HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

22 October 2014

SATIVEX, solution for oromucosal spray

10 ml vial, B/3 (CIP: 34009 276 612 0 4)

Applicant: ALMIRALL

INN	Delta-9-tetrahydrocannabinol/cannabidiol
ATC code (year)	N02BG10 (other analgesics and antipyretics)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"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."**

Actual Benefit	**low**
Improvement in Actual Benefit	**Given the reservations resulting from the level of evidence in the performed studies and the small levelof the effect observed, the Committee considers that SATIVEX does not provide an improvement in actual benefit (IAB V,none) in the treatment of symptoms related to moderate to severe spasticity due to multiple sclerosis.**
Therapeutic use	**SATIVEX is an add-on treatment in patients who are not adequately relieved by an optimal anti-spasticity treatment. Treatment will not be continued beyond 4 weeks if the clinical response is deemed insufficient.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (mutual recognition procedure): 8 January 2014 Reference Member State: United Kingdom Type IB variation (correction to the Marketing Authorisation of 27 May 2014): minor changes in the following sections: 2. Composition, 4.5 Interactions, 5.2 Pharmacokinetic properties, 6.3 Shelf life European risk management plan: observational safety study Additional risk minimisation measures: pharmacovigilance and addictovigilance monitoring, information for the healthcare professionals concerned.
Prescribing and dispensing conditions	Narcotic: prescription limited to 28 days; prescription subject to the specifications established by the decree of 31 March 1999 (or secured prescription). Initial six-month hospital prescription reserved for neurologists and physical medicine and rehabilitation specialists. Unrestricted renewal.

ATC Classification	2014	
	N	Nervous system
	N02	Analgesics
	N02B	Other analgesics and antipyretics
	N02BG	Other analgesics and antipyretics
	N02BG10	Cannabinoids

02 BACKGROUND

This is an application for inclusion on the list of proprietary medicinal products refundable by National Health Insurance and approved for use by hospitals and various public services for the proprietary medicinal product SATIVEX, solution for oromucosal spray.

This proprietary medicinal product is a solution for oromucosal spray consisting of a mixture of two extracts of Cannabis sativa L containing 2.7 mg of delta-9-tetrahydrocannabinol (THC) and 2.5 mg of cannabidiol (CBD).

Decree 2013-473[1] of 5 June 2013 amending the provisions of Article R. 5132-86 of the public health code now permits the ANSM to grant a Marketing Authorisation for proprietary medicinal products containing cannabis and its cannabinoid derivatives and allows manufacture, transport, import, export, possession, offer, sale, purchase or use of these proprietary medicinal products.

[1] Decree 2013-473 of 5 June 2013 amending, for proprietary medicinal products, the provisions of Article R. 5132-86 of the Public Health Code relative to the prohibition of operations related to cannabis or its derivatives. JORF [Official Journal of the French Republic] 0130 of 7 June 2013. See appendix.

03 THERAPEUTIC 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."

04 DOSAGE

"SATIVEX is for oromucosal use only.

SATIVEX is intended to be used in addition to the patient's current anti-spasticity medication.

Treatment must be initiated and supervised by a physician with specialist expertise in treating this patient population.

Use in adults

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.
Patients should be advised that it might take up to two weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.
To minimise variability of bioavailability in the individual patient, administration of SATIVEX should be standardised as far as possible in relation to food intake (see section 4.5). In addition, starting or stopping some concomitant medicinal products may require a new dose titration (see section 4.5).

Titration period:

A titration period is required to reach the optimal dose. The number and timing of sprays will vary between 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 one 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.

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.

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

Review by the physician

A thorough evaluation of the severity of spasticity related symptoms and of the response to standard anti-spasticity medication should be performed prior to initiation of treatment. SATIVEX is only indicated in patients with moderate to severe spasticity that have responded inadequately to other anti-spasticity medication. The patient's response to SATIVEX should be reviewed after four weeks of treatment. If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then SATIVEX treatment should be stopped. In the clinical trials this was defined as at least a 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale (see section 5.1). The value of long term treatment should be re-evaluated periodically. […]

Elderly

No specific studies have been carried out in elderly patients, although patients up to 90 years of age have been included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks.

Patients with significant hepatic or renal impairment

There are no studies in patients with impaired hepatic or renal function. However, in these sub-populations the effects of SATIVEX may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations (see section 4.4)."

05 THERAPEUTIC NEED[2,3,4,]

Spasticity is a very common symptom in multiple sclerosis; almost all patients will be concerned in their disease progression, with spastic manifestations, more or less severe, but frequently troublesome and disrupting function. Spasticity may be useful in some patients by overcoming for motor weakness and helping to maintaincertain functional capabilities such as transfer capacity, but the impact of this symptom is most often negative. Its clinical expression is very changing. It

[2] Bensmail D, Vermersch P. Épidémiologie et évaluation clinique de la spasticité dans la sclérose en plaques [Epidemiology and clinical evaluation of spasticity in multiple sclerosis]. Revue neurologique 2012;168:S45-S50.

[3] Traitements médicamenteux de la spasticité - Recommandations de Bonne Pratique [Pharmacological treatments for spasticity - Good Practice Guidelines] - Afssaps, June 2009.

[4] Anti-spasticity agents for multiple sclerosis (Review) - The Cochrane Collaboration 2009.

may simply be from a feeling of stiffness experienced by the patient when walking or making voluntary movements to major stiffness of all four extremities at an advanced stage of MS. It generally increases with disease progression, but could sometimes be severe from the early years.

A detailed analysis of the clinical situation is necessary to better evaluate the risk/benefit ratio of any anti-spastic treatment and choose the most appropriate therapeutic strategy. Pharmacological or surgical treatments should be most often considered as only one component of a therapeutic program combining physical therapy, occupational therapy, use of equipment and self-directed rehabilitation in various degrees.

In the case of focal or multifocal manifestations of spasticity, initial treatment involves local medical treatments (botulinum toxin, alcohol or phenol nerve block). In the event of widespread spasticity, oral administration of anti-spastic products such as baclofen, dantrolene, tizanidine (temporary authorisation for use) or benzodiazepines (off-label) can be proposed. These treatments used as a monotherapy or in combination have inconsistent and often moderate efficacy. Their adverse effects are significant.

Intrathecal administration of baclofen or surgical procedures (neurotomy, tenotomy or other neuro-orthopedic techniques) will be proposed at an advanced stage of the disease.

06 CLINICALLY RELEVANT COMPARATORS

The treatments listed in 06.1 and 06.2 are given for information purposes since SATIVEX is indicated in the treatment of manifestations of spasticity related to MS in combination with these standard anti-spastic treatments.

06.1 Medicinal products

Oral treatments:

- Baclofen - LIORESAL, tablet
- Dantrolene - DANTRIUM, capsule
- Tizanidine - SIRDALUD, tablet
  under a compassionate use by a cohort (May 2014): Treatment for spasticity due to brain or spinal neurological conditions in cases of failure or intolerance with other anti-spastic treatments.
- Benzodiazepines - off-label
- Anti-epileptics - off-label (treatment of the painful component of spasticity)

Intrathecal baclofen: LIORESAL solution for injection

Intramuscular botulinum toxin type A: BOTOX / DYSPORT

NAME (Date of the first Marketing Authorisation)	Wording of the indication (date of the Marketing Authorisation)	AB
LIORESAL 10 mg, tab (16/12/97)	Spastic contractures of multiple sclerosis Spastic contractures of spinal cord disorders (infectious, degenerative, traumatic or neoplastic origin). Spastic contractures of cerebral origin	moderate RI 07/09/11
DANTRIUM, capsules (29/06/78)	Treatment of advanced forms of spasticity of pyramidal origin associated with hemiplegia, paraplegia and MS. Dantrolene is especially useful in patients whose residual motor function is good and in whom spasticity is a major obstacle to rehabilitation.	moderate RI 08/09/10
LIORESAL, solution for injection Medicinal product reserved for hospital use. (26/09/94)	Adults: Treatment of severe chronic spasticity associated with multiple sclerosis, spinal or cerebral lesions after failure of oral anti-spastic treatments (including oral baclofen) or adverse effects that are too severe at effective oral doses. […]	Substantial
BOTOX Medicinal product reserved for hospital use. (22/08/2000)	Adults Treatment of neurologic detrusor overactivity leading to urinary incontinence not controlled by anticholinergic therapy in: - patients with spinal cord injury - patients with multiple sclerosis and using self catheterisation for voiding […] Adults and children 2 years of age or older (01/08/05) Symptomatic local treatment of spasticity (muscular hyperactivity) of the upper and lower extremities.	Substantial EIT (06/09/06)
DYSPORT Medicinal product reserved for hospital use. (11/10/93)	Adults […] Symptomatic local treatment of spasticity (muscular hyperactivity) of the upper and/or lower extremities. (08/09/2005) […]	Substantial EIT (06/09/06)

RI: Renewal of inclusion

06.2 Other health technologies

- Physical therapy, occupational therapy, equipment
- Neurosurgery (neurotomy, tenotomy, rhizotomy, etc.), orthopedic surgery
- Local application of alcohol or phenol (off label)

◗ Conclusion

There is no clinically relevant comparator for SATIVEX in its indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Reimbursement for SATIVEX internationally:

Country	Date of Marketing Authorisation	REIMBURSEMENT (in the indication)
		Special conditions
United Kingdom	**16/06/2010**	Reimbursement
Spain	20/07/2010	Reimbursement (hospital dispensing)
Germany	18/05/2011	Reimbursement
Denmark	06/06/2011	Individual reimbursement
Austria	19/01/2012	Individual reimbursement
Norway	22/08/2012	Individual reimbursement
Switzerland	22/11/2013	Individual reimbursement
Liechtenstein	22/11/2013	Individual reimbursement
Italy	09/04/2013	Reimbursement (hospital prescribing and dispensing)
Czech Republic	06/04/2011	Refusal
Netherlands	18/07/2012	
Finland	22/11/2012	
Portugal	19/06/2012	Assessment in progress
Belgium	21/08/2012	Assessment in progress
Ireland	11/07/2014	Assessment in progress
Sweden	15/12/2011	Dossier not submitted
Iceland	19/07/2012	
Slovakia	12/06/2012	
Poland	12/12/2012	
Luxembourg	01/01/2013	
Canada	15/04/2005	Private market
New Zealand	22/10/2010	Compassionate use
Israel	14/02/2012	Private insurance
Australia	26/11/2012	Refusal
Kuwait	11/07/2013	Not on the market

In Canada and Israel, the product also has a Marketing Authorisation in neuropathic pain due to multiple sclerosis. In Canada, a Marketing Authorisation was granted in adjunctive analgesic treatment in adults with advanced cancer.

Two synthetic THC analogues have a Marketing Authorisation outside Europe:

- MARINOL (dronabinol): USA, Canada, South Africa, Australia
- CESAMET (nabilone): Canada, Australia, United Kingdom

Dronabinol is available in France under a temporary authorisation for use by a named person granted in 2003. The ANSM has recorded 95 requests for a temporary authorisation for use in 2013 for this product. Since 1st January 2014, 105 requests were recorded, in response to which 77 treatments were initiated, mainly for neuropathic pain.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy[5]

Three phase III studies were conducted (GWMS 0106, GWCL 0403 and GWSP 0604) in the indication. These randomised, double-blind superiority studies compared the efficacy and safety of SATIVEX to those of placebo in patients with documented multiple sclerosis (MS). The use of cannabis or cannabinoids in the days prior to inclusion were a non-inclusion criterion.

Two scales for measuring spasticity are conventionally used by clinicians in daily practice, the Ashworth scale (Ashworth, 1964; Bohannon et al, 1986[6]) and the Tardieu scale (Tardieu, 1954). These scales measure the resistance occurring during passive stretching of the muscle studied. The modified Ashworth scale[7] evaluates the stiffness on stretching of a muscle group rather than spasticity. This scale has limits: it does not take into account the speed-dependent nature of spasticity and its inter-examiner reproducibility is considered poor.

In the studies described below, a different approach for evaluating spasticity[8,9] was used. This is a self-assessment done by the patient, using a numerical scale from 0 to 10 (NRS-11): 0 = no spasticity, 10 = the worst spasticity imaginable). At the same time for 7 consecutive days, the patient evaluates the average severity of spasticity experienced in the preceding 24 hours. A moderate correlation between this scale and the Ashworth and Tardieu scales has been demonstrated. The test-retest reliability was deemed good.

[5] Public Assessment Report - Decentralised Procedure - SATIVEX Oromucosal Spray.

[6] Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206-7.

[7] Score from 0 to 4 (0, 1, 1+, 2, 3, 4) - score 0 : no increase in muscle tone, score 4: the joint concerned is fixed in flexion or extension (abduction or adduction).

[8] Farrar JT, Troxel AB, Stott C et al. Validity, reliability and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: A post-hoc analysis of a randomized, double-blind, placebo-controlled trial. Clin Ther 2008;30:974-85.

[9] Anwar K, Barnes MP. A pilot study of a comparison between a patient scored numeric rating scale and clinician scored measures of spasticity in multiple sclerosis. NeuroRehabilitation 2009;24:333-40.

8.1.1 Study GWMS 0106[10]

Type of study	Randomised (2:1 ratio), double-blind, placebo-controlled superiority study.
Start and end of the study	12 June 2002 - 30 March 2004
Study location / sites	United Kingdom (8 sites), Romania (4 sites)
Inclusion criteria	Documented MS Age > 18 years Spasticity of at least two muscle groups with a score of 2 or higher on the Ashworth scale Spasticity inadequately relieved by the current anti-spastic treatment before inclusion Stable anti-spastic treatment in the 30 days prior to inclusion
Treatments	THC 2.7 mg + CBD 2.5 mg delivered by 100 µl spray (ethanol and propylene glycol solution) or placebo Auto-titration by the patient Maximum tolerated doses: 8 sprays / 3 hours and 48 sprays / 24 hours
Endpoints	Primary endpoint changed by amendment (2 December 2003)*: Change in the mean calculated spasticity score over 7 days at 6 weeks of treatment compared with the mean score calculated over the initial 7 days. These scores were collected daily by the patient using an 11-point numerical rating scale (NRS-11) Hypothesis: Difference of 1 point (standard deviation 2.1) The secondary endpoints include: - Percentage of responders (reductions in the NRS-11 score ≥ 30% and ≥ 50%) - Modified Ashworth Scale - Ordinal scale of spasm frequency (score from 0 to 4) - Mobility index - Patient global impression of change (score from 1 to 7)

* The Ashworth scale was initially the primary efficacy endpoint and was replaced by the NRS-11 score.

Study results:

In all, 189 patients, mean age 49, were randomised (ratio 2:1): THC/CBD (n=124), placebo (n=65). The mean duration of the disease was 13 years (0.5 - 41); 42% of them had previously used cannabis.
Among the patients included, 75% of patients in the THC/CBD group and 65% of patients in the placebo group received at least one concomitant anti-spastic treatment during the study: baclofen 42%, dantrolene and derivatives 4%, tizanidine 21%, benzodiazepines 20%, gabapentin 8%, botulinum toxin 2%.

Fifteen patients were prematurely withdrawn from the treatment in the double blind period: 12 in the THC/CBD group (adverse event 6, withdrawal of consent 4, noncompliance 1; lost to view 1) and 3 in the placebo group (adverse event 1; protocol deviation 1; administrative decision 1).

In all, 184 patients were analysed by ITT. Five patients were excluded from the analysis: 3 patients did not have an initial evaluation, 2 patients did not have an evaluation on treatment. The median duration of exposure was 42 days. The median number of daily doses was 7 in the THC/CBD group and 13 in the placebo group.

[10] Collin C, Davies P, Mutiboko IK, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007;14:290-6.

Results from the intention to treat analysis

Endpoints	THC / CBD n=120	Placebo n=64	p
Initial spasticity score	5.49 (1.91)	5.39 (1.91)	
Mean change	-1.18	-0.63	
Difference vs placebo*	**-0.52** (-1.03; -0.004)		0.048
% of responders (reduction ≥ 30%)	**40.0%**	**21.9%**	
Difference vs. placebo (95% CI)	18.1% (4.73; 31.52)		
OR (95% CI)	OR 2.38 (1.21; 4.91),		0.014
% patients (score reduction **≥** 50%)	17.5%	9.4%	
Initial Ashworth score	2.41 (0.45)	2.44 (0.41)	
Mean change	-0.64	-0.53	
Difference vs placebo*	-0.11		ns
Frequency of initial spasms	2.27 (1.13)	2.54 (1.13)	
Mean change	-0.39	-0.22	
Difference vs placebo*	-0.17		ns

* ANCOVA adjusted on the treatment, site and initial spasticity score

The results on the other secondary endpoints did not show any difference between the product and the placebo.

8.1.2 Study GWCL 0403[11]

Type of study	Randomised (1:1 ratio), double-blind, placebo-controlled superiority study.
Start and end of the study	9 March 2005 - 20 December 2005
Study location / sites	United Kingdom (15 sites), Romania (8 sites)
Inclusion criteria	Documented MS > 6 months and signs of spasticity > 3 months Age > 18 years Mean spasticity score on NRS-11, measured over 6 days, of at least 4 points Spasticity inadequately relieved by the current anti-spastic treatment Stable anti-spastic treatment in the 30 days prior to inclusion
Treatments	THC 2.7 mg + CBD 2.5 mg delivered by 100 µl spray (ethanol and propylene glycol solution) or placebo Auto-titration by the patient Maximum tolerated doses: 8 sprays / 3 hours and 24 sprays / 24 hours
Endpoints	Primary efficacy endpoint: Change in the mean calculated spasticity score over 14 days at 6 weeks of treatment compared with the mean score calculated over the initial 7 days. These scores were collected daily by the patient using an 11-point numerical rating scale (NRS-11) Hypothesis: Difference of 0.75 points (standard deviation 2) The secondary endpoints include: - Percentage of responders (reductions in the NRS-11 score ≥ 30% and ≥ 50%) - Modified Ashworth Scale - Caregiver global impression of change (score from 1 to 7) - 10-metre walk test - Barthel Index

Study results:

In all, 337 patients, mean age 48, were randomised: THC/CBD (n=167), placebo (n=170). The mean duration of the disease was 15 years, with a mean EDSS of 6. The mean duration of spasticity symptoms was 8 years. Among the patients included, 24% had previously used cannabis.
The percentage of patients who continued their anti-spastic treatment and their disease-modifying treatment during the study was 89%:

- anti-spastic treatments: baclofen 52%, tizanidine 22%, gabapentin 8%, benzodiazepine 22%, dantrolene 2%, tolperisone 1%;
- disease-modifying treatments: azathioprine 29%, methylprednisolone 23%, prednisone 20%, interferon 21%, glatiramer acetate 7%, cyclophosphamide 6%.

Thirty-two patients prematurely discontinued treatment before the end of the double blind period, 17 patients (10%) in the THC/CBD group (adverse events 9, withdrawal of consent 2, other 3, lack of efficacy 2, lost to view 1); 15 patients (8%) in the placebo group (adverse events 5, lack of efficacy 4, lost to view 2, other 2, withdrawal of consent 1, pregnancy 1)

In all, 335 patients were analysed by ITT. Two patients were excluded from the analysis: The median duration of exposure was 87 days. The median number of daily doses was 8.5 in the THC/CBD group and 15.4 in the placebo group.

[11] Collin C, Ehler E, Waberzinek G et al. (2010). A double-blind, randomized, placebo-controlled, parallel-group study of SATIVEX, in subjects with symptoms of spasticity due to multiple sclerosis. Neurological Research 2010;32:451-9.

Results of intention to treat analysis (patients who received at least one treatment and who were evaluated on treatment)

Endpoints	THC / CBD n=166	Placebo n=169	p
Initial spasticity score	6.77	6.48	
Mean change	-1.05	-0.82	
Difference vs placebo*	**-0.23** (-0.59; 0.14)		ns
% of responders (score reduction ≥ 30%)	**31%**	**25%**	
Difference vs. placebo (95% CI)	6% (-4; 15)		ns
OR (95% CI)	1.34 (0.83; 2.17)		
% of responders (score reduction ≥ 50%)	13%	11%	
Difference vs. placebo (95% CI)	2% (-5; 9)		ns
OR (95% CI)	1.21 (0.62; 2.37)		

* ANCOVA covariate initial spasticity score, adjustment factors on the treatment, site, ambulatory status

The results on the other secondary endpoints did not show any difference between the product and the placebo.

8.1.3 Pooled efficacy data from both studies (GWMS 0106 / GWCL 0403)

The pooled analysis of the changes in spasticity scores of both studies showed a difference between the product and the placebo of -0.34 points (95% CI [-0.64;-0.04], p=0.027) in the mean changes in spasticity scores at 6 weeks of treatment.
The percentages of responders (NRS-11 of 30%) differed between the two treatments: 35% on THC/CBD versus 24% on placebo: OR: 1.63 (95% CI 1.10; 2.41, p=0.015).

8.1.4 Study GWSP 0604[12]

The protocol for study GWSP 0604 is based on the hypothesis that a decrease of at least 20% of the NRS-11 score at 4 weeks of treatment with the THC/CBD combination is predictive of a clinically relevant response (decrease of 30% of the score) after 16 weeks of treatment. This hypothesis was suggested by retrospective analysis of the GWCL 0403 study data: 94% of patients who were "responders" (reduction of 30% of the NRS-11 score) at 14 weeks had a reduction of the NRS-11 score of 20% during the first 4 weeks of treatment.

Type of study	Randomised (1:1 ratio), double-blind, placebo-controlled superiority study.
Start and end of the study	January 2008 - 30 January 2009
Study location / sites	United Kingdom (17 sites), Spain (11), Poland (10), Czech Republic (8), Italy (5)
Inclusion criteria	Documented MS > 6 months and signs of spasticity > 3 months Age > 18 years Mean spasticity score on NRS-11, measured over 6 days, of at least 4 points Spasticity inadequately relieved by the current anti-spastic treatment Anti-spastic treatment / disease-modifying treatment in the 30 days prior to inclusion
Treatments	Two treatment periods: - Single-blind (patient) pre-inclusion period: THC/CBD for 4 weeks - Randomised double-blind period in patients with a reduction of at least 20% in the NRS-11 score at the end of the pre-inclusion period: THC/CBD versus placebo for 12 weeks THC 2.7 mg + CBD 2.5 mg delivered by 100 µl spray (ethanol and propylene glycol solution) Auto-titration by the patient (first 14 days) Maximum tolerated doses: 12 sprays / 24 hours
Endpoints	<u>Primary efficacy endpoint</u>: Change in the mean calculated spasticity score over 7 days at 16 weeks of treatment compared with the mean score calculated over the initial 7 days. These scores were collected daily by the patient using an 11-point numerical rating scale (NRS-11). Hypothesis: Difference of 0.75 points (standard deviation 1.6) <u>The secondary endpoints include</u>: - Percentage of responders (reductions in the NRS-11 score ≥ 30% and ≥ 50%) - Modified Ashworth Scale - Ordinal scale of spasm frequency - Mobility index - Patient global impression of change (score from 1 to 7) - Physician global impression of change (score from 1 to 7) - Caregiver global impression of change (score from 1 to 7) - Sleep disturbance assessment score, 10-metre walk test, Barthel index.

[12] Novotna A., Mares J., Ratcliffe S., Novakova I., Vachova M., Zapletalova O. et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (SATIVEX), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol 2011;18:1122-31.

Study results:

In all, 572 patients were included in the 4-week single-blind pre-inclusion period. Three hundred and thirty one patients (58%) were not randomised. 278 did not meet the inclusion criteria, 53 were not randomised for other reasons (including 29 adverse events, 10 withdrawals of consent and 5 insufficient efficacy). Among the patients included in the study, 85% received at least one concomitant anti-spastic treatment during this period: baclofen 54%, tizanidine 22%, benzodiazepines and derivatives 24%, antiepileptics 23%, adamantane derivatives 13% and 56% were receiving disease-modifying treatment.
Among the patients not randomised, 50% had an improvement in the NRS-11 score of at least 5% and 41% had an improvement of 5 to 20%.

In all, 241 patients, mean age 49, were randomised: THC/CBD (n=124), placebo (n=117). The mean duration of the disease was 13 years (1.5 - 42), with a mean EDSS of 6 points (1.5 to 9). The mean duration of spasticity symptoms was 8 years. 18% of them had previously used cannabis in the year preceding inclusion.
In these patients, the mean initial NRS-11 score at baseline was 6.9 points (± 1.25). After 4 weeks of single-blind treatment with THC/CBD, this mean score was 3.9 points (± 1.51).

During the double blind period, 89% of patients received at least one concomitant anti-spastic treatment: baclofen 58%, tizanidine 17%, benzodiazepines and derivatives 22%, antiepileptics 24% and adamantane derivatives 13%. Sixty-two percent of patients received a disease-modifying treatment.

Seventeen patients were prematurely withdrawn from treatment before the end of the double blind period: 15 patients (12%) in the THC/CBD group (adverse events 8, withdrawals of consent 3, pregnancy 1, disease progression, other 1); 2 patients (2%) in the placebo group (withdrawal of consent 2).

The median duration of exposure was 45 days. The median number of daily doses during the study was 9 in the two treatment groups.

Results of intention to treat analysis (patients who received at least one treatment and who were evaluated on treatment)

Endpoints	THC / CBD n=124	Placebo n=117	p
Initial spasticity score	3.87	3.92	
Mean change	-0.19	0.64	
Difference vs placebo*	**-0.84** (-1.29; -0.40)		0.0002
% of responders (reduction ≥ 30%)	**74%**	**51%**	
Difference vs. placebo (95% CI)	23% (0.11; 0.35)		
OR (95% CI)	OR 2.73 (1.59; 4.69),		0.0003
% patients (score reduction **≥** 50%)	45%	33%	
Difference vs. placebo (95% CI)	12%		ns
Initial Ashworth score	22.1 (14.82)	20.8 (13.28)	
Mean change	0.08	1.83	
Difference vs placebo	-1.75		ns
Frequency of initial spasms	5.61 (9.09)	5.29 (7.30)	
Mean change	0.03	2.56	
Difference vs placebo	-2.53		0.005

* ANCOVA covariate initial spasticity score, adjustment factors on the treatment, site, ambulatory status

Changes in the numerical rating scale for sleep disturbances were different between the two groups: -0.13 on THC/CBD versus 0.75 on placebo.

The patient global change assessment was qualified as improved (score from 1 to 3) in 77% of patients in the THC/CBD group (versus 61% in the placebo group), and the physician assessment in 78% of patients in the THC/CBD group (versus 54% of the placebo group)

The results on the other secondary endpoints (mobility index, 10-metre walk test, Barthel index, quality of life scales) did not show differences between the two treatment groups.

08.2 Safety/Adverse effects

8.2.1 Data from phase III studies[13]

The product safety profile was established from the data of 3 phase III placebo-controlled clinical studies (GWMS 0106, GWCL 0403, GWSP 0604) including the extension periods of these studies.

A total of 805 patients were exposed to the product during the controlled periods of these studies for a mean exposure duration of 67 days at a mean daily dose of 9.1 sprays per day versus 13.7 sprays in patients treated with placebo. 59% of them were between 46 and 65 years old.

The most common concomitant treatments included: baclofen 41%, amitriptyline 12%, gabapentin 15%, benzodiazepine 16%, opioids 19% and strong opioids 9%.
Seventy-six percent of patients had at least one adverse event (AE) on THC/CBD (n=805) versus 66.4% on placebo (n=741). The percentage of patients who stopped treatment for an adverse event was 9.8% on THC/CBD and 4.7% on placebo.

The adverse events occurring on THC/CBD with a greater frequency than that observed on placebo were mainly reported as follows:

- vertigo (6.5% vs 2.0%), blurred vision (1.9% vs 0.4%)
- gastrointestinal disorders: dry mouth (6.1% vs 3.1%), nausea (9.6% vs 5.7%), diarrhoea (5.5% vs 3.9%), constipation (2.4% vs 0.5%)
- general disorders: fatigue (12.5% vs 8.4%), asthenia (5.6% vs 3.1%), feeling drunk ″or abnormal″ (5.4% vs 0.9%) ; falls (1.5% vs 0.5%); anorexia (2.1% vs. 0.7%); increased appetite (1.4% vs 0.4%)
- neurological disorders: dizziness (25% vs 8.2%), somnolence (8.2% vs 2.3%), disturbance in attention (3.9% vs 0.1%), dysgeusia (3.1 % vs 0.8%), balance disorder (2.9% vs 1.8%), dysarthria (2.0% vs 0.4%), lethargy (1.5% vs 0.7%) , memory impairment / amnesia (2.5% vs 0.4%); among the psychiatric disorders: disorientation (4.1% vs 0.8%), elevated mood (2.2% vs 0.9%), dissociation (1.7% vs 0.1%).

Among adverse events considered as severe, occurred in 15.3% of patients in the THC/CBD group (versus 8.5% in the placebo group) dizziness (2.9% vs 0.4%) and asthenia (1.1% vs 0.3%) were reported in more than 1% of patients.

Serious adverse events were reported in 4.6% of patients treated with THC/CBD and 3.2% of patients in the placebo group.

[13] MHRA - Public Assessment Report - Decentralised procedure - SATIVEX Oromucosal Spray - May 2010.

8.2.2 Phase III study open-label extensions[14]

In all, 1,016 patients started or continued treatment with THC/CBD in open label. The mean exposure period was 215 days, i.e., 598 patient-years. The mean daily dose was 4 sprays per day. The incidence of adverse events was 67.5%. The incidence of adverse events considered severe was 21.3%; nausea (1.4%), diarrhoea (1.9%), vomiting (1.7%), asthenia (1.1%) and dizziness (1.4%) were the most common events. A serious adverse event was reported in 8.3% of patients.

8.2.3 Study GWSP 0702[15]

The randomised, double-blind, placebo-controlled efficacy study GWSP 0702 was performed in MS patients who received SATIVEX treatment for at least 12 weeks. Thirty-six patients were randomised over a 4 week treatment period: SATIVEX (n=18), placebo (n=18). The mean duration of prior SATIVEX treatment was 3.6 years, the mean dose was 8 sprays a day. Sixteen patients (89%) discontinued treatment in the placebo group (adverse events 44%, withdrawal of consent 6%, other 39%), 56% of them between the 1st and the 7th day. Three patients (17%) discontinued treatment in the SATIVEX group (adverse events 6%, other 11%).

8.2.4 Pharmacovigilance data[16]

SATIVEX has been sold since April 2005 in Canada and since June 2010 in Europe. On 15 April 2013, post-marketing exposure and compassionate use of the product was estimated at 19,145 patient-years.

The latest periodic pharmacovigilance report has not shown any new signal. The special warnings in the summary of product characteristics include: increased risk of falls due to adverse treatment effects or combination with a muscle relaxant such as baclofen or a benzodiazepine; risk of mouth sores at the product application site; the possible occurrence of changes in heart rate and blood pressure or dizziness during titration and psychiatric symptoms during treatment.

The RMP mentions the need to collect additional safety data, especially in hepatic impairment, renal impairment, cardiovascular disease and in the elderly.

08.3 Summary & discussion

A first double-blind, placebo-controlled study (GWMS 0106) was conducted in 189 patients with MS and inadequately relieved by their anti-spastic treatment. A difference in the NRS-11 spasticity score (primary efficacy endpoint) of -0,52 points [-1.03; -0.004], p=0.048 was observed at 6 weeks of treatment between the THC/CBD and the placebo group. This difference was less than the hypothesis defined in the protocol. A difference of 18% was observed between the two groups concerning the percentage of patients who were treatment responders (reduction of the NRS-11 score ≥ 30%). A second double-blind, placebo-controlled study (GWCL 0403) conducted in 337 patients did not reveal any difference versus placebo on the same primary efficacy endpoint at 14 weeks of treatment (-0.23 [-0.59; -0.14], ns). The pooled analysis of these two studies showed a difference of questionable clinical significance between the treated group and the placebo group at 6 weeks of treatment (-0.34 points [-0.64, -0.04], p=0.027).

GWSP 0604, a double-blind, placebo-controlled study, included 572 patients inadequately relieved by their anti-spastic treatment whose initial NRS-11 score was at least 4 points. In all, 241 patients

[14] MHRA - Public Assessment Report - Decentralised procedure - SATIVEX Oromucosal Spray - May 2010.

[15] Notcutt W, Langford R, Davies P et al. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term SATIVEX (nabiximols). Multiple Sclerosis Journal 2012;18:219-28.

[16] Date from PSUR 16 (16 October 2012 - 15 April 2013).

were randomised, or 42% of the patients included in the study. These patients were selected based on a reduction of at least 20% of the NRS-11 spasticity score during a first period of treatment with THC / CBD. During this pre-screening period, the mean change in NRS-11 scores in these patients was 3 points. During the randomised period, the difference between the mean changes in the spasticity scores observed between the two groups at 14 weeks of treatment was -0.84 points [-1.29; -0.40] p=0.0002. This difference corresponds to the 0.75 point hypothesis defined in the protocol. These results demonstrate the extent of the placebo effect in response to THC/CBD treatment during the pre-screening period.
Adjuvant treatment with THC / CBD achieved a clinically relevant improvement in spasticity (NRS-11 score reduction ≥ 30%) in about 10% of patients included in the study.

Note that the prior optimisation of treating or not treating spasticity pharmacologically before patients were included and started on treatment is not discussed in these studies.

During these placebo-controlled studies, the percentages of patients who presented at least one adverse event were 77% versus 66% and the percentages of treatment discontinuations for adverse events were 9.8% versus 4.7%, higher on THC/CBD than on placebo. The most common adverse events were neuropsychological (dizziness, somnolence / fatigue) and gastrointestinal (nausea, dry mouth).

08.4 Planned studies

As part of the European risk management plan, an observational safety study is underway in the United Kingdom and Germany. The objective of this study is to collect safety data from around 3,000 patients treated with SATIVEX. It is planned to include patients who will be treated in France in this program. A similar safety follow-up is underway in Spain.
While collecting adverse events the focus is on monitoring identified risks (memory disorders, psychiatric and psychological disorders) and potential risks (suicidal ideation / suicide, risk when driving a vehicle, misuse, abuse / addiction / withdrawal syndrome, falls, off-label use).

The marketing of SATIVEX in France will be accompanied by risk minimisation measures and pharmacovigilance and addictology monitoring set up by the ANSM.

09 THERAPEUTIC USE

Spasticity related to multiple sclerosis is part of a multifactorial symptomatology. In order to optimise its management, it must be assessed globally, which must include an assessment of associated symptoms (motor impairment, muscular contractures, cerebellar syndrome, etc.) and its functional impact.

SATIVEX is an adjuvant treatment in patients who are not adequately relieved by an optimal anti-spasticity treatment. Treatment will not be continued beyond 4 weeks if the clinical response is deemed insufficient.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Spasticity includes both hypertonic manifestations per se and phasic manifestations (clonus and muscle spasms) episodically triggered spontaneously or during voluntary movements. This symptom can impair walking and worsen the risk of falling and hinder gripping function. It can have an unfavourable effect on transfers, nursing care, dressing and grooming. It can promote the development of painful periarticular contractures, sources of additional impairment and discomfort. Spasticity can have a significant impact on quality of life.

◗ This proprietary medicinal product is intended as a symptomatic therapy.

◗ The efficacy/adverse effects ratio of this medicinal product is modest in the indication.

◗ SATIVEX is an add-on treatment for the manifestations of spasticity related to MS in patients who are inadequately relieved by reference anti-spastic treatments. There is no pharmacological treatment alternative in the indication.

◗ Public health benefit:

Today, multiple sclerosis (MS) affects between 70,000 and 90,000 patients in France, with a probable annual incidence of four to six per 100,000 inhabitants[17] and it is the leading non-traumatic cause of severe acquired disability in the young. The severity of the disease is due to the disabilities it causes, their impact on quality of life and their socio-economic impact. The public health burden represented by MS is considered to be moderate, including in the subpopulation of patients for whom SATIVEX is indicated.

Reducing the functional limitations induced by multiple sclerosis and improving the quality of life of patients with the disease are a public health need within the framework of established priorities (objective 65 of the act of 9 August 2004 on French public health policy, plan for improvement in quality of life of patients with chronic illnesses 2007-2011).

The efficacy results of three randomised, double-blind, placebo-controlled phase III studies rely on a patient self-assessment; adding SATIVEX to the usual anti-spastic treatment showed a clinically relevant improvement in spasticity in 10 to 20% of patients inadequately relieved by their treatment.

The impact of SATIVEX on the quality of life of treated patients is not demonstrated. SATIVEX has no impact on the organisation of healthcare.

[17] Guide to Long-term Disorders - HAS - September 2006

It is not certain that these results can be extrapolated to current practice, especially due to the non-inclusion criteria of the performed studies and the pre-screening of the patients to be treated.
SATIVEX thus does not meet the identified public health need.
Consequently, SATIVEX is not expected to have any impact on public health in its indication.

Consequently, the Committee considers that the actual benefit of SATIVEX is low in the Marketing Authorisation indication.

The Committee recommends inclusion of SATIVEX on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages of the Marketing Authorisation.

◗ **Proposed reimbursement rate: 15%**

010.2 Improvement in actual benefit (IAB)

Given the reservations resulting from the level of evidence in the performed studies and the small level of the effect observed, the Committee considers that SATIVEX does not provide an improvement in actual benefit (IAB V, none) in the treatment of symptoms related to moderate to severe spasticity due to multiple sclerosis.

010.3 Target population

The prevalence of people with chronic disorders for multiple sclerosis was 126/100,000 on 31 December 2012 for patients subscribed under the general health plan.[18] Applying this prevalence to the general population, the number of persons currently treated for multiple sclerosis in France is estimated to be about 83,000.

Approximately 80 to 90% of patients with multiple sclerosis will have signs of spasticity for at least a period during their disease progression (Paty[19], Rizzo[20]), i.e., 60,000 to 75,000 patients. Spasticity is considered to be moderate to severe in a third of cases.

The proportion of patients "inadequately relieved by standard anti spastic treatments" can vary greatly with the therapeutic management of the disease.
According to data from the Rizzo registry (n=20,969), the percentages of patients receiving the combination of at least two oral treatments are 35% and 46% respectively in moderate spasticity and severe spasticity. According to these data, a maximum estimate of the population likely to receive SATIVEX during an initial treatment in France may comprise between 8,000 and 10,000 patients.
According to the efficacy data from the laboratory studies conducted in the indication, 10 to 20% of these would be likely to benefit from a long-term SATIVEX treatment, thus a maximum estimate of 2,000 patients in France.

[18] Statistical data from National Health Insurance. www.ameli.fr.

[19] Paty GW. Clinical features of multiple sclerosis. Multiple sclerosis *1° Ed. 1997, FA Davis Company Philadelphia.* P:171-191.

[20] Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Multiple Sclerosis 2004;10:589–95.

Packagings

SATIVEX is packaged in a 10 ml vial for oromucosal spray. Given the administration restrictions to be respected (maximum of 12 sprays per day, an interval of at least 15 minutes between each spray), the vial could include a dose counter and a dose locking system with a refractory period (minimum time between two sprays).

Furthermore, there is a system for screwing the vial and the oromucosal tip together but the oromucosal spray does not have a safety-sealed lid to prevent accidental poisoning in children.

APPENDIX

Article R5132-86

Amended by Decree 2013-473 of 5 June 2013 - Art. 1

I. The following are prohibited: production, manufacture, transport, import, export, possession, offer, sale, purchase or use of:

1° Cannabis, its plant and its resin, products containing it or products obtained from cannabis, its plant or its resin;

2° Tetrahydrocannabinols, with the exception of delta 9-tetrahydrocannabinol, their esters, ethers and salts as well as salts of the above-mentioned derivatives and products containing these.

II. Exceptions to the provisions set forth above may be granted for research and control as well as manufacturing of derivatives authorised by the Director General of the Agence nationale de sécurité du médicament et des produits de santé

Cultivation, import, export and industrial and commercial use of cannabis strains devoid of narcotic properties or products containing such varieties may be authorised, on the proposal of the Director General of the agency or by decree of the ministers responsible for agriculture, customs, industry and health.

III. - Manufacture, transport, import, export, possession, offer, sale, purchase or use are not prohibited, when they relate to proprietary medicinal products containing one of the substances mentioned in 1 and 2 of this Article and that are the subject of a Marketing Authorisation issued in France in accordance with the provisions of Chapter I of Part II of this text or by the European Union under Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.