart Kerr
TAG Review Date:	Reviewer: Chris Ranson

TAG Recommendation Date:	

Impact on individual clinical commissioning groups		
CCG	**Population**	**Cost Impact**
Vale of York	**337,500**	£37,733-£75,546
Harrogate and Rural District	**160,100**	£17,918-£35,836
Scarborough & Ryedale	**118,000**	£13,206-£26,412
Hambleton, Richmondshire & Whitby	**141,600**	£15,848-£31,696
East Riding of Yorkshire	**320,642**	£35,886-£71,772
Hull	**295,987**	£33,127-£66,254
North Lincolnshire	**168,400**	£18,847-£37,694
North East Lincolnshire	**167,200**	£18,713-£37,426