EPILEPSY

CHI Formulary Indication Review

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Council of Health Insurance

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INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Epilepsy Clinical Guidance- Issued March 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ACTH	Adrenocorticotropic hormone
AES	American Epilepsy Society
ASM	Antiseizure Medication
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CHMP	Committee for Medicinal Products for Human Use
CKDL5	Cyclin-dependent kinase-like 5
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CPG	Clinical Practice Guideline
CRSE	Refractory Convulsive Status Epilepticus
CSE	Convulsive Status Epilepticus
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FS	Febrile Seizure
HAS	Haute Autorité de Santé
IDF	CHI Drug Formulary
IGE	Idiopathic Generalized Epilepsy
ILAE	International League Against Epilepsy
IQWIG	Institute for Quality and Efficiency in Health Care
KET	Ketamine
KSA	Kingdom of Saudi Arabia
KSUMC	King Saud University Medical City
LEV	Levetiracetam
LGS	Lennox-Gastaut syndrome
MDZ	Midazolam
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
N/A	Not Available/Not Applicable
NICE	National Institute for Health and Care Excellence

PBAC	Pharmaceutical Benefits Advisory Committee
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Propofol
PTB	Pentobarbital
RSE	Refractory Status Epilepticus
RSE	Refractory Status Epilepticus
SE	Status Epilepticus
SES	Saudi Epilepsy Society
SFDA	Saudi Food and Drug Authority
VPA	Valproic Acid

Executive Summary

Epilepsy is a chronic noncommunicable disease of the brain that affects around 50 million people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function[1].

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than one per year to several per day[1].

One seizure does not signify epilepsy; up to 10% of people worldwide have one seizure during their lifetime. Epilepsy is defined as having two or more unprovoked seizures[1].

Epilepsy is a common neurologic disorder that is characterized by recurrent unprovoked seizures which develop due to abnormal hypersynchronous activity of the neurons. **Active epilepsy** is identified as the most recent episodes of seizure that have occurred during the last 5 years or treatment with anti-epileptic drugs. In general, epilepsy affects both male and female individuals of all ages and is associated with an increased risk of psychiatric comorbidities, health problems, high economic burden, and stigma. At the clinical level, epilepsy is classified into two major types being either partial (focal), affecting one hemisphere, or generalized that originates in both hemispheres simultaneously (i.e., diffused cortical activation). However, seizures associated with dyscognitive features and impaired awareness and consciousness are known as complex partial seizures. However, during the last decades, the number of epidemiological studies investigating the prevalence and incidence of epilepsy has rapidly increased worldwide and in developed countries, in particular[2].

Epilepsy accounts for a significant proportion of the world's disease burden, affecting around 50 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1,000 people[1].

Globally, an estimated 5 million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100,000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100,000. Close to 80% of people with epilepsy live in low- and middle-income countries[1].

The global prevalence of active epilepsy is around 6.38/1,000 persons. In the Arabian region, the median prevalence of active epilepsy is 4.4/1,000 persons. In the Kingdom of Saudi Arabia (KSA), the last prevalence study for active epilepsy cases was conducted in 2001 and showed an estimate of 6.5/1,000 persons[3].

CHI issued Epilepsy guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Epilepsy report and seeks to offer guidance for the effective management of Epilepsy. It provides an **update on the Epilepsy Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update were summarized, being **the update of the clinical guidelines** namely: NICE guidelines for Epilepsies: diagnosis and management published [2022][4], in addition to **missing guidelines** such as Saudi Epilepsy Society consensus on epilepsy management during the COVID-19 Pandemic [2020][5], New guidelines for management of febrile seizures in Japan [2015][3], Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society (2016)[6], Management of convulsive status epilepticus in children: an adapted clinical practice guideline for pediatricians in Saudi Arabia [2017][7] and Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee [2020][8].

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Gastric and Esophageal Cancers therapeutic management.

Below is a table summarizing the major changes based on the different epilepsy guidelines used to issue this report.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. General Recommendations for the Management of Epilepsy

Management of Epilepsy		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Consider supplementation with calcium and vitamin D with some antiseizure medications (such as carbamazepine, phenytoin, primidone, and sodium valproate) associated with decreased bone mineral density and increased risk of osteomalacia and for people at risk.	Not graded	NICE (2022)[4]
For focal seizures treatment, consider lamotrigine or levetiracetam as first-line monotherapy.	Not graded	NICE (2022)[4]
For myoclonic seizures, offer sodium valproate or levetiracetam as a first-line treatment. If sodium valproate is unsuccessful as first-line treatment, offer levetiracetam as a second-line monotherapy or add-on treatment.	Not graded	NICE (2022)[4]
For infantile spasms not due to tuberous sclerosis, as a first-line treatment, offer combination therapy with high-dose oral prednisolone and vigabatrin. Offer vigabatrin alone in children at high risk of steroid-related side effects.	Not graded	NICE (2022)[4]
For infantile spasms due to tuberous sclerosis, offer vigabatrin alone. If vigabatrin is ineffective after 1 week, add high-dose oral prednisolone.	Not graded	NICE (2022)[4]
Valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless other options are unsuitable, and the pregnancy prevention program is in place.	Not graded	NICE (2022)[4]
Consider ketogenic diet under the guidance of a tertiary epilepsy specialist for certain	Not graded	NICE (2022)[4]

childhood-onset epilepsy syndromes and for drug resistant epilepsy.		

At the end of the report, a key recommendation synthesis section is added highlighting the use of each drug class in specific group of patients.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI epilepsy report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the March 2020 CHI Epilepsy Report and the corresponding recommendations.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision		
Old Versions		**Updated versions**
1.1.1.	NICE Guideline for Epilepsies: Diagnosis and Management [2012]	NICE Guideline for Epilepsies in Children, Young People, and Adults [2022][4]
1.1.2.	American Academy of Neurology and the American Epilepsy Society Evidence Based Guideline: Management of an Unprovoked First Seizure in Adults [2015]	N/A*
1.1.3.	American Academy of Neurology and the American Epilepsy Society Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy [2018]	Reaffirmed 2021
1.1.4.	American Academy of Neurology and the American Epilepsy Society Practice guideline update	Reaffirmed 2021

	summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy [2018]	
1.1.5.	Neurocritical care society Guidelines for the Evaluation and Management of Status Epilepticus [2012]	N/A*
1.1.6.	American Epilepsy Society Guideline Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society [2016]	N/A*
1.1.7.	European Journal of Neurology [EFNS] guideline on the management of status epilepticus in adults [2010]	N/A*
1.1.8.	American Academy of Neurology and the American Epilepsy Society Practice parameter: Treatment of the child with a first unprovoked seizure [2003]	N/A*

*: *No updated versions available*

1.1.1 NICE Guideline for Epilepsies in Children, Young People, and Adults [2022]

*Please refer to **Section 1.1** of the previous CHI March 2020 report.*

The revised 2022 edition of the National Institute for Health and Care Excellence (NICE) guideline for diagnosis and management of epilepsies in adults and pediatrics introduced a set of recommendations detailed below[4] (recommendations are ugraded).

A. Treating epileptic seizures in children, young people, and adults

1. Pharmacological treatment of **generalized tonic-clonic seizures**

Monotherapy

- Offer sodium valproate as first-line monotherapy for generalized tonicclonic seizures in:

- Boys and men
- Girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children.
- Women who are unable to have children.

- Offer lamotrigine or levetiracetam as first-line monotherapy for generalized tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children). If the first choice is unsuccessful, offer the other of these options. In April 2022, these were off-label uses of lamotrigine in children under 13 years and levetiracetam in adults and children.
- If first-line monotherapy with sodium valproate is unsuccessful for generalized tonic-clonic seizures, offer lamotrigine or levetiracetam as second-line monotherapy treatment. If the first choice is unsuccessful, try the other of these options. In April 2022, these were off-label uses of lamotrigine in children under 13 years and levetiracetam in adults and children. See NICE's information on prescribing medicines.
- Do not offer sodium valproate monotherapy for generalised tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - Other treatment options are unsuccessful.
  - The risks and benefits have been fully discussed, including the risks to an unborn child.
  - The likelihood of pregnancy has been taken into account and a pregnancy prevention program put in place, if appropriate.

<u>Add-on treatment</u>

- If monotherapy is unsuccessful in people with generalized tonic-clonic seizures, consider 1 of the following first-line add-on treatment options:
  - clobazam
  - lamotrigine
  - levetiracetam
  - perampanel
  - sodium valproate, except in women and girls able to have children
  - topiramate.

- If the first choice is unsuccessful, consider the other first-line add-on options.

  In April 2022, these were off-label uses of clobazam as add-on therapy in children under 6 months, lamotrigine in children under 2 years, levetiracetam in children under 12 years, perampanel in children under 7 years, and topiramate in children under 2 years.

- If first-line add-on treatments tried are unsuccessful in people with generalized tonic-clonic seizures, consider 1 of the following second-line add-on treatment options:
  - brivaracetam
  - lacosamide
  - phenobarbital
  - primidone
  - zonisamide
  - If the first choice is unsuccessful, consider the other second-line add-on options.

    In April 2022, these were off-label uses of brivaracetam in adults and children, lacosamide in children under 4 years, and zonisamide in adults and children.
- Do not offer sodium valproate as an add-on treatment for generalized tonic-clonic seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
  - Other treatment options are unsuccessful.
  - The risks and benefits have been fully discussed, including the risks to an unborn child.
  - The likelihood of pregnancy has been taken into account and a pregnancy prevention program put in place, if appropriate.

<u>Other treatment considerations</u>

- Be aware that the following antiseizure medications may exacerbate seizures in people with absence or myoclonic seizures, including in juvenile myoclonic epilepsy:
  - carbamazepine
  - gabapentin
  - lamotrigine (for myoclonic seizures)

- oxcarbazepine
- phenytoin
- pregabalin
- tiagabine
- vigabatrin

2. Pharmacological treatment of **focal seizures** with or without evolution to bilateral tonic-clonic seizures

<u>Monotherapy:</u>

- Consider **lamotrigine** or **levetiracetam** as **first-line** monotherapy.
- If first-line monotherapies are unsuccessful consider 1 of the following second-line monotherapy options: carbamazepine, oxcarbazepine, zonisamide. If the first choice is unsuccessful, consider the other second-line monotherapy options.
- Consider lacosamide as third-line monotherapy.

<u>If monotherapy is unsuccessful:</u>

- Consider first-line add-on treatment options: carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide.
- If first-line options are unsuccessful, consider brivaracetam, cenobamate (in line with NICE's technology appraisal guidance on cenobamate for treating focal onset seizures in epilepsy), eslicarbazepine acetate, perampanel, pregabalin, sodium valproate, except in women and girls able to have children
- If second-line options are unsuccessful, consider phenobarbital, phenytoin, tiagabine, vigabatrin.
- Sodium valproate should not be used as an add-on treatment for focal seizures in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), unless:
    - other treatment options are unsuccessful;
    - the risks and benefits have been fully discussed, including the risks to an unborn child;
    - the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.

3. Pharmacological treatment of **absence seizure** (including childhood absence epilepsy)

Without other seizure types:

- Offer **ethosuximide** as **first-line** treatment.
- Offer sodium valproate as second-line monotherapy or add-on treatment for boys of all ages, girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children and women who are unable to have children.
- Offer lamotrigine or levetiracetam as a third-line monotherapy or add-on treatment options.

With other seizures or at risk of these:

- Offer sodium valproate as a first-line treatment in:
    - boys and men;
    - girls aged under 10 years and who are unlikely to need treatment when they are old enough to have children;
    - women who are unable to have children.
- Offer **lamotrigine** or **levetiracetam** as a **first-line** option in **women and girls** able to have children (including young girls who are likely to need treatment when they are old enough to have children)
- Offer lamotrigine or levetiracetam as a second-line monotherapy or add-on treatment options or ethosuximide as a second-line add-on treatment.
- Do not offer carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin.

4. Pharmacological treatment of **myoclonic seizure**

- Offer **sodium valproate** (in boys and men, and in girls and women unable to have children) or **levetiracetam** (in girls and women able to have children) as a **first-line** treatment.
- If sodium valproate is unsuccessful as first-line treatment, offer levetiracetam as a second-line monotherapy or add-on treatment.
- If levetiracetam is unsuccessful, consider 1 of the following as monotherapy or add-on treatment options: brivaracetam, clobazam, clonazepam, lamotrigine, phenobarbital, piracetam, topiramate, zonisamide.

5. Pharmacological treatment of **tonic or atonic seizure**

   - Offer **sodium valproate** as **first-line** treatment to boys, men, and women who are not of childbearing potential. If sodium valproate is unsuitable, ineffective, or not tolerated, offer lamotrigine.
   - If lamotrigine is unsuccessful. consider one of the following as monotherapy or add-on treatment: clobazam, rufinamide, topiramate.
   - If third-line treatment is unsuccessful, consider a ketogenic diet as an add-on treatment under the supervision of a ketogenic diet team.
   - If all other treatment options are unsuccessful, consider *felbamate* as an add-on treatment under the supervision of a neurologist with expertise in epilepsy.

6. Pharmacological treatment of **idiopathic generalized epilepsy (IGE)**

   - As **first-line** treatments, offer **sodium valproate** to boys, men and women who are not of childbearing potential. If sodium valproate is unsuitable or not tolerated, offer **lamotrigine** or **levetiracetam**. *Lamotrigine can exacerbate myoclonic seizures*.
   - If first-line treatments are unsuccessful, consider lamotrigine or levetiracetam as a second-line monotherapy or add-on treatment options.
   - Offer perampanel or topiramate as third-line add-on treatment options.

B. Treating childhood-onset epilepsies

1. Dravet Syndrome

- As **first-line** treatment, offer **sodium valproate** because of the severity of the syndrome and the lack of evidence for other effective first-line treatment options.
- Sodium valproate should be used with caution in women and girls.

  If sodium valproate should be started or continued in women's and girls' able to have children (including young girls who are likely to need treatment when they are old enough to have children), weigh benefits versus risks including risks to an unborn child and takes into consideration the pregnancy likelihood and put in place a pregnancy prevention program.
- Adjunctive treatment: consider triple therapy clobazam or stiripentol as adjunctive treatment (children under 2 years)
- As a second-line treatment, if triple therapy is unsuccessful and the child is over 2 years, consider cannabidiol in combination with clobazam as an add-on treatment option.

- If other treatment options fail, consider 1 of the following add-on options under the supervision of a ketogenic diet team or a neurologist with expertise in epilepsy, as appropriate: ketogenic diet, levetiracetam, topiramate.
- If all other treatment options are unsuccessful, consider potassium bromide under the guidance of a neurologist with expertise in epilepsy.
- Do not offer carbamazepine, gabapentin lamotrigine, lacosamide oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

  NICE has produced technology appraisal guidance on fenfluramine for treating seizures. Fenfluramine was FDA approved in June 2020, and is under evaluation by EMA.

2. Lennox–Gastaut syndrome

- As a **first-line** treatment, offer **sodium valproate** to boys, men and women who are not of childbearing potential.
- Offer lamotrigine as a second line monotherapy or add-on treatment.
- Offer cannabidiol in combination with clobazam if the child is over 2 years and clobazam as third line treatment.
- Ketogenic diet as an add-on if third-line unsuccessful
- If all options fail, consider felbamate as add-on under neurologist supervision with epilepsy expertise.
- Do not offer carbamazepine, gabapentin lamotrigine, oxcarbazepine, phenobarbital, pregabalin, tiagabine or vigabatrin.

3. Infantile spasms syndrome

- *For infantile spasms not due to tuberous sclerosis*, as a first-line treatment, offer combination therapy with high-dose oral **prednisolone and vigabatrin**.

  Offer vigabatrin alone in children at high risk of steroid-related side effects.

  For infantile spasms due to tuberous sclerosis, offer **vigabatrin** alone. If vigabatrin is ineffective after 1 week, add high-dose oral prednisolone.
- Consider the following as a second-line monotherapy or add-on treatment options for infantile spasms, guided by a ketogenic diet team or tertiary pediatric epilepsy specialist, as appropriate: ketogenic diet, levetiracetam, nitrazepam, sodium valproate, topiramate.

4. Self-limited epilepsy with centrotemporal spikes

- Offer **levetiracetam** or **lamotrigine** as **first-line** treatment.
- Offer the following: carbamazepine, oxcarbazepine, zonisamide as second-line options.
- Consider sulthiame as monotherapy or add-on treatment as third line after discussion with a tertiary pediatric neurologist.
- Carbamazepine, oxcarbazepine, and lamotrigine may rarely exacerbate seizures or the development of another epilepsy syndrome, or affect cognitive performance, in a small number of children and young people.
- If there is concern about school performance, follow up with a healthcare professional at a frequency appropriate to a person's individual needs.
- Discuss discontinuing treatment if a child or young person with self-limited epilepsy with centrotemporal spikes is seizure-free for at least 2 years or at age 14 years.

5. Myoclonic-atonic seizures (Doose syndrome)

- Consider levetiracetam or sodium valproate as first-line treatments for epilepsy If either levetiracetam or sodium valproate is unsuccessful, try the other of these options.
- If sodium valproate is started or continued for epilepsy with myoclonic atonic seizures in girls or women able to have children (including young girls who are likely to need treatment when they are old enough to have children):
    - Discuss the risks and benefits of treatment, including the risks to an unborn child;
    - Take into account the likelihood of pregnancy and put in place a pregnancy prevention program, if appropriate.

Second-line treatment

- If first-line treatments for epilepsy with myoclonic-atonic seizures are unsuccessful, consider a ketogenic diet as a second-line monotherapy or add-on treatment, under the supervision of a ketogenic diet team.

Third-line treatment

- If second-line treatment for epilepsy with myoclonic-atonic seizures is unsuccessful, consider the following as third-line monotherapy or add-on treatment options: clobazam, ethosuximide, topiramate, zonisamide. If the first choice is unsuccessful, consider the other third-line options. In April 2022, these were off-label uses of clobazam as monotherapy in adults and children, and add-

on therapy in children under 6 months, and topiramate and zonisamide in adults and children.

- Do not use any of the following medications because they may exacerbate seizures in people with epilepsy with myoclonic-atonic seizures: carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, vigabatrin.

Discontinuing medication

- Consider discontinuing antiseizure medication treatment in children with epilepsy with myoclonic-atonic seizures who are seizure-free for 2 years.

C. Status epilepticus

Prolonged or repeated seizures and convulsive status epilepticus

- The International League Against Epilepsy (ILAE) proposed a new definition of **status epilepticus** meaning that all seizures **lasting longer than 5 minutes** constitute status epilepticus.

Generalized convulsive status epilepticus

- If the person has an individualized emergency department plan, administer medications accordingly.
- If the person doesn't have an individualized emergency department plan, give a **benzodiazepine** (buccal midazolam or rectal diazepam) immediately as first-line treatment in the community or intravenous lorazepam.
- Be aware of the possible underlying causes of status epilepticus, including hypoglycemia, eclampsia, and alcohol withdrawal, which may need to be treated with additional medication.
- If there is no response to first dose of benzodiazepine, seek help (call emergency services in the community or expert guidance in hospital), follow the individualized treatment plan if available or give a second dose of benzodiazepine if the seizure does not stop within 5 to 10 minutes of the first dose.
- If convulsive status epilepticus does not respond to 2 doses of a benzodiazepine, give any of the following medicines intravenously as a second-line treatment: • levetiracetam, phenytoin, sodium valproate.

  ***Take into account that levetiracetam may be quicker to administer and have fewer adverse effects than the alternative options

- Third-line treatment options under expert guidance: phenobarbital or general anesthesia

Repeated seizures or cluster seizures

Repeated or cluster (3 or more in 1 hour): consider giving a **benzodiazepine**, such as clobazam or midazolam, immediately if they do not have an individualized emergency management plan.

Prolonged (continues for more than 2 minutes than a usual seizure): consider giving a benzodiazepine, such as midazolam or clobazam. After a prolonged convulsive and non-convulsive seizure, agree on an emergency department plan with the person.

Refractory convulsive status epilepticus

- Administer intravenous **midazolam**, **propofol**, or **thiopental sodium** to treat adults with refractory convulsive status epilepticus.
- As the treatment pathway progresses, the expertise of an anesthetist/ intensivist should be sought.

Non-convulsive status epilepticus is uncommon, and management is less urgent.

D. Non-pharmacological treatment

- Consider **ketogenic diet** under the guidance of a tertiary epilepsy specialist for certain childhood-onset epilepsy syndromes and for drug resistant epilepsy.
- Resective epilepsy surgery: refer to tertiary epilepsy services for consideration assessment. Not to exclude people with learning disabilities or underlying genetic abnormalities.
- If the surgery is not suitable, consider vagus nerve stimulation as an add-on treatment to antiseizure medication.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI epilepsy report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Saudi Epilepsy Society Consensus on Epilepsy Management During the COVID-19 Pandemic [2020][5]
New Guidelines for Management of Febrile Seizures in Japan [2015][8]
Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society (2016)[6]

Management of Convulsive Status Epilepticus in Children: An Adapted Clinical Practice Guideline for Pediatricians in Saudi Arabia [2017][7]

1.2.1 KSA Guidelines

1.2.1.1 Saudi Epilepsy Society (SES) Consensus on Epilepsy Management During the COVID-19 Pandemic [2020]

The Saudi Epilepsy Society (SES), in collaboration with the Saudi Patient Safety Center, has initiated a priority care classification in epilepsy management practice. In addition, the SES COVID-19 task force has established a consensus for the best evidence-based practice related to epilepsy during the pandemic[5]. The main recommendations are listed below:

Epilepsy and the risk of COVID-19

- There is no evidence that patients with epilepsy are at any increased risk for COVID-19 or that epilepsy is associated with a risk of having a severe infection.
- Antiepileptic medications themselves are not immunosuppressive, but the rare patients who develop a neutropenia related to their antiepileptic medications may theoretically be at increased risk. In extremely rare cases, some epileptic patients who take an immunomodulatory medication such as a steroid or another immunosuppressant may have more severe symptoms of COVID-19.
- Antiepileptic medication interactions with drugs used for COVID-19. Several drugs are used in COVID-19 management, ranging from antiviral to antimalarial drugs. Many interactions are evident between antiepileptic medications and drugs used for COVID-19. In the current climate of frequently changing information, it is recommended to review the COVID-19 drug interaction literature and resources.
- Based on the above, potentially significant interactions with several drugs used for COVID-19 can occur when used with phenobarbitone, primidone, phenytoin, and carbamazepine. Expectedly, the least frequent interactions have been found with levetiracetam, lacosamide, gabapentin, retigabine, topiramate, vigabatrin, zonisamide, valproate, and lamotrigine. It is not recommended to alter the antiepileptic regimen as a potential preventive measure during the pandemic in anticipation of starting a COVID-19 medication. Consultation with an epileptologist may help upon prescribing a COVID-19 medication for a patient with epilepsy.

1.2.1.2 Management of Convulsive Status Epilepticus in Children: An Adapted Clinical Practice Guideline for Pediatricians in Saudi Arabia [2017]

Members of the Saudi Pediatric Society, Saudi Pediatric Neurology Society, Saudi Epilepsy Society and the Gulf League Against Epilepsy formed a committee to review and endorse this CPG. This guideline is expected to improve the quality and safety of care for children with convulsive status epilepticus (CSE) in Saudi Arabia[7]. The main recommendations (ungraded) are detailed below:

- Status epilepticus (SE) is a common and serious neurological problem in children, particularly those under 2 years of age. It is a life-threatening condition needing early recognition and intervention to prevent significant neurological sequelae.
- SE is defined as a seizure activity longer than 5 minutes or two or more seizures, without a return to consciousness between seizures.
- SE in children has been identified as a high priority health topic at the King Saud University Medical City (KSUMC) based on hospital records.
- The International League Against Epilepsy (ILAE) Task Force on the Classification of SE, recently defined SE as a condition resulting from either a failure of the seizure termination mechanisms or a failure of the initiation mechanisms, both which would lead to abnormally prolonged seizures (after time point t1)
    - The first time point (t1) is the length of the seizure (t1); it represents 'continuous seizure activity' and identifies the time when treatment should be started. The second time point (t2) is the time of ongoing seizure activity beyond which there is a risk of long-term sequelae or consequences. Identification of t2 highlights the importance of SE prevention.
- *Management of CSE in children.*
    - Prehospital management. Early treatment for CSE is associated with cessation of the convulsion and an improved outcome; treatment should start prehospital, at home or in the community, with the administration of **buccal midazolam or rectal diazepam**. Prehospital management is associated with a shorter SE duration Buccal midazolam is as effective as rectal diazepam in terminating the acute attack of the seizure. Discussing administration of these medications with the parents of any child with epilepsy is crucial.
    - Prehospital medications should be made available for use in the ambulance and emergency care services and be prescribed for children

who have a history of frequent seizures. Paramedical personnel should also be trained to administer these medications.

- *In hospital management.*
    - Stabilization of the patient and termination of the seizure.
    - Benzodiazepines remain the drug of choice as a first line therapy, having a high strength of evidence; IV lorazepam and diazepam are effective initial medications.
    - Buccal or intramuscular midazolam, or rectal diazepam can be used if the IV line cannot be established rapidly.
    - If a seizure continues 5-10 minutes from the initial dose, then a second dose can be administered.

Second-line therapy for CSE do not currently exist

- Phenytoin, fosphenytoin, phenobarbital, valproic acid, levetiracetam, and recently lacosamide, are frequently prescribed for the treatments of CSE.
- Although fosphenytoin has greater tolerability than phenytoin, the availability and cost of fosphenytoin in KSA precludes its recommendation in this CPG. The NICE-CPG recommends the use of either phenytoin or phenobarbitone as second-line therapy; the AES-CPG (American Epilepsy Society – Clinical Practice Guidelines) also recommends phenobarbitone if phenytoin, valproic acid, or levetiracetam are not available.
- Valproic acid is as effective as phenytoin in aborting CSE. While recognizing the side effects of valproic acid, especially in children less than two years of age due to hepatotoxicity, and a major concern in children with inborn errors of metabolism, particularly those with mitochondrial disorder, valproic acid is still considered as one of the alternative therapies.

Refractory Status Epilepticus (RSE)

Midazolam infusion, sodium thiopental, or pentobarbital. Treatment of RSE requires intubation and admission to the Pediatric Intensive Care Unit (PICU).

1.2.2 North American Guidelines

1.2.2.1 Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society [2016]

The goal of this guideline published by the AES in 2016 is to provide evidence-based answers to efficacy, safety, and tolerability questions regarding the treatment of convulsive status epilepticus. This guideline focuses on convulsive status epilepticus

because it is both the most common type of status epilepticus and is associated with substantial morbidity and mortality.

Anticonvulsant “efficacy” is the ability of the drug to stop convulsive status epilepticus, “tolerability” involves the “incidence, severity and impact” of anticonvulsant related adverse effects, “effectiveness” encompasses both anticonvulsant efficacy and tolerability, and “safety” refers to life-threatening adverse events.

The main recommendations are summarized below[6].

Table 4. American Epilepsy Society 2022 Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Translation of Evidence to Recommendation	**Conclusion and Recommendation**
Level A	
One or more class I studies or two or more consistent class II studies	Established as effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be done or should not be done
Level B	
One or more class II studies or three or more consistent class III studies	Probably effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be considered or should not be considered
Level C	
Two or more consistent class III studies	Possibly effective, ineffective, or harmful for the given condition in the specified population Recommendation: May be considered or may not be considered
Level U	
Lack of studies meeting level A, B, or C designation	Data inadequate or insufficient. Given current knowledge, treatment is unproven. Recommendation: None

- In adults with convulsive status epilepticus, intramuscular midazolam, intravenous lorazepam, intravenous diazepam and intravenous phenobarbital are established as efficacious as initial therapy (Level A).

- Intramuscular midazolam has superior effectiveness compared to intravenous lorazepam in adults with convulsive status epilepticus without established intravenous access (Level A).
- In children, intravenous lorazepam and intravenous diazepam are established as efficacious at stopping seizures lasting at least 5 minutes (Level A) while rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam are probably effective (Level B).
- No significant difference in effectiveness has been demonstrated between intravenous lorazepam and intravenous diazepam in adults or children with convulsive status epilepticus (Level A).
- Respiratory and cardiac symptoms are the most commonly encountered treatment-emergent adverse events associated with intravenous anticonvulsant drug administration in adults with convulsive status epilepticus (Level A).
- The rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convulsive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus (Level A).
- When both are available, fosphenytoin is preferred over phenytoin based on tolerability but phenytoin is an acceptable alternative (Level A). In adults, compared to the first therapy, the second therapy is less effective while the third therapy is substantially less effective (Level A).
- In children, the second therapy appears less effective and there are no data about third therapy efficacy (Level C).

Figure 1 is a clinical algorithm proposed by the AES to assist clinicians by providing an analytical framework for evaluating and treating patients with SE.

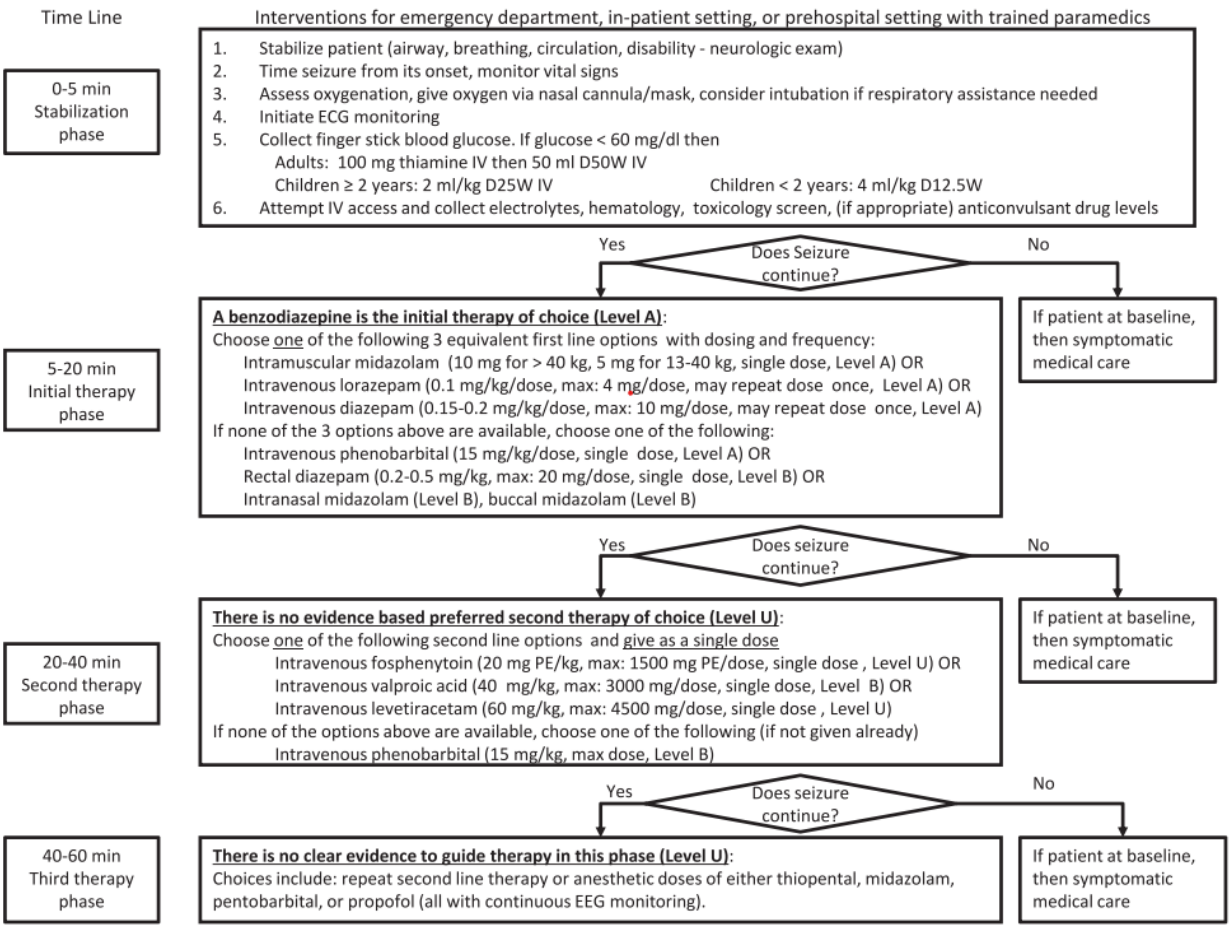

Figure 1. *Proposed treatment algorithm for status epilepticus. Retrieved from the AES 2016 guidelines.*

1.2.2.2 Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee [2020]

The main recommendations from the guidelines published by the American Epilepsy Society are summarized below[9].

The goals of this review were firstly to identify, analyze, and grade all the research literature on the efficacy of BRV, ketamine (KET), LCM, LEV, VPA, MDZ, PTB, and PRO at stopping CRSE and secondly to examine 5 other IV ASMs used in the treatment of special populations (e.g., children, pregnant women) with hard-to-control seizures.

Articles were classified into 4 classes as per the table below:

Table 5. American Epilepsy Society's Grading of recommendations

Grading Scheme for Recommendations
Articles were classified as: ➢ **Class I (triple masked, prospective, randomized controlled trials)** ➢ **Class II (prospective matched group cohort study)** ➢ **Class III (all other controlled trials)** ➢ **Class IV (evidence from uncontrolled studies, case series or reports, or expert opinions) according to the American Academy of Neurology Clinical Practice Guideline Process Manual**

Adrenocorticotropic Hormone, Corticosteroids, and IVIg

- No studies exist on the use of ACTH (Adrenocorticotropic hormone), corticosteroids, or ACTH (Adrenocorticotropic hormone), for the treatment of CRSE (Refractory Convulsive Status Epilepticus). Small series and case reports exist on the use of these agents in the treatment of RSE (Refractory Status Epilepticus) of suspected immune etiology, severe epileptic encephalopathies, and rare epilepsy syndromes.

Brivaracetam

- For adults with CRSE, insufficient evidence exists on the effectiveness of brivaracetam (level U; 4 class IV studies).

Lacosamide

- For children and adults with CRSE, it is possible that lacosamide is effective at stopping RSE (level C; 2 class III, 14 class IV studies).

Levetiracetam

- For children with CRSE, insufficient evidence exists that LEV (Levetiracetam) and VPA (Valproic Acid) are equally effective (level U, 1 class III study).
- For adults with CRSE, insufficient evidence exists to support the effectiveness of LEV (level U; 2 class IV studies).

Magnesium sulfate

- Magnesium sulfate may be effective in the treatment of eclampsia, but there are only case reports of its use for CRSE.

Midazolam

- For children with CRSE, insufficient evidence exists to support either that MDZ (Midazolam) and diazepam infusions are equally effective (level U; 1 class III study) or that MDZ infusion and PTB (Pentobarbital) are equally effective (level U; 1 class III study).

- For adults with CRSE, insufficient evidence exists to support either that MDZ infusion and PRO (Propofol) are equally effective (level U; 1 class III study) or that low-dose and high-dose MD infusions are equally effective (level U; 1 class III study).

Ketamine

- For children and adults with CRS, E insufficient evidence exists to support the effectiveness of KET (Ketamine) (level U; 25 class IV studies)
- For children and adults with CRSE, insufficient evidence exists to support that MDZ is effective as the last drug added (level U; 29 class IV studies).

Propofol and Pentobarbital

- For adults with CRSE, insufficient evidence exists to support that PTB and PRO are equally effective (level U; 1 class III study).
- For adults and children with CRSE, insufficient evidence exists to support that PTB is effective as the last ASM added (level U; 42 class IV studies).
- For CRSE, insufficient evidence exists to support that PRO is effective as the last ASM (Antiseizure Medication) used (level U; 26 class IV studies).
- No pediatric-only studies exist on the use of PRO for CRSE, and many guidelines do not recommend its use in children aged <16 years. Pyridoxine-dependent and pyridoxine responsive epilepsies should be considered in children presenting between birth and age 3 years with refractory seizures and no imaging lesion or other acquired cause of seizures. For children with CRSE, insufficient evidence exists that VPA and diazepam infusion are equally effective (level U, 1 class III study).
- No class I to III studies have been reported in adults treated with VPA for CRSE. In comparison, for children and adults with established convulsive SE (i.e., not RSE), after an initial benzodiazepine, it is likely that loading doses of LEV 60 mg/kg, VPA 40 mg/kg, and Fos phenytoin 20 mg PE/kg are equally effective at stopping SE (level B, 1 class I study).
- In conclusion, there is a lack of substantial evidence regarding the effectiveness of using medications such as BRV, LCM, LEV, valproate, KET, MDZ, PTB, and PRO either as the last resort anti-seizure medication or in comparison to other drugs for the management of clinical Continuous Refractory Status Epilepticus (CRSE). Adrenocorticotropic hormone, IVIg, corticosteroids, $MgSO_4$, and pyridoxine have been employed in specific situations, but their use in CRSE has not been thoroughly researched. When it comes to treating confirmed Convulsive Status Epilepticus (CSE) that is not refractory, LEV, VPA, and Fosphenytoin are likely equally effective, though whether this holds true for CRSE remains uncertain. To address these

uncertainties, rigorous triple-masked, randomized controlled trials are essential to assess the comparative effectiveness of anesthetic and non-anesthetic parenteral anti-seizure medications in the treatment of CRSE.

1.2.3 International Guidelines

1.2.3.1 The Japanese Society of Child Neurology Guidelines for the Management of Febrile Seizures in Japan [2015]

The main recommendations from the guidelines published by the Japanese Society of Child Neurology are summarized below[8].

The grade of recommendation was assessed based on the grading system of the Agency for Health Care Policy and Research (AHCPR, now Agency for Healthcare Research and Quality (AHRQ)). The clinical questions covered the topics of emergency.

Table 6. The Japanese Society of Child Neurology Grading Scheme for Recommendations

Grading Scheme for Recommendations			
Level	**Evidence**	**Grade**	**Evidence**
Level I	Meta-analysis of multiple studies	**A**	Strongly recommend; Good evidence
Level II	Experimental studies	**B**	Recommend; At least fair evidence
Level III	Well-designed, quasi-experimental studies	**C**	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
Level IV	Well-designed, non-experimental studies	**D**	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
Level V	Case reports and clinical examples	**E**	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.

- The 2015 guidelines define febrile seizures (FS) as a seizure accompanied by fever (temperature 38 degrees C or higher), without central nervous system

(CNS) infection, that occurs in infants or children 6–60 months of age. Cases with a history of epilepsy prior to the seizure with fever are excluded from FS.

- Complex FS is defined as a seizure with focal manifestations, prolonged (15 min or longer) duration, and/or recurrent within 24 hours. Simple FS is defined as a seizure without the characteristics of complex FS.

Emergency care

- Lumbar puncture should be considered for children with FS and signs of CNS infections, such as meningeal signs, altered consciousness longer than 30 min, or bulging anterior fontanel. (Grade A)
- Blood examination is not routinely needed for children with FS; Blood examination should be considered in cases of poor general condition, prolonged altered consciousness, or signs of dehydration". In the 2015 guideline, due to the risk of cerebral herniation, we recommend CT or MRI before lumbar puncture in children with FS.

Febrile status epilepticus

- A new definition with shorter seizure duration has been proposed as an operational definition. Recently the Task Force of the International League Against Epilepsy proposed a new definition of SE including definitions with short and long seizure durations: The new definition has two operational dimensions: the time point (t1) beyond which the seizure should be regarded as "continuous seizure activity" and a second time point (t2) after which there is a risk of long-term consequences. The time points are different for each seizure type.
- The 2015 guidelines define the first time point for starting first line medication as 5 minutes.
- Intravenous diazepam or midazolam are recommended as the first-line treatment of febrile status epilepticus. (Grade A) 2) Attention to respiratory depression is needed. (Grade B).
- MRI (Magnetic Resonance Imaging) re-examination should be reconsidered in children who do not have full recovery of consciousness after febrile.

Prophylactic diazepam

Prophylactic diazepam can be used in children with the following criteria: (Grade B)

1. Children with a history of a prolonged febrile seizure lasting 15 minutes or longer.

Or

2. Children with repeated FS and two of the following risk factors: (1) focal or repeated seizures within 24 hours (2) preexisting neurological abnormality or developmental delay (3) family history of FS or epilepsy (4) age younger than 12 months (5) seizure within 1 h after onset of fever (6) seizure occurring with body temperature less than 38C.

Vaccines

Children with a history of FS can receive all currently available vaccines if the caregiver understands both the benefits and risks of the vaccines. (Grade A)

Section 2.0 Drug Therapy in Epilepsy

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 New Drugs

Since March 2020, new drugs have been added to the guidelines for the management of epilepsy and have been registered by the SFDA.

2.1.1 Brivaracetam

Table 7. Brivaracetam Drug Information

SCIENTIFIC NAME **Brivaracetam**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes, add-on treatment to other medications to treat partial onset seizures in patients aged 16 years and older with epilepsy
EMA	Yes, add-on to other epilepsy medicines to treat partial-onset seizures (epileptic fits starting in one specific part of the brain). It can be used in patients from the age of 2 years with partial-onset seizures with or without secondary generalisation (where the abnormal electrical activity spreads through the brain).
MHRA[10]	Yes
PMDA[11]	Yes
Indication (ICD-10)	G40.0, G40.1, G40.2, G40.3
Drug Class	Antiseizure Agent
Drug Sub-class	Miscellaneous
ATC Code	N03AX, N03AX23
Pharmacological Class (ASHP)	Anticonvulsants
DRUG INFORMATION	

Dosage Form	Film-coated tablet Oral solution Solution for injection/infusion
Route of Administration	Oral and IV use
Dose (Adult) [DDD]*	**Partial-onset seizures (monotherapy or adjunctive therapy): Oral, IV: Initial: 50 mg twice daily; may decrease to 25 mg twice daily or increase up to 100 mg twice daily based on individual patient response and tolerability (maximum: 200 mg/day). Note: Use injection when oral administration is temporarily not feasible; clinical study experience with brivaracetam injection is limited to 4 consecutive days of treatment.**
Maximum Daily Dose Adults*	200 mg per day
Dose (pediatrics)	**Partial-onset seizures; adjunct or monotherapy:** **Note: Avoid abrupt withdrawal; decrease dose gradually. Use injection when oral administration is temporarily not feasible; clinical study experience with brivaracetam injection is limited to 4 consecutive days of treatment.** **Infants,** **Children, and Adolescents <16 years:** **<11 kg:** Oral, IV: Initial: 0.75 to 1.5 mg/kg/dose twice daily; adjust dose based on individual patient response and tolerability (gradual dose escalation not required); maximum daily dose: 6 mg/kg/day in 2 divided doses. **11 to <20 kg:** Oral, IV: Initial: 0.5 to 1.25 mg/kg/dose twice daily; adjust dose based on individual patient response and tolerability (gradual dose escalation not required); maximum daily dose: 5 mg/kg/day in 2 divided doses.

	20 kg to <50 kg: Oral, IV: Initial: 0.5 to 1 mg/kg/dose twice daily; adjust dose based on individual patient response and tolerability (gradual dose escalation not required); maximum daily dose: 4 mg/kg/day in 2 divided doses. **≥50 kg**: Oral, IV: Initial: 25 to 50 mg twice daily; adjust dose based on individual patient response and tolerability (gradual dose escalation not required); maximum daily dose: 200 mg/day in 2 divided doses. **Adolescents ≥16 years:** Oral, IV: Initial: 50 mg twice daily; may decrease to 25 mg twice daily or increase up to 100 mg twice daily based on individual patient response and tolerability (gradual dose escalation not required); maximum daily dose: 200 mg/day in 2 divided doses.
Maximum Daily Dose Pediatrics*	200 mg/day
Adjustment	• No dose adjustment for altered kidney function. **For Hepatic Impairment: Adult** Mild to severe impairment (Child Pugh classes A, B, and C): Initial: 25 mg twice daily, up to a maximum of 75 mg twice daily. **For Hepatic Impairment: Pediatric** Mild to severe impairment: Infants, Children, and Adolescents <16 years: Oral, IV: <11 kg: Initial: 0.75 mg/kg/dose twice daily; maximum daily dose 4.5 mg/kg/day in 2 divided doses. 11 to <20 kg: Initial: 0.5 mg/kg/dose twice daily; maximum daily dose: 4 mg/kg/day in 2 divided doses.

	20 kg to <50 kg: Initial: 0.5 mg/kg/dose twice daily; maximum daily dose: 3 mg/kg/day in 2 divided doses. ≥50 kg: Initial: 25 mg twice daily; maximum daily dose: 150 mg/day in 2 divided doses. Adolescents ≥16 years: Oral, IV: Initial: 25 mg twice daily; maximum daily dose: 150 mg/day in 2 divided doses.
Prescribing edits*	MD, AGE, ST, CU, PA
AGE (Age Edit): Given to patients with partial onset seizures who are ≥1 month of age	
CU (Concurrent Use Edit): Recommended as a second-line **add-on option** for the treatment of partial-onset seizures if the first-line add-on options fails	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only neurologists should prescribe Brivaracetam wih appropriate experience in the treatment of epilepsy	
PA (Prior Authorization): Brivaracetam, a controlled substance V should be prior authorized because it can be misused or abused. Brivaracetam requires monitoring for hepatic function which in case of impairment imposes dose adjustement. In addition to the hepatic function, symptoms of depression and suicidality, CBC with differential should also be monitored	
QL (Quantity Limit): N/A	
ST (Step Therapy): Recommended as monotherapy or add-on therapy if Levetiracetam fails as a **second-line** or **add-option** for myoclonic seizure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Nervous system: Dizziness (12%), drowsiness (≤16%), psychiatric disturbance (13%; includes psychotic and nonpsychotic), sedated state (≤16%) **Most serious**: Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with

	or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat. • Hallucinations (seeing or hearing things that are not there). • Change in balance. • Trouble walking. • Clumsiness. • Not able to control eye movements. • Like other drugs that may be used for seizures, this drug may rarely raise the risk of suicidal thoughts or actions. The risk may be higher in people who have had suicidal thoughts or actions in the past.
Drug Interactions*	**Category X**: • Azelastine (Nasal) • Bromperidol • Flunarizine • Kratom • Olopatadine (Nasal) • Orphenadrine • Oxomemazine • Paraldehyde • Thalidomide
Special Population	• CYP2C19 poor metabolizers: Poor metabolizers of CYP2C19 may require dose reduction. • Hepatic impairment: Use caution in patients with hepatic impairment; dosage adjustment recommended. • Renal impairment: Not recommended in patients with end-stage renal disease (ESRD) undergoing dialysis.
Pregnancy	Brivaracetam crosses the placenta

Lactation	Brivaracetam is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to brivaracetam or any component of the formulation
Monitoring Requirements	CBC with differential, liver and renal function, and symptoms of depression and suicidality (baseline and as clinically indicated)
Precautions	***Concerns related to adverse effects:*** • CNS depression: May cause CNS depression (impaired coordination, ataxia, abnormal gait, dizziness and dose-related fatigue, and somnolence), which may impair physical or mental abilities. Risk is greatest early in treatment, but may occur at any time. Patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery, driving). • Hematologic effects: May cause hematologic abnormalities; significant decreased white blood cell count (<3.0 x 10^9/L) and decreased neutrophil count (<1.0 x 10^9/L) have been reported. • Hypersensitivity: Bronchospasm and angioedema have been reported. Discontinue therapy if a hypersensitivity reaction develops. Multiorgan hypersensitivity syndrome (also known as Drug Rash Eosinophilia and Systemic Symptoms or DRESS), is a serious condition sometimes induced by antiseizure drugs. DRESS initially

	presents with fever and rash, then with other organ system involvement that may include eosinophilia, lymphadenopathy, hepatitis, nephritis, and/or myocarditis. If any of these hypersensitivity reactions are suspected and an alternative cause cannot be established, discontinue brivaracetam. • Psychiatric symptoms: Psychosis, paranoia, hallucinations, and behavioral symptoms (including abnormal behavior, adjustment disorder, affect liability, aggression, agitation, altered mood, anger, anxiety, apathy, belligerence, depression, irritability, mood swings, nervousness, psychomotor hyperactivity, restlessness, and tearfulness) may occur; clinical trials reported events in 13% of adult patients receiving brivaracetam compared with 8% receiving placebo (adverse events in pediatric patients were similar to those observed in adult patients). • Suicidal ideation: Pooled analysis of trials involving various antiseizure medications (regardless of indication) showed an increased risk of suicidal thoughts/behavior (incidence rate: 0.43% treated patients compared with 0.24% of patients receiving placebo); risk observed as early as 1 week after initiation and continued through duration of trials (most trials ≤24 weeks). Monitor all patients for notable changes in behavior that might indicate suicidal thoughts or

	depression; notify the health care provider immediately if symptoms occur. ***Other warnings/precautions:*** • Withdrawal: Antiseizure medications should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency unless safety concerns require a more rapid withdrawal.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Epilepsy treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 8. Brivaracetam HTA Analysis

Medication	Agency	Date – HTA Recommendation
Brivaracetam	NICE	N/A
	CADTH[12]	01/2017: The CADTH Canadian Drug Expert Committee (CDEC) **recommends that brivaracetam be reimbursed** for adjunctive therapy in the management of partial-onset seizures (POS) in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy, **if the following clinical criteria and conditions are met:** Clinical criteria: • Patients are currently receiving two or more antiepileptic drugs (AEDs). • Patients are not receiving concurrent therapy with levetiracetam.

		• Patients are those for whom less costly AEDs are ineffective or not clinically appropriate. Conditions: • Patients are under the care of a physician experienced in the treatment of epilepsy. • The daily cost of treatment with brivaracetam should not exceed the daily cost of alternative adjunctive therapies.
	HAS[13]	12/2022: **Opinion in favor of reimbursement** in combination in the treatment of partial onset seizures with or without secondary generalization in children and adolescents aged 2 to 15 inclusive with epilepsy.
	PBAC[14]	***For the 25 mg dose,*** continuing therapy only: • Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition. • Intractable partial epileptic seizures. The treatment must not be given concomitantly with levetiracetam. ***For the 50 mg*** dose, intractable partial epileptic seizures, initial treatment **Clinical criteria:** • The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent. **AND** • The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents. **AND** • The treatment must not be given concomitantly with levetiracetam, except for cross titration. ***For the 10mg/ml oral liquid:*** Intractable partial epileptic seizures, Initial treatment **Clinical criteria:**

		• The treatment must be in combination with two or more anti-epileptic drugs which includes one second-line adjunctive agent. **AND** • The condition must have failed to be controlled satisfactorily by other anti-epileptic drugs, which includes at least one first-line anti-epileptic agent and at least two second-line adjunctive anti-epileptic agents. **AND** • Patient must be unable to take a solid dose form of this drug, **AND** • The treatment must not be given concomitantly with levetiracetam, except for cross titration.
	IQWIG[15]	Document published in german.

Conclusion Statement – Brivaracetam

As per **HAS**, the use of Brivaracetam is recommended to be used in combination in the treatment of partial onset seizures with or without secondary generalization in *children and adolescents aged 2 to 15* inclusive with epilepsy. **CADTH** recommends **that brivaracetam be reimbursed for** adjunctive therapy in the management of partial-onset seizures (POS) in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy if certain conditions are met. Its use as an adjunct is also backed up by **PBAC**. No data that shows its cost effectiveness but according to **CADTH**, the daily cost of treatment with brivaracetam should not exceed the daily cost of alternative adjunctive therapies. According to **NICE** guidelines 2022, Brivaracetam can also be used for myoclonic seizure as a monotherapy or add-on treatment. Brivaracetam is present in breast milk so benefits versus risks to the infant and to the mother should be weighed before prescribing it to a breastfeeding mother.

2.2 Modifications

No modifications have been made since March 2020.

2.3 Delisting

The medications below are no longer SFDA registered[16], therefore, it is recommended to delist the following drugs from CHI formulary:

- Zonisamide
- Cenobamate
- Escilicarbazepine
- Phenobarbital
- Tiagabine
- Ethosuximide
- Rufinamide
- Felbamate
- Stiripentol
- Cannabidiol

2.4 Other Drugs

After March 2020, there have been novel drugs that have received FDA or EMEA approval. However, these drugs are not yet registered by the SFDA.

2.4.1 Fintepla (Fenfluramine)

FDA: June 25, 2020: The U.S. Food and Drug Administration approved Fintepla (fenfluramine), a Schedule IV controlled substance, for the treatment of seizures associated with Dravet syndrome in patients age 2 and older[17].

EMA: February 8, 2023 – FINTEPLA®▾ (fenfluramine) oral solution has been approved in the European Union (EU) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) as an add-on therapy to other anti-epileptic medicines for patients two years of age and older[18].

2.4.2 Ztalmy (Ganaxolone)

FDA: March 21, 2022: The FDA has approved ganaxolone (Ztalmy) for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder, also known as CDD, in patients aged 2 years and older[17].

EMA: On 25 May 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Ztalmy, intended for the treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder in children and adolescents[18].

Section 3.0 Key Recommendations Synthesis

Treatment should be started with an antiseizure medication once the diagnosis of epilepsy is confirmed. Consider starting treatment after a first unprovoked seizure if any of the following apply: an examination identifies signs of neurological deficit, the electroencephalogram (EEG) shows unequivocal epileptic activity after a discussion of the risk of further seizures, the person or their family or carers consider the risk unacceptable, brain imaging shows a structural abnormality[4].

Long-term treatment with some antiseizure medications (such as carbamazepine, phenytoin, primidone, and sodium valproate) is associated with decreased bone mineral density and increased risk of osteomalacia. Vitamin D and calcium supplementation should be considered for people at risk[4].

The risks to an unborn child of taking antiseizure medications during pregnancy, such as congenital malformations, neurodevelopmental impairments and fetal growth restriction should be discussed with women and girls with epilepsy who are able to have children (including young girls who are likely to need treatment when they are able to have children), and their families or carers if appropriate. Specifically, the risks to the unborn child of using sodium valproate during pregnancy, including the increased risk with higher doses and polytherapy, should be assessed[4].

- Pharmacological treatment of **myoclonic seizure**[4]
    - ⇨ Offer sodium valproate or levetiracetam as a first-line treatment.
    - ⇨ If sodium valproate is unsuccessful l as first-line treatment, offer levetiracetam as a second-line monotherapy or add-on treatment
    - ⇨ If levetiracetam is unsuccessful, consider 1 of the following as monotherapy or add-on treatment options: *brivaracetam*, clobazam, clonazepam, lamotrigine, phenobarbital, piracetam, topiramate, zonisamide.
    - ⇨ Consider discontinuing antiseizure medication treatment in children with epilepsy with myoclonic-atonic seizures *who are seizure-free for 2 years*.
- Pharmacological treatment of **tonic or atonic seizure**[4]
    - ⇨ Offer sodium valproate as first-line treatment to boys, men and women who are not of childbearing potential. If sodium valproate is unsuitable, ineffective or not tolerated, offer lamotrigine.
    - ⇨ If Lamotrigine is unsuccessful. consider one of the following as monotherapy or add-on treatment: clobazam, rufinamide, topiramate.

- ⇨ If the third line is unsuccessful, consider a ketogenic diet as an add-on treatment under the supervision of a ketogenic diet team
- ⇨ If all other treatment options are unsuccessful, consider *felbamate* as an add-on treatment under the supervision of a neurologist with expertise in epilepsy.

Status epilepticus [4]

- ⇨ The International League Against Epilepsy (ILAE) proposed a new definition of **status epilepticus** meaning that all seizures ***lasting longer than 5 minutes*** constitute status epilepticus.
- ⇨ If convulsive status epilepticus does not respond to 2 doses of a benzodiazepine, give any of the following medicines intravenously as a second-line treatment: • levetiracetam, phenytoin, sodium valproate

  ***Take into account that levetiracetam may be quicker to administer and have fewer adverse effects than the alternative option

Non-pharmacological treatment[4]

- ⇨ Consider ketogenic diet under the guidance of a tertiary epilepsy specialist for certain childhood-onset epilepsy syndromes such as (Lennox–Gastaut syndrome, Dravet Syndrome, Infantile spasms syndrome) and for drug resistant epilepsy.
- ⇨ Resective epilepsy surgery: refer to tertiary epilepsy services for consideration assessment. Not to exclude people with learning disabilities or underlying genetic abnormalities
- ⇨ If the surgery is not suitable, consider vagus nerve stimulation as an add-on treatment to antiseizure medication.

From a pharmacoeconomic perspective, recommendations issued by multiple Health Technology Assessment (HTA) bodies were reviewed. Briefly, **most favor the use of Brivaracetam** in combination in the treatment of partial onset seizures with or without secondary generalization in adults and in children and adolescents aged 2 to 15 inclusive with epilepsy.

Section 4.0 Conclusion

This report serves as an annex to the previous CHI Epilepsy report and aims to provide recommendations to aid in the management of Epilepsy. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Epilepsy. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:

Age Edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing: failure of combination of behavioral and alarm therapy
Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after: First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks

Appendix B. MeSH Terms Pubmed Search

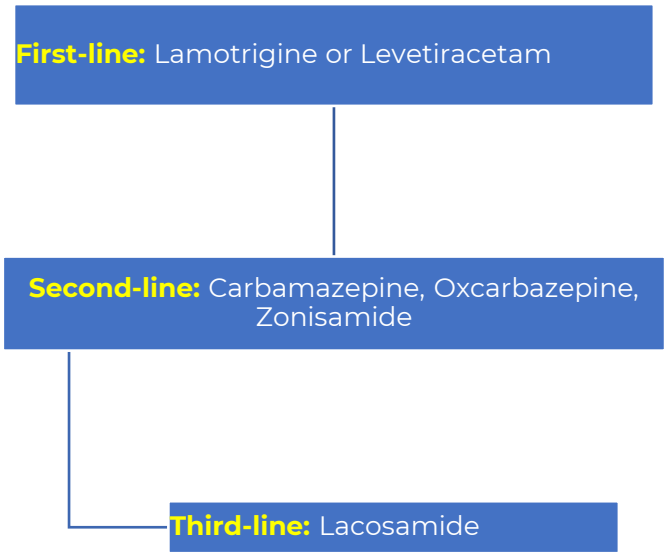
The following is the result of the PubMed search conducted for Epilepsy Guideline search:

Query	Filters	Search Details	Results
((((((((((Epilepsy[MeSH Terms]) OR (Epilepsies[Title/Abstract])) OR (Seizure Disorder[Title/Abstract])) OR (Seizure Disorders[Title/Abstract])) OR (Awakening Epilepsy[Title/Abstract])) OR (Epilepsy, Awakening[Title/Abstract])) OR (Epilepsy, Cryptogenic[Title/Abstract])) OR (Cryptogenic Epilepsies[Title/Abstract])) OR (Cryptogenic Epilepsy[Title/Abstract])) OR (Epilepsies, Cryptogenic[Title/Abstract])) OR (Aura[Title/Abstract])) OR (Auras[Title/Abstract])	Guideline, in the last 5 years	("Epilepsy"[MeSH Terms] OR "Epilepsies"[Title/Abstract] OR "seizure disorder"[Title/Abstract] OR "seizure disorders"[Title/Abstract] OR "awakening epilepsy"[Title/Abstract] OR "epilepsy awakening"[Title/Abstract] OR "epilepsy cryptogenic"[Title/Abstract] OR "cryptogenic epilepsies"[Title/Abstract] OR "cryptogenic epilepsy"[Title/Abstract] OR "epilepsies cryptogenic"[Title/Abstract] OR "Aura"[Title/Abstract] OR "Auras"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	16

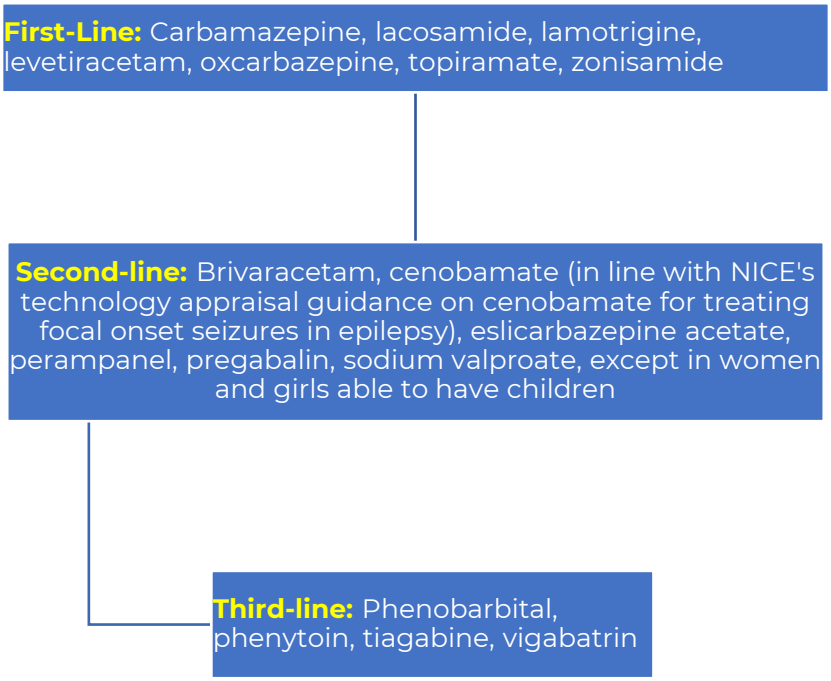
Appendix C. Treatment Algorithms

1. Focal seizures treatment

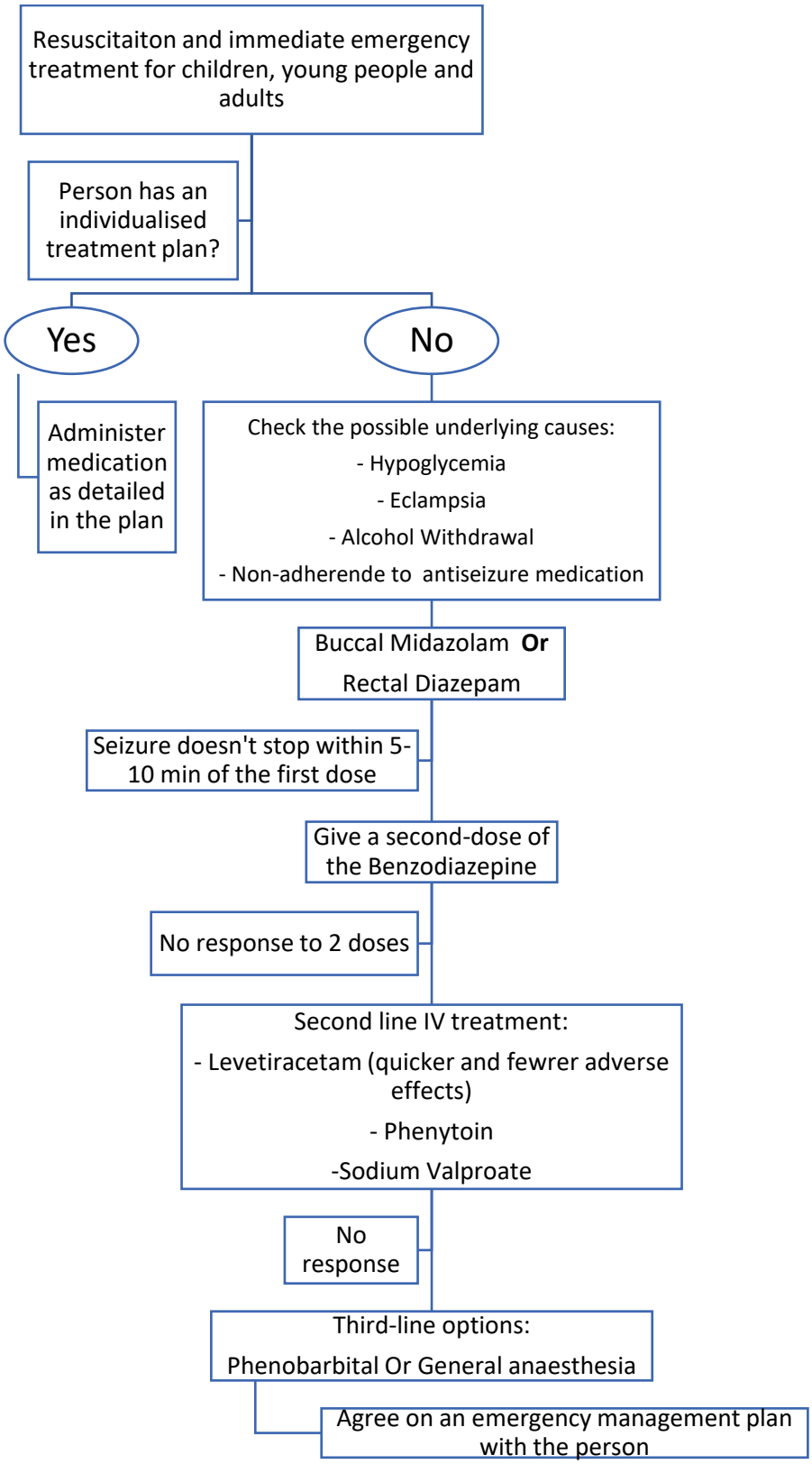
- Monotherapy



- If monotherapy is unsuccessful



2.Generalized convulsive status epilepticus's initial treatment


Resuscitaiton and immediate emergency treatment for children, young people and adults
Person has an individualised treatment plan?
Yes
No
Administer medication as detailed in the plan
Check the possible underlying causes:
- Hypoglycemia
- Eclampsia
- Alcohol Withdrawal
- Non-adherende to antiseizure medication
Buccal Midazolam Or
Rectal Diazepam
Seizure doesn't stop within 5-10 min of the first dose
Give a second-dose of the Benzodiazepine
No response to 2 doses
Second line IV treatment:
- Levetiracetam (quicker and fewrer adverse effects)
- Phenytoin
-Sodium Valproate
No response
Third-line options:
Phenobarbital Or General anaesthesia
Agree on an emergency management plan with the person