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EPAR summary for the public

Xyrem
sodium oxybate

This document is a summary of the European Public Assessment Report (EPAR) for Xyrem. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Xyrem.

What is Xyrem?

Xyrem is an oral solution that contains the active substance sodium oxybate (500 mg/ml).

What is Xyrem used for?

Xyrem is used to treat adults who have narcolepsy with cataplexy. Narcolepsy is a sleep disorder that causes excessive daytime sleepiness. Cataplexy is a symptom of narcolepsy involving sudden muscle weakness in response to an emotional reaction such as anger, fear, joy, laughter or surprise. Cataplexy can sometimes cause a patient to collapse.

The medicine can only be obtained with a special prescription.

How is Xyrem used?

Xyrem treatment should be started and given under the guidance of a doctor who has experience in the treatment of sleep disorders. Because sodium oxybate can be abused, doctors should check for a history of or susceptibility to drug abuse before treatment, and monitor for misuse and abuse during treatment.

Xyrem is given at a dose of 4.5 to 9 g per day in two equally divided doses. The maximum daily dose is 9 g. Patients should usually start with two doses of 2.25 g (4.5 ml) per day. The dose is then adjusted at one- to two-week intervals depending on the patient’s response. The starting dose should be halved in patients who have problems with their liver. The dose of Xyrem should also be reduced by
a fifth if patients are taking the medicine valproate for another condition at the same time as they are taking Xyrem. Patients who have problems with their kidneys should consider a low sodium diet. Patients taking Xyrem should avoid alcohol, as it can increase Xyrem’s effects.

Xyrem is supplied with a measuring device and a cup. Before taking the medicine, the patient should dissolve the dose in water to make up a drink. The first dose of the day is taken at bedtime, at least two to three hours after food. The second dose is taken 2.5 to 4 hours later. Both doses should be prepared at the same time before the patient goes to bed. For more information, see the package leaflet.

**How does Xyrem work?**

The active substance in Xyrem, sodium oxybate, is a central nervous system depressant. The precise way in which it works is not known, but it is thought to attach to receptor molecules on the surface of some cells in the brain. This leads to changes in the activity of the brain, bringing about ‘delta’ (slow) brain waves and night-time sleep. When taken at bedtime, Xyrem increases deep sleep and increases the amount of time spent asleep at night, whilst reducing the number of sleeping periods during the day. This improves the symptoms of narcolepsy.

**How has Xyrem been studied?**

The effects of Xyrem in narcolepsy and cataplexy have been studied in 707 patients in four studies. In all of the studies, Xyrem was given at a daily dose between 3 and 9 g and was compared with placebo (a dummy treatment). The first study (136 patients) examined the effects of Xyrem on the number of cataplexy attacks over four weeks of treatment. The second study, including 56 patients who had been taking Xyrem for at least six months, compared the effects of continuing to take Xyrem at the same dose as before, with the effects of switching to placebo. The study measured the number of cataplexy attacks over two weeks. The other two studies (516 patients) examined the effects of Xyrem on excessive daytime sleepiness and other symptoms of narcolepsy, either taken alone or as an add-on to the patient’s existing dose of modafinil (a stimulant medicine used to treat narcolepsy). The main measure of effectiveness was the change in daytime sleepiness.

The effects of Xyrem have also been studied in fibromyalgia patients with moderate to severe symptoms in two short-term (12-week) studies in 1,121 patients, and one long-term (up to nine months) study in 560 patients. Fibromyalgia is a disease of unknown origin causing long-lasting, widespread pain and painful responses to touch. The main measure of effectiveness was based on reduction of pain severity and improvement in function.

**What benefit has Xyrem shown during the studies?**

Xyrem was more effective than placebo in reducing symptoms. In the first study, a daily dose of 9 g reduced the number of cataplexy attacks by 16.1 (from 23.5 to 8.7) per week, compared with a fall of 4.3 per week in the patients taking placebo. The second study showed that Xyrem continued to prevent cataplexy attacks after long-term treatment: there was no change over two weeks in the number of attacks in the patients continuing to take Xyrem, compared to an increase of 21.0 attacks in those switching to placebo. Xyrem also reduced excessive daytime sleepiness in patients who continued to take modafinil, as well as in those who took Xyrem alone.

The data obtained in the fibromyalgia studies did not support the use of Xyrem in this condition in the European population.
What is the risk associated with Xyrem?

The most common side effects with Xyrem (seen in more than 1 patient in 10) are dizziness, headache and nausea (feeling sick). Nausea is more common in women than in men. Xyrem can also cause respiratory depression (inhibition of breathing). For the full list of all side effects reported with Xyrem, see the package leaflet.

Xyrem must not be used in patients with major depression, in patients with ‘succinic semialdehyde dehydrogenase deficiency’ (a rare metabolic disease), or in patients being treated with opioids (such as some painkillers) or barbiturates (such as some anaesthetics and medicines used to prevent seizures). Because sodium oxybate can be abused, doctors must carefully monitor patients using Xyrem. Patients are also advised against taking alcohol while on treatment with Xyrem. For the full list of restrictions, see the package leaflet.

Why has Xyrem been approved?

The CHMP decided that Xyrem’s benefits are greater than its risks. Although the 9-g dose was the most effective, it was linked to high levels of side effects, so the Committee recommended a starting dose of 4.5 g per day. Since the effective dose is close to the dose at which side effects become serious, increases in dose must be carried out strictly and under the supervision of a doctor specialised in the treatment of sleep disorders. The Committee recommended that Xyrem be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Xyrem?

A risk management plan has been developed to ensure that Xyrem is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Xyrem, including the appropriate precautions to be followed by healthcare professionals and patients.

The company that makes Xyrem will minimise the risk of abuse of Xyrem by providing educational materials to healthcare workers and patients, strictly controlling the distribution of the medicine, and monitoring its use.

Other information about Xyrem:

The European Commission granted a marketing authorisation valid throughout the European Union for Xyrem on 13 October 2005.

The full EPAR for Xyrem can be found on the Agency’s website: ema.europa.eu/Find_medicine/Human medicines/European_Public_Assessment_Reports. For more information about treatment with Xyrem, read the Package Leaflet (also part of the EPAR) or contact your doctor or pharmacist.

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