# Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children and adolescents aged 7 until 19 years)

**Reference: NHS England: 210301/P**

# Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children and adolescents age 7 until 19 years)

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**Prepared by NHS England Specialised Services Clinical Reference Group for Paediatric neurosciences**

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## Contents

## Policy Statement

NHS England will commission sodium oxybate for symptom control of narcolepsy with cataplexy (children and adolescents, aged 7 until they are 19 years old) in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

## Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

## Plain Language Summary

### About narcolepsy

Narcolepsy is a condition that affects sleep and wake cycles and impacts on all aspects of life. The symptoms include:

- feeling very sleepy during the day
- seeing or hearing things that are not there (hallucinations)
- not being able to move or speak when you are waking up or falling asleep (sleep paralysis)
- having problems sleeping at night (disturbed sleep).

Narcolepsy may occur with cataplexy - this is a sudden, temporary muscle weakness. Signs range from jaw dropping to total collapse on the floor. It is usually triggered by an emotion and may last between a few seconds and several minutes.

**About current treatment**

Treatment usually starts with making changes to behaviour and a person's environment. The treatment includes medicines called 'stimulants' that help to stop the patient feeling so sleepy during the day.

If the patient does not respond to this treatment, the next step will involve treatment with other medicines.

**About the new treatment**

Sodium oxybate is a medicine that is licensed for treating narcolepsy with cataplexy in adults, adolescents and children from 7 years. However, it is not licensed for use in children under 7 years. The following side effects happen often:

- feeling sick (nausea)
- headache
- bed wetting
- confusion.

**What we have decided**

NHS England has carefully reviewed the evidence to treat narcolepsy with cataplexy in children with sodium oxybate. We have concluded that there is enough evidence to make the treatment available for children and adolescents aged 7 until they are 19 years old. It can only be used in children who have not responded to current treatments, or children who cannot have current treatments.

# 1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission sodium oxybate for a defined group of children and adolescents (aged 7 until they are 19 years old) suffering from narcolepsy with cataplexy and who have not responded, or are intolerant to, first and second line medications.

Narcolepsy and cataplexy are lifelong disorders, often diagnosed in childhood. Narcolepsy with cataplexy (otherwise known as narcolepsy-cataplexy complex) is a neurological condition affecting the regulation of sleep/wake cycles characterised by excessive day-time sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and fragmented night-time sleep. Narcolepsy may occur without cataplexy but virtually all patients with cataplexy have narcolepsy.

Sodium oxybate is derived from the neurotransmitter GABA and suppresses dopaminergic neuronal activity. It has been shown to be effective in controlling symptoms of both narcolepsy and cataplexy in adults and is licenced for such use. Sodium oxybate is known to be associated with frequent side effects (e.g. nausea, headache, bed wetting, and confusion including withdrawal effects) and may not be appropriate for all patients.

Sodium oxybate is licensed to treat adults, adolescents and children aged 7 until they are 19 years old, who have narcolepsy with cataplexy by both the European Medicines Agency (EMA/602260/2020) and for adults by the U.S. Food and Drug Administration (NDA 21-19).

# 2 Definitions

**Narcolepsy** is a chronic neurological condition affecting the brain's ability to regulate normal sleep/wake cycles. This can lead to symptoms such as disturbed night-time sleep and excessive sleepiness throughout the day.

**Cataplexy** is an episode of muscular weakness triggered by strong emotions such as laughter, anger and surprise. The loss of muscle tone ranges from a just-perceptible weakening of the facial muscles through weakness at the knees, to total collapse on the floor, which may cause injury.

**Hypnagogic hallucinations** are sensory phenomena experienced just before sleep. They can be vivid and frightening episodes of seeing, hearing or feeling phantom sensations.

**Sleep paralysis** is a state in which the patient is physically immobile, but fully conscious. Whilst it does not cause direct harm, sleep paralysis can be frightening.

**Polysomnography** is an investigation of sleep, carried out at a specialist sleep centre. The study usually involves staying overnight at the sleep centre so sleeping patterns can be analysed.

## 3 Aims and Objectives

The policy aims to define NHS England's commissioning position for sodium oxybate for the treatment of children and adolescents (aged 7 until they are 19 years old) suffering from narcolepsy with cataplexy.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for children suffering from narcolepsy with cataplexy.

## 4 Epidemiology and Needs Assessment

Narcolepsy and cataplexy impact on all aspects of life. For this patient group problems related to tiredness (e.g. poor concentration and memory; interference with life and education; daytime sleepiness) and cataplexy attacks may particularly affect educational attainment (and associated future employment and economic outcomes), social/personal relationships and general well-being. Falls can occur during cataplexy attacks which may cause injury. Frequent or prolonged hallucinations occur and vivid nightmares can occur

and can be frightening as patients cannot separate reality from dreams. Additionally, there is a high risk of obesity and metabolic syndrome.

The estimated incidence rate is 1.37/100,000 per year for both narcolepsy with cataplexy and narcolepsy without cataplexy and 0.74/100,000 per year for narcolepsy with cataplexy (Silber et al., 2002).

The prevalence of paediatric narcolepsy is likely to be underestimated due to misdiagnosis (Stores G, 2006) and early studies reported a median delay between symptom onset and diagnosis of more than 10 years (Morrish et al., 2004). It is thought that half the adults with narcolepsy-cataplexy will have had symptoms during childhood but not diagnosed until later (Dauvilliers et al., 2001) although this pattern is improving with increased understanding of the condition. The overall prevalence of narcolepsy (paediatric and adult) in Western countries is estimated to be 20-50 per 100,000 population (Longstreth et al., 2007).

Clinical experience suggests c. 12 paediatric patients have severe and uncontrolled narcolepsy with cataplexy in England each year,. As such, it is estimated that c. 12 paediatric patients per year are likely to be the cohort for this policy.

# 5 Evidence base

NHS England has concluded that there are sufficient grounds to support a policy for the routine commissioning of sodium oxybate for children and adolescents, aged 7 until they are 19 years old, suffering from narcolepsy with cataplexy and who have not responded, or are intolerant to, first and second line medications.

**Evidence summary**

NB. This policy was revised in January 2021 to reflect changes to the license for sodium oxybate extending its use to children aged 7 years and above. The evidence review summarised below was carried out prior to this and therefore does not include evidence in pre-pubescent children.

**1a. Is sodium oxybate safe and clinically effective in the reduction in number and intensity of cataplexy attack, excessive day-time sleepiness (diurnal naps), nocturnal awakenings, terrifying dream experiences, insomnia, hypnagogic hallucinations, sleep paralysis, and improvement in quality of life in adult patients with narcolepsy and cataplexy compared to no intervention, combined treatment or with only standardised treatments?**

There is evidence from meta-analyses of RCTs and open-label extension studies for statistically significantly better results for sodium oxybate compared to placebo for cataplexy attacks, daytime sleepiness, sleep attacks, nocturnal awakenings and symptom improvement. There is evidence of a reduction in sleep paralysis and hypnagogic hallucinations in some RCTs, and approximately two-thirds of patients in one 12-week open-label study reported a reduction in sleep paralysis and hypnagogic hallucinations. The review did not identify any studies comparing sodium oxybate to combined treatment or standardised treatments. One open-label study attempted to define a clinically relevant reduction for cataplexy attacks and daytime sleepiness and this criteria was achieved by a high proportion of patients in that study. The other study authors did not address the clinical relevance of their results and did not present data in a way that supported an assessment of clinical relevance. It is therefore difficult to assess the clinical relevance of the results.

In a meta-analysis of safety outcomes in adults, rates of nausea, vomiting and dizziness were statistically significantly higher with sodium oxybate compared to placebo. In one open-label study, 56% adults reported an adverse event of which 2% were considered serious. Study withdrawals due to adverse events were reported and were all less than 10% of participants.

**1b. Is there evidence that sodium oxybate is clinically effective in patients with narcolepsy and cataplexy who have reached puberty (and weigh >40kgs) compared with no intervention, combined treatment or with only standardised treatments?**

The review did not identify any studies comparing sodium oxybate with no intervention, combined treatment or standardised treatments in children who have reached puberty.

There is limited evidence from three, small uncontrolled observational studies (n=23 combined) whose populations are of an age which suggests they have reached puberty, for statistically significant reductions from baseline for cataplexy attacks. In one study (n=13) the reduction in mean daily attacks was 3.7 (from a baseline of 3.9) and in another study (n=8) the reduction in median weekly attacks was 34 (from a baseline of 38.5). There was also some evidence for statistically significant improvements from baseline in daytime sleepiness and nocturnal sleep. There were reported improvements (statistical tests not performed) for some patients in hypnogogic hallucinations, sleep paralysis and quality of life related outcomes. Limited information on the safety of sodium oxybate in children who have reached puberty comes from two small studies (n=10 combined). In one study, two of the eight patients withdrew due to adverse effects (nightmares, suicidal ideation and dissociated feelings) and another two patients experienced terminal insomnia. Individual patients from both studies experienced a range of other effects.

Because this evidence is from a very small number of patients in uncontrolled observational studies it is not possible to draw any strong conclusions about the effectiveness of sodium oxybate in patients with narcolepsy and cataplexy who have reached puberty and the results should be treated with caution.

**2. Is sodium oxybate cost-effective in controlling the symptoms of narcolepsy and cataplexy in patients with narcolepsy?**

The review did not identify any studies assessing the cost-effectiveness of sodium oxybate for narcolepsy.

# 6 Criteria for Commissioning

**Inclusion criteria:**

Sodium oxybate will be prescribed for children and adolescents, aged 7 until they are 19 years old, where attempts to control symptoms of narcolepsy with cataplexy have failed despite a trial of first and second line medications from each symptom group for at least three months. Specifically:

i. Patients who present with narcolepsy with cataplexy according to International Classification of Sleep Disorders 3 (ICSD) criteria; AND

ii. Adequately treated co-morbid sleep disorders (such as obstructive sleep apnoea and restless legs syndrome) as assessed by polysomnogram; AND

iii. Show incomplete response to trial of more than one medication from each symptom group (Narcolepsy: methylphenidate, lisdexamphetamine, modafinil and atomexetine. Cataplexy: venlafaxine, clomipramine and other SSRIs. See section 8: patient pathway for more information); OR

iv. Have significant adverse effects as a result of second line medication in each symptom group; AND

v. Are assessed as able to benefit from sodium oxybate by a properly constituted MDT (see section 9: governance arrangements for more information).

**Exclusion criteria:**

i. Patients who do not fit the above criteria and for whom this treatment is contraindicated, including exclusion as advised by manufacturer.

**Stopping criteria:**

ii. Serious adverse effects including signs of respiratory depression; OR

iii. Show evidence of incomplete response at three months as assessed by clinical examination according to:
For cataplexy: the severity and frequency criteria below; AND
For narcolepsy: the Epworth or Paediatric sleepiness scale below.

At least one of the cataplexy scores (either severity or frequency) should improve after 3 months of treatment.

Severity of cataplexy

1 = moderate weakness
2 = can maintain posture with external support
3 = loses posture and falls to the ground

Frequency of cataplexy

0 = <1 episode per year
1 = ≥1 attack per year
2 = more than one attack per month
3 = >1 attack per week
4 = >1 per day

Improvements in narcolepsy should be monitored by using either the Epworth Sleepiness Scale or the Paediatric Sleepiness Scale.

# 7 Patient Pathway

As a disease diagnosed in childhood, narcolepsy and cataplexy requires special arrangements for the transition of care from paediatric to adult neurological services.

First line of treatment consists of behavioural and environmental adaptations including stimulants for daytime sleepiness. Failure to respond to these interventions will progress to second line therapies.

Referrals to specialist sleep services can be made only from secondary care.

Once diagnosis is confirmed by the specialist sleep service, the patient is prescribed one of the following first or second medications, conventionally divided into medications that improve narcolepsy and cataplexy. (Note that medications that are classed as ‘first’ and ‘second’ line in the list below are based on clinical consensus. This varies across countries and there is a lack of head-to-head studies to evidence such choices).

Narcolepsy:
First line: Methylphenidate preparations (immediate and prolonged release)
Second line: Dexamphetamine, lisdexamphetamine, modafinil and atomoxetine

Cataplexy:
First line: Venlafaxine
Second line: Clomipramine and other SSRIs

If the patient shows incomplete response within three months and/or has significant associated adverse effects after trial of first and second line medications treatment options in each treatment group, sodium oxybate is classed as third-line treatment.

Sodium oxybate should only be initiated following an MDT discussion, which should explicitly consider the psychological support arrangements that need to be put in place for the individual child, including psychological assessment where the child is deemed to be at higher risk of harm.

Dosage: Initially two doses of 2.25g per day and adjusted at one- to two-week intervals depending on response up to a maximum daily dose of 9g (in two equally divided doses) (EMA/602260/2020). In addition, prescribing consultant will regularly monitor the patient’s BMI.

Treatment duration: For some patients this will be a life-long treatment.

# 8 Governance Arrangements

Patients in secondary care should be referred to the designated tertiary service.

Treatment should be conducted by services with previous and ongoing experience in the diagnosis and management of young people with narcolepsy. Such services must have access to a sleep laboratory that can conduct standard polysomnography and multiple sleep latency tests to AASM standards.

MDT in such services will comprise a paediatrician and a psychologist, with the paediatrician having relevant training and experience in paediatric narcolepsy. Typically this includes paediatricians with neurodisability, neurology, and respiratory sleep training backgrounds. In some instances, the paediatrician will be supported by a consultant colleague from an adult (usually neurology) service. Treatment should be conducted in accordance with the SEND Code of Practice.

Such services must have access to specialised paediatric pharmacy. Psychology support can come from within the sleep services, or externally such as local child and adolescent mental health services (CAMHS). Children deemed to be at higher risk of harm need to be registered with CAMHS services. Health services should collaborate with education and social care services to ensure patients get appropriate support.

Sodium oxybate is a controlled drug and appropriate training and safeguards must be in place (e.g. lockable storage).

# 9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

Commissioning of sodium oxybate in patients after their 19th birthday is the responsibility of Clinical Commissioning Groups (CCGs). Guidance to facilitate decision making by CCGs in whether to commission sodium oxybate for patients after their 19th birthday has been published by the Regional Medicines Optimisation Committee (https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/).

# 10 Audit Requirements

Sodium oxybate should only be available in experienced centres that audit and publish their results using established narcolepsy outcome measures. This should include complication rates related to the use of sodium oxybate. Use of software systems (e.g. Blueteq) to track and audit use of sodium oxybate by clinicians to be mandated, in order to ensure it is administered according to the Criteria for Commissioning.

In addition, centres without an in-house database will be invited to participate in the European Narcolepsy Network (EU-NN) database to enhance the scientific understanding of this rare disease.

# 11 Documents which have informed this Policy

European Public Assessment Report, Xyrem (Sodium Oxybate) EMA/602260/2020

Scottish Medicine Consortium No. (246/06). August 10, 2007

Department for Education & Department of Health, Special educational needs and disability code of practice: 0 to 25 years, January 2015

## 12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

## References

Dauvilliers, Y, Montplaisis J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. Neurology. 2001; 57:2029-33

Longstreth WT, Koepsell TD, Ton TG, Henrickson AF, van Belle G. The epidemiology of narcolepsy. Sleep 2007 Jan; 30 (1): 13-26

Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004 Jan; 5 (1): 37-41

Silber MH, Krahn LE, Olsen EJ. Diagnosing narcolepsy: validity and reliability of new diagnostic criteria. Sleep Med 2002 Mar; 3 (2):109-13

Stores G. The protean manifestations of childhood narcolepsy and their misinterpretations. Dev Med Child Neurology 2006 Apr; 48 (4):307-10

# Appendix: Change form

**Change form for published Specifications and Products developed by Clinical Reference Group (CRGs)**

**Product name:** NHS England Clinical Commissioning Policy: Sodium Oxybate for symptom control of narcolepsy with cataplexy (children)

**Publication number:** formerly 16065/P

**Description of changes required**

| Describe what was stated in original document | Describe new text in the document | Section/Paragraph to which changes apply | Describe why document change required | Changes made by | Date change made |
|---|---|---|---|---|---|
| Age range revised throughout clinical commissioning policy from post-pubescent children to children over 7 years.<br><br>Clarification included that the evidence review was carried out prior to the current errata and therefore was limited to evidence in post-pubescent children. | | Pages 6, 8, 9, 11, 13 | To reflect license extension to cover children aged 7 years and above. | Policy Clinical Lead<br><br>National Programme of Care Manager, Women & Children | January 2021 |