THE SOUTH YORKSHIRE & BASSETLAW

Shared Care Protocol
For
Epilepsy in Adults

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Approved by: **Sheffield Area Prescribing Group**

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Anti-epileptic drugs
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 and GPs for many years with GPs taking prescribing responsibility where appropriate. 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.

Blood tests for monitoring of patients on anti-epileptic drugs are very rarely required, and the practice of adjusting drug dose according to the results of anti-epileptic drug levels is strongly discouraged unless there is a question of adherence. 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. Routine blood tests for monitoring of liver function or white cell count are not indicated for any anti-epileptic medication, except felbamate.

Doctors should be aware that anti-epileptic drugs, 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). Such induction of liver function means these drugs interact with oral contraceptives and may reduce their efficacy (see page 4). Lamotrigine also has modest effects on hormone levels, it is unclear if this affects contraceptive efficacy. NICE guidance states that prescribers may wish to undertake baseline blood tests including blood count, electrolytes, vitamin D and calcium and repeat every 2-5 years in patients on enzyme-inducing drugs. As the risk of bone demineralization is probably greater in patients taking enzyme-inducing anti-epileptic drugs, it is worth considering bone densitometry in older patients taking these drugs.

Procedure for Initiating Shared Care Arrangements

Specialist education, training, ongoing advice and support is available from the specialist team. Patients seen in the 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-epileptic 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 outpatient clinic will be notified in writing to the GP and letters countersigned by the Consultant Neurologist.
Sharing of care assumes communication between the specialist 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.

Specialist Team Responsibilities:

- 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, prior to the initiation of medication.
- Ensure patient is fully informed of potential benefits and side effects of treatment.
    - Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. If valproate is being used in woman of child bearing age, ensure the woman is made aware and supplied with relevant literature https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials
- Initiate treatment and provide one month supply of medication (for medication initiated during clinic appointments, see below* for medication changes made between clinic appointments).
- If the patient agrees, Epilepsy Nurse Specialist will contact the patient to offer a clinic appointment/home visit for follow up. The timescale for this follow up will vary according to patient need and the medication being prescribed. The GP will be notified of the outcome of the follow up discussion.
- Provide all patients with contact details of the Epilepsy Nurse Specialist so they can contact the service if needed before the nurses contact them.
- Consultant Neurologist writes to GP within 10 days of initiating new medication, detailing individual patient plan (dose and titration).
- Letter from Consultant Neurologist to state that the request for GP to continue prescribing is in accordance with this shared care guideline.
- Any dose changes once the patient is established on treatment will be conveyed in writing to the GP for the GP/specialist service** to prescribe.
- *Where a change in medication is required between clinic appointments, for example if a drug has not been tolerated, the following procedure will be followed:
    - Epilepsy Nurse Specialist will liaise with Consultant Neurologist to decide on a suitable medication.
    - Epilepsy Nurse Specialist** will send a written request to ask the GP to issue a prescription for the medication. The request will also detail the individual patient plan (dose and titration) and state the request for GP to prescribe is in accordance with this shared care guideline.
    - If the GP has concerns regarding the prescription of an anti-epileptic drug they will seek advice from the patient's Consultant Neurologist.
- **Where the epilepsy nurse service is commissioned to prescribe medicines (e.g. Doncaster), they will issue the prescription and provide a written update for the GP.
- Monitor side effects of medication via routine out-patient visits with Epilepsy Nurse Specialists
- Report adverse events to the MHRA
- Monitor patient's response to treatment via routine out-patient visits with Epilepsy Nurse Specialists

Baseline Tests

See individual drugs in Appendix B.

Disease monitoring

The patient will be reviewed by the specialist team when necessary. The time interval will differ depending on the patient.

Primary Care Team Responsibilities:

- 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.
- Check drug interactions with any new medication started or any new conditions diagnosed. Contact the specialist team if possible interactions found and discuss with Consultant Neurologist if necessary.
- Undertake drug specific monitoring, where applicable, as detailed within Appendix B.
- Amend prescription as per requests from secondary care for dose changes in patients on established treatment.
- Where a change in medication is required between clinic appointments, for example if a drug has not been tolerated, the following procedure will be followed:
    - Epilepsy Nurse Specialist will liaise with Consultant Neurologist to decide on a suitable medication.
    - Epilepsy Nurse Specialist** will send a written request to ask the GP to issue a prescription for the medication. The request will also detail the individual patient plan (dose and titration) and state the request for GP to prescribe is in accordance with this shared care guideline.
    - Anti-epileptics appropriate for a GP to initiate and prescribe, under the guidance of the specialist, are listed in Appendix B.
    - If the GP has concerns regarding the prescription of an anti-epileptic drug they will seek advice from the patient's Consultant Neurologist.

  **Where the epilepsy nurse service is commissioned to prescribe medicines (e.g. Doncaster), they will issue the prescription and provide a written update for the GP.
- Report adverse events to the MHRA.
- Report adverse events to the consultant sharing the care of the patient.

Routine Monitoring

See Appendix B for information relating to individual drugs.

Disease Monitoring

The patient will be reviewed by the specialist team when necessary. The time interval will differ depending on the patient.

Communication

Specialist to GP

The Consultant Neurologist will inform the GP when they have initiated an anti-epileptic drug and will provide a summary of dosage and titration instructions for the GP to follow.

GP to specialist

If the GP has concerns over the prescribing of the relevant anti-epileptic drug, they will contact the specialist team as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
Consultant Neurologists		
Dr A Brockington (Doncaster & Sheffield)	01142712619	Alice.brockington@sth.nhs.uk
Dr G Dennis (Bassetlaw & Sheffield)	01909502712 0114 2712769	Gary.dennis@sth.nhs.uk
Dr R A Grunewald (Chesterfield & Sheffield)	0114 2712306	richard.grunewald@nhs.net
Dr SJL Howell (Sheffield)	0114 2712942	
Prof M Reuber (Sheffield)	0114 2268688	
Dr P Shanmugarajah (Rotherham & Sheffield)	0114 2713708	Priya.shanmugarajah@sth.nhs.uk
Dr S Wong (Barnsley & Sheffield)	01142711977	Siew.wong@sth.nhs.uk

Epilepsy Nurse Specialist Service Sheffield, Rotherham, Chesterfield Epilepsy Nurse Specialist Service Doncaster Epilepsy Nurse Specialist Service Barnsley Epilepsy Nurse Specialist Service Bassetlaw	0114 2713488 01302 796215 01226 645180 01777 863507	epilepsyservice@sth.nhs.uk (do not send patient identifiable data)
Lead Pharmacist Sheffield-Ben Dorward	0114 2263225	Ben.dorward@sth.nhs.uk

STH intranet website: http://nww.sth.nhs.uk/nhs/NeuroScience/Neurology/

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 who is being asked to take over the prescribing. 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.

Management and referral guidelines
First unprovoked seizure (i.e. not caused by alcohol, anoxia due to syncope, etc.):

- Do not initiate anti-epileptic drugs.
- Refer for investigation.
- Give advice about driving (stop and inform DVLA www.gov.uk/epilepsy-and-driving), bathing, swimming, working at heights, working with dangerous machinery

Second seizure before outpatient appointment
If urgent treatment is required, therapeutic options may be discussed with consultant or on-call SpR for Neurology. Advise about driving, and in women teratogenic risk of drugs (high risk with valproate – **avoid valproate in women with childbearing potential**).

Please note:
[1] Drug interaction between anticonvulsant and oral contraceptives exists with: carbamazepine, eslicarbazepine, felbamate, oxcarbazepine, perampanel, phenytoin, phenobarbital, primidone, rufinamide and topiramate. The Faculty of Sexual and Reproductive Health (FSRH) gives detailed advice: https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/drug-interactions-final-15feb.pdf The guidance currently recommends that women starting enzyme-inducing anti-epileptic drugs (AEDs) should be advised to use a reliable form of contraception unaffected by enzyme-inducing AEDs e.g. progestogen only

injectable, copper-bearing intrauterine devices or the levonorgestrel containing intrauterine system. The interaction also applies to post-coital oral contraceptives and the contraceptive implant (see FSRH and MHRA guidance).

- Double dose of oestrogen combined pill equivalent to a minimum of ethinyloestradiol 50mcg is required for those women who wish to continue on combined oral contraceptive (COC), and FSRH suggests continuous or tricycling regimen with a pill-free interval of 4 days or to use alternative contraception.
- 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. The COC also reduces the blood level of lamotrigine (and thus there is a risk of breakthrough seizures when a COC is taken by women on a stable dose of lamotrigine and of toxicity in the pill free week).
- Depo contraceptives such as Depo-Provera injection and intrauterine coils are acceptable. However contraceptive implants should be avoided.

[2] Warn about risk of allergic reactions, which can be serious (Stevens Johnson syndrome) with phenytoin, carbamazepine, phenobarbital and lamotrigine.

[3] Warn about an increased risk of suicidal ideation (1-2%) with anti-epileptic drugs.

Criteria for referral of patients established on treatment

Any of the following:

- When patient or general practitioner is **not** comfortable to continue with the existing regime due to either continuing seizures or drug side effects.
- Advice in respect of concordance.
- Special situations, e.g.
    - pregnancy, preconception counselling
    - occupational advice
    - driving
    - discontinuing medication

Dispensing – Continuity of supply

Appendix C specifies the MHRA guidance relating to minimising risk when changing between different manufacturer's supplies of anti-epileptic treatment.

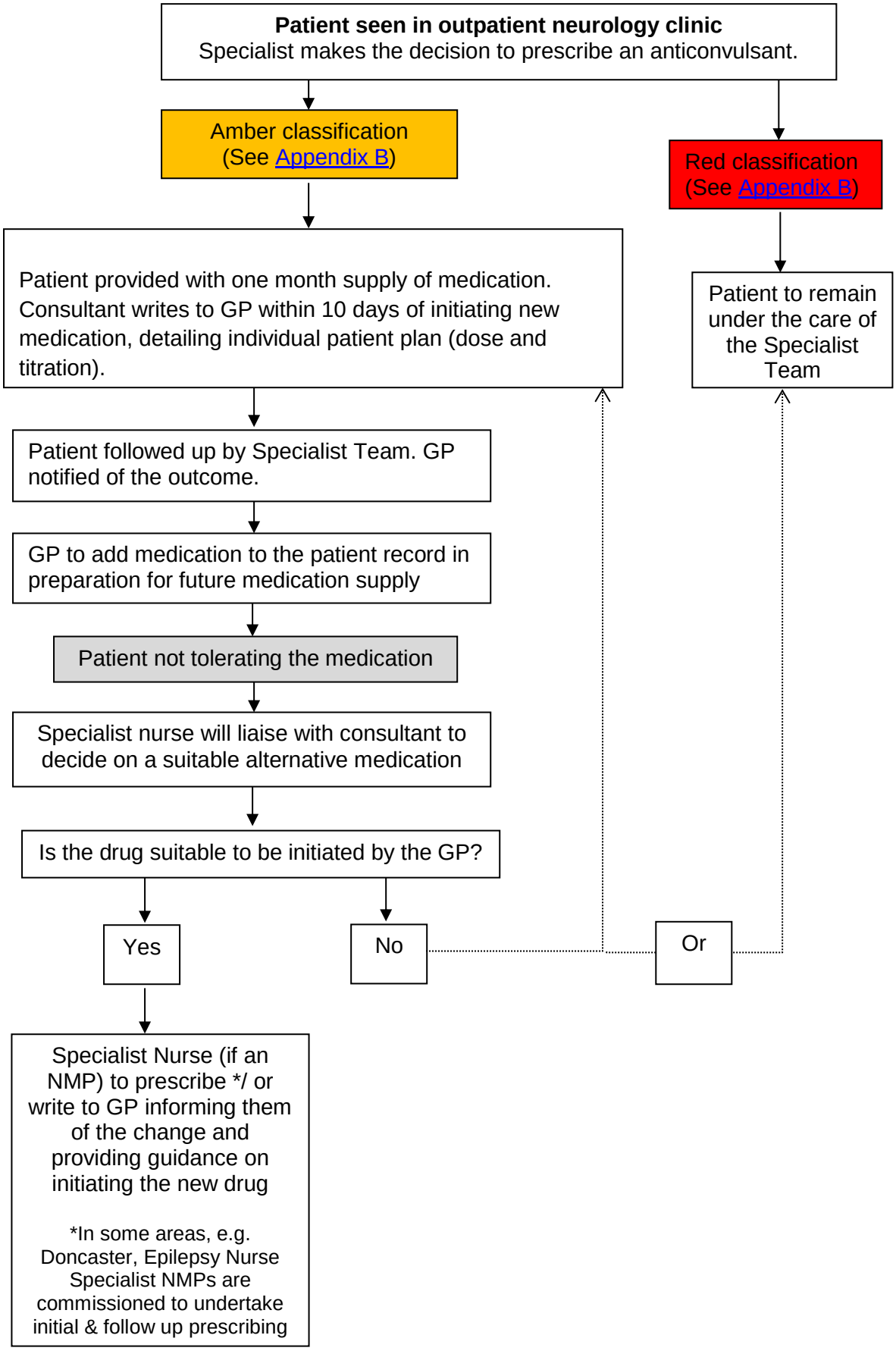
Specific MHRA advice to the dispensing pharmacist is that they "should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that AED. Such cases should be discussed and agreed with both the prescriber and patient (or carer)".

In the circumstances whereby a pharmacy is unable to ensure continuity of supply and

- the prescriber cannot be contacted and
- as a result the patient would be at risk of a break in treatment

Then the opinion of the named specialist neurologists in this document is that a supply of the medicine should be made regardless of brand, i.e. a change in brand if required is preferable to a break in treatment.

Appendix A – Process for initiating Shared Care



Appendix B – Drug summaries (emergency drugs used in conjunction with emergency care plan)

Drug	**MHRA category (see Appendix C) Advice on brand prescribing**	**Traffic light status**
Acetazolamide	NA	Amber
Benzodiazepines	2	Amber
Brivaracetam	NA	Amber
Carbamazepine	1	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	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
Retigabine	2	Red
Topiramate	2	Amber
Sodium valproate	2	Amber
Vigabatrin	3	Amber
Zonisamide	2	Amber

Acetazolamide

SPC available at: http://www.medicines.org.uk/emc/medicine/22217/SPC/Diamox+Tablets+250mg/

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

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

Benzodiazepines

(i.e. clobazam, lorazepam, diazepam. For rectal diazepam see separate entry below)
SPCs available at: http://www.medicines.org.uk/emc/

Licensed Indications: These may be used in accordance with an individual care plan as an oral rescue medication to prevent seizure clusters or secondary generalisation particularly in partial seizures.

Licensed Dose: Maximum doses are tailored to the individual
Clobazam 10mg (may also be used for catamenial seizures) maximum doses 60mg daily
Lorazepam 1mg. Maximum dose 4mg (2mg in the elderly)
Diazepam 5mg-10mg. Maximum dose 30mg (15mg in the elderly)

Dose Titration: Doses are titrated according to response

Side Effects: Drowsiness, confusion, ataxia, headache, vertigo, GI disturbance, urinary retention,

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.

Brivaracetam

SPC available at: http://www.medicines.org.uk/emc/medicine/31452

Licensed Indications: Adjunctive therapy in the treatment of focal onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy

Licensed Dose: Initial daily dose 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

Carbamazepine

SPC:
http://www.medicines.org.uk/emc/medicine/1328/SPC/Tegretol+Tablets+100mg%2c+200mg%2c+400mg/

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
(Higher doses may be used in pregnancy due to significant reductions in serum dose)

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 rash may require admission and immediate withdrawal of Carbamazepine.

Side Effects: Dry mouth, nausea, vomiting, rash, oedema, dizziness, drowsiness, fatigue, headache, hyponatraemia, blood disorders, dermatitis, urticaria.

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.

Clonazepam

SPC: http://www.medicines.org.uk/emc/medicine/25745

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: Withdraw at a rate of 2mg per month

Side Effects: Drowsiness, fatigue, dizziness, muscle hypotonia, co-ordination disturbances, poor concentration, restlessness, confusion, amnesia

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)

SPC available at: http://www.medicines.org.uk/emc/

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; Child 1-2 years 5mg; Child 2-12 years 10mg.

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

SPC available at: / http://www.medicines.org.uk/emc/medicine/22376

Licensed Indications: 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.

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

May **reduce effect of combined oral contraceptive, warfarin** & simvastatin (weak CYP3A4 inducer)

Caution should be exercised in the treatment of patients with renal impairment and the dose should be adjusted according to creatinine clearance

Ethosuximide

SPC available at: http://www.mhra.gov.uk/spc-pil/

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,

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.

Felbamate (hospital only drug) - Red Drug

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. Two 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

SPC available at:
http://www.medicines.org.uk/emc/medicine/24646/SPC/Gabapentin+300mg+Capsules/

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

Licensed Dose: 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

SPC available at:
http://www.medicines.org.uk/emc/searchresults.aspx?term=lacosamide&searchtype=QuickSearch

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.

Monitoring: Caution in severe hepatic impairment. Titrate dose with caution in patients with renal impairment. Maximum dose of 250mg daily if eGFR<30ml/min/1.73^2.

Lamotrigine

SPC available at: http://www.medicines.org.uk/emc/medicine/4228/SPC/Lamictal/

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:
- Lamotrigine theoretically increases the metabolism of hormones in the COC and thus may have the potential to reduce its efficiency.
- In patients established on lamotrigine treatment addition of oral contraceptives to their drug regime may lower the effectiveness of the anti-epileptic medication. In these circumstances an increase of lamotrigine dose of about 30% should be considered.
- Warn patients to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop.

Levetiracetam

SPC available at:
http://www.medicines.org.uk/emc/searchresults.aspx?term=levetiracetam&searchtype=QuickSearch

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: Halve dose in severe hepatic impairment if eGFR<60ml/min/1.73m^2. Reduce dose in renal impairment.

Methsuximide (hospital only drug) – Red Drug

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)

SPCs available at:
http://www.medicines.org.uk/emc/medicine/25538/SPC/BUCCOLAM+10+mg+oromucosal+solution/
http://www.medicines.org.uk/emc/medicine/33476 (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: Used as rescue medication with a BRAND SPECIFIC 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:

- ***Midazolam 10mg in 1ml Oromucosal solution (Epistatus®) for adults (currently licensed for use in children from 10 to < 18 years of age).***
- ***Midazolam 5mg in 1ml Oromucosal solution (Buccolam®) for children (currently licensed for use from 3 months to < 18 years of age).***

Oxcarbazepine

SPC available at:
http://www.medicines.org.uk/emc/medicine/2673/SPC/Trileptal+150+mg%2c+300+mg%2c+600+mg+Film-coated+tablets/

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.

Paraldehyde – Red drug (area dependent)

Rectal solution (50:50) in olive oil

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

SPC available at:
http://www.medicines.org.uk/emc/medicine/26951/SPC/Fycompa+2mg%2c4mg%2c6mg%2c8mg%2c10mg%2c12mg+film-coated+tablets/

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

SPC available at:
http://www.medicines.org.uk/emc/medicine/24078/SPC/Phenobarbital+Tablets+BP+60mg/

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 impairment. Use with caution in renal impairment.

Phenytoin

SPC available at:
http://www.medicines.org.uk/emc/searchresults.aspx?term=phenytoin&searchtype=QuickSearch

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 250 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

SPC available at: http://www.medicines.org.uk/emc/medicine/30815

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

Primidone

SPC available at: http://www.medicines.org.uk/emc/medicine/27348/SPC/PRIMIDONE+250mg+tablet/

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

SPC available at:
http://www.medicines.org.uk/emc/medicine/20165/SPC/Inovelon+Tablets+and+Oral+Suspension/

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 50–70 kg max. 1.2 g twice daily; body-weight over 70 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 50–70 kg max. 1.2 g twice daily; body-weight over 70 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.

Retigabine – Red Drug –being withdrawn by manufacturer

SPC available at: http://www.medicines.org.uk/emc/medicine/24527/SPC/Trobalt/

Licensed Indications: Adjunctive treatment of drug-resistant focal seizures with or without secondary generalisation; it should only be prescribed when other appropriate drug combinations have proved inadequate or have not been tolerated.

NICE TA232: Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (July 2011)
Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, and topiramate has not provided an adequate response, or has not been tolerated.

Licensed Dose: Usual maintenance dose is 600mg-1200mg daily.

Dose Titration: Retigabine is initiated at a dose of 100mg TDS, which is titrated to response, and the expected maintenance dose is expected to be between 600mg and 1200mg a day.

Drug Withdrawal: Retigabine is withdrawn at the rate it was introduced. This may be undertaken more quickly if severe adverse effects are experienced.

Side Effects: See below.

Monitoring: SPC recommends caution with drugs which could prolong QT interval and certain patient groups at elevated risk such as those with known prolonged QT intervals; structural heart disease and those over 65 should have an ECG before starting treatment and one at maintenance dose. Reduce dose in hepatic impairment. Reduce dose in renal impairment.

Pigment changes (ie, discolouration) of ocular tissue—including the retina—have been reported in two long-term clinical studies of retigabine and a compassionate use programme. These studies also observed blue-grey discolouration of the nails, lips, or skin. Patients who are currently receiving retigabine treatment should be reviewed at next appointment. Comprehensive ophthalmic examination should be done at the start of treatment and at least every 6 months thereafter during treatment. This will need to be performed by secondary care ophthalmology. Treatment should only continue after a careful reassessment of the balance of benefits and risks if pigment changes are detected.

Topiramate

SPC available at:
http://www.medicines.org.uk/emc/searchresults.aspx?term=topiramate&searchtype=QuickSearch

Licensed Indications: Alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation.

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.

Sodium Valproate

SPC available at:
http://www.medicines.org.uk/emc/searchresults.aspx?term=sodium+valproate&searchtype=QuickSearch

Licensed Indications: All forms of epilepsy; in female children, female adolescents, women of childbearing potential and pregnant women treatment should only be initiated if other treatments are ineffective or not tolerated

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. TERATOGENIC. Ensure women of child bearing potential made aware & supplied with relevant literature https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials

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

Vigabatrin

SPC available at: http://www.medicines.org.uk/emc/medicine/26956/SPC/Sabril+500+mg+film-coated+tablets/

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 normally be arranged by secondary care. Consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73m^2.

Zonisamide

SPC available at:
http://www.medicines.org.uk/emc/medicine/16240/SPC/Zonegran+25%2c+50%2c+100+mg+Hard+Capsules/

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

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)

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:

MHRA/CHM advice (Available at: https://www.gov.uk/drug-safety-update/antiepileptic-drugs-new-advice-on-switching-between-different-manufacturers-products-for-a-particular-drug

Anti-epileptic drugs: new advice on switching between different manufacturers' products for a particular drug (November 2013)

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of anti-epileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

- Different anti-epileptic drugs 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;
- 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;
- 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);
- Please report on a Yellow Card any suspected adverse reactions to anti-epileptic drugs (see https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/
- 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

Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate. 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

Category 3

Levetiracetam, 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, and risk of confusion or dosing errors