Cambridgeshire & Peterborough Integrated Care System

NHS Cambridgeshire & Peterborough

Management Pathway

Treatment of epilepsy in adults

Executive Summary

This is a reference document to supplement information provided in the clinic letter from specialists in Hospital, Community and Learning Disability services to Primary Care. It outlines responsibilities for initiation, ongoing prescribing and monitoring of antiseizure medication (ASM) between Primary Care, Community and Hospital teams.

The choice of treatment for epileptic seizures is influenced by patient factors as well as epilepsy syndrome, both of which can be complex.

Initiation of ASM should only be on advice of a specialist, and can take place in Primary care unless there are specific restrictions on prescribing.

ASMs within the first year of licence in the UK will be initiated by the specialist to the initial target maintenance dose or for 3 months, whichever is longer. Other ASMs, if initiated by the specialist due to clinical urgency, will usually be for 4 weeks, with the GP taking on prescribing thereafter.

The specialist should provide information on indication for new antiseizure medication, with specific details on starting dose, titration schedule and initial maintenance dose, as well as important side effects and monitoring requirements.

The Appendix contains information on usual titration regimes, maintenance doses and withdrawal regimes.

Guidance is provided for suspected first unprovoked seizure and second seizure before specialist review as well as referral of those established on ASM (See section 20).

Key Messages

- NICE recommends a consistent supply of a particular manufacturer's ASM preparation, unless decided with the patient or carer, that this is not a concern. MHRA has classified all ASMs into three categories to help decide if it is necessary to avoid change in manufacturer's products (See Section 20).
- All women with the potential to fall pregnant should be prescribed Folic Acid 5mg, unless on highly effective contraception (IUD, contraceptive implant), and for at least 3 months preconception as a minimum. Folic acid should be continued for at least the first 12 weeks of pregnancy.

- There is specific advice for the care of women with epilepsy (irrespective of whether prescribed ASM) who wish to conceive, or pregnant women with epilepsy to improve maternal and pregnancy outcomes (see Section 17).
- Serum levels of ASMs is not routinely indicated for monitoring except for Phenytoin and Lamotrigine (preconception and during pregnancy). Routine blood tests are generally advised on an annual basis if required, except for specific monitoring requirements.

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1. Scope

Cambridgeshire and Peterborough Integrated Care System (ICS) across tertiary care, secondary care, mental health and community services and primary care.

2. Purpose

Aim of the pathway is to ensure:

- Patients with seizures are assessed appropriately and in a timely manner.
- Drug treatment for seizures is performed in a systematic manner based on current national guidance.
- Access to newer antiseizure medications for patients whose seizures persist despite accepted first line therapies.
- A robust and acceptable line of responsibility for initiation, ongoing prescription and monitoring between primary care, community and hospital teams.

3. Definitions

CUHFT	Cambridge University Hospitals Foundation Trust
NWAFT	North West Anglia Foundation Trust
CPFT	Cambridgeshire and Peterborough NHS Foundation Trust
ASM	Antiseizure medication
OD	Once daily
BD	Twice daily

TDS	Three times daily
PRN	As required (needed)
SCG	Shared care guidance

4. Introduction

Patients with epilepsy have been cared for jointly between consultants and GPs for many years with GPs taking prescribing responsibility. The introduction in recent years of a number of new drugs with which GPs may be unfamiliar has led to concern about clinical responsibility. These drugs include Zonisamide, Eslicarbazepine, Lacosamide, Perampanel Rufinamide, Brivaracetam, Cenobamate and cannabinoids. Their use is no different in principle from older drugs already prescribed by GPs.

It is also important to note that newer drugs are generally only initiated after failure or intolerance to more established drug treatments or in particular patient populations (such as women at risk of potential teratogenic effects). The current NICE guidance (NICE NG217 Epilepsies in children, young people and adults 27 April 2022) provides a framework for appropriate use of first, second and subsequent trials of antiseizure medication. The newer drugs are most commonly used after failure of 2 to 3 antiseizure medications.

There is a common misconception about the cost of continued trials of newer ASM. However, most of the newer drugs are comparable in price, and are commonly used in substitution with each other. It is also worthwhile to recognise the burden of epilepsy on the patient both from medical and psychosocial impact, and that the direct medical costs of patients who achieve seizure freedom are significantly less than those with ongoing seizures (Jacoby et al 1998). The difference in non-medical costs (loss of earning potential, social care, welfare) between seizure free and non-seizure free patients is even greater.

Bearing this in mind, the drug and therapeutics committee of each hospital and integrated clinical system should have in place procedures where access to new ASMs for drug refractory patients are not unduly delayed due to bureaucratic processes, if used within this accepted management pathway.

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6. Management and referral guidelines for Primary Care

First unprovoked seizure (i.e. not caused by alcohol, anoxia due to syncope, etc.)

a) Do not initiate antiseizure medication.
b) Refer all patients **urgently** for assessment and investigation. An eye witness of the attack should be asked to accompany the patient to the appointment or be available for remote consultations.
c) With the patient's permission, family members or carers should be requested to take videos of further events on a mobile device for clinical review.
d) Perform an ECG, particularly checking QT interval, and refer to cardiologist if the ECG is abnormal.
e) Give advice about driving regulations referring to current DVLA regulations.
f) Information and Support is available at NICE NG217 Epilepsies in children, young people and adults.

Second seizure before outpatient appointment

a) Normal practice would be to discuss therapeutic options by Advice and Guidance (preferred route to get the fastest response) or letter with consultants or Epilepsy Nurse Consultant (see below).

b) Immediate drug initiation, after specialist advice, may be appropriate and would involve first line treatment as per NICE guidance (NICE NG217 Epilepsies in children, young people and adults 27 April 2022), taking account of patient preference, characteristics and lifestyle (valproate NOT for women of childbearing age).

c) Advise about current DVLA guidance on Epilepsy Regulations.

d) Advise about teratogenic risk of drugs in women (doubling of risk of major congenital abnormalities (from 1 -2 in 100 background risk to 2-3 in 100 on exposure to single ASM, except for valproate where the risk is much higher). The risk of minor abnormalities, including learning difficulties are unknown, except for valproate which has an increased risk of particularly verbal learning deficits. MHRA has provided a patient information leaflet on Epilepsy Medicines in Pregnancy to be given to women started on ASM.

e) Consider impact of ASM on contraceptive choices in women;

i) Note the interaction of carbamazepine, phenytoin, phenobarbital, primidone and topiramate with oral contraceptive pill (double dose of oestrogen combined pill equivalent to a minimum of ethinylestradiol 50mcg required).

ii) Lamotrigine also interacts with the oral contraceptive pill to a limited degree, and we recommend warning the patient that the contraceptive efficacy *might* be affected.

iii) Depo contraceptives such as Depo Provera injections and intrauterine coils are acceptable however contraceptive implants should be avoided. Depo injections should be given every 12 weeks even to patients taking antiseizure medications.

f) Warn about risk of allergic reactions, which can be serious (Stevens Johnson syndrome) with phenytoin, carbamazepine, phenobarbital and lamotrigine (can be delayed up to 6-8 weeks after initiation or dose increase).

g) Warn about an increased risk of suicidal ideation (1-2%) with ASM and more commonly behavioural and mood change.

h) Inform patients that medication should be taken continuously, and changes or withdrawal made only after recommendation at the time of medical review (by GP or Epilepsy specialist). Criteria for referral of patients established on treatment. Any of the following:

   i. When patient or general practitioner is **not** comfortable to continue with the existing regime due to continuing seizures or drug side effects.
   ii. Ongoing seizures despite trials of >2 ASMs at optimum doses and not had a specialist epilepsy review in last 5 years. Refer urgently for assessment if the patient has a seizure recurrence after a period of remission.
   iii. Patients new to the county with Epilepsy diagnosis.
   iv. Women with epilepsy (irrespective of whether they are currently prescribed antiseizure medication) planning to start a family or who fall pregnant.
   v. All patients on sodium valproate not under specialist epilepsy care (community, secondary or tertiary) at reproductive risks (55 years and under) and not exempted from the Valproate Pregnancy Prevention Programme (ie previous completion of Valproate Acknowledge of Risk form, ARAF) as per regional MHRA valproate referral pathway.
   vi. Advice in respect of concordance.
   vii. Special situations, e.g. pregnancy, preconception counselling
   viii. Occupational advice
   ix. Driving
   x. Discontinuing medication.

7. Drug treatment – general principles of initiation of treatment

a) Consultant Neurologists/Nurse, GPSiE, Epilepsy Specialist Nurses (with independent prescribing qualifications or, if without NMP, after discussion with supervising clinician) and Consultant Psychiatrists in Learning Disability will recommend initiation of treatment with ASM treatment to the GP after consultation with the patient, or patient's family or carers (if appropriate) or initiate treatment especially if delay in starting treatment is considered to be a clinical risk for the patient.

b) Generally, if initiated by a specialist, the first four weeks of treatment will be provided, with the GP taking on responsibility for the monitoring and prescribing thereafter.

c) If there is a novel ASM, in the first year of being licensed in the UK, unless there are specific NHSE or NICE guidance or funding arrangements to the contrary, the hospital will initiate treatment and provide the first three months' supply or until dose escalation is completed, whichever is longer.

d) Thereafter, treatment of the novel ASM should be continued from primary care, unless there are specific NHSE or NICE guidance or funding arrangements to the contrary.

8. Drug Treatment – Indications, general principles and recommended treatment regimens:

Indications, cautions, contraindications, side effects, doses and formulations are listed in the British National Formulary. These guidelines may differ slightly from the regimes stated in the British National Formulary, but represent acceptable clinical practice in the UK. They are endorsed by the consultant neurologists at North West Anglia Foundation Trust, Cambridge University Hospitals NHS Foundation Trust and Cambridgeshire and Peterborough NHS Foundation Trust -all listed in the appendix to this protocol.

9. Drug treatment – treatment regimens

a) Patients seen in the epilepsy or general neurology clinic are provided with a personalised care plan and titration schedule outlined in the letter to the GP. Epilepsy nurse specialists (if not independent prescribers themselves) could assist in titration of ASM within limits recommended by the Consultant Neurologist/Nurse, GPSiE or Consultant Psychiatrist in Learning Disability.
b) Changes in treatment advised by the Epilepsy Nurse Specialists will be notified in writing to the GP and letters countersigned by the Consultant Neurologist or Epilepsy Nurse Consultant in charge of the case or explicit reference will be made to discussion and agreement of the treatment plan by the Consultant Neurologist, GPSiE, Epilepsy Nurse Consultant or Consultant Psychiatrist in Learning Disability in charge of the case.
c) Treatment plans will include:
    - Indication for new drug regime.
    - Current seizure frequency.
    - Potential side effects and need for specific monitoring.
    - Contact details in case of difficulties.
    - Time for review by Epilepsy Team (reviews can be done remotely if a face-to-face appointment is not suitable for the patient).
    - Statement to the effect that the GP should contact the clinician recommending initiation of treatment for further advice if they have any concerns.
d) At an interval no later than six months after completion of dose escalation, the patient should be evaluated by the specialist team who recommended or initiated treatment and the decision made to continue or withdraw therapy. This should be made explicit in the patient record and communicated to the GP.
e) At review, the hospital will provide the GP with a further summary to include:
    - Ongoing drug regime, indication for continuation or change in regime.
    - Impact of drug regime on seizure frequency and/or quality of life.
    - Time for next review.
f) The specialist will endeavour to ensure that continuation of drug regimens will be supported by evidence of positive impact on seizure frequency and/or quality of life for the patient.

g) Where a decision is made to continue a therapy, if the patient is on polytherapy, then a decision should be made as to whether any other therapy can be withdrawn. Since new ASMs are generally only licensed for polytherapy, it is likely that this will only be possible for patients taking three or more ASMs.

10. Monitoring of treatment

a) Most drugs are titrated to tolerance and clinical effectiveness. Where intoxication is suspected, the Epilepsy Nurse Specialist, Consultant Neurologist or Consultant Psychiatrist in Learning Disability involved should normally be consulted for advice. Routine blood tests for monitoring of liver function or white cell count are not indicated for any ASM, but NICE guidance states that prescribers may wish to undertake baseline blood tests including blood count, liver enzymes, electrolytes, vitamin D and calcium and repeat every 2 to 5 years.
b) Blood tests for monitoring of patients on ASMs are very rarely required, and the practice of adjusting drug dose according to the results of ASM levels is strongly discouraged unless there is a question of adherence (except in the case of particular ASMs in pregnancy).
c) Where specific monitoring is required, for example ophthalmological monitoring in patients taking vigabatrin, it will be the responsibility of the secondary care physician to ensure this is undertaken. Where there is more minor monitoring required, for example with blood tests or ECG, the primary care physician may agree to take responsibility but, an explicit request by the epilepsy specialist should be made in each case.

11. Drug treatment - choice of antiseizure medication

The choice of antiseizure medication will depend on:

a) The type of epilepsy; in adults the distinction is usually between focal and generalised epilepsies, although occasional patients may have specific conditions such as Lennox Gastaut syndrome, Dravet Syndrome or Tuberous Sclerosis for which specific drugs are indicated.
b) Other antiseizure medication being taken; for example, combining sodium channel blocking drugs tends to increase the risk of side-effects such as ataxia.
c) Adverse effect profile: for example, some drugs may cause weight increase or weight loss, which may be particularly problematic given the profile of the patient.
d) Some drugs have a greater risk of particular neuropsychiatric side-effects which may need to be considered in individual patients.
e) Non-adherence to the licensed indications of new antiseizure medication may be justified, for instance where the licenced indications do not reflect current knowledge, the indications do not include well proven uses of the drug, or the licensed indications are overly restrictive. The Consultant Neurologist, GP with specialist interest in Epilepsy (GPSiE), or the Epilepsy Nurse Consultant, who is an independent non-medical prescriber, may recommend the use of drugs beyond the licensed indications and will detail this in the correspondence to the General Practitioner who is being asked to take over on going prescription of the drug. Wherever the specialist clinician considers such a use to be indicated, they will explain the drug's unlicensed status to the patient involved.

f) In general, the aim is to treat patients with the fewest number of antiseizure medication as possible to achieve seizure freedom, or if this is not possible, a reasonable compromise between seizure frequency and tolerability as determined by patient choice. Combinations of more than 3 ASMs rarely provide additional efficacy.

12. Assessment of the efficacy of an antiseizure medication

a) Patients starting an ASM, particularly a novel drug, in a non-emergency situation, should ideally complete a seizure diary for at least four weeks prior to initiating treatment and continue the diary during the assessment period.
b) The time taken to judge the efficacy of a new ASM depends in part on seizure frequency; those with a low seizure frequency will need longer to assess the impact of a new medication. We recommend that the efficacy of an ASM is assessed no later than 6 months after reaching optimal dosage.
c) There is no single measure which can be used in all cases to measure the efficacy of ASMs. Several factors have to be taken into account:
    i. Seizure frequency.
    ii. Seizure severity; for example reduction in clustering of seizures especially that requires admission to hospital; reduction in tonic clonic or other more dangerous seizure types; reduction in incontinence, post ictal confusion or other socially disabling aspects of seizures.
d) Maintenance of seizure control with clinically useful reduction in adverse effects from medication, such as sedation, cognitive, psychiatric or behavioural symptoms.

13. Effects of liver induction/inhibition

a) Doctors should be aware that ASM, especially phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine and topiramate, induce liver enzymes and that this process is harmless but has a bearing on the outcome when prescribed together with other drugs with similar liver enzyme inducing or inhibitory effects. Some drugs such as lacosamide or perampanel do not affect liver enzymes themselves, but affected by liver enzyme inducers or inhibitors and so dose adjustment may be required when adding or removing such medication.
b) Such induction of liver function means some ASMs interact with oral contraceptives. Lamotrigine also has modest effects on hormone levels. It is unclear if this affects contraceptive efficacy, but if so, the effect is likely to be small. **Note: lamotrigine efficacy does get minimised by the oestrogen component of the combined oral contraceptive pill thus caution should be exercised requiring increase to the ASM.**

14. Hyponatraemia with some Antiseizure medications (particularly carbamazepine and oxcarbazepine)

a) Some ASMs cause hyponatraemia by Syndrome of Inappropriate anti-diuretic hormone secretion (SIADH). In the majority of these cases, the hyponatraemia is not clinically significant,

and in the order of 125 mmol/L -135 mmol/L. Serum sodium levels below 125mmol/L may need adjustment in the dose of ASM. The Specialist team should be contacted for advice if there is concern.

b) If serum sodium levels need to be monitored (especially with oxcarbazepine), the hospital will advise the GP by letter when the drug is initiated or doses adjusted at hospital review.

15. Co-administration of antiseizure medication with sodium channel blocking properties

a) It is well recognised that coadministration of two sodium channel blocking ASMs (such as carbamazepine and lamotrigine) or the combination of certain ASMs with a sodium channel blocking antiseizure medication (e.g. levetiracetam and carbamazepine/ phenytoin/ lamotrigine/ oxcarbazepine) can increase problems with tolerability.

b) This is particularly observed when a new ASM is added to existing treatment with sodium channel blocking ASM. This may require reduction in dose of the existing ASM (or even its withdrawal) to allow titration of the new ASM to a therapeutic dose. Where this may be a possibility the Hospital team will warn the GP of potential interaction and provide advice on the dosage adjustments that are required.

16. MHRA Advice on switching between different manufacturers' products for a particular ASM

a) Different ASMs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers' products of a particular drug may cause adverse effects or loss of seizure control. No switching between manufacturers should occur without the patient being informed and consented.

b) ASMs have been divided into three categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. Antiepileptic drugs: New advice on switching between different manufacturers' products for a particular drug (November 2017)

c) If it is felt desirable for a patient to be maintained on a specific manufacturer's product, this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the marketing authorisation holder).

d) This advice relates only to ASM use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain and primary headache disorders).

17. Use of valproate in women and men with epilepsy

The MHRA has issued further guidance on the use of sodium valproate in women and men unless other treatments are ineffective or not tolerated: Valproate: reminder of current Pregnancy Prevention Programme requirements; information on new safety measures to be introduced in the coming months (12 Dec 2022). Further updates to the guidance are anticipated, so prescribers and epilepsy specialists will need to ensure practice is in line with current guidance at the time of prescribing.

The MHRA information leaflets for patients, GPs, pharmacists and epilepsy specialists should be used to guide discussion with patients and amongst professionals.

For women:

There is a dose dependent effect with a:

- 10% risk of congenital malformations.
- 30 to 40% risk of serious developmental disorders (delays in early development with talking, low intellectual abilities, poor language skills and memory problems) in preschool children exposed to valproate in utero.
- Possibility of risk throughout pregnancy cannot be excluded.
- Risk with high dose valproate monotherapy could be reduced with combination ASM therapy, if this allows reduction in dose of valproate.

Hence all women able to have children must comply with the pregnancy prevention programme (PREVENT). These regulatory measures also include a ban on the use of valproate to treat epilepsy during pregnancy unless there is no other effective medication available.

The benefits of valproate must be balanced against the risks, when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

If a woman is already on valproate, the decision to withdraw treatment must be made in consultation with a specialist in epilepsy.

All female patients on valproate must be informed of and understand:

- Risks associated with valproate during pregnancy.
- The need to use effective contraception throughout treatment with valproate if pregnancy is possible (Pregnancy Prevention Plan (PPP)).
- Advice on contraceptive options and implementation of PPP is the responsibility of the GP.
- Need for annual review of treatment by a specialist (Neurologist, Epilepsy Specialist Nurse, GPSiE, Consultant Psychiatrist in Learning Disability) to inform the prescriber of the appropriateness of ongoing treatment with valproate.
- The need to rapidly consult if she is planning a pregnancy or becomes pregnant.
- Be provided with the MHRA Patient Guide on valproate.
- Use the MHRA checklist on valproate to guide discussion and document the discussion has taken place on an annual basis unless the requirements the valproate pregnancy prevention programme are not necessary because there are compelling reasons to indicate that there is no risk of pregnancy.

There is a further Guidance Document on Valproate Use in Women and Girls of Childbearing Years on behalf of the Royal College of General Practitioners and Association of British Neurologists latest version 2019 with practical advice on implementation of the regulatory measures.

Women on Valproate who need to comply with the PPP and annual review of ARAF form, once under the care of specialist services (community, secondary or tertiary services), will continue to be offered review on an annual basis at a minimum as long as the current MHRA guidance on Valproate remains in place.

For men:

Current product information already indicated that valproate may impair male fertility, and there is some evidence that this is reversible upon discontinuation. In addition, the MHRA have considered data from studies in juvenile rats and adult rats and dogs reporting adverse effects to the male reproductive system in animals receiving valproate, as well as non-clinical studies on the potential for epigenetic effects of valproate and transgenerational risks. There are currently limited data available on these risks in humans and further studies are planned. There is also an ongoing retrospective study on the outcomes of babies exposed to valproate via paternal use.

Once further guidance has been provided by the MHRA on the use valproate in women and men 55yrs old and under, local referral and monitoring pathways will be implemented to support the safe prescribing of valproate in this population.

18. Antiseizure medication with specific NHS England commissioning arrangements and/or NICE appraisal

Cannabidiol with Clobazam for treating seizures associated with Dravet Syndrome (NICE TA614) and Lennox-Gastaut syndrome (NICE TA615)

Prescribing Classification: Hospital Only

There is no evidence from the published clinical trials that cannabidiol, when used in adults, poses an additional risk or need for monitoring compared to other licenced ASMs.

However current NHS England commissioning arrangements require prescribing to be restricted to designated specialist centres only (via Blueteq), with Addenbrookes Hospital and Norfolk and Norwich University Hospital being recognised centres within East of England.

In the longer term, it is anticipated initiation, ongoing prescribing and monitoring will follow the same principles as previous novel ASMs (as in 8 – 11 above), whilst complying with NICE TA614 and TA615.This will also allow for the prescribing of cannabidiol at other hospitals in the region by epilepsy specialists who are currently only able to do so at Addenbrookes Hospital.

Initial prescription and further dose adjustments as well as supply will be by a Consultant neurologist or Epilepsy Nurse Consultant at Addenbrookes Hospital. When prescribing cannabis-based medicinal products, the patient should be advised to stop any non-prescribed cannabis, including over-the-counter, online and illicit products.

Monitoring of treatment will take place at 6 monthly intervals by the GP or at Addenbrookes Hospital if timing coincides with a face-to-face appointment in the Epilepsy clinic. Blood tests including LFT / FBC will need to be done at baseline, 1 month, 3 month, and 6 months and then intermittently thereafter (6 or 12 monthly, as advised by the Epilepsy specialist) unless taking valproate or have a raised ALT or AST at baseline.

Adverse treatment effects: Cannabidiol's adverse effects are mostly, but not always, mild and tolerated. The most common adverse events are somnolence or sedation, decreased appetite, diarrhoea, fever, fatigue and vomiting.

Treatment will be withdrawn if:

- the frequency of drop/convulsive seizures has not fallen by at least 30% compared with the 6 months before starting treatment.
- Adverse events are not tolerated or manageable.

Everolimus for epilepsy in patients with Tuberous Sclerosis Complex (TSC)

Prescribing Classification: Hospital Only

Everolimus is licenced for adjunctive treatment of focal epilepsy in patients with TSC who have failed to respond to 2 antiseizure medications, in addition to its indication for enlarging renal and hepatic angiomyolipomas and cerebral subependymal giant astrocytomas. Patients being considered for Everolimus will have been assessed and considered not suitable for epilepsy surgery by the Epilepsy Surgery MDT at Addenbrookes Hospital, or where VNS is not considered suitable or has failed as next treatment choice.

Current NHS commissioning arrangements require prescribing to be restricted to designated specialist centres (via Blueteq), currently Addenbrookes Hospital and Norfolk and Norwich University Hospital within East of England. Different preparations are licenced for different indications to ensure correct dosing regimens. Everolimus dispersible tablets (Votubia) are licenced for adjunctive treatment of refractory focal epilepsy in association with Tuberous Sclerosis Complex (TSC). **Votubia dispersible tablets are not interchangeable with Votubia tablets.**

Initial prescription and further dose adjustments as well as supply will be by a Consultant Neurologist at Addenbrookes Hospital. Treatment doses are calculated by Body Surface Area and titrated to achieve therapeutic Everolimus serum levels.

Since Everolimus is considered an immune suppressive therapy, baseline blood tests required before starting treatment include FBC, clotting, CRP, fasting glucose, renal and liver function, fasting lipids as well as confirming viral serology/immunity status for HIV/hepatitis B&C/CMV/EBV/VZV/Measles, Mumps and Rubella. Full Covid19 vaccination schedule is strongly recommended. Live vaccines should be avoided or completed before initiation of Everolimus. Baseline pulmonary function tests may be considered by the prescribing specialist.

Monitoring of treatment: Everolimus whole blood trough concentrations should be assessed at least 1 week after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. Once a stable dose is attained, trough concentrations should be monitored every 3 to 6 months in patients with changing Body Surface Area (BSA), or every 6 to 12 months in patients with stable BSA, for the duration of treatment. Repeat FBC, glucose, U&Es, LFTs, lipid profile will be repeated alongside Everolimus whole blood trough concentrations. If there are any significant abnormalities on the blood tests, GPs are advised to contact the specialist prescribing team within 24 hours.

Adverse treatment effects: The most common adverse events are: Stomatitis, mouth ulcers, GI side effects, tingling peripheries, rash, headache, myalgia, fevers, seizures, myelosuppression (i.e. leukopenia and thrombocytopenia), hyperuricemia, hyperlipidaemia, hyperglycaemia, and non-infectious pneumonitis (rare).
Most common blood disorders: leukopenia, anaemia, neutropenia, thrombocytopenia.
Most common electrolyte disturbances: hypophosphatemia, hypokalaemia, hypocalcaemia.
Patients commonly benefit from concomitant Vitamin B and Zinc supplementation together with Chlorhexidine mouthwash and local anaesthetic gel to reduce the incidence of and ameliorate mouth ulcers.

Treatment will be withdrawn if:

- if no longer clinically beneficial with 50% reduction at 28 weeks or additional outcome criteria on a per-patient basis where it is felt appropriate such as reduction in hospital admission frequency, use of rescue medications, or reduction in the number of falls.
- Adverse events are not tolerated or manageable.

Cenobamate for treating focal onset seizures in epilepsy (NICE TA753)

Prescribing Classification: Specialist initiation NO SCG

Cenobamate has been recommended for treating focal onset seizures with or without secondary generalisation in adults with drug-resistant epilepsy that has not been adequately controlled by at least 2 antiseizure medicines. Ongoing prescribing can be transferred to Primary Care.

It is recommended only if:

- It is used as an add-on treatment, after at least 1 other add-on treatment has not controlled seizures, and

- Treatment is started within a tertiary epilepsy service.

Tertiary epilepsy clinics in C&P ICS are currently delivered at Addenbrookes Hospital (Dr T Mitchell, Dr T Ham, Dr T Cope, Dr R Thornton, Sr E Chisanga) and Peterborough City Hospital (Dr T Mitchell). Across the East of England region, Tertiary epilepsy clinics are also provided at West Suffolk Hospital (Dr A Kelso) and Norfolk and Norwich Hospital (Dr J Cochius, Dr E Staufenberg). The tertiary service may also provide assessment of patients' eligibility for cenobamate through a Complex Cases MDT with partner secondary care and specialist community epilepsy services in the region, for those who do not need further tertiary specialist evaluation such as epilepsy surgery. It would be anticipated that the initial prescription will be provided by a Consultant Neurologist or experienced Specialist Epilepsy nurse non-medical prescriber sharing care with a Consultant Neurologist.

The initial prescription will be provided by the hospital specialist until the initial target dose has been achieved. The hospital will provide the first three months' supply or until dose escalation to the initial target dose is completed, whichever is longer.

Once the initial target dose has been achieved, and there have been no adverse events or tolerability issues, ongoing prescribing will be continued in Primary Care. This follows the general principles of medication initiation for all antiseizure medications already set out in this document (see Section 8).

The most common reported adverse events are somnolence, dizziness and fatigue.

Cenobamate is not recommended for use in pregnancy and women of childbearing potential not using contraception. All women with the potential to fall pregnant should be counselled about the potential increased risk of birth defects and neurodevelopmental effects if cenobamate is used in pregnancy, and appropriate use of effective contraception during use of cenobamate and until 4 weeks after treatment discontinuation. Women using oral contraceptives should practice additional or alternative non-hormonal measures of birth control.

However, if a woman on cenobamate falls pregnant, she should not stop cenobamate abruptly. The GP should inform the Epilepsy team urgently, to seek expedited review.

There are no treatment specific monitoring requirements.

Fenfluramine for treating seizures associated with Dravet Syndrome (NICE TA808)

Prescribing Classification: Hospital only

Fenfluramine is recommended as an add-on to other antiseizure medicines for treating seizures associated with Dravet syndrome in people aged 2 years and older, only if:

- Seizures have not been controlled after trying 2 or more antiseizure medicines.

- the frequency of convulsive seizures is checked every 6 months, and fenfluramine is stopped if it has not fallen by at least 30% compared with the 6 months before starting treatment.
- the company provides fenfluramine according to the commercial arrangement.

Monitoring requirements: an echocardiogram should be performed before starting treatment, then every 6 months for the first 2 years, and annual thereafter, if pathological valvular changes or pulmonary arterial hypertension develop, a follow- up echocardiogram should be performed at an earlier timeframe- consult product literature. Echocardiograms will be organized and monitored by the hospital specialist.

Body-weight also needs monitor during treatment.

19. Patients with drug resistance/ drug refractory epilepsy

a) 60 -70% of patients with epilepsy will become seizure free on the first or second tolerated ASM. Patients who are seizure free on medication are unlikely to need a change in medication, unless published research suggests one is particularly successful above older ASMs, or new information is available about their existing medication leading to a higher risk of adverse events.

b) Those who do not become seizure free after trials of the first two tolerated ASMs are considered to be 'drug refractory', and in these patients continuing trials of ASM need to be considered, if the patient wishes, due to the medical and psychosocial impact of ongoing epileptic seizures (termed 'active' epilepsy) which includes increased mortality as well as morbidity. There is evidence for increased medical costs and non-medical costs in those with continuing seizures compared to those who achieve seizure freedom, also providing a health economic reason to continue trials of ASMs to achieve seizure freedom (Jacoby et al 1998).

c) Patients with drug refractory active epilepsy should be referred for specialist epilepsy assessment (NICE NG127), usually in a tertiary epilepsy service, to be considered for reassessment of diagnosis, treatment plans and potentially other therapies (including epilepsy surgery or vagal nerve stimulator).

20. Education, information, advice and support

The epilepsy nurse specialists or epilepsy nurse consultant may be contacted for advice to GPs and for information, advice and support for patients. For medical advice and drug changes the consultant neurologists should be contacted (Advice and Guidance is preferred route) who may refer enquirers to the Epilepsy Nurse Specialists if appropriate.

Addenbrooke's Hospital

Consultant neurologists:
Dr T Mitchell, Dr T Cope and Dr R Thornton

Telephone: 01223 216759

Dr T Ham
Telephone: 01223 256349

Or On call neurology specialist registrar at Addenbrooke's Hospital

CUH Epilepsy Nurses:
Nurse Consultant, Erica Chisanga, or Specialist Nurse, Lucy Ginn
Telephone: 01223 217992

North West Anglia NHS Foundation Trust

Peterborough City Hospital

Consultant Neurologists:
Dr T Mitchell, Dr J Thorpe, Dr D Baumer, Dr S Stacpoole, Dr T Stoker
Telephone: 01733 673549
Email: nwangliaft.neurosecretaries@nhs.net

Hinchingbrooke Hospital

Consultant Neurologist:
Dr T Graves
Telephone: 01480 847533
Email: nwangliaft.mfopneurohh@nhs.net

Cambridgeshire and Peterborough NHS Foundation Trust

Consultant Neurologist:
Dr T Cope

Consultant Psychiatrists in Learning Disability:
Hollies- The Cavell Centre, Peterborough
Dr S Ghosh, Dr N Khalil
Telephone: 01733 776058/776059
Email: Cpm-tr.admin.holliesld@nhs.net

Community Epilepsy Specialist Nurses:
Karen Wilkins, Aubrey Chawira, Joanne Hamm, Andy Hall,
Simi Cherian, Melissa Taylor-Reid
Telephone: 0330 7260077
Email: Cpm-tr.Epilepsy@nhs.net

21. References

- NICE NG217 Epilepsies in children, young people and adults, 27 April 2022

- Jacoby et al 1998, Epilepsia:39(7):776-86. Uptake and costs of care for epilepsy: findings from a U.K. regional study
- Antiepileptic drugs: New advice on switching between different manufacturers' products for a particular drug (November 2017).
- Valproate use by women and girls Guidance (GOV.UK) (Updated 11 February 2021).
- Guidance Document on Valproate Use in Women and Girls of Childbearing Years (December 2020)
- MHRA: Epilepsy medicines and pregnancy safety leaflet (January 2021)
- NICE Technology Appraisal Guidance: Cannabidiol with clobazam for treating seizures associated with Dravet syndrome
- NICE Technology Appraisal Guidance: Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome
- NHS England Clinical Commissioning Policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above)
- NICE Technology Appraisal Guidance: Cenobamate for treating focal onset seizures in epilepsy

22. Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust and North West Anglia NHS Foundation Trust service equality and diversity statement.

23. Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

24. Document ratification details

Ratification Process	**Details**
Authored by:	Cambridge University Hospitals NHS Foundation Trust North West Anglia NHS Foundation Trust Cambridgeshire and Peterborough Integrated Care Board
Ratified by:	Cambridgeshire and Peterborough Joint Prescribing Group
Date ratified:	August 2023
Review date:	August 2026
Version number:	3

Appendix 1: Antiseizure Medication Regimes

These documents outline information about drugs where local recommendations may vary from those in British National Formulary and may need to be individualised to patient circumstances, including significant adverse effects, withdrawal recommendations, precautions and any requirement for blood testing. The BNF remains the authoritative resource. Further information on antiseizure medication can be found on the Cambridgeshire and Peterborough system-wide formulary.

1. **Acetazolamide immediate release tablets (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin at a dose of 250mg daily, increasing in 250mg steps every one to four weeks until seizures are controlled, intoxication becomes unacceptable or a dose of 1g is reached in three divided doses. Withdraw at a rate of 250mg every week or so. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

2. **Brivaracetam (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Start prescribing at 50mg BD in most patients. This can be reduced to 25mg BD in the elderly or in those with hepatic impairment or otherwise vulnerable to sedative side effects. The maximum dose is 150mg BD, 75mg BD in those with hepatic impairment. Main adverse effects are sedation or dizziness. Withdrawal by 25mg per week. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

3. **Cannabidiol (Prescribing Classification: Hospital only): (as per NICE TA614, TA615 and TA873)** in Dravet syndrome and Lennox Gastaut syndrome with clobazam (no minimum dose) or Tuberous Sclerosis if seizures not controlled well enough after trying two or more antiseizure medications. It is administered orally as 100 mg/ml cannabidiol solution. The recommended starting dosage is 2.5 mg/kg taken twice daily for 1 week. After 1 week, this should be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dosage can be further increased in weekly increments of 2.5 mg/kg taken twice daily up to a maximum recommended dosage of 10 mg/kg twice daily (20 mg/kg/day). Any dosage increases above 10 mg/kg/day should take into account individual benefit and risk. Dose reductions may be needed in moderate or severe hepatic impairment and/or excessive sedation.

4. **Carbamazepine including modified release preparations (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin at 200mg once or twice daily, increasing in 200mg steps every two weeks until a dose of 200mg BD is reached. Thereafter increase only if further seizures occur at a rate of 200mg every two to four weeks until seizures are controlled, or symptoms of intoxication become unacceptable. In case of rash (unless severe) withdraw at a

rate of 200mg per week. Severe rash may require admission and immediate withdrawal of carbamazepine. In non-urgent withdrawal, withdraw at a rate of 200mg every two to four weeks. Ensure the patient is maintained on a specific manufacturer's product. Tegretol is the preferred brand.

Specific considerations: Section 13 Enzyme induction; Section 14 Hyponatraemia; Section 15 Co-administration of sodium channel blocking ASMs and Section 16 Maintaining manufacturer's products.

5. **Cenobamate (Prescribing Classification: Specialist initiation NO SCG): (as per NICE TA753)** for add on therapy after failure of at least 2 antiseizure medications. Currently, treatment has to be started in tertiary services, but can be continued in Primary care. The recommended starting dose of cenobamate is 12.5 mg per day, titrated gradually to the recommended target dose of a single dose of 200 mg per day (Two weekly increases to 25mg, 50mg, 100mg, 150mg and 200mg). Based on clinical response, dose may be increased to a maximum of 400 mg per day (50mg/day every 2 weeks). In clinical practice, the titration schedule may be slower than recommended, but should not be exceeded due to risk of severe adverse reactions (DRESS). Dose adjustments may be needed in patients with renal or hepatic impairment.
Specific considerations: Section 15 Co-administration of sodium channel blocking ASMs.

6. **Clobazam (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Can be used as adjunct on a daily basis, or short courses (PRN) for clusters of seizures including catamenial seizures. Start at 10mg OD, can increase one week later to 10mg BD. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

7. **Clonazepam (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin at a dose of 0.5-1mg nocte, increasing in 0.5-1mg steps every two to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 2mg TDS is reached. Some patients may require even smaller increments because of sedative effects. Withdraw at a rate of 2mg per month. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

8. **Diazepam (rectal) (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Used as a rescue medication with an individualised care plan. BNF guidelines recommend 0.5mg /kg body weight, maximum 30mg daily**.**

9. **Eslicarbazepine (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin at 400mg nocte, increasing by 400mg every 2-4 weeks to 800mg nocte if continuing seizures. Can be increased in 400mg steps to 1600mg until seizures are controlled or symptoms of intoxication become unacceptable. Base the need for continued supply of a

particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

Specific considerations: Section 13 Enzyme induction; Section 14 Hyponatraemia; Section 14 Co-administration of sodium channel blocking ASMs

10. **Ethosuximide (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin at a dose of 250mg BD (only for absence seizures in idiopathic generalised epilepsy). Maximum dose 1g BD. Withdraw at a rate of 500mg every two to four weeks. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

11. **Everolimus (Prescribing Classification: Hospital only):** dosing is individualised based on Body Surface Area (BSA) using the Dubois formula with a starting dose adjusted for coadministration with a CYP3A4/PgP inducer. Individualised dosing should be titrated by increasing the dose by increments of 1 to 4 mg to attain the target trough concentration for optimal clinical response. Dosing should be titrated to attain trough serum concentrations of 5 to 15 ng/ml.

12. **Fenfluramine (Prescribing Classification: Hospital only) as per NICE TA808:** Initially 0.1mg/kg twice daily for 1 week, then increased if necessary to 0.2mg/kg twice daily for 1 week, adjusted according to response; maintenance 0.35mg/kg twice daily, for patients requiring more rapid titration, the dose may be increased every 4 days; maximum 26g per day.
When used with stiripentol, a lower maintenance dose of 0.2mg/kg twice daily is recommended; maximum 17mg per day.

13. **Gabapentin (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 300-400mg OD, increasing in 300-400mg steps every one to four weeks until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 1.2g TDS is reached. A small number of patients may benefit from (and tolerate) higher doses even up to 4.8g daily. Withdraw gabapentin at a rate of 400mg every one to four weeks. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

14. **Lacosamide (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at a dose of 50mg once or twice daily and increase in 50-100mg daily every one to two weeks to a maximum of 200mg BD (polytherapy) or 300mg BD (monotherapy). Some patients may benefit from doses up to 400mg BD. Withdraw at a rate of 50-100mg every 1 to 2 weeks. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

Specific consideration: Section 15 Co-administration of sodium channel blocking ASMs.

15. **Lamotrigine (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

    For patients not taking other antiseizure drugs:
    Introduce at 25mg daily for two weeks before increasing further as follows.
    Increase to 50mg daily for two weeks.
    Then increase in steps of 25mg- 50mg per fortnight can be until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 200mg BD is reached.

    For patients taking Sodium Valproate:
    Introduce at 25mg on alternate days for two weeks, then 25mg once daily for two weeks, then increase by 25mg every two weeks until symptoms of toxicity become unacceptable or a dose of 100mg BD is reached. (Doses up to 300mg/day may also be given in a single undivided daily dose). Patients who are also taking Sodium Valproate sometimes tolerate higher doses, but monitor closely for intoxication above 200mg daily.

    For those patients taking an enzyme inducing antiseizure medication (Carbamazepine, Phenytoin, Phenobarbital, and Primidone):
    Introduce at 50mg of Lamotrigine daily and increase in 50mg steps every two to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 200mg BD is reached. Some patients on enzyme inducing drugs will tolerate higher doses.

    Withdraw Lamotrigine at a rate of 25mg-50mg every one to four weeks: NOTE Lamotrigine theoretically increases the metabolism of hormones in the OCP and thus may have the potential to reduce its efficiency.

    Oral contraceptives: In patients established on lamotrigine treatment addition of combined oral contraceptives to their drug regime may lower the effectiveness of the ASM. In these circumstances an increase of lamotrigine dose of about 30% should be considered.
    Specific considerations: Section 15 Co-administration of sodium channel blocking ASMs

16. **Levetiracetam (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 250mg a day and increase in 250mg steps every fortnight to 1500mg BD. If seizures persist and patient can tolerate higher dosage, this can be increased to 1750mg bd up to a maximum of 2000mg BD. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
    Specific considerations: Section 15 Co-administration of sodium channel blocking ASMs.

17. **Midazolam (oromucosal solution buccal administration) (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Rescue or PRN medication for prolonged (≥5 minutes) seizures / clusters of seizures with an individualised care plan and training of carers by Epilepsy Nurse Consultant/Epilepsy Nurse Specialists or Learning Disability Community Nurses. Prescribe by brand – Epistatus and Buccolam are not interchangeable.

18. **Oxcarbazepine (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 300mg once a day, increase by 300mg every fortnight to 600mg BD, unless further seizures when it can be increased if tolerated up to a maximum of 1.2g BD. Withdraw at a rate of 300mg every 1-2 weeks. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
Specific considerations: Section 13 Enzyme induction; Section 14 Hyponatraemia; Section 15 Co-administration of sodium channel blocking ASMs.

19. **Paraldehyde (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Available as a rectal solution (50:50) in olive oil from Stockport Pharmaceuticals (details under Special-order Manufacturers in BNF). Adult dose 5-10ml (i.e. 10-20ml of solution). Patients will be provided with an individualised care plan.

20. **Perampanel (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 2 mg at bedtime and increase by 2 mg every fortnight until seizures are controlled or as tolerated up to a maximum dose of 8 mg nocte in mild hepatic impairment and 12 mg nocte in other patients. Withdraw at 2mg per month. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
Specific considerations: for doses of 12mg or more Section 13 Enzyme induction.

21. **Phenobarbital (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 30mg nocte and increase in 30mg steps every four weeks until seizures are controlled, or symptoms of intoxication become unacceptable. Maximum dose usually around 240mg daily. Withdraw at a rate of 30-60mg per month. Ensure that the patient is maintained on a specific brand.
Specific considerations: Section 13 Enzyme induction; Section 16 Maintaining manufacturer's products.

22. **Phenytoin (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 300mg daily, increasing in 25mg steps every four to eight weeks until seizures are controlled, or symptoms of intoxication become unacceptable. Withdraw at a rate of 50 -100mg per month. Ensure that the patient is maintained on a specific brand.
Specific considerations: Section 13 Enzyme induction; Section 15 Co-administration of sodium channel blocking ASMs; Section 16 Maintaining manufacturer's product.

23. **Pregabalin (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Initially 25mg TDS, increase every few weeks until seizures are controlled to maximum 600mg daily. Pregabalin has a similar therapeutic profile to gabapentin which is cheaper but is easier to take at therapeutic doses. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

24. **Primidone (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin with 125mg lying flat in bed at night first dose. Increase in 125mg steps every fortnight until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 750mg BD is reached. Withdraw at a rate of 250mg per month. Ensure that the patient is maintained on a specific brand.
    Specific considerations: Section 13 Enzyme induction; Section 16 Maintaining manufacturer's production.

25. **Rufinamide (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 100mg once or twice daily and increase in 100-200mg increments every 1-2 weeks. Target dose 900mg BD but can be increased further depending on body weight. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
    Specific consideration: Section 13 Enzyme induction.

26. **Sodium valproate (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Use standard or slow-release preparation. Begin at a dose of 300-500mg once or twice daily, increasing after two to four weeks to 500mg BD. Thereafter increase only if further seizures occur and at a rate of 500mg each month until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 1.5g BD is reached. Withdraw at a rate of 500mg per month unless serious adverse event demands more rapid withdrawal. Note this drug interacts with lamotrigine. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
    Specific consideration: Section 18 Use of valproate in women and men.

27. **Stiripentol (Prescribing Classification: Specialist initiation with NO SCG):** Dose is calculated on an mg/kg body weight to a maximum of 50mg/kg/day. Usually initiated as an adjunct to sodium valproate or clobazam (0.5mg/kg/day) in Dravet's Syndrome. A dose reduction in clobazam may be required if tolerability becomes problematic on introduction of stiripentol.

28. **Tiagabine (Prescribing Classification: Specialist initiation with NO SCG*):***
    With enzyme-inducing medication:
    - Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every week; maintenance 30–45 mg daily in 2–3 divided doses.

With non enzyme-inducing medication:

- Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every week; maintenance 15–30 mg daily in 2–3 divided doses. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

29. **Topiramate (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Introduce at 25mg OD. Increase in steps of 25-50mg every one to two weeks to an initial dose of 50mg BD. Consider further dose increases in steps of 25-50mg every one to two weeks until seizures are controlled or maximum dose of 400mg BD is reached. Withdraw topiramate at a rate of 50mg every two to four weeks. Adverse effects include weight loss, ataxia, slowed thought and speech and mood disturbances. Note: Dosage of 200mg or more daily renders oral contraceptives ineffective. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.
    Specific consideration: Daily dose of 200mg or more Section 13 Enzyme Induction.

30. **Vigabatrin (Prescribing Classification: Specialist initiation NO SCG):** Introduce at a dose of 500mg OD, increasing in 500mg steps every one to four weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 1.5g BD is reached. Withdraw at a rate of 500mg per month. ***Test visual fields arranged by hospital prior to introduction and check 3 monthly for first year and six monthly thereafter***. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

31. **Zonisamide (Specialist ADVICE, can be initiated in Primary Care on the advice of a specialist):** Begin with 25mg OD, increasing in 25-50mg increments every two to four weeks until seizures are controlled to maximum 400mg OD. Withdraw at the same rate. Warn patients about measures to mitigate risk of hyperthermia in addition to other more common side effects. Base the need for continued supply of a particular brand on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency, treatment history and patient specific issues.

    Felbamate is no longer licenced for use in epilepsy in the UK, but is still available in other countries. If a patient has already been commenced on Felbamate, it would not be recommended for it to be withdrawn before seeking advice from the tertiary epilepsy service. Ongoing prescribing would need discussion between tertiary epilepsy service and Primary Care.

Appendix 2: Treatment Pathway

