Anti-Epileptic Drug (AED) Pharmacotherapy Algorithm

NICE Guidance

The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication, co-morbidity, the child/ young person/adult's lifestyle, the preferences of the person and their family and/or carers as appropriate 1.9.1.2*

Consistent supply to patient of a particular manufacturer's AED preparation is recommended. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects. 1.9.1.4*

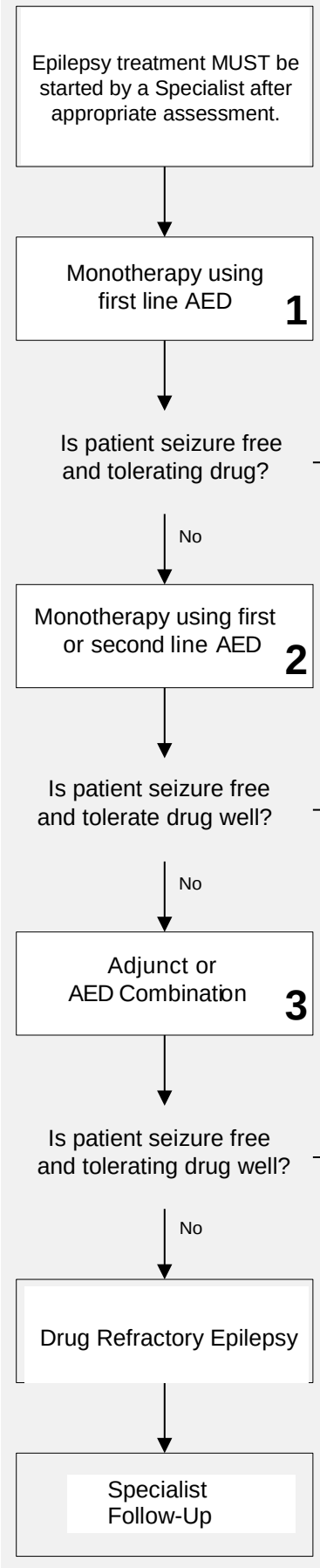
The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first -line AED 1.9.1.3*

If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first -line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly. 1.9.1.6*

It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects. 1.9.1.8*

* NICE Guidelines CG137

AED Pathway



Communication between Consultant and GP

Consultant or Epilepsy Specialist will assess the Patient's epilepsy, arrange necessary investigations and recommend a treatment approach.

Consultant or other member of the Epilepsy Clinical Team will write to GP providing details of recommended drug regime including starting dosage, rate of dose increase, potential target dose, etc. Letter to advise on the action to be taken if seizures stop, or if intolerable side effects occur.

Patient will be followed up by the hospital's secondary care team until they are seizure-free or maximally treated on a stable dose of anti-epileptic drug, or further treatment changes are declined by the patient.

If a newly-licensed anti-epileptic is recommended, a shared care guideline will be sent to the GP. For this purpose, "newly-licensed" drugs are those which have been granted a UK license within the last 4 years. Prescribing and dispensing for the first 3 months will be carried out by the hospital. The GP will be asked to maintain the on-going prescription once the treatment has been optimised.

Discharge to GP

GP Responsibility:
Amend maintenance prescription as per letter following patient's hospital appointments. May be rarely asked to titrate in line with a titration schedule. Organise blood tests when indicated. Monitor for development of adverse effects to medication and where appropriate & alert the hospital's Epilepsy Clinical Team.

Waltham Forest and East London Medicines Optimisation and Commissioning Committee (WEL MOCC)
NHS Newham CCG, NHS Tower Hamlets CCG, NHS Waltham Forest CCG
Primary Care Anti-Epileptic Pathway. Date approved: March 2019. Review date: March 2021

The Annual Primary Care Clinical Review

Agree a comprehensive care plan with the patient, family and carers:

- Lifestyle issues
- Drug Review
- Epilepsy Specialist Nurse Contact

Discuss Sudden Unexplained Death in Epilepsy (SUDEP) – This should be discussed to show why preventing seizures is important and importance of concordance with medication. Tailored information on the person's relative risk of SUDEP should be part of the counselling checklist for children, young people and adults with epilepsy and their families and/or carers. Information can be found from the SUDEP charity: www.sudep.org

Annual review should include an enquiry about side effects and a discussion of the treatment plan to ensure concordance and adherence to medication.

Women and girls with epilepsy

Women and girls must be given accurate information and counselling about contraception, conception, pregnancy, breastfeeding, caring for children and menopause.

Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There is limited data on risks to the unborn child associated with newer drugs. See appendix 4.
Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800mg/day) and polypharmacy, particularly with sodium valproate, are associated with greater risk.

The Medicines and Healthcare products Regulatory Agency (MHRA) changed the license of valproate medicines to reflect the significant risk of birth defects and persistent developmental disorders to children born to women who take valproate during pregnancy.
Valproate medicines must not be used in women and girls of childbearing potential including young girls below the age of puberty unless the conditions of the Pregnancy Prevention Programme are met (see below) and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist. Valproate must not be used in pregnant women.

The Pregnancy Prevention Programme is a system to ensure all female patients taking valproate:
•have been told and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form
•are on highly effective contraception if necessary
•see their specialist at least every year

Resources:
The MHRA toolkit provides safety advice and resources to ensure female patients are better informed about the risks of taking valproate during pregnancy.
https://www.gov.uk/guidance/valproate-use-by-women-and-girls
http://www.gov.uk/government/news/valproate-banned-without-the-pregnancy-prevention-programme

This includes the Acknowledgement Form – for the specialist and patient (or their parent / caregiver / responsible person) to sign at initiation and at treatment reviews at least every year. The patient should receive a copy of the form; one copy should be filed in the specialist notes, and one copy sent to the patient's GP.

Contraception

In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. See Appendix 2 for contraception information.

All women and girls on AEDs should be offered 5mg per day of folic acid before any possibility of pregnancy.

Pregnancy

This should be planned where possible and in conjunction with the Specialist. In the event of an unplanned pregnancy, **DO NOT STOP taking AEDs** and contact the Epilepsy Clinic and Pregnancy Clinic. Often the drug treatment will remain the same but at lower doses. More information can be found in appendix 4 of risks of individual drugs.

Status Epilepticus

This is prolonged or repeated seizures and convulsive status epilepticus.

Buccal midazolam is the first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Rectal diazepam is a preferred option if buccal midazolam is not available. Treatment is only required in certain circumstances and not every patient will require it. This will be determined by the Epilepsy Clinic and where information will be provided, as drug treatment is only part of the management plan (includes care plan, counselling, training etc). Buccal midazolam should not be prescribed in the absence of a management plan. Advice can be sought from the Epilepsy Clinic. Epilepsy clinic has a direct number and it is available at core time and out of hours (i.e. evenings and weekend) provision of information.

Treatment

The aim of treatment is to maximize the chance of reducing seizure frequency and severity. Seizures severely affect quality of life, but are also at risk of death (SUDEP). Choice of drug will be based upon evidence of efficacy (in clinical outcome terms) and the risks (potential for doing harm, adverse effects.).

Most patients will respond to either the first or second anti-epileptic drug (AED) but some patients will require multiple AEDs to reduce or stop seizures (termed drug refractory).

Where the older established drugs have failed to be successful in controlling the seizures, newer drugs need to be tried, usually as add-on therapy.

In these patients response to AEDs can be idiosyncratic. The choice of AED combinations in these patients is complex, and may be guided by the epilepsy syndrome (group of features that occur together e.g. types of seizures, age when seizures began, part of the brain involved, genetic information etc), response, concomitant, tolerability of previous AEDs, and patient preference.

Prescribing of AEDs

Initiation: Anti-epileptic treatment will be initiated by specialists in secondary care. GPs will **NEVER** be asked to initiate or make changes to treatment regimens.

Specialists should make the diagnosis and initiate treatment choice. Primary Care clinicians should not initiate or make changes to existing drug regimens without advice from a specialist.

A table of the recommended AEDs by epilepsy type as recommended by NICE has been included for information in appendix 1. It is recognised that NICE choices have an economic slant and may not always fit the best clinical choice for the patient. The choice of medication will depend on the patient and place on pathway. Deviations to the pathway /recommended AEDs may occur for specific patients based on national and international guidelines (e.g. SIGN etc.) and clinical expertise depending on clinical factors and co-medications.

Continuation treatment:

- Dose regimens will be instructed by specialists.
- Prescribing and dispensing for the first 3 months will be carried out by the hospital to assess efficacy and tolerance to the drug, identify adverse effects and dose titration.
- Primary care will then be requested to continue prescribing thereafter.

In *general* primary care clinicians will not be asked to titrate regimes. However it may be possible that titration has not been completed after the initial 3 months and primary care may be requested to *continue* titration, but **ONLY WHERE A TYPED DATED FULL PERSONALISED TITRATION SCHEDULE HAS BEEN PROVIDED**. Primary care clinicians should expect the Trust to always include a titration schedule with the hospital letter and should not prescribe in the absence of one or where it is has not been specified to follow one.

Most AEDs are amber drugs; requiring initiation only on the advice of a specialist. Newer agents will have Shared Care Guidelines (SCG) available and supplies for the first 3 months of initiation will be supplied by the hospital. The SCG available are at the end of the document for Brivaracetam and Perampanel.

Information about standard titration and doses has been included for information in appendix 2.

Adverse effects

Adverse effects are common and can be severe enough to necessitate withdrawal of a drug. It is recognised that the newer drugs often have fewer side effects and it is reasonable that they are tried before the older agents, some of which could be potentially serious.

Although most patients will respond to either the first or second anti-epileptic drug (AED), some patients will require multiple AEDs to reduce or stop seizures. In these patients (termed drug refractory), response to AEDs can be idiosyncratic.

Management: Most adverse effects occur early in treatment.

If a patient has been on a stable dose and develops new symptoms, it is unlikely to be due to adverse effects of the drugs and the advice is to contact the Epilepsy Team.

If a patient is on a titrating regime and develops a new symptom, it may be due to an adverse effect. In the first instance contact the Epilepsy Team and check for concurrent interacting drugs. The usual management in such circumstances may be to reduce the dose back one step in the regime as per the titration plan and reviewed in two weeks as guided by the Epilepsy Team.

Interactions: Many AEDs will interact with other medication. Please refer to the latest National BNF for an up to date list of interactions. Queries on interactions and co-morbidities can be directed to the Epilepsy Team**.** See BNF for information https://bnf.nice.org.uk/

Therapeutic Drug Monitoring

In general there are very few situations where this is helpful and in general is not necessary. Monitoring is often thought necessary if adverse effects are present; however adverse effects can still occur within normal therapeutic parameters. The exception would be use of high dose phenytoin. Where specific monitoring is required this will be advised and carried out by the Epilepsy Team. However in all circumstances please contact the Epilepsy Team.

Advice & Support:

Epilepsy Team Contact Details: 0203 5940701 or epilepsy.nurse@bartshealth.nhs.uk

Available: Monday to Friday 9-5pm (usually 30-45min response time depending on day /demand.)

Out-of-hours: Neurology registrar on-call (via switch), or can leave an answerphone message or send an email for next working day (for non-urgent).

Also available under Neurology Advice and Guidance on ERS.

Generic AEDs and switching between different manufacturer's products

Drugs should be prescribed by **BRAND or BRANDED GENERICs**, as differences can exist between generic drugs. Differences in adverse effects exist between different manufacturers which can lead to non-concordance.

The commission on human medicines (CHM[1]) reviewed adverse reactions arising from generic anti-epileptic products. The CHM considered characteristics of anti-epileptic drugs and classified them into three categories based on therapeutic index, solubility and absorption to help prescribers and patients decide whether it was necessary to maintain continuity of supply of a specific manufacturer's product.

These categories are listed below:

	Advise for doctors	Antiepileptic drugs in category
Category 1	Doctors are advised to ensure that their patient is maintained on a specific manufacturer's product	Carbamazepine, Phenobarbital, Phenytoin, Primidone
Category 2	Doctors are advised to use their judgement (in consultation with their patient and/or their carer) to determine whether it would be advisable for them to be maintained on a specific manufacturer's product.	Clobazam, Clonazepam, Eslicarbazepine, Lamotrigine, Oxcarbazepine, Perampanel, Rufinamide, Topiramate, Valproate, Zonisamide
Category 3	Doctors are advised that it is usually unnecessary to ensure that their patients are maintained on a specific manufacturer's product	Ethosuximide, Gabapentin, Levetiracetam, Lacosamide, Pregabalin, Tiagabine, Vigabatrin

1. CHM- service alert letter November 2013

References:

NICE. Clinical Guideline CG137. Epilepsies: diagnosis and management. April 2018. https://www.nice.org.uk/Guidance/CG137

MHRA. Valproate banned without the pregnancy prevention programme. 24 April 2018. https://www.gov.uk/government/news/valproate-banned-without-the-pregnancy-prevention-programme

MHRA Guidance. Valproate use by women and girls. Last updated 18 December 2018. https://www.gov.uk/guidance/valproate-use-by-women-and-girls

FSRH UK Medical Eligibility Criteria for Contraceptive Use (UK MEC). https://www.fsrh.org/ukmec/

NHS Drug Tariff. December 2018. https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

Appendix 1 - Recommended AED by epilepsy type NICE CG137

Seizure Type	First Line	Second Line	Adjunct
Focal	Carbamazepine Lamotrigine 1.9.3.1	Levetiracetam Oxcarbazepine Sodium Valproate 1.9.3.2	Clobazam, Gabapentin Valproate Topiramate 1.9.3.4
Generalized Tonic Clonic	Sodium Valproate Lamotrigine Carbamazepine Oxcarbazepine 1.9.4.1-3		Clobazam Lamotrigine Levetiracetam Topiramate 1.9.4.4
Absence Seizures	Ethosuximide Sodium Valproate 1.9.5.1	Lamotrigine 1.9.5.2	Combination of first line and second line 1.9.5.3
Myoclonic Seizures	Sodium Valproate 1.9.6.1	Levetiracetam Topiramate 1.9.6.2	Combination of first line and second line 1.9.6.3
Tonic or Atonic Seizures	Sodium Valproate 1.9.7.1		Lamotrigine 1.9.7.3
Infantile Spasms	Steroid Vigabatrin 1.9.8.2		
Dravet Syndrome	Sodium Valproate Topiramate 1.9.9.2		Clobazam Stiripentol 1.9.9.3
Lennox – Gastaut Syndrome	Sodium Valproate 1.9.10.2		Lamotrigine Rufinamide Topiramate 1.9.10.3
Centrotemporal / Panayiotopoulos / Late onset occipital (Gastaut type)	Carbamazepine Lamotrigine 1.9.11.1	Levetiracetam Oxcarbazepine Sodium Valproate 1.9.11.2	Carbamazepine Clobazam Gabapentin Sodium valproate Topiramate 1.9.11.5
Idiopathic generalized epilepsy (IGE)	Sodium valproate 1.9.12.1	Lamotrigine Topiramate 1.9.12.2-3	Lamotrigine Levetiracetam Sodium valproate Topiramate 1.9.12.4 Clobazam, clonazepam, Zonisamide 1.9.12.5

Juvenile myoclonic epilepsy (JME)	Sodium valproate 1.9.13.1	Lamotrigine Levetiracetam Topiramate 1.9.13.2	Lamotrigine Levetiracetam Sodium valproate Clobazam, clonazepam, Zonisamide 1.9.13.4

Appendix 2 - Standard titration and dosage tables for AED

In general, during titration of anti-epileptic drugs almost all side effects are predictable and dose related. Serious and idiosyncratic side effects (e.g. rash with lamotrigine) are listed in the British National Formulary, and will be highlighted by the specialist team when a drug is recommended.
Anti-epileptic drugs should be started at the lowest possible dose, and titrated up in the smallest possible steps no faster than every two weeks, until the initial target dose (according to the BNF) is reached. Thereafter, if seizures continue, the dose can be increased further in the same small increments every time the patient has a seizure (no faster than every two weeks) until:

- the seizures stop, or
- the maximum tolerated dose is reached, or
- the maximum licensed dose is reached, whichever happens first

Occasionally doses in excess of the maximum licensed dose can be used safely. The specialist team will specifically indicate in the clinic letter if this is the case and state the maximum dose that should not be exceeded.

Brivaracetam	Dosage is increased gradually by 25mg every two weeks up to a maximum of 100mg twice daily.
Carbamazepine	Carbamazepine is most frequently given as the prolonged-release formulation twice daily. In patients on high doses, the dose may be given three times daily. Dosage is increased gradually, normally by 200mg every two weeks. The usual maintenance dose is 800-1200mg daily. Sometimes, dosages up to 2000mg daily may be necessary. It may be helpful to monitor the plasma concentration of carbamazepine. If using carbamazepine, offer controlled released preparations.
Clobazam	Usual starting dose is 20-30mg/day (as per BNF) but can be 5-10 mg/day. This may be gradually increased up to a maximum of 60mg daily. This drug is often used on a “prn” basis for 3-5 days at the start of an anticipated cluster of seizures.
Eslicarbazepine	Dosage is increased gradually, usually by 400mg every four weeks, up to 800mg once daily. If necessary, may be further gradually increased up to 1200mg once daily.
Gabapentin	Dosage is increased gradually, usually by 300mg every two weeks, up to a maintenance dose in the range 900 to 3600 mg/day. Dosages up to 4800 mg/day have been used. The total daily dose should be divided in three single doses.

Lamotrigine	Monotherapy: Dosage is increased gradually, usually by 50mg every two weeks. Usual maintenance dose is 100 - 200 mg/day (once a day or two divided doses). In some patients 500 mg/day has been required to achieve desired response. Adjunctive therapy with valproate: Dosage is increased gradually, usually by 50mg every two weeks. Usual maintenance dose is 100 - 200 mg/day (once a day or two divided doses) Adjunctive therapy without valproate and with inducers of lamotrigine glucuronidation (eg. phenytoin, carbamazepine, phenobarbital, primidone, rifampicin, lopinavir/ritonavir): Dosage is increased gradually, usually by 50mg every two weeks. Usual maintenance dose is 200 - 400 mg/day (two divided doses). In some patients 700 mg/day may be required to achieve desired response. Adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation: Dosage is increased gradually; maintenance dose is 100 - 200 mg/day (once a day or two divided doses).
Levetiracetam	The dosage is increased gradually, usually by 250mg every two weeks. Maximum licensed dose is 1500mg twice daily. Dosages higher than this are used occasionally.
Lacosamide	It is necessary to take lacosamide twice daily. The dosage is increased gradually, usually by 50mg every two weeks. Maximum licensed dose is 200mg twice daily.
Oxcarbazepine	The dosage is gradually increased, usually by 150mg every two weeks. Therapeutic effects are normally seen at doses between 600 mg/day and 2400 mg/day. The total daily dose should be given in two divided doses
Perampanel	Perampanel should be taken orally once daily before bedtime. Dosage should be gradually increased by 2mg every four weeks. Normal dose range: 4mg to 12mg at night. If a patient misses a dose, they should wait and take their next dose as scheduled as perampanel has a long half-life.
Pregabalin	Dosage should be gradually increased by 25mg to 50mg every two weeks (taken in two daily divided doses). The maximum recommended total daily dose is 600mg.
Sodium Valproate	The Epilepsy Clinical Team at Barts Health generally recommends the sustained-release formulation (Epilim Chrono). This reduces peak concentration and ensures more even plasma concentrations throughout the day. Dosage should be gradually increased by 200mg to 300mg every two weeks. The sustained release formulation can be given once or twice daily. The usual maintenance dose is 1000mg to 2000mg per day. Sometimes, total daily dosages of 2500mg are used. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary.
Topiramate	Dosage should be gradually increased by 25mg every two weeks. The normal maintenance dose is 50mg to 100mg twice daily. The maximum dose is 500mg twice daily
Zonisamide	The dosage is increased gradually by 25mg to 50mg every two weeks; maximum licensed dose is 500mg per day taken once a day or in two divided doses.

Appendix 3 - Epilepsy and Contraception

Interactions between anti-epileptic drugs (AEDs) and contraceptive hormones are clinically important due to the risk of contraceptive failure, teratogenicity or reduced seizure control.

The metabolism of oestrogen and progestogen is increased by AEDs that induce cytochrome P450.

Strong enzyme inducers	Less potent enzyme inducers	No significant effect
Carbamazepine Eslicarbazepine Oxcarbazepine Phenytoin Phenobarbital Primidone	Lamotrigine Perampanel Rufinamide Topiramate	Benzodiazepines Ethosuximide Gabapentin Lacosamide Lamotrigine Pregabalin Sodium valproate Tiagabine Vigabatrin Zonisamide

The FRSH has updated its guidance on drug interactions with hormonal contraception and can be found here:
https://www.fsrh.org/standards-and-guidance/current-clinical-guidance/drug-interactions/

AEDs and contraception (from UKMEC) https://www.fsrh.org/ukmec/

Anticonvulsant	**Combined hormonal methods**	**Progestogen only pill**	**Progestogen only implant**	**Progestogen only injectable**	**Levonorgestrel releasing intrauterine system**	**Copper bearing intrauterine device**
Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	**Category** 3*	**Category** 3*	**Category** 2*	**DMPA Category** 1 **NET-EN Category** 2*	**Category** 1	**Category** 1
Lamotrigine	**Category** 3	**Category** 1	**Category** 1	**Category** 1	**Category** 1	**Category** 1
*The consistent use of condoms is recommended						
UKMEC Category 1: A condition for which there is no restriction for the use of the contraceptive method with the condition or in that circumstance						
UKMEC Category 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks						
UKMEC Category 3: A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgment and/or referral to a specialist provide, since use of the method is not usually recommended unless other methods are not available or not acceptable.						
UKMEC Category 4: A condition which represents unacceptable health risk if the method is used						
DMPA, depot medroxyprogesterone acetate; NET-EN, Norethisterone enanthate						

The medication SPC and recent British National Formulary should be consulted for up-to-date information on drug interactions. The most recent information from the Faculty of Sexual and Reproductive healthcare clinical effectiveness unit is available at www.fsrh.org

Depot injections: The efficacy of the progestrogen-only injectable, depot medroxyprogesterone acetate is not reduced.

Emergency contraception:

Women who require emergency contraception while using liver enzyme inducing AEDs should be advised that an intrauterine device (UID) is the preferred option if appropriate. The Faculty of Sexual & Reproductive Healthcare (FRSH) recommends a copper IUD where appropriate.

Those who prefer to use oral progestogen-only emergency contraception may be advised to double the dose of levonorgestrel as a single dose as soon as possible and licensed within the first 72 hours of unprotected sexual intercourse. Evidence suggests that it is ineffective if taken more than 96 hours after Un-Protected Sexual Intercourse (UPSI).

The emergency contraceptive, uliprsital acetate is metabolised by cytochrome P450 and its efficacy may be reduced by enzyme-inducing AEDs. Increasing the dose of ulipristal is not currently recommended. A 3 mg dose of levonorgestrel can be considered but women should be informed that the effectiveness of this regimen is unknown.

The licence for Levonelle® and ellaOne® do not recommend use in women using enzyme-inducing AEDs.

Clinicians should always counsel regarding the effectiveness of emergency contraception.

FRSH have updated guideline on Emergency Contraception: https://www.fsrh.org/documents/ceu-clinical-guidance-emergency-contraception-march-2017/

Appendix 4 - Epilepsy in Pregnancy

Anti-epileptic drugs (AEDs) may increase the risk of Major Congenital Malformations (MCM) in the developing baby. Patients who are pregnant should be referred to the Obstetric Neurology clinic via the Epilepsy Nurse Specialists (020 3594 0701) clinic so that the patient can be entered onto the UK epilepsy and Pregnancy register and manage the care of the epilepsy and its treatment. Patients planning a pregnancy (or all women of child-bearing age if not already explicitly discussed) should be referred to the Epilepsy Specialist Nurses for pre-pregnancy counselling (020 3594 0701).

In general, the risks of seizures, both to the mother and the unborn child, outweigh the risks of AEDs in pregnancy. It is always recommend that mothers continue their AEDs during pregnancy. Not to do so can be fatal.

Folic Acid, 5mg, may prevent MCMs in women taking AEDs therefore it is recommended that all women of child bearing age are prescribed folic acid 5mg OD routinely.

All AEDs carry some risk during pregnancy. Specific risks attributable to individual drugs are detailed in the table below. Data from the UK Epilepsy and Pregnancy Register suggests that, in general, AED monotherapy is associated with a 3.7% MCM rate, and polypharmacy with a 6.0% MCM rate. The risks of individual drugs may be substantially lower or higher than this (see below).

Drug	Risks during Pregnancy
Carbamazepine	Carbamazepine is considered one of the safest drugs to use in pregnancy, but is known to increase the risk of spina bifida, microcephaly and hypospadia. Carbamazepine may be used in pregnancy to treat epilepsy when the risks are considered. The UK Epilepsy and Pregnancy Register reports a 2.2% risk of MCM in monotherapy, and 4.1% risk in polypharmacy. There may be a higher risk on higher doses of carbamazepine. The dose should be kept as low as therapeutically justifiable.
Clobazam	Treatment is permitted even in the first trimester. After long-term treatment, withdrawal effects in the newborn must be expected and the child observed closely during the first days of life.
Eslicarbazepine	There is limited data on the use in pregnancy and minimum effective doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity to antenatal screening.
Ethosuximide	Recommended for absence seizures in pregnancy. Exposure does not require termination of pregnancy but a detailed ultrasound diagnosis should confirm normal development of the foetus.
Gabapentin	Data is limited. Available data do not indicate a substantial teratogenic risk with gabapentin monotherapy.
Lacosamide	There is limited data on the use in pregnancy. Lacosamide should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the foetus.

Lamotrigine	Lamotrigine may be used instead of older AEDs, but if possible the daily dosage should not exceed 200mg. The UK Epilepsy and Pregnancy Register reports a 3.2% risk of MCM in monotherapy, and 4.8% risk in polytherapy. Higher dose of lamotrigine appear to be associated with a higher risk.
Levetiracetam	There is limited data on the use in pregnancy but decrease in plasma concentrations have been observed during pregnancy. This decrease is more pronounced during the third trimester. The UK Epilepsy and Pregnancy Register reports a 0.7% risk of MCM in monotherapy, and 5.6% in polytherapy.
Oxcarbazepine	There is limited data on the use in pregnancy but in animal studies increased embryo mortality, delayed growth and malformations were observed.
Perampanel	There is limited data on the use in pregnancy but embryotoxicity was observed in rats.
Phenytoin	Phenytoin pharmacokinetics (extensively metabolised by Cytochrome P450, high degree of protein binding) make it an unsuitable drug to use during pregnancy if possible. However, when epilepsy if well-controlled with phenytoin, therapy should be continued, with monotherapy the goal. The UK Epilepsy and Pregnancy Register reports a 3.2% MCM rate with phenytoin monotherapy. The daily dose should be as low as possible.
Pregabalin	There is limited data on the use in pregnancy.
Primidone/ phenobarbitone	Limited high quality data for use in pregnancy. May be used in pregnancy for focal epilepsy, grand-mal seizure and less severe forms of pre-eclampsia. When treatment continues until delivery the newborn should be observed for clinical signs of drug withdrawal.
Rufinamide	There is limited data on the use in pregnancy.
Sodium Valproate	Caution in prescribing to women considering becoming pregnant if suitable treatment alternatives are available. Any attempt to change treatment should be accomplished prior to conception. The UK Epilepsy and Pregnancy Register has reported a 7% risk of MCM in monotherapy, Higher doses of sodium valproate may be associated more strongly with MCMs. There is a less well quantified risk (up to 40%) of reduced IQ and behavioural problems for children exposed to valproate *in utero*. **MHRA update: Valproate and the risk of abnormal pregnancy outcomes** In January 2015 and 2018 the MHRA issued strengthened warnings related to safety of medicines related to valproate (sodium valproate, valproic acid [brand leader: Epilim®] and valproate semisodium [brand leader: Depakote®]), following completion of a Europe-wide review. **Summary of risks and precautions** • Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and congenital malformations (in approximately 10% of cases). • 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. • Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.

	• Carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
	• You must ensure that all female patients are informed of and understand:
	  • the risks associated with valproate during pregnancy;
	  • the need to use effective contraception;
	  • the need for regular review of treatment;
	  • the need to rapidly consult if she is planning a pregnancy or becomes pregnant

Tiagabine	There is limited data on the use in pregnancy.
Topiramate	The UK Epilepsy and Pregnancy Register has reported that Topiramate is associated with approximately 5% risk of MCMs in monotherapy, and 11% in polytherapy.
Zonisamide	There is limited data on the use in pregnancy.

AEDs that increase hepatic metabolism (including Phenytoin, Phenobarbitone, Carbamazepine, Oxcarbazepine, Topiramate, Zonisamide, Perampanel, Rufinamide) may increase the risk of neonatal haemorrhage. Women taking these medications may be prescribed oral Vitamin K 10mg daily for the last month of pregnancy, and the baby should receive IM vitamin K 1mg as usual at delivery as directed by the specialist.

BRIVARACETAM ▼ for Epilepsy

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AS AND FILED IN NOTES

Patient name	
Date of Birth	
NHS No.	
Referring Consultant	
Contact Details	

INTRODUCTION – Indication and Licensing

Brivaracetam is licensed in the UK as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age.

PATIENT PATHWAY- *brief explanation of why planned arrangements for prescribing and monitoring between primary and secondary care are appropriate*

Clinical Speciality / Indication	Prescribing Initiated by	Prescribing Continued by *(detail when suitable for transfer to occur)*	Monitored by *(detail when suitable for transfer to occur IF APPROPRIATE)*	Duration of treatment
Neurology: Epilepsy	Consultant Neurologist	GP after treatment assessed as effective and tolerated and dose is stable (usually within 3 months)	Effect on seizure control monitored by hospital and GP	If therapy is effective and tolerated, duration is indefinite. Once dosage is stable, on-going prescribing will be provided by the patient's GP

DOSE AND ADMINISTRATION

Brivaracetam should be taken twice daily.

Normally treatment is initiated at a dose of 25mg daily.
Thereafter it is gradually increased in 25mg increments every two weeks up to a maximum of 100mg twice daily depending on effectiveness and the occurrence of side effects.

Available as: 10mg, 25mg, 50mg, 75mg, 100mg tablets
Oral solution 1mg/mL
(Solution for injection 10mg/mL)

Brivaracetam may be taken with or without food. Tablets should be swallowed whole with a glass of liquid.

MONITORING STANDARDS FOR MEDICATION AT BARTS HEALTH NHS TRUST

Seizure frequency/nature

Adverse Effects (see below)

This patient will be monitored regularly in the Epilepsy Clinic for tolerance to the drug and its effects on his epilepsy. The patient has our contact details if he/she has any concerns with his their anti-epileptic medication.

Barts Health NHS Trust will be responsible for prescribing Brivaracetam for the first twelve weeks or until stable, by which time an appropriate maintenance dosage should be established. Providing the addition of Brivaracetam is well tolerated by the patient, we ask that the GP then continues prescription for this drug. It may take longer to establish the degree of benefit in controlling seizures and this patient will therefore continue to be monitored by Barts Health NHS Trust for at least six months.

KEY ADVERSE EFFECTS & ACTIONS

This section should be read in conjunction with the manufacturer's data sheet.

Adverse effects	Frequency	Actions
Dizziness, somnolence	(very common ≥ 1:10)	Reduce dose if severe
Fatigue, insomnia, vertigo	(common ≥ 1:100 to < 1:10)	Reduce dose if severe
Nausea, vomiting, constipation	(common ≥ 1:100 to < 1:10)	Reduce dose if severe
Decreased appetite	(common ≥ 1:100 to < 1:10)	Reduce dose if severe
Depression, anxiety, irritability	(common ≥ 1:100 to < 1:10)	Reduce dose if severe
URTI, cough	(common ≥ 1:100 to < 1:10)	Reduce dose if severe
Seizure	(common ≥ 1:100 to < 1:10)	Reduce dose and consider withdrawal of drug
Neutropenia	(uncommon ≥ 1:1000 to < 1:100)	Withdraw drug
Suicidal ideation, psychotic disorder, aggression, agitation	(uncommon ≥ 1:1000 to < 1:100)	Withdraw drug

This only lists the key important ADRs – For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

For information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

PREGNANCY AND BREAST FEEDING

Contact the Epilepsy Clinical Team if patient becomes pregnant or is planning to become pregnant; see also – "Managing drug therapy between Primary and Secondary Care, July 2013" Appendices B and C on the use of contraceptives, and pregnancy in epilepsy.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

CAUTIONS

- Suicidal ideation and behaviour
- Hepatic impairment
- Lactose intolerance (Brivaracetam film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine)

CONTRA-INDICATIONS

- Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients

KEY INTERACTIONS

See Summary of Product Characteristics (SPC)

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first three months of treatment or until patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
7. Where the GP is not performing the monitoring (hospital will usually do the monitoring) , the blood test form MUST be annotated to request that blood results are also copied to the GP
8. Evaluation of any reported adverse effects by GP or patient.
9. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient, and inform GP.
10. Inform GP of patients who do not attend clinic appointments.

11. Ensure that backup advice is available at all times.

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA, where appropriate.
5. Prescribe the drug treatment as described.

CCG/ CSU

1. To provide feedback to trusts via Trust Medicines Committee.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy
5. Take/ administer the medication as prescribed

COST

Drug Product	Cost in primary care
Brivaracetam Tablets [Briviact film-coated tablets]	£129.64 per month (Drug Tariff. December 2018 prices). (Note: same price for all dosages up to 100mg twice daily due to cost of all tablet strengths being the same).

RESOURCES AVAILABLE

Barts Health NHS Trust	
Consultant via switchboard Registrar on-call out of hours	Barts Health NHS Trust Switchboard: 020 3416 5000 Ask switchboard to air call
Clinical Pharmacist, Neurology	020 3246 0140
Clinical Nurse Specialist, Epilepsy	020 3594 0701
Barts Health Medicines Information Pharmacist	020 8535 6971
Prescribing Advice for Tower Hamlets CCG	020 3688 2556
Prescribing Advice for Newham CCG	020 3688 2316
Prescribing Advice for Waltham Forest CCG	020 3688 2654

Version control:

Version	Date	Prepared	Approval status
Original	May 2016	Ann Dougan (Clinical Pharmacist, Neurology) Dr Andrew Kelso (Consultant Neurologist)	D&TC approved 2016
Update 1	Updated template	Ann Dougan, Clinical Pharmacist	WELMOCC March 2019 DTC April 2019

PERAMPANEL
Epilepsy

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AS AND FILED IN NOTES

Patient name	
Date of Birth	
NHS No.	
Referring Consultant	
Contact Details	

INTRODUCTION – Indication and Licensing

Perampanel is licensed in the UK as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalised seizures in adult and adolescent patients from 12 years of age with epilepsy. It is indicated for the adjunctive treatment of primary generalised tonic-clonic seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy.

PATIENT PATHWAY- brief explanation of why planned arrangements for prescribing and monitoring between primary and secondary care are appropriate

Clinical Speciality / Indication	Initiated by	Prescribing continued by	Monitored by	Duration
Neurology: Epilepsy	Consultant Neurologist	GP after treatment assessed as effective and tolerated and dose is stable (usually within 3 months)	Effect on seizure control monitored by hospital and GP	If therapy is effective and tolerated, duration is indefinite. Once the dosage is stable, on-going prescribing will be provided by the patient's GP

ORAL DOSE AND ADMINISTRATION

Perampanel should be taken once daily just before going to bed

Treatment is initiated at a dose of 2mg daily. This is gradually increased in 2mg increments up to a maximum of 12mg daily depending on effectiveness and the occurrence of side effects.

Available as: 2mg, 4mg, 6mg, 8mg, 10mg, 12mg tablets

Perampanel may be taken with or without food. Tablets should be swallowed whole with a glass of water.

MONITORING STANDARDS FOR MEDICATION AT BARTS HEALTH NHS TRUST

Seizure frequency/nature

Adverse Effects (see below)

This patient will be monitored regularly in the Epilepsy Clinic for tolerance to the drug and its effects on his epilepsy. He has our contact details if he has any concerns with his anti-epileptic medication.

Barts Health NHS Trust will be responsible for prescribing perampanel for the first 3 months, by which time an appropriate maintenance dosage should be established. Providing the addition of perampanel is well tolerated by the patient, we ask that the GP then continues prescription for this drug. It may take longer to establish the degree of benefit in controlling seizures and this patient will therefore continue to be monitored by Barts Health NHS Trust for at least six months.

KEY ADVERSE EFFECTS & ACTIONS

This section should be read in conjunction with the manufacturer's data sheet (SPC www.medicines.org).

Adverse effects	Symptoms/signs	Actions
Dizziness, somnolence	[very common ≥ 1/10]	Reduce dose if severe
Ataxia, dysarthria, irritability	[common ≥ 1/100 to <1/10]	Reduce dose if severe
Nausea	[common ≥ 1/100 to <1/10]	Reduce dose if severe
Diplopia, blurred vision	[common ≥ 1/100 to <1/10]	Reduce dose if severe
Weight increase	[common ≥ 1/100 to <1/10]	Reduce dose if severe
Fatigue, gait disturbance	[common ≥ 1/100 to <1/10]	Reduce dose if severe

This only lists the key important ADRs – For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

For information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

PREGNANCY AND BREAST FEEDING

Contact the Epilepsy Clinical Team if patient becomes pregnant or is planning to become pregnant; see also – "Managing drug therapy between Primary and Secondary Care, July 2013", Appendices B and C on the use of contraceptives, and pregnancy in epilepsy.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

CAUTIONS

- Suicidal ideation and behaviour
- Aggressive and hostile behaviour
- Lactose intolerance (Perampanel film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine)

CONTRA-INDICATIONS

- Hypersensitivity to the active substance or to any of the excipients

KEY INTERACTIONS

See Summary of Product Characteristics (SPC)

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum supply the first three months of treatment or until patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
7. Where the GP is not performing the monitoring (hospital will usually do the monitoring), the blood test form MUST be annotated to request that blood results are also copied to the GP.
8. Evaluation of any reported adverse effects by GP or patient.
9. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient, and inform GP.
10. Inform GP of patients who do not attend clinic appointments.
11. Ensure that backup advice is available at all times.

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA, where appropriate.
5. Prescribe the drug treatment as described.

CCG/ CSU

1. To provide feedback to trusts via Trust Medicines Committee.
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease eg. plans for pregnancy
5. Take/administer the medication as prescribed

COST

Perampanel	All tablet strengths from 4mg upwards (Fycompa®) £140 for 28 (N.B. 20% VAT to be added on medication dispensed from the hospital). (Drug Tariff. December 2018 prices).

RESOURCES AVAILABLE

Barts Health NHS Trust	
Consultant via switchboard Registrar on-call out of hours	Barts Health NHS Trust Switchboard: 020 3416 5000 Ask switchboard to air call
Clinical Pharmacist, Neurology	020 3246 0140
Clinical Nurse Specialist, Epilepsy	020 3594 0701
Barts Health Medicines Information Pharmacist	020 8535 6971
Prescribing Advice for Tower Hamlets CCG	020 3688 2556
Prescribing Advice for Newham CCG	020 3688 2316
Prescribing Advice for Waltham Forest CCG	020 3688 2654

Refer to the local intranet to obtain the latest version of this guideline

Version control:

Version	Changes	Date	Prepared	Approval status
Original		Nov 2013	Chalers Tugwell	JPG approved Nov 2013
Update 1	Updated template		Ann Dougan, Clinical Pharmacist	WELMOCC March 2019 DTC April 2019