THE SOUTH YORKSHIRE & BASSETLAW

Shared Care Protocol
For
Epilepsy in Adults

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Shared Care Guideline for the prescribing of drugs used to treat epilepsy in adults.

This guideline has been subject to consultation with the Epilepsy Services Group, Sheffield Teaching Hospital NHS Foundation Trust (which includes Neurologists with a special interest in epilepsy and epilepsy nurse specialists)

Background

Patients with epilepsy have been cared for jointly between consultants, epilepsy nursing service and GPs for many years with GPs taking prescribing responsibility where appropriate. This shared care protocol provides a framework to support the three parties involved. The introduction in recent years of a number of new drugs with which GPs may be unfamiliar has led to concern about clinical responsibility. Their use is no different in principle from older drugs already prescribed by GPs and therefore it is appropriate for there to be a shared care guideline.

Procedure for Initiating Shared Care Arrangements

Specialist education, training, ongoing advice and support is available from the specialist teams. Patients seen in the consultant led epilepsy clinic are provided with a treatment plan outlined in the letter to the GP and copied to the Epilepsy Nurse Specialist. Epilepsy Nurse Specialists will normally assist in titration of anti-seizure medication within limits recommended by the Consultant Neurologist. The Consultant Neurologist will usually prescribe the first month's medication for patients seen in the outpatient clinic and GPs would be expected to continue prescribing after this.

Changes in treatment (i.e. prescribing of an alternative anti-epileptic medication) advised by the Epilepsy Nurse Specialists outside the consultant lead outpatient clinic will be notified in writing to the GP. Sharing of care assumes communication between the consultant, specialist nursing team, GP and patient and/or patient's carers. The shared care arrangements should be explained to the patient/carer and accepted by them. The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

See Appendix A for summary of initiation of shared care.

Consultant Team Responsibilities

Initial assessment and treatment

- Diagnosis and assessment, ensuring there are no interactions with concurrent therapy or disease states at the time of the initial consultation and subsequent reviews.
- Undertake baseline testing, if applicable (see individual drugs in Appendix B), prior to the initiation of medication.
- Ensure patient and/or carer is fully informed of potential benefits and side effects of treatment.
- Initiate first antiepileptic drug treatment and provide one month supply of medication (however see Specialist Nursing Service Responsibilities section regarding process for any changes in medication, including prescribing of a new alternative antiepileptic medication,)
- Write to GP within 10 days of initiating new medication, detailing individual patient plan (dose and titration), and stating the request for GP to continue prescribing in accordance with this shared care guideline
- Provide patients with contact details of the Epilepsy Nurse Specialist so they can contact the service if needed, if the patient meets the service referral criteria

- With patient consent, refer to epilepsy nursing service for follow up if the patient meets the specialist nursing referral criteria for the relevant Place. Contact service(s) for current criteria.

Disease monitoring

- Oversee monitoring patient's response to treatment, and side effects of medication until the patient is stable either directly or via Epilepsy Nurse Specialists. Arrangements for follow up, and time intervals of follow up appointments will vary, depending on the patient.
- Report any identified adverse events to the MHRA
- Any dose or drug changes once the patient is established on treatment to be conveyed in writing to the GP.

Special considerations that apply to valproate

From January 2024, valproate must not be initiated in new patients (male or female) younger than 55 years, unless two specialists* independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. This decision must be documented, and a Risk Acknowledgement Form (female or male) completed and shared with the GP and patient.
See below for the additional responsibilities required for female patients.

Note: Male patients only require a Risk Acknowledgement form at initiation, NOT annually.
Male patients established on valproate prior to January 2024 should be informed about a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception. As a precaution, male patients should be advised to use effective contraception throughout the valproate treatment period and for 3 months after stopping valproate. The MHRA visual risk communication diagram and Patient Guide for men can be used to support discussions. More details can be found in the MHRA alert.

*A specialist prescriber, who initiates treatment, is a consultant neurologist, psychiatrist or paediatrician who regularly manages complex epilepsy or bipolar disorder.
The second specialist signatory, and those who can support other aspects of the PPP, could include the following:

- Consultant adult or paediatric neurologists
- Consultant psychiatrists
- Speciality and associate specialist doctors in psychiatry and neurology
- Speciality doctors in psychiatry
- Paediatrician with special interest in epilepsy
- Paediatrician who regularly manages complex epilepsy or bipolar disorder
- Epilepsy Nurse Consultant
- Specialist Nurses in relevant disciplines
- Specialist Pharmacists in relevant disciplines

Three infographics describe circumstances where review by two specialists may be required:

- for female patients under 55 years old
- for male patients under 55 years old
- for male and female patients 55 years and older

Special considerations for female patients

At initiation, and where relevant during follow up appointments, discuss with females patients (or their carers), the risks associated with anti-epileptic drugs and untreated epilepsy in pregnancy (See MHRA drug safety update and safety information leaflet to assist discussion), and any interactions that treatment may have with hormonal contraception. See Contraception section below.

- **Valproate**
  - From January 2024, at their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate. Subsequent annual reviews only require one specialist signature.
  - The valproate decision support tool can be used to support discussions: **Is valproate the right epilepsy treatment for me?**
  - If valproate is being used, the conditions of the Pregnancy Prevention Programme (PPP) must be fulfilled, as applicable, ensuring:
    - Pregnancy is excluded before treatment initiation.
    - The patient (or their carer) is made aware of, and understands, the risks and is supplied with the Patient Guide for Women.
    - The patient understands the need to comply with effective contraception throughout treatment (if necessary) and undergo pregnancy testing when required. See the Contraception section below and the MHRA aide-memoir table.
    - All patients are reviewed at least annually to re-evaluate treatment, contraception (if necessary), discuss risks and sign an updated Annual Risk Acknowledgement Form. Copies must be forwarded to the patient's GP and epilepsy nursing service.
    - If the PPP is not required*, the reason is documented in Step 1 of the Annual Risk Acknowledgement Form and shared with the patient and GP.
  - Further details on the responsibilities of the specialist are given in the Guide for Healthcare professionals.

    *** PPP not required**

    If the reason is permanent (e.g. hysterectomy, bilateral oophorectomy, post menopause) Step 1 of the updated ARAF only needs to be completed on one occasion. Where the absence of risk may change (e.g. pre-menarche, long-term monogamous relationship with a vasectomised male partner, same sex relationship and not planning pregnancy, intellectual disability with lack of mental capacity[*]), at least Step 1 of the ARAF should be completed annually.

    The decision around the absence of risk of pregnancy can be made by the specialist prescriber alone on consideration of the patient's individual circumstances (without the need for countersignature). See MHRA infographics for details.

    Female sterilisation (tubal ligation) is a highly effective form of contraception. However, locally it is classed as a permanent exemption form the PPP. GPs must inform secondary care if a reversal procedure is performed.

- **Topiramate**
  - From June 2024, an Annual Risk Awareness Form for Epilepsy must be completed with all female patients of childbearing potential receiving topiramate (or their responsible person).
  - If topiramate is being used, the conditions of the Pregnancy Prevention Programme (PPP) must be fulfilled, as applicable, ensuring:
    - Pregnancy is excluded before treatment initiation.
    - The patient (or their carer) is made aware of, and understands, the risks and is supplied with the Topiramate Patient Guide - Epilepsy
    - The patient understands the need to comply with highly effective contraception throughout treatment (if necessary) and undergo pregnancy testing when required. See the Contraception section below and the MHRA aide-memoir table.

[*] In some cases, clinicians and their parents/legal guardians can agree that the patient lacks capacity to consent for sexual activity and therefore agree there are compelling reasons that the absence of pregnancy risk is permanent. Examples may include patients with genetic/structural developmental epileptic encephalopathies (DEE), severe congenital brain malformation, severe acquired brain injury following hypoxic-ischaemic encephalopathy.

NOTE: Topiramate can potentially reduce the efficacy of hormonal contraception. Acceptable forms of contraception include an intrauterine method (Cu-ICD or LNG-IUS), or the medroxyprogesterone acetate depot (MDPA) injection PLUS a barrier method.

- All patients are reviewed at least annually to re-evaluate treatment, contraception (if necessary), discuss risks and sign an Annual Risk Awareness Form. Copies must be forwarded to the patient's GP and epilepsy nursing service.
- If the PPP is not required, the reason is documented in Step 1 of the Annual Risk Awareness Form and shared with the patient and GP.

- Further details on the responsibilities of the specialist are given in the Guide for Healthcare professionals.

Specialist Nursing Service Responsibilities

Initial assessment and treatment

- To contact the patient to offer a clinic appointment once referral from Consultant service is received. The timescale for this follow up will vary according to patient need and the medication being prescribed.
- Monitor patient's response to treatment, and side effects of medication. (The time interval and mode of contact will differ depending on the patient). Report any identified adverse events to the MHRA.
- Where a change in medication is identified by the nursing service, for example if a drug has not been tolerated, the epilepsy nurse specialist will decide on a suitable medication, either if this has already been specified in the consultant clinic letter, or by discussion with the consultant service. They will then follow a procedure that varies according to whether or not the service is a commissioned nurse prescribing service:

FOR A NURSE PRESCRIBING SERVICE (EG DONCASTER)

Epilepsy nurse specialist will issue a prescription for the medication, and will write to the responsible consultant, and to the GP to inform them of this change. Once the patient is on a stable dose of medication, the epilepsy nurse specialist will ask the GP in writing, to take over the repeat prescription of medication.

FOR A NON PRESCRIBING EPILEPSY NURSING SERVICE (EG SHEFFIELD, BARNSLEY, ROTHERHAM)

Epilepsy nurse specialist will send a written request to ask the GP to issue a prescription for the medication. The request will detail the individual patient plan (dose and *titration), and state that the request for the GP to prescribe is in accordance with this shared care guideline. If this is following discussion with a consultant, the letter will be countersigned by the consultant. If this is following a plan in a consultant clinic letter, the letter will be referenced.

*When a drug has been initiated by the epilepsy nursing service the GP may be asked to titrate the medication according to this shared care protocol. If during this process there are any uncertainties about tolerability of the medication or other adverse effects, the patient should be asked to consult the epilepsy nurse specialist team or consultant's secretary for advice

Special considerations for female patients

- At initiation, and where relevant during follow up appointments, discuss with women who are of childbearing potential, the risks associated with anti-epileptic drugs and untreated epilepsy in pregnancy (See MHRA drug safety update and safety information leaflet to assist discussion), and any interactions that treatment may have with hormonal contraception.
- **Valproate**

Valproate is contraindicated in female patients aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the Pregnancy Prevention Programme are fulfilled. See above for details.

- **Topiramate**
  Topiramate is contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled. See above for details.

Primary Care Team Responsibilities

Initial treatment

- The GP will add the drug to the patient's repeat prescription within 2 weeks of receipt of the information from the Consultant Neurologist and issue ongoing prescriptions. (See Dispensing and continuity of supply regarding brand vs generic prescribing. If the primary care prescriber feels unable to act under this shared care protocol, they should discuss with the specialist requesting the care in the first instance. If after discussion they still feel unable to prescribe then the primary care clinician must notify the specialist in writing, stating/confirming the reasons for not prescribing.
- When a drug has been initiated by the Epilepsy Specialist Nursing Service the GP may be asked to initiate and titrate the medication according to this shared care protocol (see appendix B). If during this process there are any uncertainties about tolerability of the medication or other adverse effects, the patient should be asked to consult the epilepsy nurse specialist team or consultant's secretary for advice.
- In some regions, where there is a commissioned prescribing epilepsy nursing service (e.g. Doncaster), GPs may request that the nursing service continue to prescribe the patient's antiepileptic medications until such point as they are on a stable dose. This should be done in writing, within 2 weeks of receipt of the information from the Consultant Neurologist, or from another service (such as an inpatient discharge summary).
- For medication supplied from another provider (e.g. red drugs) prescribers are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems

Disease monitoring

- Check drug interactions with any new medication started or any new conditions diagnosed. Contact the specialist nursing team or consultant if potential interactions found.
- Amend prescription as per requests from secondary care (consultant or nurse led service) for dose changes and new medication (as per appendix A). To make minor changes to medication, if within competence. If the GP has concerns regarding the prescription of an anti-epileptic drug they will seek advice from the patient's Consultant Neurologist or the specialist nursing service.
- Anti-epileptics appropriate for a GP to prescribe, under the guidance of the consultant and the specialist nursing service, are listed in Appendix B.
- Report adverse events to the specialist (consultant and / or specialist nursing service) sharing the care of the patient, and to the MHRA.
- All adults with epilepsy should have a structured review, on at least an annual basis, by either a generalist or specialist as per NICE guidelines (recommendation 1.6. Where patients are not under regular follow up by the consultant team and or the epilepsy specialist nurses, this should be carried out in general practice.
- Consider re-referral to or discussion with the specialist team (consultant or nursing) in the following circumstances: Where seizures are not controlled on medication; where the patient is experiencing unacceptable side effects; when the diagnosis is in question or a new seizure type

occurs; when the patient becomes pregnant or is planning pregnancy (see notes below); if the patient wishes to withdraw from antiseizure medication.
- Undertake drug specific monitoring, where applicable, as detailed within Appendix B.

Special considerations that apply to valproate

From January 2024, **all new requests** to prescribe valproate should be accompanied by a completed Risk Acknowledgement Form (female or male), signed by two specialists. See above for the definition of appropriate specialists.

See below for the additional responsibilities required for female patients.

Note: Male patients only require a Risk Acknowledgement form at initiation, NOT annually.

Male patients established on valproate prior to January 2024 should be informed about a possible increased risk of neurodevelopmental disorders in children born to men treated with valproate in the 3 months prior to conception. As a precaution, male patients should be advised to use effective contraception† throughout the valproate treatment period and for 3 months after stopping valproate. Patients only require referral to the specialist if they are planning a family in the next 12 months or if they wish to discuss alternative treatment options.

The MHRA visual risk communication diagram and Patient Guide for men can be used to support discussions. More details can be found in the MHRA alert.

Special considerations for female patients

- Ensure that women taking antiseizure medication are given appropriate contraceptive advice, taking into account the considerations detailed in the contraception section below.
- Urgently refer women who are pregnant or planning to become pregnant for specialist advice on their anti-seizure treatment, if they have not previously been counselled about this.
- All women using seizure medication who are planning to become pregnant should be offered 5mg per day of folic acid (Note. 5mg strength is prescription only - POM) before any possibility of pregnancy.

- **Valproate**
  - Ensure that all women of childbearing potential and girls, who are taking valproate for the treatment of epilepsy, have been reviewed by a specialist in the last 12 months, and a valid Annual Risk Acknowledgement Form has been received and uploaded to the patient record. If they have not been reviewed, refer them urgently for assessment. An appropriate SNOMED code should be assigned – see Valproate Guidance for Primary Care for more information.
  - Ensure all women of childbearing potential and girls receiving valproate who are reviewed by a specialist after January 2024 have been reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate. Subsequent annual reviews only require one specialist signature.
  - Put in place a robust mechanism to ensure the ARAF is in date when prescriptions are issued and to ensure that patients are recalled or referred back to secondary care before the expiry date. However, a prescription for valproate should not be stopped, simply due to a delay in specialist review/ ARAF completion, as this may put the patient at risk.
  - Ensure women of childbearing potential who are taking valproate are complying with the pregnancy prevention programme (where applicable) and:
    - Have a copy of the Patient Guide for Women.
    - Are using effective contraception and understand the need to comply with effective contraception throughout treatment with valproate. For patients not using highly effective contraception, the risk of pregnancy should be assessed prior to issuing each valproate prescription; pregnancy testing may be required.

† Effective contraception is classed as condoms, plus contraception used by the female sexual partner. If there is no pregnancy risk or if the woman is already using highly effective contraception, then condom use is not required to prevent pregnancy.

See the contraception section below and the MHRA aide-memoir table for details on contraceptive efficacy and pregnancy testing requirements.
    - Remind the patient to contact you immediately if they suspect there has been a problem with their contraception or if they may be pregnant.
  - Further details on the responsibilities of the GP are given in the Guide for Healthcare professionals. Seek specialist advice if concerned.
  - Ensure appropriate PPP SNOMED codes are assigned to all patients – see Valproate Guidance for Primary Care for more information.

- **Topiramate**
  - Ensure all women of childbearing potential and girls receiving topiramate who have been reviewed by a specialist after June 2024 are being treated in line with the new topiramate Pregnancy Prevention Programme, and a valid Annual Risk Awareness Form (ARAF) has been received and uploaded to the patient record.
  - Put in place a robust mechanism to ensure the ARAF is in date when prescriptions are issued and to ensure that patients are recalled or referred back to secondary care before the expiry date. However, a prescription for topiramate should not be stopped, simply due to a delay in specialist review/ ARAF completion, as this may put the patient at risk.
  - Ensure women of childbearing potential who are taking topiramate are complying with the pregnancy prevention programme (where applicable) and:
    - Have a copy of the Topiramate Patient Guide - Epilepsy
    - Are using highly effective contraception and understand the need to comply with this throughout treatment with topiramate and for 4 weeks after stopping. For patients not using highly effective contraception, the risk of pregnancy should be assessed prior to issuing each topiramate prescription; pregnancy testing may be required.
    - See the contraception section below and the MHRA aide-memoir table for details on contraceptive efficacy and pregnancy testing requirements.
      NOTE: Topiramate can potentially reduce the efficacy of hormonal contraception. Acceptable forms of contraception include an intrauterine method (Cu-ICD or LNG-IUS), or the medroxyprogesterone acetate depot injection PLUS a barrier method.
    - Remind the patient to contact you immediately if they suspect there has been a problem with their contraception or if they may be pregnant.
  - Further details on the responsibilities of the GP are given in the Topiramate Healthcare Professional Guide - Epilepsy. Seek specialist advice if concerned.
  - Ensure appropriate PPP SNOMED codes are assigned to all patients.

General information

Drug treatment - indications and recommended treatment regimes

Indications, cautions, contraindications, side effects, doses and formulations are listed in the British National Formulary; however, these guidelines may differ slightly but represent acceptable practice in the UK.

There are occasions when non-adherence to the licensed indications of anti-epileptic drugs or use of unlicensed preparations may be justified, for instance where the licence indications do not reflect current knowledge, the indications do not include well proven uses of the drug or the licence indications are over restrictive. The Consultant Neurologist may recommend the use of drugs beyond the licensed indications and will detail this in the correspondence to the GP and specialist nurse led service, where appropriate. Wherever the consultant neurologists consider it to be indicated and, if appropriate, they will explain the drug's unlicensed status to the patient or carer.

Communication

Expected communications between specialist teams and GP practices are detailed above (see Consultant, specialist nursing team and primary care team responsibilities)

Contact names and details

Contact Details	Telephone number	Email
Consultant Neurologists		
Dr G Dennis (Bassetlaw & Sheffield)	01909502712 0114 2712769	gary.dennis1@nhs.net
Dr R A Grunewald (Chesterfield & Sheffield)	0114 2712306	richard.grunewald@nhs.net
Prof M Reuber (Sheffield)	0114 2268688	markus.reuber@nhs.net
Dr P Shanmugarajah (Rotherham)	0114 2713708	priya.shanmugarajah1@nhs.net
Dr S Wong (Barnsley & Sheffield)	01142711977	siew.wong2@nhs.net
Epilepsy Nurse Specialist Service Sheffield, Rotherham, Chesterfield	0114 2713488 (for professionals)	sth.epilepsyservice@nhs.net
Epilepsy Nurse Specialist Service Doncaster and Bassetlaw	01302 796217	rdash.rehabservices@nhs.net
Epilepsy Nurse Specialist Service Barnsley	01226 645180	epilepsyservice @swyt.nhs.
Lead Pharmacist Sheffield - Natasha Hoyle	0114 2713225	natasha.hoyle@nhs.net

General information about anti-seizure medication side effects and monitoring

General principles regarding monitoring of side effects of anti-seizure medications are given below. This is not a comprehensive list, and drug-specific side effects can be found in Appendix B, or in the British National Formulary or Summary Product Characteristics.

Contraception

The effectiveness of *combined* oral contraceptives, *progestogen-only* oral contraceptives, contraceptive patches, vaginal rings, progestogen implants, and emergency hormonal contraception can be considerably reduced by interaction with antiseizure drugs that induce hepatic enzyme activity, including: carbamazepine, eslicarbazepine, felbamate, lamotrigine[‡], oxcarbazepine, perampanel, phenytoin, phenobarbital, primidone, rufinamide and topiramate. The Faculty of Sexual and Reproductive Health (FSRH) gives detailed advice: Drug Interactions with Hormonal Contraception

During use of a teratogen that is NOT an enzyme inducer (and no other enzyme-inducing drug being taken) use of the progestogen implant, the copper IUD or a levonorgestrel-releasing

[*] Lamotrigine interacts to a limited degree, and it is recommended patients are warned that contraceptive efficacy might be affected. Lamotrigine concentrations can also be affected by contraceptives, with the risk of reduced seizure control or lamotrigine toxicity. Combined hormonal contraceptives (CHC) can reduce the blood level of lamotrigine; progestogen-only contraceptives may increase lamotrigine concentrations. See the BNF for more information.

IUS is recommended. If combined hormonal contraception, a progestogen-only pill or depot medroxyprogesterone acetate is used, condoms should be used reliably in addition.

During use of a teratogen that is an enzyme inducer or a potential enzyme inducer (or if an enzyme-inducing drug is also being taken) use of the copper IUD, a levonorgestrel-releasing IUS, or depot medroxyprogesterone acetate PLUS condoms is recommended. Use of CHC, progestogen-only pills and the progestogen implant is not recommended.
See FSRH CEU guidance (Contraception for women using known teratogenic drugs or drugs with potential teratogenic effects**)** and MHRA guidance (Medicines with teratogenic potential) for more information.

During use of an enzyme-inducer (and no teratogenic medications) use of a contraceptive method that is unaffected by the enzyme inducer is recommended. Intrauterine contraception and depot medroxyprogesterone acetate are appropriate options. In exceptional circumstances, where alternative effective contraception is not acceptable, consider the use of two ethinylestradiol (EE) monophasic combined oral contraceptive pills together containing a total of 50µg of EE (30µg + 20µg). These should be used in a continuous regimen (or tricycled with a shortened hormone-free interval of 4 days).

Allergic reactions

Patients commenced on anti-seizure medications should be warned about risk of allergic reactions, which can be serious (Stevens Johnson syndrome) with phenytoin, carbamazepine, zonisamide and lamotrigine in particular, but can occur with any anti-seizure medication.

Depression and suicidality

People with epilepsy are at increased risk of depression and suicidality. Patients should be warned that some anti-seizure medications, for example levetiracetam, may increase this risk further. (https://www.sign.ac.uk/our-guidelines/diagnosis-and-management-of-epilepsy-in-adults/ 4.6.5 p19). The relatively low risk of antidepressants affecting seizure threshold rarely outweigh the risk of leaving depression untreated. Antidepressants can be used in people with epilepsy, see link for further information, specialist advice can be sought as needed.

Blood tests for monitoring

Serum levels of anti-seizure medications are very rarely required, and the practice of adjusting drug dose according to the results of anti-epileptic drug levels is discouraged unless there is a question of adherence and sometimes during pregnancy**.** Instead most drugs are titrated to tolerance. Where intoxication is suspected, the Epilepsy Nurse Specialists or Consultant Neurologist involved should normally be consulted for advice.

Several anti-epileptic drugs (enzyme inducing AEDs), especially phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine and topiramate, induce liver enzymes but that this process is generally harmless to the liver (although significant hepatotoxicity can rarely occur with all of these agents). Eslicarbazepine also induces liver enzymes to some degree.

Routine blood tests for monitoring of liver function or white cell count are not indicated for any anti-epileptic medication, except felbamate and cannabidiol.

Bone health.

NICE guidance states that a high level of vigilance should be maintained for emergence of treatment-related adverse effects such as those on bone health. Bone demineralization is a risk for

patients taking enzyme-inducing anti-epileptic drugs (phenytoin, phenobarbitone, carbamazepine), and sodium valproate.

Patients on these medications should be offered / recommended to take vitamin D supplementation, (see local CCG vitamin D/self-care guidance for specific advice – note higher doses may be needed) https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention/background-information/risk-factors/) and tests of full blood count, electrolytes, liver function, vitamin D and calcium should be considered every 2-5 years according to NICE guidelines (https://www.nice.org.uk/guidance/cg137/chapter/1-Guidance#pharmacological-treatment).

Bone densitometry should be considered for patient taking these medications, in older patients and those with other risk factors for osteoporosis, or a history of fragility fractures.

Dispensing and continuity of supply

MHRA guidance relating to minimising risk when changing between different manufacturer's supplies of anti-epileptic treatment can be found here at https://www.gov.uk/drug-safety-update/antiepileptic-drugs-updated-advice-on-switching-between-different-manufacturers-products**.** Also see additional advice from SPS, - The Use of Generic Anti-Epileptics Drugs in Patients with Epilepsy

Key advice for prescriber / dispensing pharmacies:

- Anti-epileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product. These categories are listed below.
- Differences between alternative products (for example, product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.
- 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);
- This advice relates only to anti-epileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that anti-epileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);
- Usual dispensing practice can be followed when a specific product is not stated.

CATEGORY 1

Phenytoin, carbamazepine, phenobarbital, primidone.

For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer's product.

CATEGORY 2

Clobazam, Clonazepam, Eslicarbazepine, Lamotrigine, Oxcarbazepine, Perampanel, Rufinamide, Topiramate, Valproate, Zonisamide

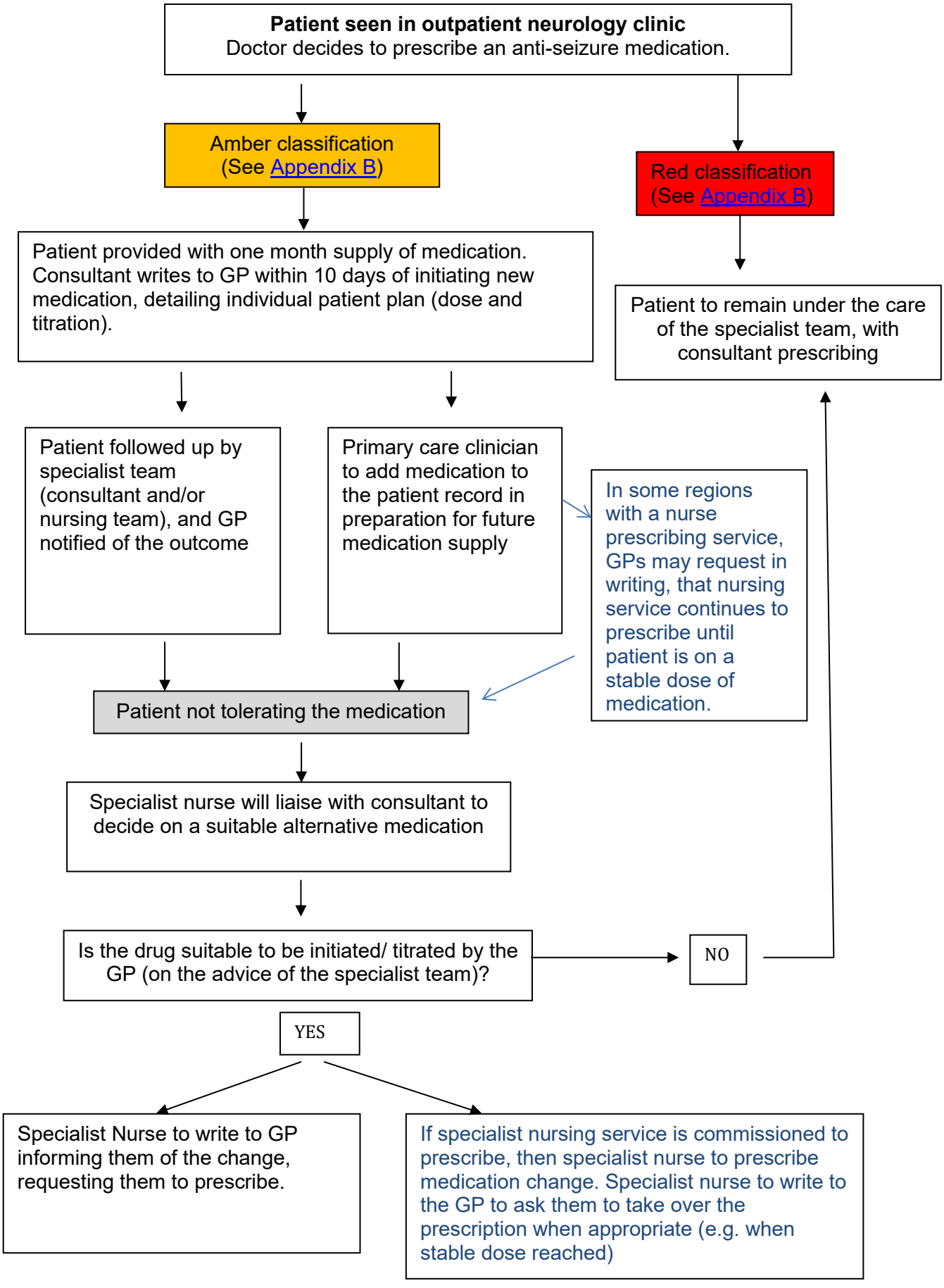
For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgment and consultation with the patient and/or carer taking into account factors such as seizure frequency and treatment history. Patient/carer-related factors such as their negative perceptions about alternative products and/or other issues related to the patient should also be taken into account. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.

CATEGORY 3

Levetiracetam, brivaracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin.

For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns such as patient anxiety, risk of confusion or dosing errors, negative perceptions about alternative products and/or other issues related to the patient. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered.

Appendix A – Process for initiating Shared Care



Appendix B: Drug summaries

The details below in each drug summary are not a comprehensive list of all clinically relevant information and, see the BNF and the SPC for full details. See BNF for all drug interactions. Note - Some anti-epileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some anti-epileptics may be affected by hormonal contraceptives. For more information, see above and *Conception and contraception* in the individual drug monographs in the BNF.
Some of the doses/titration and withdrawal regimens included in the monographs are based on clinical expertise/local practice.

Drug	**MHRA category (see Dispensing and continuity of supply)**	**Traffic Light Drug List (TLDL) status***
Acetazolamide	NA	Amber
Brivaracetam	3	Amber
Cannabidiol	NA	Red
Carbamazepine	1	Amber
Cenobamate (see appendix info for community pharmacy re ordering)	Not relevant (one brand)	Amber
Clobazam	2	Amber
Clonazepam	2	Amber
Diazepam (rectal)	NA	Amber
Eslicarbazepine	2	Amber
Ethosuximide	3	Amber
Felbamate	NA	Red
Gabapentin	3	Amber
Lacosamide	3	Amber
Lamotrigine	2	Amber
Levetiracetam	3	Amber
Methsuximide	NA	Red
Midazolam (Buccal)	Brand prescribing recommended due to differences in formulations/strength	Amber
Oxcarbazepine	2	Amber
Paraldehyde	NA	Red
Perampanel	2	Amber
Phenobarbital	1	Amber
Phenytoin	1	Amber
Pregabalin	3	Amber
Primidone	1	Amber
Rufinamide	2	Amber
Sodium Valproate	2	Amber
Stiripentol	NA	Red
Topiramate	2	Amber
Vigabatrin	3	Amber
Zonisamide	2	Amber

*Area prescribing group traffic light drug lists exist for each region. See link to Sheffield TLDL. Neighbouring CCGs can be found here. Barnsley, Rotherham and Doncaster and Bassetlaw.
Whilst it is the intention that this shared care protocol will facilitate alignment of these lists across the places, with respect to epilepsy medications, regional differences may persist.

Acetazolamide

The details below are not a complete list see the BNF and the SPC for full details

Licensed Indications: Epilepsy, diuresis and glaucoma

Licensed Dose: 250mg – 1g daily in divided doses

Dose Titration: 250mg daily, increasing in 250mg steps every one to four weeks until seizures are controlled, side effects become unacceptable or a total dose of 1g (taken in three divided doses) is reached.

Drug Withdrawal: Withdraw at a maximum rate of 250mg weekly.

Side Effects: Nausea and vomiting, taste disturbance, loss of appetite, thirst, headache, dizziness, paraesthesia, nephrolithiasis, electrolyte disturbances. Blood disorders, rashes, and other sulfonamide-related side-effects occur occasionally.

Monitoring: Blood count and plasma electrolyte concentrations should be monitored if patient taking acetazolamide long term. Acetazolamide is a sulfonamide derivative therefore patients should be told to report any unusual skin rash. Avoid in hepatic impairment. Avoid in renal impairment.

Brivaracetam

The details below are not a complete list see the BNF and the SPC for full details

Licensed Indications: Adjunctive therapy in the treatment of focal onset seizures with or without secondary generalisation in adult and adolescent patients with epilepsy

Licensed Dose: Recommended starting dose is 50 mg/day. The dose should be administered in two equally divided doses, once in the morning and once in the evening. Final total daily dose range of 50 mg/day to 200 mg/day.

Dose Titration: Doses titrated according to response in 50mg steps 2-4 weekly

Side Effects: Somnolence, dizziness, fatigue, depression, anxiety, irritability, reduced appetite, nausea
Taken with carbamazepine, brivaracetam increases concentration of carbamazepine epoxide, an active metabolite of carbamazepine

Monitoring: A maximum daily dose of 150 mg administered in 2 divided doses is recommended for all stages of hepatic impairment

Cannabidiol (RED DRUG)

The details below are not a complete list see the BNF and the SPC for full details

Licensed Indications: Lennox Gastaut syndrome https://www.nice.org.uk/guidance/ta615 and Dravet syndrome https://www.nice.org.uk/guidance/ta614 . Must be prescribed alongside clobazam (dose not specified) to be eligible for NHS funding. Funding application and Blueteq registration required.

Licensed Dose: 2.5 to 10mg/kg twice daily. Available as 100mg/ml oral solution (hospital only).

Dose Titration: Start at 2.5mg/kg twice daily (adults). After one week, increase to 5mg/kg twice daily (10 mg/kg/day). If required & tolerated titrate in increments of 2.5 mg/kg twice daily (5 mg/kg/day) to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Dose reduction may be required in those with moderate or severe hepatic impairment.

Drug Withdrawal: Little experience of rapid withdrawal, but generally withdrawn over a few weeks.

Side Effects: Somnolence, appetite change, behaviour changes, diarrhoea, vomiting, abnormal liver function. Concomitant use of valproate increases risk of diarrhoea and decreased appetite.

Monitoring: Manufacturer advises monitor liver function at baseline, at 1 month, 3 months, and 6 months of treatment, then periodically thereafter; more frequent monitoring is recommended in patients with raised baseline ALT or AST or taking valproate. Restart monitoring schedule if dose increased above 10 mg/kg/day. If transaminase or bilirubin levels increase significantly or symptoms of hepatic dysfunction occur, treatment should be withheld or permanently discontinued based on severity - consult SPC.

Carbamazepine

The details below are not a complete list see the BNF and the SPC for full details

Licensed Indications: Focal and secondary generalised tonic clonic seizures

Licensed Dose: 100-200mg 1-2 times daily, increasing slowly to usual dose of 0.8-1.2g daily in divided doses. In some cases 1.6-2g may be needed. Use a prolonged release preparation.

Unlicensed doses commonly used: Some patients may need 2.4g daily in divided doses

Dose Titration: Use a prolonged release preparation. Introduce at 100mg once or twice daily, increasing in 100mg steps every one to two weeks until a dose of 300mg bd is reached. Thereafter increase only if further seizures occur at a rate of 100mg every two to four weeks until seizures are controlled or symptoms of intoxication become unacceptable.

Drug Withdrawal: In non-urgent withdrawal, withdraw at a rate of 200mg every two to four weeks.
In case of rash (unless severe) withdraw at a rate of 200mg per week. Severe dermatological problems (including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and Stevens Johnson syndrome (SJS)) and aggravated liver dysfunction or acute liver disease requires the drug to be withdrawn immediately, this may require admission.

Side Effects: Dry mouth, nausea, vomiting, rash, oedema, dizziness, drowsiness, fatigue, headache, hyponatraemia, blood disorders, dermatitis, urticaria. Caution in cardiac disease. Avoid if AV conduction abnormal

Monitoring: Manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value uncertain). Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders and be advised to seek medical attention if symptoms such as fever, rash, mouth ulcers, bruising or bleeding develop.

Cenobamate (see appendix C for ordering information for community pharmacies)

The details below are not a complete list see the BNF and the SPC for full details

Licensed Indications: Adjunctive treatment of focal seizures with or without secondary generalisation. It should only be used as an add-on treatment, after at least 1 other add-on treatment has not controlled seizures and treatment is started in a tertiary epilepsy service.

Licensed Dose: 200 mg once daily is the usual target dose; increased if necessary up to 400 mg once daily.

Dose Titration (TO BE DONE BE THE SPECIALIST) **:**. Initially 12.5 mg once daily for 2 weeks, followed by 25 mg once daily for a further 2 weeks, then 50 mg once daily for a further 2 weeks, then increased in steps of 50 mg every 2 weeks, according to response;

Drug Withdrawal: Avoid abrupt withdrawal—withdraw treatment gradually over at least 2 weeks.

Side Effects: The most common side effects in clinical trials were somnolence, dizziness and fatigue. Rashes can occur, but DRESS was not reported at slow dose titrations. Disturbance of mood, anxiety or sleep problems were uncommon (<3%).

Cenobamate has significant interactions with several anti-epileptic medications- in particular, a potential 2 fold increase in PHT levels, so PHT dose should be reduced during Cenobamate titration. Efficacy of CBZ and LTG may be reduced, and adverse effects of PHB and Clobazam may be increased.

Monitoring:
Patients started on cenobomate require:
Baseline LFTS, Repeat LFTs at 3-4 months. Additional reviews to be at clinician discretion, eg more frequently if patient has condition or co-prescribed medication that may predispose to hepatic derangement, or LFTs begin to destabilise.

Dose reductions required in hepatic and renal impairment, See SPC or BNF for dosing advice. At the time of prescription, patients should be advised of the signs and symptoms of DRESS and monitored closely for skin reactions.

Clobazam

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Clobazam is licensed as an adjunctive therapy in epilepsy. It is most often used with an individual care plan as an oral rescue medication to prevent seizure clusters or secondary generalisation particularly in focal seizures.

Licensed Dose: Maximum doses are tailored to the individual. Clobazam 10mg (may also be used for catamenial seizures) to maximum dose 60mg daily

Dose Titration: Doses are titrated according to response

Drug Withdrawal: Withdrawal of clobazam (a benzodiazepine) should be gradually because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. See product literature for suggested withdrawal regime.

Side Effects: Drowsiness, confusion, ataxia, headache, vertigo, GI disturbance, urinary retention, rash, rarely agitation and aggression.

Monitoring: Benzodiazepines can precipitate coma if used in hepatic impairment. Start with smaller initial doses or reduce dose; avoid in severe hepatic impairment.
Renal impairment: Patients with renal impairment have increased cerebral sensitivity to benzodiazepines; start with small doses in severe impairment.

Clonazepam

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: All forms of epilepsy

Licensed Dose: 0.5-1mg initially at night for 4 nights increased according to response over 2-4 weeks to usual maintenance dose of 4-8mg usually at night but can be given in 3-4 divided doses if necessary.

Dose Titration: Introduce at a dose of 0.5mg-1mg nocte, increasing in 0.5mg- 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 due to sedative effects

Drug Withdrawal: Withdrawal of clonazepam (a benzodiazepine) should be gradually because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. Withdraw at a rate of 2mg per month

Side Effects: Drowsiness, fatigue, dizziness, muscle hypotonia, co-ordination disturbances, poor concentration, restlessness, confusion, amnesia, rash, rarely agitation and aggression

Monitoring: Benzodiazepines can precipitate coma if used in hepatic impairment. If treatment is necessary, benzodiazepines with shorter half-lives are safer, such as temazepam or oxazepam. Start with smaller initial doses or reduce dose; avoid in severe impairment.

Renal impairment: Patients with renal impairment have increased cerebral sensitivity to benzodiazepines; start with small doses in severe impairment.

Diazepam (rectal)

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Used as rescue medication with an individualised care plan.

Licensed Dose: Adult and child over 12 years 10-20mg repeated once after 10-15 minutes if necessary; Elderly 10mg; then 10 mg after 10–15 minutes if required

Dose Titration: Not applicable

Drug Withdrawal: Not applicable

Side Effects: Hypotension and apnoea as well as the side effects listed for benzodiazepines in general.

Eslicarbazepine

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Monotherapy or Adjunctive therapy in adults with focal seizures with or without secondary generalisation.
Licensed Dose and Dose Titration: Starting dose is 400 mg once daily, increased to 800 mg once daily after one or two weeks. The dose may be increased to 1,200 mg once daily if necessary and if tolerated. Some patients on monotherapy regimen may benefit from a dose of 1,600 mg once daily

Side Effects (similar to carbamazepine and oxcarbazepine): Dizziness, somnolence, rash, nausea, ataxia, tremor, diplopia, blurred vision, reduced appetite, hyponatraemia, prolonged PR interval

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance, avoid use if CRCL<30 ml/min. Avoid in 2nd & 3rd degree AV block as eslicarbazepine associated with AV prolongation.

Ethosuximide

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Absence attacks in idiopathic generalised epilepsy. NOT for convulsive seizures.

Licensed Dose: Usual dose is 1g-1.5g daily in 2 divided dose up to a maximum of 1g bd.

Dose Titration: Introduce at a dose of 250mg once or twice daily. Increase by 250mg every 5-7 days to a usual dose of 1g-1.5g daily in 2 divided doses. Occasionally, up to 2g per day may be needed.

Drug Withdrawal: Withdraw at a rate of 500mg every two to four weeks.

Side Effects: GI disturbance, headache, fatigue, drowsiness, rash, aggression

Monitoring: Patients and/or their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, mouth ulcers, bruising or bleeding develop.

Everolimus (RED DRUG)

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indication: add on treatment for refractory focal seizures in people with Tuberous sclerosis

Licensed Dose: 5mg/m2 if not taking CYP3A4 inducer, 8mg/m2 if taking CYP3A4 inducer (eg CBZ, PHT, PHB)

Dose Titration: depending upon trough blood level, target trough blood level and patient response. Lower doses required in hepatic impairment.

Side Effects: Alopecia; anaemia; appetite decreased; arthralgia; asthenia; cough; decreased leucocytes; dehydration; diabetes mellitus; diarrhoea; dry mouth; dyslipidaemia; dysphagia; dyspnoea; electrolyte imbalance; eye inflammation; fever; gastrointestinal discomfort; haemorrhage; headache; hyperglycaemia; hypertension; increased risk of infection; insomnia; menstrual cycle irregularities; mucositis – **stomatitis**, pneumonitis; nail disorders; nausea; neutropenia; oral disorders; peripheral oedema; proteinuria; renal impairment; respiratory disorders; skin reactions; taste altered; thrombocytopenia; vomiting; weight decreased. Congestive heart failure; embolism and thrombosis; flushing; healing impaired; hepatitis B reactivation; musculoskeletal chest pain; pancytopenia; sepsis; urinary frequency increased

Monitoring: *Votubia*® manufacturer advises everolimus blood concentration monitoring, beginning after 1st week of treatment, to allow dosage adjustment to target.
Monitor for symptoms and signs of infection, renal function, blood-glucose concentration, complete blood count, serum-triglycerides and serum-cholesterol before treatment and 'periodically thereafter'

Felbamate (RED DRUG)

See BNF for details / place in therapy. Also see product details available from the FDA

Licensed Indications: Unlicensed. Only available on a named patient basis
Licensed Dose: Unlicensed

Unlicensed doses commonly used: not applicable

Dose Titration: Introduce at a dose of 400mg three times daily, increasing in 400mg steps every 2 weeks until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 2.4g in three divided doses is reached.

Drug Withdrawal: Withdraw at a rate of 400mg every one to two weeks.

Side Effects: decreased appetite, vomiting, insomnia, nausea, dizziness, somnolence, and headache. Many patients report increased alertness with the drug. Rare but very serious effects include aplastic anaemia and hepatic failure.

Monitoring: Patients need counselling about the risks of aplastic anaemia and liver failure prior to commencing treatment. Nurse to monitor for signs of bleeding, bruising, symptoms of anaemia or infection indicative of bone marrow suppression. FBC and LFTs every two weeks for the first year then three monthly thereafter. Responsibility for monitoring resides with the prescriber in secondary care; however the GP should record on patients clinical system as hospital only drug to facilitate clinical checking and safety warnings.

Gabapentin

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation

Licensed Dose: In clinical trials, the effective dosing range was 900 to 3600 mg/day. A small number of patients may benefit from and tolerate higher doses even up to 4.8g daily

Dose Titration: Introduce at 300mg-400mg daily, increasing in 300mg-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.

Drug Withdrawal: Withdraw gabapentin at a rate of 300mg- 400mg every one to four weeks.

Side Effects: Nausea, vomiting, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, **weight gain, increased appetite**, anorexia, hypertension, vasodilatation, oedema, dyspnoea, cough, drowsiness, dizziness.

Monitoring: Reduce dose in renal impairment.

Lacosamide

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation.

Licensed Dose: Maximum dose of 300mg bd (monotherapy); 200mg bd (adjunctive).

Unlicensed doses commonly used: Some patients may require up to 300mg bd as adjunctive

Dose Titration: Initiate at 50mg bd, increasing weekly by 50mg bd to maximum of 200mg bd.

Drug Withdrawal: Withdraw by 50mg every one to two weeks.

Side Effects: Nausea and vomiting, constipation, flatulence, dizziness, headache, impaired coordination, drowsiness, tremor, depression, fatigue, AV block.

Monitoring: Contraindicated if 2nd or 3rd degree heart block. ECG prior to treatment initiation. Caution in severe hepatic impairment and cardiac disease. Titrate dose with caution in patients with renal impairment. Maximum dose of 250mg daily if eGFR<30ml/min/1.73^2.

Lamotrigine

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Focal seizures and primary and secondary generalised tonic-clonic seizures.

Licensed Dose and Titration:
For patients not taking other anti-epileptics:
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 until seizures are controlled, symptoms of toxicity become unacceptable or a dose of 300mg 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 150mg 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 patients taking an enzyme inducing anti-epileptic drug (carbamazepine, felbamate, oxcarbazepine, perampanel, phenytoin, phenobarbital, primidone, rufinamide and topiramate)
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 300mg bd is reached. Some patients on enzyme inducing drugs will tolerate higher doses.

Unlicensed doses commonly used: Some patients may require up to 400mg bd

Drug Withdrawal: Withdraw Lamotrigine at a rate of 25mg-50mg every one to four weeks.

Side Effects: Nausea, vomiting, diarrhoea, dry mouth, aggression, agitation, headache, dizziness, tremor, insomnia, back pain.

Monitoring:
- Warn patients to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop.
- Caution in cardiac disease, particularly Brugada. ECG prior to treatment.

Levetiracetam

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation and for adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures.

Licensed Dose: Introduce at 250mg once or twice daily. Maximum dose of 1.5g bd.

Unlicensed doses commonly used: Some patient may require a dose of up to 2g bd.

Dose Titration: Introduce at a rate of 250mg once or twice daily, increasing in 250mg-500mg increments one to four weekly until seizures are controlled, symptoms of intoxication become unacceptable or a maximum of 2g bd is reached.

Drug Withdrawal: Withdraw at a rate of 250mg-500mg every two to four weeks.

Side Effects: Mood disturbance (depression, irritability), anorexia, weight changes, abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, cough, drowsiness, amnesia, ataxia, convulsion, dizziness.

Monitoring: Reduce dose in renal impairment (CrCl <80ml/min/1.73m^2). In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m^2.
Refer to SPC for full details.

Methsuximide (RED DRUG)

For prescribing information see Pfizer medical information

Licensed Indications: Unlicensed

Licensed Dose: Unlicensed

Unlicensed doses commonly used: Introduce at 300mg once or twice daily. Increase by 300mg per week until seizures stop, symptoms of intoxication occur, or a dose of 1200mg/day is reached. However the dose could be increased up to 1800mg daily if patient not optimally controlled and tolerates a higher dose.

Dose Titration: Increase by 300mg per week.

Side Effects: Constipation, diarrhoea, dizziness, drowsiness, headache, loss of appetite, loss of coordination, nausea, stomach pain, trouble sleeping, vomiting, weight loss.

Monitoring: No special monitoring required but patients should be counselled regarding haematological adverse effects presenting as fever, sore throat, lethargy, unexplained bruising /bleeding. These should be reported and investigated for evidence of myelosuppression.

Midazolam (Buccal)

The details below are not a complete list, see the BNF and the SPC for full details (Buccolam® and Epistatus®)

Licensed Indications: Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (Buccolam® from 3 months to < 18 years; Epistatus® from 10 years to < 18 years)

Unlicensed Indication and Dose: Use in adults as rescue medication with an individualised care plan. Usual adult dose is 10mg administered into buccal cavity. Usual maximum dose 20mg in 24-hours.

Dose Titration: Not applicable **Drug Withdrawal:** Not applicable

Side Effects: GI disturbance, dry mouth, hiccups, increased appetite, jaundice, hypotension.

Please note:

Prescribers need to be aware that there are two different strengths of buccal midazolam in common use, brand prescribing is therefore recommended:

- ***Midazolam 10mg in 1ml Oromucosal solution (Epistatus®) (currently licensed for use in children from 10 to < 18 years of age).***
- ***Midazolam 5mg in 1ml Oromucosal solution (Buccolam®) (currently licensed for use from 3 months to < 18 years of age).***
- *Any care plans for buccal midazolam provided by the STH neurology service (mainly the epilepsy specialist nurses) will be* ***generic*** *and not brand specific****, but will make it clear that there are different brands/strengths available and this should be carefully checked prior to prescribing /administration to ensure consistency in the brand***
- *The epilepsy specialist nurses will no longer provide training to care providers/care homes on the use of buccal midazolam. They will signpost any requests for this training to other available resources, to be used in conjunction with Epilepsy Awareness Training, ensuring that carers know how to recognise epileptic (and non-epileptic) seizures and when it is appropriate to administer rescue medication.*

Oxcarbazepine

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures.

Licensed Dose: Usual dose range 0.6–2.4 g daily in divided doses.

Dose Titration: Introduce at a dose of 150mg – 300mg daily, increasing in 150mg – 300mg steps two to four weekly until seizures are controlled, there are signs of intoxication or a dose of 1200mg bd is reached.

Drug Withdrawal: Withdraw at a rate of 150mg – 300mg two to four weekly.

Side Effects: Nausea, vomiting, constipation, diarrhoea, abdominal pain, dizziness, headache, drowsiness, agitation, amnesia, asthenia, ataxia, confusion, impaired concentration, depression, tremor, hyponatraemia, acne, alopecia, rash, nystagmus, visual disorders including diplopia.

Monitoring: Avoid in patients taking carbamazepine and those with cardiac conduction defects.
Monitor plasma-sodium concentration in patients at risk of hyponatraemia.
Monitor body-weight in patients with heart failure.

Paraldehyde (RED DRUG)

Rectal solution (50:50) in olive oil

For prescribing information see BNFC

Licensed Indications: Unlicensed. Rectal paraldehyde is used for the treatment of tonic-clonic seizures.

Licensed Dose: Unlicensed.

Unlicensed doses commonly used: Dose expressed as 50% paraldehyde in olive oil:
Adults (5-10ml diluted 50% to) 10-20ml of the diluted rectal solution as a single dose.
Children (1 month – 18 years) 0.8ml/kg up to a maximum of 20ml

Dose Titration: Not applicable

Drug Withdrawal: Not applicable

Perampanel

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Perampanel is licensed for adjunctive treatment of partial onset seizures with or without secondary generalised seizures.

Licensed Dose: 2 mg once daily before bedtime, increased according to response and tolerability in 2mg steps at intervals of at least 2 weeks; usual maintenance 4–8 mg once daily; max. 12 mg once daily

Dose Titration: Introduce at 2mg once daily and titrate monthly in 2mg steps.

Drug Withdrawal: Perampanel should be withdrawn by halving the dose every two weeks.

Side Effects: Nausea, changes in appetite, weight increase, aggression, dizziness, drowsiness, dysarthria, gait disturbance, irritability, anxiety, confusion, suicidal ideation and behaviour, malaise, ataxia, back pain, vertigo, blurred vision, diplopia

Monitoring:

- Note interaction with oral contraceptive above 8mg/day, making the contraceptive less effective.
- In patients with hepatic impairment: increase at intervals of at least 2 weeks, up to max. 8 mg daily in mild or moderate impairment; avoid in severe impairment.
- Renal impairment: avoid in moderate or severe impairment.

Phenobarbital

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: All forms of epilepsy except typical absence seizures.

Licensed Dose: 60-180mg at night

Unlicensed doses commonly used: Some patients may require up to 240mg at night.

Dose Titration: Introduce at 30-60mg at night. Increase by 30mg every 2-4 weeks.

Drug Withdrawal: Sudden withdrawal should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, fits and delirium) may be precipitated

Side Effects: Hepatitis, cholestasis; hypotension; respiratory depression; behavioural disturbances, nystagmus, irritability, drowsiness, lethargy, depression, ataxia, paradoxical excitement, hallucinations, impaired memory and cognition, hyperactivity particularly in the elderly and in children; osteomalacia (see Cautions); megaloblastic anaemia (may be treated with folic acid), agranulocytosis, thrombocytopenia; allergic skin reactions.

Monitoring: Avoid in severe hepatic and renal impairment. Use with caution in mild to moderate renal impairment.

Phenytoin

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Tonic-clonic seizures; partial seizures; combination of these.

Licensed Dose: Usual dose 200-500mg daily

Unlicensed doses commonly used: Occasionally doses above 500mg may be used.

Dose Titration: Introduce at 150 mg- 300mg daily. Increasing in 25mg steps every two to eight weeks until seizures are controlled or symptoms of intoxication become unacceptable.

Drug Withdrawal: Withdraw at a rate of 25 mg - 100mg per month.

Side Effects: Nausea, vomiting, constipation, drowsiness, insomnia, transient nervousness, tremor, paraesthesia, dizziness, headache, anorexia; gingival hypertrophy and tenderness (maintain good oral

hygiene); rash (discontinue; if mild re-introduce cautiously but discontinue immediately if recurrence), acne, hirsutism, coarsening of facial appearance.

Monitoring: Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal.

Pregabalin

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Adjunctive therapy for focal seizures with or without secondary generalisation

Licensed Dose: Maximum dose 300mg bd

Dose Titration: Introduce at 25mg -75mg once or twice daily. Increase in steps of 25mg-75mg every one to two weeks to an initial dose of 150mg twice daily, then increase in steps of 25mg –75mg every one to two weeks until seizures stop, side effects intervene or a maximum dose of 300mg twice daily is reached.

Drug Withdrawal: Withdraw pregabalin at a rate of 25mg -100mg every one to two weeks

Side Effects: Dry mouth, constipation, vomiting, flatulence, oedema, dizziness, drowsiness, irritability, impaired attention, disturbances in muscle control and movement, speech disorder, impaired memory, paraesthesia, euphoria, confusion, malaise, appetite changes, insomnia, **weight gain,** sexual dysfunction, visual disturbances (including blurred vision, diplopia, visual field defects)

Monitoring: Reduce dose in renal impairment, see BNF for full details

Primidone

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: All forms of epilepsy except typical absence seizures

Licensed Dose: Usual maintenance 0.75–1.5 g daily in 2 divided doses

Dose Titration: Introduce at 125mg at night first dose. Increase in 125mg steps each week until seizures are controlled, symptoms of intoxication become unacceptable or a dose of 750mg bd is reached.

Drug Withdrawal: Withdraw at a rate of 250mg per month

Side Effects: Nausea, visual disturbances; less commonly vomiting, headache, dizziness; rarely psychosis, lupus erythematosus, arthralgia; also reported Dupuytren's contracture

Monitoring: Reduce dose in hepatic impairment

Rufinamide

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Adjunctive treatment of seizures in Lennox-Gastaut syndrome.

Licensed Dose: Maximum dose of 900mg bd but can be increased further dependant on body weight (body-weight 30–50 kg max. 900 mg twice daily; body-weight 50.1–70 kg max. 1.2 g twice daily; body-weight over 70.1 kg max. 1.6 g twice daily)

Dose Titration: Introduce at 100mg once or twice daily and increase in 100mg-200mg increments every one to two weeks. Maximum dose of 900mg bd but can be increased further dependant on body weight (body-weight 30–50 kg max. 900 mg twice daily; body-weight 50.1–70 kg max. 1.2 g twice daily; body-weight over 70.1 kg max. 1.6 g twice daily)

Drug Withdrawal: Rufinamide is withdrawn at a rate of 100-200mg increments every one to two weeks. This may be undertaken more quickly if severe adverse effects are experienced.

Side Effects: Nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain, weight loss, anorexia; rhinitis, epistaxis; dizziness, headache, drowsiness, insomnia, anxiety, fatigue, increase in seizure frequency, impaired coordination, hyperactivity, tremor, gait disturbances; influenza-like symptoms; oligomenorrhoea; back pain; nystagmus, diplopia, blurred vision; rash and acne; hypersensitivity syndrome also reported

Monitoring: Caution in mild to moderate hepatic impairment. Avoid in severe hepatic impairment.

Sodium Valproate

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: All forms of epilepsy; must not be initiated in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply; female children, female adolescents, women of childbearing potential and pregnant women must meet the conditions of the Pregnancy Prevention Programme.

Licensed Dose: Usual maintenance dose 1–2 g daily (20–30 mg/kg daily), max. 2.5 g daily

Unlicensed doses commonly used: Occasionally some patients may need up to 3g daily in divided doses

Dose Titration: Introduce at a rate of 300-500mg once or twice daily, increasing to an initial dose of 800-1,000mg daily. Titrate if required in 300-500mg increments every 2-4 weeks until seizures stop, side effects become unacceptable or a maximum dose of 1.5g bd is reached.

Drug Withdrawal: Withdraw at a rate of 300-500mg every 2-4 weeks unless serious adverse event demands more rapid withdrawal.

Side Effects: Nausea, gastric irritation, diarrhoea; **weight gain**; hyperammonaemia, thrombocytopenia; transient hair loss (regrowth may be curly), deafness, encephalopathy, Parkinsonism. Highly **TERATOGENIC**. Ensure patients are made aware & supplied with relevant literature: **Valproate – reproductive risks**

Monitoring: Avoid in hepatic impairment. Reduce dose in renal impairment.

Stiripentol (RED DRUG)

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Adjunctive treatment of refractory generalised tonic clonic seizures in severe myoclonic epilepsy of infancy (Dravet syndrome), in combination with clobazam and valproate

Licensed Dose: up to 50mg/kg in 2-3 divided doses. Note: Stiripentol capsules and oral powder sachets are **not bioequivalent,** caution when changing formulation

Dose Titration: start at 20mg/kg and increase to 30mg/kg after 1-4 weeks. Then titrate up by 5mg/kg every 1-4 weeks depending upon response. Adults may not tolerate 50mg/kg. Dose of clobazam may need to be reduced. Take with food, but avoid dairy products, carbonated drinks, fruit juice & caffeine containing drinks & theophylline.

Side Effects: Nausea, vomiting, diarrhoea,, abdominal pain, weight loss, anorexia; dizziness, drowsiness, insomnia, anxiety, fatigue, impaired coordination, hyperactivity, hyperkinesia, gait disturbances; diplopia, blurred vision; rash including photosensitivity, neutropenia, raised liver enzymes, rarely thrombocytopenia. Hyperammonaemia with valproate. Many drug interactions related to CYP450 enzymes.

Monitoring: Full blood count and liver enzymes before treatment and every 6 months thereafter. Avoid if history of psychosis. Manufacturer advises avoid in severe hepatic or renal impairment.

Topiramate

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation. **Women and girls of childbearing potential and pregnant women** must meet the conditions of the Pregnancy Prevention Programme.

Licensed Dose: Monotherapy: Usual adult dose 100–200 mg daily in 2 divided doses, adjusted according to response; max. 500 mg daily (doses of 1 g daily have been used in refractory epilepsy);
Adjunctive therapy: Usual dose 200–400 mg daily in 2 divided doses; max. 400 mg daily;

Unlicensed doses commonly used: Some patients may require up to 400mg bd

Dose Titration: Introduce at 25mg once or twice daily. Increase in steps of 25mg-50mg every one to two weeks to an initial dose of 50mg twice daily. Consider further dose increases in steps of 25mg-50mg every one to two weeks until seizures stop, side effects intervene or a maximum dose of 400mg twice daily is reached.

Drug Withdrawal: Withdraw topiramate at a rate of 50mg every two to four weeks.

Side Effects: nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, dry mouth, taste disturbance, gastritis, appetite changes, dyspnoea, impaired attention, cognitive impairment, movement disorders, seizures, tremor, malaise, impaired coordination, speech disorder, drowsiness, dizziness, sleep disturbance, anxiety, confusion, paraesthesia, aggression, mood changes, depression, agitation, irritability, nephrolithiasis, urinary disorders, anaemia, arthralgia, muscle spasm, myalgia, muscular weakness, visual disturbances including **acute glaucoma**, nystagmus, tinnitus, epistaxis, alopecia, rash, pruritus

Monitoring: Use with caution in hepatic impairment or renal impairment.

Vigabatrin

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: In combination with other anti-epileptic treatment for focal epilepsy with or without secondary generalisation. It should not be prescribed unless all other appropriate drug combinations are ineffective or have not been tolerated, and it should be initiated and supervised by an appropriate specialist.

Licensed Dose: Usual range 2–3 g daily (max. 3 g daily);

Dose Titration: Introduce at a dose of 250mg- 500mg daily, increasing in 250mg- 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.

Drug Withdrawal: Withdraw at a rate of 250mg- 500mg per month.

Side Effects: Nausea, abdominal pain; oedema; drowsiness (rarely encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG—reduce dose or withdraw), fatigue, excitation (in children), agitation, dizziness, headache, nervousness, depression, aggression, irritability, paranoia, impaired concentration, impaired memory, tremor, paraesthesia, speech disorder, weight gain; visual field defects (see under Cautions), blurred vision, nystagmus, diplopia

Monitoring: Visual fields must be tested prior to introduction and checked three monthly for first year and six monthly thereafter. This will be arranged by secondary care.
Consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73m^2.

Zonisamide

The details below are not a complete list, see the BNF and the SPC for full details

Licensed Indications: Used alone for the treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy, and as adjunctive treatment for refractory focal seizures with or without secondary generalisation.

Licensed Dose: Monotherapy usual maintenance 300 mg once daily; max. 500 mg daily.
Adjunctive therapy usual maintenance 300–500 mg daily in 1–2 divided doses
Note In adjunctive therapy, increase dose at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin or phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4.

Dose Titration: Introduce at 25mg-50mg once or twice daily. Increase in steps of 25mg – 100mg every two to four weeks to an initial dose of 150mg daily. Consider further dose increases in steps of 25mg every 1 to 2 weeks until seizures stop, side effects intervene or a maximum dose of 500mg daily is reached.

Drug Withdrawal: Withdraw zonisamide at a rate of 50mg every one to two weeks.

Side Effects: Nausea, diarrhoea, abdominal pain, constipation, dyspepsia, anorexia, weight loss, peripheral oedema, drowsiness, dizziness, confusion, agitation, irritability, depression, psychosis, ataxia, speech disorder, impaired memory and attention, fatigue, nystagmus, paraesthesia, tremor, pyrexia, insomnia, diplopia, ecchymosis, alopecia, pruritus, rash (consider withdrawal) visual disturbances including **acute glaucoma**,

Monitoring: Hepatic impairment -initially increase dose at 2-week intervals if mild or moderate impairment; avoid in severe hepatic impairment.

Renal impairment -initially increase dose at 2-week intervals; discontinue if renal function deteriorates

Appendix C

Cenobamate (Ontozry®) Information for Community Pharmacies

Background

Cenobamate (Ontozry®) is licensed for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products.[1]

NICE TA 753 recommends cenobamate as an option for treating focal onset seizures with or without secondary generalised seizures in adults with drug-resistant epilepsy that has not been adequately controlled with at least 2 antiseizure medicines.[2] 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 in a tertiary epilepsy service.

Cenobamate has been classified as amber within South Yorkshire (Barnsley, Doncaster, Rotherham and Sheffield) and Bassetlaw http://www.barnsleyformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=4&SubSectionRef=04.08.01&SubSectionID=A100&drugmatch=5103 for use in line with the NICE TA and the South Yorkshire and Bassetlaw Adult Epilepsy Shared Care Guideline.

This information has been produced to support community pharmacies with the ordering of cenobamate to ensure continuity of supply for patients in the community.

Ordering Information (correct at time of update – December 2022)

Cenobamate (Ontozry®) is currently only available from Phoenix Healthcare.[3] Pharmacies who currently hold Phoenix Accounts may order via the Phoenix Reordering System or by calling Customer Services. Alternatively, pharmacies who hold accounts with both Alliance and Phoenix can order via Alliance using the Third Party Ordering System (TPOS). It is also anticipated that pharmacies who hold accounts with both AAH and Phoenix will be able to order via AAH using TPOS in the near future.

If a pharmacy does not currently hold a Phoenix Account please contact their Customer Services via the contact details below.

Phoenix Contact Information

General Customer Services (order status/delivery queries/order placement):

Tel: 0844 736 2287

Email: customerservice@phoenixmedical.co.uk

Web Portal (pharmacy and Doctors): https://www.myp-i-n.co.uk/pms/design/hframe.htm

PIP Codes

Product Description	PIP Code
Cenobamate Ontozry 12.5mg 1x14 & 25mg 1x14 Tablets 28	6773691
Cenobamate Ontozry 50mg tablets 1x14 Tablets 14	6773683
Cenobamate Ontozry 50mg tablets 2x14 Tablets 28	6773675
Cenobamate Ontozry 100mg tablets 1x14 Tablets 14	6773667
Cenobamate Ontozry 100mg tablets 2x14 Tablets 28	6773642
Cenobamate Ontozry 150mg tablets 1x14 Tablets 14	6773634
Cenobamate Ontozry 150mg tablets 2x14 Tablets 28	6773659
Cenobamate Ontozry 200mg tablets 1x14 Tablets 14	6773626
Cenobamate Ontozry 200mg tablets 2x14 Tablets 28	6773618

Further Information

Should a pharmacy require further information or encounter any issues in ordering the medication, please liaise with a member of the Medicines Management Team (either linked to the GP practice/PCN or within the place based team within the ICB) who can advise and/or support the patient in obtaining the medication from an alternative pharmacy as necessary.

References

1. Ontozry® SPC. Available at: https://www.medicines.org.uk/emc/product/13010/smpc. Date accessed<1st August 2022>.
2. NICE TA 753. Cenobamate for treating focal onset seizures in epilepsy (December 2021). Available at: https://www.nice.org.uk/guidance/ta753. Date accessed <1st August 2022>.
3. Information provided by Angelini Pharma.

References used during review September 2021

British National Formulary - https://bnf.nice.org.uk/

Electronic Medicines Compendium - https://www.medicines.org.uk/emc#gref

NICE Epilepsies: diagnosis and management CG137 - https://www.nice.org.uk/guidance/cg137

NICE TA753: Cenobamate for treating focal onset seizures in epilepsy - https://www.nice.org.uk/guidance/ta753

MHRA Drug Safety Update - https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review

MHRA Drug Safety Update - https://www.gov.uk/drug-safety-update/antiepileptic-drugs-updated-advice-on-switching-between-different-manufacturers-products

MHRA Drug Safety Update – https://www.gov.uk/drug-safety-update/valproate-pregnancy-prevention-programme-actions-required-now-from-gps-specialists-and-dispensers and https://www.gov.uk/guidance/valproate-use-by-women-and-girls

RCPCH Guidance Document on Valproate Use in Women and Girls of Childbearing Years - https://www.rcpch.ac.uk/sites/default/files/2021-01/Pan_College_Guidance_Document_on_Valproate_Use%20V2.1.pdf

PHE Dependence and withdrawal associated with some prescribed medicines - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940255/PHE_PMR_report_Dec2020.pdf

Additional references accessed – interim update Dec 2022
MHRA Drug Safety Update - Topiramate (Topamax): start of safety review triggered by a study reporting an increased risk of neurodevelopmental disabilities in children with prenatal exposure - GOV.UK (www.gov.uk)

SPC for cenobamate - Ontozry 200 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Additional references accessed – interim updates in 2024/2025
MHRA Valproate safety measures - https://www.gov.uk/government/collections/valproate-safety-measures

MHRA Drug Safety Update - https://www.gov.uk/drug-safety-update/valproate-belvo-convulex-depakote-dyzantil-epilim-epilim-chrono-or-chronosphere-episenta-epival-and-syonellv-review-by-two-specialists-is-required-for-initiating-valproate-but-not-for-male-patients-already-taking-valproate

MHRA Valproate - reproductive risks - https://www.gov.uk/guidance/valproate-reproductive-risks

Topiramate (Topamax): introduction of new safety measures, including a Pregnancy Prevention Programme - https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme