PAIN RELEAF

While cannabis' health risks prompted its reclassification in January, the drug looks set to become the key ingredient of a new pain relief medicine. **Katrina Megget** reports on the emergence of Sativex

After 10 years in development and travelling a rocky legislative road, pharmaceutical company GW Pharmaceuticals will this spring submit its cannabis-based medicine, Sativex, for marketing authorisation as a treatment for multiple sclerosis (MS) symptoms. The product provides a legal alternative for many people who have been seeking pain relief and symptom management in the form of an illegal joint.

Already approved in Canada for the treatment of multiple sclerosis and cancer pain, the drug, self-administered as an oral spray, is made up of a 50-50 mix of the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD).

Cannabis was medically available in the UK until 1971, when the government moved to make it illegal under the Misuse of Drugs Act. However, the use of cannabis for medicinal purposes merely went underground. The Medicines and Healthcare products Regulatory Agency (MHRA) says a "substantial proportion" of MS patients use cannabis to relieve symptoms. A survey of readers carried out by the magazine *Disability Now* found a quarter of disabled people use cannabis.

In 1998, the House of Lords Science and Technology Committee concluded there was an "unmet medical need" and backed the use of cannabis for medicinal purposes. The Committee said the evidence in the case of MS was "enough to justify a change in the law". At the time, the government maintained that evidence was weak over the medicinal properties of cannabis. Three years later GW Pharmaceuticals presented new Sativex trial results showing that of the first 53 patients in three trial centres, 41 derived clinically significant benefit. The trial also found the drug had an excellent safety profile. The Home Office then announced it would change the law to allow the prescription of cannabis-based medicines if they were approved by the MHRA.

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"As many as one-third of the 85,000 MS sufferers in the UK have said they would seriously consider taking cannabis illegally to reduce symptoms," says GW Pharmaceuticals spokesman Mark Rogerson. "We take that as strong evidence of an unmet need."

GW's first attempt at getting Sativex approval failed in 2004 when the MHRA cited a lack of clinical evidence. However, GPs were given permission to prescribe Sativex on a named-patient basis and more than 2,000 MS patients have received the drug to date. In 2006, GW again submitted an application only to withdraw it almost a year later after outstanding issues required new data to be generated. At the end of 2007, the company started a new 'Phase III' trial to resolve the concerns. But in April last year, the company released results showing an "unexpectedly strong placebo response" where patients on the dummy drug showed an almost similar response to those taking the real one. The trials have since been redesigned. GW is "confident" requirements have now been met and "hopeful" that Sativex will finally be approved this year.

Sativex was approved in Canada in 2005 as a treatment for neuropathic pain for multiple sclerosis patients and in 2007 as an additional analgesic for cancer patients. Last year Sativex sales in Canada increased by 15 per cent. Rogerson says that based on "anecdotal evidence and clinical work" with patients in Canada, the company is confident the drug is being well received. Canadian MS patients have reported "improvements in pain management, relief from spasticity and improved function".

Are there any cannabis-like side effects to Sativex? There have been reports in the Canadian press of some patients struggling with the taste, texture and method of administration. Concerns have also been raised that the drug is not being metabolised properly, has no analgesic properties and creates the dizziness, sleepiness and paranoia associated with cannabinoids. "Patients may also experience symptoms of cannabinoid intoxication, including dizziness when they first take Sativex," stipulated a fact sheet handed to doctors by Health Canada when the drug was initially unveiled. GW's own research found 3.8 per cent of patients experienced a euphoric mood, 2.6 per cent a depressed mood, 1.8 per cent anxiety, 0.9 per cent hallucination and 0.8 per cent paranoia. GW has not undertaken formal studies looking at the dose-response relationship of Sativex, but studies do show the response to the drug differs between patients. "In theory, yes, you can abuse the medicine," Rogerson says. "But in practice, MS sufferers don't want to do that, they want to treat their symptoms."

Meanwhile, the Wiltshire-based company notes the abuse potential is limited because peak plasma levels of THC are far lower with Sativex than smoked cannabis. Each spray of Sativex delivers a fixed dose of 2.7mg THC and 2.5mg CBD, with a mean daily dose of nine sprays based on placebo-controlled studies. Results showed plasma levels of THC are around 30-times lower than those obtained by smoking cannabis. "In the context of the proposed indication and patient population, abuse of Sativex is not considered to be an issue of great concern, subject to sensible precautions," the MHRA has concluded.

Derek Williams, Webmaster of the UK Cannabis Internet Activists (UKCIA), says feedback to the UKCIA has been that the drug works very well. However, he says there may be the potential for the product to emerge on the black market. "I suspect the side effects of Sativex would be one of its attractions for some people. Introducing this product is bound to create a black market," he says. "The profits to be made from diverting supplies are huge. Unless the demand for social use of cannabis is allowed, black market trading of NHS Sativex is certain. We can expect the laws of supply and demand to work as normal."

Rogerson disagrees. He believes profiteering from Sativex is "extremely unlikely" and is not aware of the medicine being diverted from its proper use. Indeed, Canada's drug approval body Health Canada says: "To date there have been no reports of abuse or problems of a social consequence related to the use of Sativex reported to the Canada Vigilance Programme." The authority adds: "Health Canada monitors the benefit-to-risk profile of medications in Canada on an ongoing basis. Should a safety concern be identified with Sativex, Health Canada will take appropriate action."

The Home Office views the "attractiveness" of the drug as low because it is non-smoked, prescription-only and contains low levels of THC. "That's not to say there is no risk, there is always a risk of abuse, but tests of Sativex show the risk of danger to health is negligible."

Katrina Megget is a freelance journalist