



Northern Treatment
Advisory Group

Sativex® oromucosal spray for the management of pain (non-MS)

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Summary

- Sativex® is an oromucosal spray containing cannabis-derived active ingredients. It is not licensed in the UK for use as an analgesic and its use for the treatment of chronic non-MS related pain would be an off-license indication. There are currently no licensed non-opioid treatments for patients with chronic pain who have an inadequate response to opioids, or experience significant adverse effects with these medications.
- A number of randomised and non-randomised controlled studies of varying quality have examined the efficacy of sativex in the management of chronic non-MS related pain conditions. The main evidence base is for the use of Sativex in the treatment of chronic refractory cancer-related pain, and neuropathic pain of various origins.
- The results of studies in patients with cancer are inconsistent, but suggest that Sativex may have a role as an adjunct to opioid therapy for the treatment of cancer-related pain. In patients with neuropathic pain of various origins the evidence for efficacy is limited, with only one study demonstrating that Sativex has a positive analgesic effect when used in addition to existing analgesic therapy.
- Adverse effects with Sativex are frequent but are generally mild to moderate in severity, well tolerated and only led to withdrawal from studies in a few occasions. The most commonly reported adverse effects are dizziness, fatigue, somnolence, nausea, and dry mouth. Local oral lesions associated with application of Sativex have been reported.
- The maximum recommended number of doses is 12 sprays per day. The mean dose in clinical trials for patients with chronic-opioid refractory cancer pain was around nine sprays per day. In clinical trials in patients with chronic neuropathic pain of various origins, the mean dose was around 11 sprays per day.
- The mean annual cost of sativex per patient for the treatment of cancer pain is estimated at £4,750. For the treatment of neuropathic pain the estimated annual cost is £5,625 per patient. As the likely place in therapy of Sativex is as an adjunct to opioid therapy, the cost will be in addition to existing therapy. If provision of Sativex occurs primarily through acute services then the cost of Sativex will be significantly higher, as VAT at the rate of 20% will be applicable.
- Sativex is intended to address an unmet need in patients who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy. The non-opioid mechanism of action offers the prospect of pain relief without increasing opioid-related adverse side effects.
- The anticipated place in therapy of Sativex in the treatment of chronic pain associated with cancer and other non-MS related conditions is as an adjunct to existing opioid therapy and is not expected to replace current treatments.

Introduction and background

Chronic pain is a severe, debilitating condition resulting in a significant reduction in function and quality of life. Pain is generally described as chronic when it persists or recurs beyond the point that healing would be expected to have occurred, or when it has been ongoing for more than three months. Patients may present with nociceptive pain (due to injury or tissue damage), neuropathic pain (due to damage or dysfunction of the nerves, spinal cord or brain), or a combination of both. Chronic pain can be attributed to a wide range of identifiable causes including, musculoskeletal, neurological, psychological, and from general medical or disease processes.¹⁻⁴

Chronic pain is a common symptom associated with cancer, particularly during the more advanced stages. Cancer pain is complex and multifactorial in origin, involving inflammatory, neuropathic, ischaemic and compressive mechanisms. The majority of cancer pain occurs as a result of direct tumour invasion of local tissues resulting in inflammation, visceral obstruction and nerve compression. Additional pain may result from cancer treatments such as radiotherapy, chemotherapy and surgery. Many patients with otherwise stable cancer pain often experience transitory episodes of acute moderate to severe breakthrough pain.^{1,3-7}

Selecting an effective treatment for chronic pain can be problematic since the extent to which pain responds to analgesics varies depending on both patient and pain characteristics. Since each patient's pain is unique, pain management treatment plans must be tailored to address individual needs. A number of different analgesic drug groups, and drugs within each group, are used to manage chronic pain. The severity of pain determines the strength of analgesic required and the type and underlying cause of the pain will influence the choice of adjuvant analgesic.^{1,3,4,6-9}

Non-opioids analgesics such as paracetamol and NSAIDs are generally effective for mild to moderate pain. Opioids such as codeine and oxycodone are the mainstay approach to the management of moderate to severe pain. Treatment of breakthrough pain in cancer patients with background pain that is otherwise well controlled on a fixed schedule opioid regimen is with supplemental doses of opioids. Opioids can be combined with adjuvant analgesics, steroids antidepressants and anticonvulsants for difficult to treat pain, especially neuropathic pain. The final step in pain management is generally considered to be the use of strong opioid drugs, such as morphine. However, many patients still experience inadequate pain relief despite being treated with strong opiates, and dose-limiting side effects and fear of dependence often limit their use at higher and potentially more effective doses. There are currently no licensed non-opioid treatments for patients with chronic pain who have an inadequate response to opioids, or experience significant adverse effects with these medications.^{1-6,8-10}

The endocannabinoid system plays an important role in the modulation of pain states and elements of the endocannabinoid system are present at many levels of pain pathways. Hence, cannabinoids have emerged as potential adjuvant analgesics in chronic pain treatment. Cannabinoids are thought to alleviate pain through a variety of mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.^{3,4,11-14}

Sativex® (GW Pharma) is a cannabis-based oromucosal spray containing 27 mg/ml delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).¹⁵ Each 100 µL Sativex spray actuation provides 2.7 mg of THC and 2.5 mg of CBD. Sativex has been available as an unlicensed medicine on a named patient basis since December 2005, since which time it had been used principally to treat pain associated with MS. In June 2010 it was licensed for use 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.¹⁵ Sativex® is not licensed in the UK for use as an analgesic, and it is not currently under regulatory review for this indication.

In August 2007, Sativex was approved in Canada (with conditions) as an adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.¹⁶ In April 2014, the FDA granted Sativex fast track status for cancer pain.¹⁷

Sativex is a Schedule 4 Part 1 controlled drug. There are no additional requirements for prescription in the NHS other than those that apply to all POMs. Acquisition or disposal of Sativex must be recorded for a minimum of two years. Pharmacists do not need to record Sativex in their controlled drug registers, although this is strongly recommended by the Home Office.

This document will review the evidence for the efficacy, safety and place in therapy of Sativex in the management of refractory pain associated with cancer and other non-MS related conditions.

Clinical evidence

A number of randomised and non-randomised controlled studies of varying quality have examined the efficacy of sativex in the management of chronic non-MS related pain conditions. The main evidence base is for the use of Sativex in the treatment of chronic refractory cancer-related pain, and neuropathic pain of various origins. There are limited published data regarding its use in rheumatic disease.

In the majority of studies pain intensity was measured on an 11-point scale Numerical Rating Scale (NRS) where 0 was 'no pain' and 10 was worst possible pain or similar. The NRS is a widely used and validated measure of pain severity and is capable of showing clinically and statistically significant changes in pain.^{18,19} In chronic pain trials, it is recommended that the proportion of subjects obtaining a reductions in pain intensity of at $\geq 30\%$ on a pain NRS (responders) should be documented.²⁰ A reduction in pain NRS of approximately 30% is considered to represent a clinically significant difference.¹⁹

Cancer Pain

Portenoy et al, 2012

A phase IIb, randomized, double-blind, placebo-controlled, parallel-group, graded-dose study evaluated the analgesic efficacy of Sativex in opioid-treated cancer patients with refractory chronic cancer pain.²¹ The study was designed to explore the optimal dose-range and consisted of a 5-14 day baseline period, a one-week titration and four-week stable dose treatment period, and a post study visit after two weeks. The study population included adult patients with active cancer and moderate or severe chronic pain (NRS score 4-8) despite a stable opioid regimen (oral MR preparations or transdermal fentanyl) that could not be made more effective by further dose titration. Patients taking long-term methadone therapy were excluded.

Patients were randomised to receive placebo (n=91) or Sativex titrated to a low dose (1-4 sprays, n=91), medium dose (6-10 sprays, n=88), or high dose (11-16 sprays, n=90). The primary efficacy outcome was pain response status, with a positive response defined as $\geq 30\%$ reduction in the mean 11-point NRS. Secondary pain outcomes included continuous responder rates, mean change in daily average pain, worst pain and sleep disturbance.

In total 263 (73%) patients completed the study, including 71, 67 and 59 patients assigned to the low-, medium- and high-dose groups respectively, and 66 to the placebo group. Randomised patients had a mean age of 58 years, 48.3% were male and mean duration of cancer was 3.6 years. The most common sites were gastrointestinal, lung, breast and prostate. All patients had chronic pain with the most common reported as mixed (42%), bone (24%), visceral (15%) and neuropathic (11%). At baseline the median daily dose of opioids received was 120 to 180 mg.

Overall, there was no statistically significant difference between Sativex and placebo in the primary endpoint of $\geq 30\%$ relief from baseline pain at study end. However, the secondary outcome of continuous responder rate comparing the proportion of responders across the full spectrum of response (0 to 100%), reported a significant treatment effect in favour of the combined Sativex groups vs. placebo ($p=0.35$). This effect was significant only in the low- and mid-dose groups ($p=0.08$ and $p=0.038$, respectively). In the low-dose group, the change in average pain ($p=0.006$), worst pain ($p=0.011$) and sleep disturbance ($p=0.003$) were also greater with Sativex. There was no notable difference between treatments groups on overall QoL.

Johnson et al. 2010

A phase IIa, randomized, double-blind, placebo-controlled, parallel-group study evaluated the analgesic efficacy of sativex and THC extracts in patients with intractable cancer-related pain refractory to strong opioids.²² The study consisted of a two-day baseline period and a two-week treatment period. The study population included adult patients with cancer and at least moderately severe cancer-related pain (NRS ≥ 4) despite using strong opioids for at least one week to relieve pain. Patients taking fentanyl were excluded.

Patients were randomised to receive placebo, Sativex or THC extract (2.7 mg/spray) self-titrated to their optimal dose over week one. The maximum permitted dose was eight actuations in any three-hour period, and 48 actuations in any 24-hour period.

The co-primary efficacy outcomes were change from baseline in NRS pain score (including proportion of patients with $\geq 30\%$ improvement), and use of breakthrough analgesia. Secondary outcomes included use of opioid background medication and patient assessment of sleep quality.

Just over 81% of patients completed the study, including 48, 45 and 51 patients assigned to the placebo, sativex and THC, respectively. Randomised patients had a mean age of 60 years, 54% were male and mean duration of cancer was 3.5 years. The primary cancer sites were breast, prostate and lung. The most common type of cancer pain was reported as mixed (50%), bone (37%), neuropathic (22%), visceral (21%) and somatic/incident (10%). The baseline median morphine equivalents/day was 80 mg in the Sativex group and 120 mg in both the placebo and THC groups. Overall, for the entire treatment period the mean number of sprays used daily in the Sativex group was 9.26 (± 5.53).

There was a significant reduction in mean NRS pain scores with Sativex compared with placebo (-0.67 points, $p=0.014$), but not with THC (-0.32 points, $p=0.245$). Almost twice as many patients in the Sativex group showed an improvement of $\geq 30\%$ in mean NRS pain scores compared with placebo (23 [43%] vs. 12 [21%], corresponding to an odds ratio of 2.81 (95% CI 1.22 - 6.5; $p=0.006$). The difference in response rates between the THC and placebo groups was not statistically significant. There was no significant change in the dose of breakthrough or background medications across the treatment groups. Sleep quality (mean NRS) with Sativex did not differ significantly from placebo (-0.31, $p=0.346$).

Johnson et al. 2013 extension

An open-label extension of the Johnson et al, phase II study evaluated the long-term safety and tolerability of Sativex in patients with advanced cancer.²³ Patients who had completed the two-week parent study without unacceptable adverse effects (in the opinion of the investigator) were invited to continue with sativex or THC in the extension study. The study duration was unspecified, with visits at the end of the parent study, then 7-10 days later, then every four weeks until study completion or withdrawal. Inclusion was irrespective of previous treatment allocation.

Patients self-titrated Sativex ($n=39$) or THC ($n=4$) to symptom relief or maximum dose, and were allowed to vary their concomitant analgesic medications including morphine. The primary outcomes were safety and change from baseline in BPI-SF (Brief Pain Inventory Short-Form) and EORTC (European Organisation for Research and Treatment of Cancer) QLQ-30 scores. The study was non-comparative and no formal hypothesis testing was performed.

Overall, the mean duration of cancer was 5.2 years. The most commonly reported primary disease sites were breast, prostate, rectum, lung and bone. The most common type of cancer pain was reported as mixed, neuropathic and bone. The median duration of treatment with Sativex was 25 days (range: 2 - 579 days) while the mean duration of treatment with THC was 151.5 days (range: 4 - 657 days). The mean number of sprays used daily in the Sativex group during the last seven days of dosing was 5.4 (± 3.28).

A decrease from baseline in mean BPI-SF score was observed for "pain severity" and "worst pain" domains at each study visit in the Sativex group. However, at each

visit the investigators considered that patients' pain control was sub-optimal. There was little or no change in mean scores from the EORTC QLQ-30, except for a worsening in physical functioning.

Ongoing Phase III Studies

In November 2010, GW initiated a phase III clinical trial programme in the EU and US for Sativex as an adjunctive treatment for cancer pain. The programme includes three randomised, placebo-controlled phase III studies which plan to enrol around 1,300 patients, and a long-term extension study which is expected to enrol 760 patients. It is anticipated that top-line results from at least one of these Phase III trials will be reported towards the end of 2014. The studies will form the basis for future regulatory applications in the US and the rest of the world.^{24,25}

Neuropathic Pain

Nurmikko et al, 2007

A phase III, randomized, double-blind, placebo-controlled, parallel group trial evaluated the analgesic efficacy of Sativex in patients with neuropathic pain characterised by allodynia.²⁶ The study consisted of a 7-10 baseline period and a five-week treatment period, and an open-label extension option. The study population included adult patients with a current history of unilateral peripheral neuropathic pain (NRS score ≥ 4) and allodynia. Concomitant analgesia including strong opioids and adjuvant analgesics was maintained at a stable dose for the duration of the study.

Patients were randomised to receive placebo (n=62) or Sativex (n=63) self-titrated to a maximum dose of eight actuations in any three-hour period, and 48 actuations in any 24-hour period. The primary outcome measure was change from baseline in NRS mean intensity of global neuropathic pain score. Secondary outcomes included Neuropathic Pain Scale (NPS) composite scores, allodynia, Pain Disability Index (PDI), quality of sleep, and Patients Global Impression of Change (PGIC).

Randomised patients had a mean age of 53 years, 59% were female, with a mean duration of pain of six years, and a baseline NRS of 7.2. The background use of concomitant analgesics was high, with 69% receiving opioids, of which 12% were receiving strong opioids. Over the study period, patients receiving Sativex used a mean of 10.9 (SD 6.8) sprays daily. There was a significant reduction in mean NRS pain intensity scores with Sativex compared with placebo (-0.96; p=0.004). Improvements in NPS composite score (p=0.007), sleep NRS (p=0.001), dynamic allodynia (p=0.042), punctate allodynia (p=0.021), PDI (p=0.003) and PGIC (p<0.001) were similarly greater with Sativex vs. placebo. In the open-label extension study in which 89 patients underwent re-titrated with Sativex the reduction in mean NRS pain intensity scores was -1.4 at 52 weeks. The daily number of sprays did not increase appreciably during this period 10.2 (6.0) at the end of re-titration vs. 12.2 (7.6) at 52 weeks.

Selvarajah et al, 2010

A randomized, double-blind, placebo-controlled trial (n=30) evaluated the analgesic efficacy of Sativex as an adjunctive analgesic in the treatment of intractable diabetic peripheral neuropathy (DPN).²⁷ The study consisted of a two-week titration period and a 10-week treatment period. The study population included adult patients with

chronic painful DPN (neuropathy Total Symptom Score >4 and <16) for at least six months with stable glycaemic control (A1C <11%). Those with persistent pain despite an adequate trial of tricyclic antidepressants were recruited. Patients continued pre-existing neuropathic pain treatments throughout the study.

Patients were randomised to receive placebo (n=62) or Sativex (n=63) administered in divided doses up to four times per day. The primary outcome measure was change from baseline in mean daily Neuropathic Pain Scale (NPS) scores. Secondary outcomes included quality of life measures. At week-10 there were no significant differences in mean change in pain scores between Sativex and placebo. There were no significant differences in secondary outcomes.

Berman et al, 2004

A phase III, randomised, double-blind, placebo-controlled, crossover study evaluated the analgesic efficacy of Sativex and THC extracts in patients with chronic pain associated with brachial plexus root avulsion.²⁸ The study consisted of a two-week baseline period, followed by three two-week treatment periods. The study population included adult patients with at least one avulsed root and chronic pain (NRS score ≥ 4) regardless of current analgesic therapy. No analgesics were prohibited, but patients were not permitted to use concomitant fentanyl during the study.

Patients were randomised to receive placebo (n=48), Sativex (n=46) or THC extract (n=47). The maximum permitted dose was eight actuations in any three-hour period, and 48 actuations in any 24-hour period. The primary outcome measure was change from baseline in NRS pain score, with a difference ≥ 2 points between active treatment and placebo assumed to represent a clinically significant change.

Randomised patients had a mean age of 39 years, 96% were male, mean time since last surgical repair was five years, and 48% were taking at least one concomitant analgesic. The difference in mean pain scores between both study drugs and placebo was statistically significant, but failed to reach the assumed level of clinical significance.

Lynch et al 2013

A randomized, placebo-controlled crossover pilot study (n=18) evaluated the efficacy of Sativex in the treatment of chemotherapy-induced neuropathic pain.²⁹ To be included, participants had to have neuropathic pain (NRS ≥ 4) persisting for three months after completing chemotherapy. Concomitant analgesia had to be stable for two weeks prior to entry into the trial. The primary efficacy outcome was change from baseline in NRS pain score. Patients self-titrated Sativex up to maximum of 12 sprays per day. A total of 16 patients completed the study. The mean dose of Sativex used was eight sprays per day (range 3-12). There was no statistically significant difference between the treatment and the placebo groups in NRS pain scores.

Rheumatic Disease.

Blake et al, 2006

A phase II, randomized, double-blind, placebo-controlled, parallel group trial evaluated the efficacy of Sativex in the treatment of pain due to rheumatoid arthritis

(RA).³⁰ The study consisted of a two-week titration period followed by a three-week stable dose treatment period. The study population included adult patients with a diagnosis of RA meeting ACR criteria, with active arthritis not adequately controlled by standard medications. NSAIDs and prednisolone regimens had to have been stabilised for one month, and DMARDs for three months prior to enrolment.

Patients were randomised to receive placebo (n=27) or Sativex (n=31) at a starting dose of one spray within 30 minutes of retiring for bed, which was increased by one spray every two days to a maximum of six sprays according to individual response. The primary outcome measure was pain on movement measured using a NRS each morning. Secondary outcomes included NRS measures of pain at rest, sleep quality, and pain at present (measured by the Short Form McGill Pain Questionnaire).

Randomised patients had a mean age of 63 years and 79% were female. The mean number of Sativex sprays used in the final treatment week was 5.4 (SD 0.84). Sativex recipients showed significant improvement, relative to placebo in pain on movement (p=0.044) morning pain at rest (p=0.018), quality of sleep (p=0.027), disease activity score (p=0.002), and pain at present (p=0.016).

Cochrane Review 2012

A recent Cochrane Collaboration review concluded that Sativex appears to improve pain and sleep to a modest degree in patients with RA, but given the CNS side effects profile, the potential harms appear to outweigh the modest benefits.³¹ It should be noted that this conclusion was based solely on the phase II study described above.

Safety

The available safety data on Sativex is comprehensive. Sativex has been studied in over 2,500 patients with MS and in other conditions, in placebo controlled trials and in long-term open-label studies in which some patients used up to 48 sprays per day (i.e. four times the maximum recommended dose). The other indications studied have largely involved patients with cancer and chronic neuropathic pain of various origins. Sativex has been available as a prescription medicine in the UK since June 2010.^{15,32}

The profile of adverse events with Sativex is broadly in line with that expected of the pharmacology of cannabis. The main safety and tolerability issues are related to central nervous system events. Psychiatric symptoms such as anxiety, illusions, mood changes and paranoid ideas have been reported with Sativex. The majority of cases were generally mild to moderate in severity and resolved on reduction or interruption of Sativex. Disorientation (or confusion), hallucinations and delusional beliefs have also been reported.^{15,32}

In the MS population (licensed indication), the most common adverse events reported by patients taking Sativex are dizziness, fatigue, nausea, urinary tract disorder, somnolence, vertigo, headache, dry mouth, asthenia, and diarrhoea. These adverse events tend to occur in the first four weeks of treatment, and become less frequent over time. Common application site reactions include application site pain, oral pain and discomfort, taste disturbance, mouth ulcers and tongue pain.^{15,32}

Data on the withdrawal from Sativex treatment in patients with chronic pain is lacking. However, studies into long-term use of Sativex in patients with MS showed that sudden discontinuation of treatment did not result in any significant withdrawal-like symptoms. Some people reported temporary changes in their sleeping patterns, emotional status and appetite following discontinuation. The lack of withdrawal symptoms suggests that dependence on the treatment is unlikely. There have been no reports of drug abuse associated with Sativex.^{15,32,33}

Cancer Pain

In the phase IIb study, which incorporated a forced titration to a given dose range, the incidence of adverse events with Sativex was dose-related, with only the highest dose group (11-16 spays/day) comparing unfavourably to placebo.²¹ The most common adverse events occurring in >10% of Sativex recipients versus placebo were nausea (22% vs. 13%), dizziness (19% vs. 13%), neoplasm progression (18% vs. 14%), disorientation (17% vs. 1%), vomiting (16% vs. 8%) and somnolence (15% vs. 4%). Discontinuations from study treatment were also dose-related, with a higher rate (28%) in the high-dose group compared with the medium-dose (17%), low-dose (14%), and placebo (18%) groups. Serious adverse events (SAEs) were more common in the low-dose group. In total, 30% of Sativex treated patients experienced an SAE, compared with 24% in the placebo group. The higher incidence of death observed in the low-dose group was not thought to be treatment-related.

In the phase IIa study adverse events were similar to those reported in other clinical trials of Sativex.²² The most common treatment emergent adverse events occurring in >5% of Sativex recipients versus placebo were somnolence (13% vs. 10%), dizziness (12% vs. 5%), nausea (10% vs. 7%), confusion (7% vs. 2%), vomiting (5% vs. 3%), and hypertension (5% vs. 0%). Most were of mild or moderate severity. Adverse events lead to discontinuation from study treatment in 17% and 3% of patients, respectively. SAEs were experienced by 8% of subjects receiving Sativex, all of which were deemed to be unrelated to the study drug. There were no SAEs reported in the placebo group.

The pattern of adverse events seen in the long-term extension study was generally similar to that seen in the short-term parent study.²³ The most commonly reported adverse events with Sativex were dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. Adverse events lead to discontinuation from study treatment in 59% of patients. Of these, just over half had previously been randomised to the placebo group in the parent study. At least one SAE was experienced by 51% of patients receiving Sativex, but only 8% of patients had an SAE that was considered to be treatment-related. SAEs leading to death were observed in 31% of patients receiving Sativex, but all were reportedly caused by the patients underlying cancer.

Neuropathic Pain

Sativex therapy was generally well tolerated in patients with peripheral neuropathic pain characterised by allodynia. At least one adverse event was experienced by 91% of patients in the Sativex group during the study compared with 77% in the placebo group. Most were mild in severity and occurred at the onset of treatment.

The most common adverse events reported were CNS-related or gastrointestinal. All reported gastrointestinal adverse events (nausea, vomiting diarrhoea and constipation) combined irrespective of severity were more common in the Sativex group ($p=0.03$), whereas CNS adverse events were not. No difference was seen between groups for cognitive function at the beginning and end of treatment using the Brief Repeatable Battery of Neuropsychological tests (BRB-N). Intoxication scores remained low for both groups throughout the study. In the long-term extension study, efficacy was maintained for 52 weeks without an appreciable increase in adverse events.

In patients with chronic NP associated with brachial plexus root avulsion more adverse events were experienced during the Sativex treatment periods than during the placebo period.²⁸ The most common adverse events were dizziness, somnolence, dysgeusia, nausea and feeling drunk. However, the majority of these were mild to moderate in severity and resolved spontaneously. The number of patients reporting adverse events suggesting intoxication did not differ greatly across the treatment groups.

Adverse events were reported by the majority of patients with chemotherapy-induced NP receiving Sativex. The majority of these were mild and transient, and did not lead to discontinuation of Sativex or withdrawal from the study. The nature of adverse events was similar to that reported in other trials of Sativex in NP. The most common were fatigue, dizziness, dry mouth and nausea. No treatment emergent SAEs were reported.

No safety data are available regarding the use of Sativex in the treatment of patients with painful diabetic neuropathy.²⁷

Rheumatic Disease.

In patients receiving Sativex for the treatment of pain caused by RA the nature of adverse events was similar to that reported in other trials of Sativex in the treatment of pain.³⁰ The most common adverse events occurring in >5% of Sativex recipients versus placebo were dizziness, light-headedness, dry mouth, nausea and fall. The majority of adverse events were mild or moderate in severity, and occurred during the initial two-week titration period. There were no withdrawals due to adverse events and no SAEs in the Sativex group, compared to 11% and 7%, respectively in the placebo group.

Cost analysis

No published economic analyses on the use of Sativex in the treatment of pain were identified.

Sativex® is available in a 10 millilitre spray bottle providing up to 90 doses each of 100 microlitres, with the excess lost due to priming the pump mechanism. It will be

assumed that maximum dose extraction is achieved. Each metered dose of Sativex® delivers 2.7 mg of THC and 2.5 mg of CBD. Unopened spray bottles must be stored in a refrigerator. Once opened, a spray bottle does not need to be refrigerated but must be used within 42 days. It will be assumed that use of Sativex incurs no waste, i.e. that all spray bottles are completely used within the 42 day expiry limit.

A pack of three 10-mL units (90 dose) Sativex spray bottles costs £375.00 (excluding VAT). Dosing with Sativex for patients with MS is described in the SPC along with a titration method for proper treatment initiation. Initially, one spray in the evening increased as necessary over two weeks up to a maximum of 12 sprays per day, or until they achieve optimum symptom relief. However, it should be noted that considerably higher numbers of sprays per day (up to 48) have been documented in clinical studies. The annual cost per patient of Sativex if used at the maximum recommended dose of 12 sprays per day would be £6,083.

Cancer Pain

In clinical trials, patients with cancer-related pain used an average of up to 9.3 sprays per day, meaning that one 90-dose spray bottle will provide sufficient for around ten day's treatment. The anticipated duration of treatment has not been established, and response to therapy will need to be monitored on an on-going basis. Assuming that treatment is maintained in the relative long-term, it is assumed that 38 Sativex spray bottles are required per annum. This equates to an estimated mean annual cost per patient of £4,750. Doses above 10 sprays have not been shown to provide any significant additional benefit in patients with cancer pain and have increased adverse effects.

Accurately estimating the number of patients who might be considered for treatment with Sativex for chronic cancer-related pain is difficult. In Northern England in 2012, there were approximately 642 people per 100,000 of the population diagnosed with cancer (European age-standardised incidence rate). A conservative estimate based on the most recent surveys would suggest that around 30% of cancer patients receive inadequate pain relief despite treatment with strong opiates.³⁴⁻³⁷ If the patients who experience significant dose-limiting adverse events during opioid therapy are also considered, then the number of patients who might receive treatment with Sativex for cancer pain is likely to be significantly higher.

Neuropathic pain

In patients with neuropathic pain of various origins, the average number of sprays used in the short-term was 10.9 sprays per day and in the subsequent long-term open-label extension 12.2 sprays per day were used. Thus one 90-dose spray bottle will provide sufficient for around eight day's treatment. Assuming that treatment is maintained in the relative long-term, it is assumed that 45 Sativex spray bottles are required per annum. This equates to an estimated mean annual cost per patient of £5,625.

Given the diverse aetiology and varied treatment pathways involved, it has not been possible to estimate the number of patients who might be considered for treatment with Sativex for neuropathic pain.

As the likely place in therapy of Sativex in the treatment of chronic pain is as an adjunct to opioid therapy, the cost will be in addition to existing therapy. However, it is possible that some of the additional cost of Sativex could be offset against potential savings realised through a reduction in opioid-related adverse events, and use of concomitant laxatives and anti-emetics

VAT will be applicable to the provision of Sativex from acute services (e.g. specialist pain services and hospital pharmacy dispensaries). If provision of Sativex occurs primarily through acute services then the cost of Sativex will be significantly higher, as VAT at the rate of 20% will be applicable.

Patient impact

Sativex is not licensed in the UK for use as an analgesic and its use for the treatment of chronic non-MS related pain would be an off-license indication. There are currently no licensed non-opioid treatments for patients with chronic pain who have an inadequate response to opioids, or experience significant adverse effects with these medications.

The pharmacological effects of Sativex are dose-related and subject to considerable inter-patient variability. Patients will need to take responsibility to a certain extent for dose-titration and should be advised that it may take several weeks to establish the optimal dose for pain relief.

The maximum recommended number of doses is 12 sprays per day, or until optimum symptom relief is achieved. The mean dose in clinical trials for patients with chronic-opioid refractory cancer pain was 9 sprays per day. In clinical trials in patients with chronic neuropathic pain of various origins, the mean dose was around 11 to 12 sprays per day. Doses should initially be divided between morning and evening, such that administration corresponds to twice daily. Once the optimal dose has been defined, dose can then be spaced throughout the day as required. A minimum 15-minute interval between each spray is recommended.

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 significant adverse effects develop.

The use and manipulation of the Sativex spray device requires a degree of manual dexterity, strength and co-ordination that some patients experiencing chronic pain may not possess. In addition, use of Sativex requires a level of cognitive ability that may not be present in some patients with advanced stages of cancer. Training and support in the use of the device will be required which may need to be extended to carers as well as patients.

Sativex has generally been well tolerated in patients with chronic pain, with an acceptable adverse event profile. Common application site reactions include application site pain, oral pain and discomfort, taste disturbance, mouth ulcers and tongue pain. Consequently, application of the spray should be directed at different sites on the oromucosal surface each time it is used.

Sativex is contraindicated in patients with a history or family history of significant psychiatric disorder. Sativex is not recommended in patients with serious cardiovascular disease, and caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.

Sativex is a controlled drug, the responsibility for prescribing and monitoring of Sativex may present issues relating to shared-care between specialists and general practitioners. If shared-care arrangements are not possible then patients may have to attend acute services to obtain prescriptions for Sativex.

Points to consider

The anticipated place in therapy of Sativex in the treatment of chronic pain associated with cancer and other non-MS related conditions is as an adjunct to existing opioid therapy and is not intended to replace current treatments. Sativex is intended to address an unmet need in patients who experience moderate to

severe pain despite the highest tolerated dose of strong opioid therapy. The non-opioid mechanism of action offers the prospect of pain relief without increasing opioid-related adverse side effects. There is some evidence that Sativex may offer additional benefits beyond analgesia, such as anti-emetic effects, and improvements in sleep.

A number of randomised and non-randomised controlled studies of varying quality have examined the efficacy of sativex in the management of chronic non-MS related pain conditions. The main evidence base is for the use of Sativex in the treatment of chronic refractory cancer-related pain, and neuropathic pain of various origins. There are limited published data regarding its efficacy in rheumatic disease. There are no data regarding the use of Sativex in the treatment of breakthrough cancer pain.

The results of studies in patients with cancer are inconsistent, but suggest that Sativex may have a role as an adjunct to opioid therapy for the treatment of cancer-related pain. However, the existing data are only preliminary; a clearer understanding of the role of Sativex in the treatment of cancer pain should be confirmed upon completion of the comprehensive ongoing phase III study programme. In patients with neuropathic pain of various origins the evidence for efficacy is limited, with only one study demonstrating that Sativex has a positive analgesic effect when used in addition to existing analgesic therapy.

Adverse effects with Sativex are frequent but are generally mild to moderate in severity and manageable. The most common adverse effects are dizziness, fatigue, somnolence, nausea, and dry mouth. These adverse events tend to occur in the first four weeks of treatment, and become less frequent over time. Common application site reactions include application site pain, oral pain and discomfort, taste disturbance, mouth ulcers and tongue pain.

The degree to which Sativex is likely to be adopted into adjunctive pain management practices remains to be determined. Given the diverse aetiology and varied treatment pathways involved, it has not been possible to estimate the number of patients who might be considered for treatment with Sativex for chronic pain.

Sativex is a costly treatment, with an estimated mean annual cost per patient of £4,750 for the treatment of cancer pain, and £5,625 for the treatment of neuropathic pain. As the likely place in therapy of Sativex is as an adjunct to opioid therapy, the cost will be in addition to existing therapy. If provision of Sativex occurs primarily through acute services then the cost of Sativex will be significantly higher, as VAT at the rate of 20% will be applicable.

Sativex may present issues relating to shared care with an attendant impact of the cost of therapy.

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