COMPENDIUM ANTIEPILEPTIC DRUGS

2019/2020

Pharmacotherapy of epilepsy
9th revised international edition

Steinhoff · Bast

IMPORTANT - VALPROATE

Valproate may only be used in women of childbearing potential, pregnant women, female adolescents and girls if no other drug is effective or tolerated.

Children who have been exposed to valproate during pregnancy are at high risk for developmental disorders (in 10-40% of the cases) and severe congenital malformations (in about 10% of the cases).

For epilepsy the following contraindications during pregnancy and for women of childbearing age apply:

Valproate is contraindicated during pregnancy unless no other appropriate alternatives are available.
Valproate is contraindicated in women of childbearing age unless they participate in the pregnancy prevention programme as described below:

Pregnancy prevention programme
The pregnancy prevention programme contains the individual education and evaluation of the patient as well as controlling the patient for using at least one effective contraceptive method. This includes pregnancy tests (before starting the therapy and if necessary during therapy). The information material as well as the risk acknowledgement form are part of the pregnancy prevention programme. It requires that the treating physician controls the treatment regularly (at least once a year) and completes, together with the patient, the risk acknowledgement form.

More information can be found on the homepage of the European Medicines Agency (https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0). For information material and risk acknowledgement form please refer to your local competent authority.

The publication of this compendium has been supported by
DESITIN Arzneimittel GmbH, Hamburg.
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Publisher
German Society of Epileptology
(Deutsche Gesellschaft für Epileptologie e. V.)
Reinhardtstr. 27c · D-10117 Berlin · www.dgfe.info

Throughout the ages epilepsy sufferers and their families have sought divine aid (detail from Raphael's "Transfiguration": a father brings his epileptic son to Christ).

Note

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Information in this Compendium is based on German guidelines and experience of the authors.

Important

A strict liability for imported preparations not licensed in Germany is not assumed by the manufacturer or the importer.

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1.1 Instructions for non-professionals or carers

Helpful measures

- Move the patient to a safe location (e.g., away from traffic, sharp objects and edges).
- Loosen clothing, particularly around the neck.
- Place the patient in the recovery position to keep airway clear and prevent choking, if possible.
- Keep calm and observe the course of the seizure closely.
- Time the duration of seizure.
- If it is a prolonged major epileptic seizures (grand mal), of longer than 3 minutes, then administer drug therapy:

Rectal diazepam (rectal tubes 5 mg and 10 mg)
onset of action usually after 5-10 mins.

Infants and children < 15 kg weight	5 mg
Children > 15 kg weight	10 mg
Adults	10 - 20 mg

- Repeat administration after an additional 5-10 minutes at the earliest if seizure persists or in the case of a new seizure. Always call the emergency services and inform relatives, if possible.
- In principle, buccal lorazepam (e.g., Tavor® Expidet), oral clonazepam (e.g., Rivotril® drops) or buccal midazolam (e.g., Buccolam®) can also be administered by non-professionals or carers as emergency medication. This applies in

particular for adults, for whom rectal administration of diazepam is often impractical and always a traumatic experience in public. Study data are very scarce. In patients under the age of 18 years, official authorisation is only available for Buccolam®. For intra-nasal application or for use of other diazepines, previous consultation with the attending physician is essential. In adults efficacy and convenience of oral midazolam have been shown convincingly in the literature. At the time of manuscript preparation nasal or intramuscular aplications for lay persons were in preparation.

Buccal lorazepam (e.g., Tavor® expidet 1.0 mg and Tavor® expidet 2.5 mg)*

Recommended dose: 0.05 mg/kg body weight, but not more than 1 mg in children and 2.5 mg in adults as initial treatment

Infants >4 months	0.5 mg
Toddlers >15 kg weight	1 mg
School children	1-2.5 mg**
Adults	2.5 (5 mg)*

* If the medication shows no effect after 10-15 minutes, an additional dose of 2.5 mg can be administered if necessary following prior consultation with the attending physician.

** The approved maximum dose in children and adolescents is 1 mg. In the acute and emergency therapy higher doses might be necessary for adolescents.

Buccal clonazepam (e.g., Rivotril® drops)
Highest authorised dose in children: 1 mg

Infants >4 months	2 - 5 drops
Toddlers >15 kg weight	5 - 10 drops
School children	10 - 15 drops
Adults	10 - 30 drops

Buccal midazolam (e.g., Buccolam®) or nasal*:

3 month - < 1 year	2.5 mg**
1 year - < 5 years	5 mg
5 years - < 10 years	7.5 mg
10 years - < 18 years	10 mg

* Nasal and/ or buccal midazolam solution for injection (Dormicum® solution for injection) might be effective and practicable.

** At the age of 3 to 6 months application in a hospital setting is mandatory.

Emergency medication with Diazepam Desitin® rectal tubes especially in early childhood, continues to be the first-line medication, even though a number of studies suggest a possible superiority of midazolam. Other medicines can be considered when diazepam is ineffective or if rectal application is not allowed. In adults the use of midazolam is off-label. In adult patients the use of buccal lorazepam (Tavor® expidet) in a dose of 1 - (2.5) - 5 mg is accepted and socially tolerated. However this also represents an off-label use.

Unnecessary measures

- Restraining convulsing limbs.
- Forceful separation of clenched jaws and prying open of clasped fingers - no bite block!
- Cardiac massage; mouth-to-mouth resuscitation.
- Restraining the patient in case of impulsive restlessness (calming support instead).

1.2 Treatment recommendations for the first aiding physician

A situation is considered to be an emergency if a convulsive status epilepticus (bilateral tonic-clonic- or hemi-seizures) impends (prolonged or rapidly succeeding seizures) or is already present. This convulsive state can quickly become life-threatening for patients and requires immediate admission to the nearest hospital.

Emergency treatment prior to inpatient admission to hospital

Treatment of first choice:

Diazepam or clonazepam ampoules for intravenous (i.v.) administration (e.g., Rivotril®), midazolam (e.g. Dormicum®), lorazepam (e.g., Tavor® for injection). If unavailable, or if venous access is not possible: diazepam rectal tubes. Buccal midazolam (e.g., Buccolam®) is also approved for treatment of acute prolonged seizures in diagnosed epilepsy. The buccal administration of lorazepam is still an off-label use (see page 9).

Treatment of second choice:

Phenobarbital (PB) ampoules i.v. (e.g., Luminal®/Phenaemal®).
For phenytoin (PHT)* i.v. (e.g., Phenhydan®) see p. 17.
VPA** i.v. (e.g., Orfiril®/Episenta® solution for injection) as treatment of second choice for convulsive and non-convulsive status epilepticus.

Treatment of third choice:

VPA** i.v. (e.g., Orfiril®/Episenta® solution for injection) for generalised convulsive seizures (grand mal status), levetiracetam (LEV) i.v. (e.g. Levetiracetam DESITIN®, Keppra®).
LEV, brivaracetam (BRV, Briviact®)and lacosamide (LCM, e.g., Vimpat®) are not officially licensed for the treatment of status epilepticus.

* Fosphenytoin is labeled in several countries outside Germany. Due to a lack of personal experience we do not want to give advice concerning this compound.

** VPA is contraindicated in mitochondrial diseases

Acute and emergency treatment

Medicine Dosage recommendations for the first aiding physician	Infants	Toodlers and school children	Adults****
Lorazepam* If possible i.v.**, otherwise i.m. (1 ampoule 1 ml = 2 mg), alternative with delayed onset of action: (Tavor® Expidet)***	0.05 - 0.1 mg/kg	0.05 - 0.1 mg/kg repeat if needed after 10-15 mins.	4 mg repeat after 10-15 mins. if needed; max. dose in 12 h: 8 mg
Clonazepam (e.g., **Rivotril®**) If possible i.v.**, otherwise i.m. (mixed ampoule 2 ml = 1 mg), alternative with delayed onset of action: solution orally by syringe without cannula	0.01-0.05 mg/kg up to 0.5 mg	0.01-0.05 mg/kg equals 1-2 mg	1-2 mg
Diazepam If possible i.v.**, (1 ampoule 0.2 ml = 10 mg), alternative with delayed onset of action: rectal (1 rectal tube = 5 mg or 10 mg)	0.3-0.5 mg/kg up to 5 mg*	0.2-0.4 mg/kg equals 10-20 mg*	10-30 mg
Midazolam (1 ampoule 5 ml = 5 mg - 10 mg i.m. or oral (Buccolam®)	0.15-0.2 mg/kg i.m. or 0.15 mg/kg i.v. bolus **Infants, toodlers and school children and adults:** Then infusion: 0.05-0.2 mg/kg per hour; intravenous administration due to respiratory depression with equipment ready for intubation		5-10 mg i.m. or i.v.
Valproate (e.g., **Orfiril®/Episenta® solution for injection**) Only i.v. (3 ml ampoule = 300 mg, 10 ml ampoule = 1000 mg)	**Infants and toddlers:** Use with special caution only	**School children and adults:** 10-20 mg/kg within the space of 5-10 mins. followed by continuous infusion with max. rate of 6 mg/kg/h*****	
Phenobarbital (e.g., **Luminal® solution for injection**) If possible i.v.**, otherwise i.m. (1 ampoule = 1 ml = 200 mg)	4-10 mg/kg up to 100 mg	5-6 mg/kg up to 200 mg	200-400 mg

* Not for infants under 4 months

** i.v. injection very slowly: 1 ampoule in 10 mins.

*** Off-label use

**** Careful with elderly individuals, choose more cautious and lower doses (respiratory depression, cardiovascular risks etc.)

***** If the patient is taking lamotrigine or felbamate, the maintenance dose should not exceed 100 mg sodium valproate/hour. The infusion should be administered for at least 24 hours

Contraindications:

Myasthenia: no benzodiazepines

Hepatic porphyria: no benzodiazepines, no phenobarbital, no phenytoin and no valproate; use rectal chloral hydrate instead; (possible alternative in exceptions: magnesium i.v.).

1.3 Treatment suggestions for the clinician

If the patient has been previously treated with a benzodiazepine (lorazepam [e.g., Tavor® for injection], diazepam [e.g., Valium®] clonazepam [e.g., Rivotril®], midazolam [e.g., Dormicum®]), with PB (e.g., Luminal®/Phenaemal®) or PHT (e.g., Phenhydan®) and the seizure has been controlled clinically, it is not necessary to administer further antiepileptic drugs. However, the patient should be closely monitored.

If no previous treatment has been administered or in case of seizure recurrence, lorazepam, clonazepam or diazepam i.v., PHT i.v., PB i.v. or VPA i.v., (e.g., Orfiril®/Episenta® solution for injection) should be administered initially as outlined under "Treatment recommendations for emergency physicians". Off-label use of LEV or LCM can be considered.

Caution: There is a risk of respiratory depression at high doses and at high total doses, during severely prolonged seizures, and following use of PB after lorazepam, clonazepam, midazolam or after diazepam and vice versa. Tonic seizures can also be induced or triggered by benzodiazepines.

Due to its complicated application and high cardiovascular risk, phenytoin lost its importance during the last few years especially outside of the hospital setting. Its availability as intravenous formulation is limited. It should only be used in a hospital setting. If higher doses of benzodiazepines (BZP) or PB have been previously administered or if respiration and circulation are impaired as a result of the status, PHT is

usually the treatment of first choice. VPA (e.g., Orfiril®/ Episenta® solution for injection) can be considered in this situation (for dosage see p. 17). Given their low rate of interactions and lacking respiratory depression, it is conceivable that the antiepileptic drugs LEV i.v. (e.g., Levetiracetam DESITIN®, Keppra®) and LCM (e.g., Vimpat®), which are at present not licensed for the treatment of a status epilepticus, are an alternative. PHT (e.g., Phenhydan®) is administered undiluted and at a very slow rate (i.v. 0.5 ml/minute) via a one-way safe i.v. access (see p. 17). It has no depressant effect on respiration or circulation at the indicated doses.

Since the onset of action is delayed by 15 to 20 minutes, PHT cannot be dosed in the same way as benzodiazepines or PB i.v., which cause an immediate block of the seizure, to reach the same effect.

In a persistent convulsive status without response to BZP and a second, adequate substance (PB, PHT):
Intubation anaesthesia by an anaesthetist.

General measures

- **Keep airways clear, monitor cardiovascular status, if necessary administer of O_2, ventilation.**
- Monitor bladder status.
- At temperatures above 38.5° C, **lower temperature** by physical and/or pharmacological means.
- Treatment of cerebral oedema.
- **Treatment of dehydration and acidosis.**
- Monitor blood glucose levels (marked fall in blood sugar possible in grand mal [status]).
- **Infection prophylaxis (risk of aspiration).**
- **Close monitoring or intensive care.**

Acute and emergency treatment

Medicine Dosage recommendation for hospital physician	Infants	Toddlers and school children	Adults
Lorazepam (1 ampoule 1 ml = 2 mg)	0.05-0.3 mg/kg	0.05-0.1 mg/kg repeat after 10-15 mins. if necessary	4 mg repeat after 10-15 mins. if necessary; max. dose within 12 h 8 mg
Clonazepam (e.g., **Rivotril®**)* (mixed ampoule 2 ml = 1 mg)	0.01-0.05 mg/kg	0.01-0.05 mg/kg	1-3 mg
Diazepam* (1 ampoule = 2 ml = 10 mg)	0.15-0.3 mg/kg	0.15-0.3 mg/kg	10-30 mg
Midazolam (1 ampoule 5 ml = 5 mg)	0.15-0.2 mg/kg i.m. or 0.15 mg/kg i.v. bolus Infants, toddlers, school children and adults: Then infusion: 0.05-0.2 mg/kg per hour; intravenous administration due to respiratory depression with equipment ready for intubation		5-10 mg i.m. or i.v.
Phenobarbital (e.g., **Luminal®/Phenaemal®** solution for injection) i.v., in emergency i.m. (1 ampoule = 1 ml = 200 mg)	6-15 mg/kg	6-10 mg/kg	200-400 mg
Phenytoin[1] (e.g., **Phenhydan®**)** i.v., (cannot be dosed according to effect), (1 ampoule = 5 ml = 250 mg [Phenhydan®])	–	10-15 mg/kg	
Valproic acid*** (e.g., **Orfiril®/Episenta®** solution for injection) (3 ml ampoule = 300 mg; 10 ml ampoule = 1000 mg)	–	Authors recommendations: Single dose: 15-30 mg/kg, 5 mg/kg/min. max. Perfusor: 10-20 mg/kg within the space of 10-20 mins., then 1.5-3 mg/kg/h School children and adults: according to SmPC: 10-20 mg/kg within the space of 5-10 mins., followed by continuous infusion with max. rate of 6 mg/kg/h***	1200-1800 mg within the space of 10 mins. 2400-5100 mg in 24 h (2-4 mg/kg/h)
Levetiracetam**** (e.g., **Levetiracetam Desitin®**) (1 ampoule = 5 ml = 500 mg)	10-20 mg/kg	Single dose: 20-30 mg/kg	Authors recommendation: Single dose of 30-60 mg/kg; repeat if necessary

[1] Fosphenytoin is labeled in several countries outside Germany. Due to a lack of personal experience we do not want to give advices concerning this compound.

* ** *** **** See page 16 for explanations

See specialist literature for other antiepileptic drugs for treating a grand mal status such as chloral hydrate in aqueous (not oily) solution, clomethiazole, flunitrazepam, lidocaine, paraldehyde (not a commercial preparation), and thiopental.

* Diazepam solutions for injection should not be mixed with other medicinal products in the injection syringe and can usually only be administered as a bolus injection. Clonazepam (Rivotril®) can also be administered as an infusion:

Rivotril® at a ratio of 2-3 ampoules per 250 ml infusion of aqueous solution of glucose 5 or 10%, of NaCl 0.9% or Ringer's solution. These mixtures must remain clear and must be used immediately. Polyvinyl chloride (PVC) infusion bags should not be used. During infusions made of other solutions, diazepam (e.g., Valium®) and clonazepam (Rivotril®) can be injected into the lower injection chamber during a temporary interruption of the infusion.

** No other infusion through the same cannula during the Phenhydan® injection.

*** If the patient is taking lamotrigine or felbamate, the maintenance dose should not exceed 100 mg sodium valproate/hour. VPA inhibits the metabolism of LTG. VPA can increase felbamate serum levels by 50%.The infusion should be administered over a space of at least 24 hours.

**** Levetiracetam is not licensed for the treatment of status epilepticus. Lacosamide i.v. and brivaracetam i.v. are also not licensed for the treatment of status epilepticus. For lacosamide a single dose of 400 mg in adults can be recommended. Toddlers and school children receive 5-8 mg/kg as short infusion over a space of 15 mins, max. 200 mg as single dose. For brivaracetam an initial dose of 2 mg/kg can be recommended (Personal recommendations from Authors).

1.4 Rapid oral/intramuscular titration: Recommendations for secondary care clinicians

If the situation is not an emergency (see p. 12-18), rapid oral (i.m.) titration with PB or PHT or rapid intramuscular titration with PB can also be carried out for a rapid initiation of treatment instead of i.v. therapy (e.g., in the case of a dramatic onset or acute deterioration of epilepsy with grand mal or focal seizures or if a change of drug is necessary at short notice due to an allergy).

Phenobarbital

- **Toddlers:** initially 10-15 mg/kg twice weekly (BW) i.m. or orally; after 12 hours and then every 24 hours 5 mg/kg BW i.m. or orally (or permanent oral therapy in two daily doses).
- **Adolescents/adults:** initially 5 mg/kg BW i.m. or orally; after 12 hours and then every 24 hours 3 mg/kg BW i.m. or orally (or permanent oral therapy in two daily doses).

Phenytoin

- On Day 1, two to three times the calculated permanent treatment dose (= 5-7 mg/kg) orally (but not more than 400 mg for children or 700 mg for adults).
- On Day 2, 75% of the first dose.
- On Day 3, the calculated permanent dose (= 5-7 mg/kg). A rapid titration with PHT can promote the incidence of an allergic exanthema. Due to 100% bioavailability oral application should be preferred.

A rapid titration is easier with anticonvulsants that quickly reach a plasma steady state and/or can be applied intravenously. Neither for LEV nor for BRV parenteral application is necessary as in principal both drugs can be started with an effective maintenance dose. For LCM it was generally shown that switching to an oral maintenance dose is possible, however larger practical experience is missing. Rapid up titration for LTG, CBZ, OXC and ESL are not possible due to a lack of parenteral application forms and a significantly higher risk for allergic reactions and hyponatremia (the last only under CBZ, OXC and ESL).
In clinically challenging situations it can be justifiable to titrate anticonvulsants with a long half life much faster than usual, to judge the clinical effect as fast as possible and therefore rather accept adverse events in a hospital setting. However, adequate systematic data for such drugs like TPM, ZNS or PER are missing.

1.5 Rectal and parenteral replacement medication for oral antiepileptic drugs

If the oral long-term medication has to be interrupted for more than 24 hours (e.g., a requirement for pre-surgical or post-surgical fasting, increased vomiting or strict parenteral nutrition), the following rectal or parenteral replacement medications are available as alternative treatments:

- Instead of carbamazepine orally: carbamazepine syrup rectally (e.g., via the tip of a gastric feeding tube – not a rectal tube), undiluted; identical dose as with oral administration.
- Instead of clonazepam orally (or other benzodiazepines): clonazepam or diazepam i.m./i.v. or diazepam rectally or lorazepam or midazolam i.v..
- Instead of OXC CBZ rectally, dose 1:1 (OXC is not reabsorbed rectally).
- Instead of primidone (PRM) orally: PB i.m./i.v. (250 mg PRM is equivalent to 50 mg phenobarbital).
- Instead of LTG orally: dissolve and apply rectally (orodispersible tablet), increase dose 2x if necessary.
- Instead of LCM, LEV, BRV, VPA, PHT and PB orally: identical dose intravenously.
- All other anticonvulsants: bypass with benzodiazepines intravenously (diazepam, lorazepam, clonazepam, midazolam) or rectally (diazepam) and continue further administration as fast as possible.

When calculating the appropriate dose for these alternatives, the increased elimination resulting from (higher) infusion quantities must be taken into account.

If oral medication can be resumed within less than 24 hours after surgery, the brief interruption of tablets on the day of the surgery can be compensated by the additional administration of a single oral dose in the evening before or after surgery.

1.6 Premedication and anaesthesia in diagnostic procedures and surgeries

Where possible, use **benzodiazepine derivatives** for basic sedation, premedication and to induce parenteral anaesthesia, e.g.,:

- Orally: clobazam (CLB), clonazepam, diazepam, flunitrazepam, lorazepam, midazolam or nitrazepam.
- Buccally: lorazepam or midazolam.
- Rectally: diazepam as a suppository or solution.
- i.m.: clonazepam, diazepam, flunitrazepam or midazolam.
- i.v.: clonazepam, diazepam, flunitrazepam or midazolam to induce anaesthesia.

2.1 Diagnosis – indication for treatment

- The diagnosis of epilepsy must be definite.
  Non-epileptic cerebral or extracerebral seizures should be ruled out (e.g., affective respiratory spasms, syncopes, cardiac arrhythmias [e.g. long QT-syndrome], narcoleptic seizures, parasomnias [e.g. pavor nocturnus], paroxysmal movement disorders, dissociative seizures).

- In the case of epileptic seizures be aware of:
  – Provoked seizures, e.g., febrile seizures, or acute symptomatic seizures within the scope of correctable metabolic derailments, e.g., hypocalcaemia and hypoglycaemia.
  – Local or diffuse cerebral processes, e.g., brain tumour.

- If an epilepsy disposing constellation is present during acute symptomatic seizures, therapy for a few months is recommended.

- Only treat clinically manifest forms of epilepsy. Electroencephalography (EEG) patterns typical of epilepsy without manifest seizures are normall not a clear indication for long-term drug therapy. (Important exceptions: continuous spike wave status during sleep [CSWS], Landau-Kleffner syndrome). However, such a constellation is uncommon and might give reason to run a long-term-video-EEG to discover unnoticed seizures that require treatment.

- Always consult a neuropaediatric specialist or neurologist with experience in treating epilepsy at the beginning and in the case of problems/complications during the course of the disease.

2.2 Patient motivation

- Inform patients and their relatives extensively about the need to take medication regularly, the therapeutic goal and the risks associated with treatment.

- No treatment can be administered without the consent of the patient or their carer.

2.3 Therapeutic goals

- Freedom from seizures without impaired physical or psychological abilities.

- Unrestricted integration at school, at work and socially.

- In children: stable basis for further socio-emotional and cognitive development.

2.4 Monotherapy – polytherapy

- Follow the treatment plan consistently – do not try out different treatments at random.
- Give only one antiepileptic drug to start with (= initial monotherapy) and utilise its full potential, if necessary until you reach the limit of clinical tolerability, which is not necessarily identical with the upper limit of the so-called therapeutic blood level range.
- Before assessing the efficacy of the drug, wait until the steady state of the final dose is reached (see p. 69 ff.); if the effect is inadequate, wait for a possible late onset of action (can occur after 4-6 weeks, especially when administering VPA and all other anticonvulsants that only reach a steady state in weeks, such as TPM, ZNS or PER), provided the seizure frequency allows this.
- If the first-line medication does not result in the desired outcome, consider an "alternative monotherapy" wherever possible.
- If polytherapy is required, use no more than two or at most three antiepileptic drugs if tolerance is at best.
- If seizure freedom under polytherapy persists, combination therapy can be continued.
- Gradually discontinue medications that have proved to be ineffective.

- Avoid changing generic medication during the course of long-term therapy without a good reason, especially if the patient is seizure-free.

2.5 Start of treatment and monitoring

- As a general rule, the dose should be increased gradually.
- Keep the amount of individual daily doses small (e.g., by using prolonged-release drug formulations).
- Where possible, take the medicine during or immediately after meals, or otherwise with a large amount of liquid, at least take medication at similar times and under similar circumstances
- Ask patients to keep a seizure diary.
- Ask patients to use a dosing box, if possible.
- Use smart phone alert for improvement of adherence.
- Patients should attend regular follow-up appointments even if the results of the treatment are satisfactory (about once or twice to three times per year, see p. 79-80).

2.6 Determining blood levels of antiepileptic drugs

- Determining the blood levels is particularly important to assess **dosage reserves**, to detect **intoxications**, to collect information about **drug interactions** (see p. 35-39 as well as p. 68 ff.), to identify blood level fluctuations (e.g., self-induction of a medication, **pregnancy, intercurrent diseases**) and to assess **compliance**.

- Determination of the free fraction that is not bound to protein, particularly during pregnancy, hepatic and renal diseases, hypo- and dysproteinaemia and when adding VPA to PHT (VPA leads to a displacement of PHT from protein binding → increase of the free fraction of PHT with an otherwise unchanged total concentration → risk of overdose/intoxication).

- Consider determination of metabolites such as carbamazepine-epoxide that can increase in combination therapy (e.g. when switching from LEV to BRV).

- As a general rule, blood samples should only be drawn once the **steady state** is reached (see p. 68 ff.).

- **Single** daily blood sample should be taken in the morning before taking tablets or immediately after a recurrent seizure or – in the case of antiepileptic drugs with a short half-life – when absorption is expected to be at its peak. At least it should be taken at the same time every day.

- **Multiple** daily blood samples (daily profile) enable a more precise estimate of dosage reserves and a better detection of toxic blood level peaks for antiepileptic drugs with a short half-life. This applies in particular to non-prolonged release VPA (at least three blood level values), standard CBZ formulations and PRM.

- As a general rule, determining blood levels of benzodiazepines, gabapentin (GBP), LEV, pregabalin (PGB), tiagabin (TGB), topiramate (TPM), vigabatrine (VGB), Zonisamide (ZNS), retigabine (RTG), rufinamide (RUF), stiripentol (STP) and perampanel (PER) can be omitted because of the lack of, or (as yet) unknown correlation with the antiepileptic effect and clinical side effects. The same applies to **sulthiam** (STM): in this case the clinical signs of **hyperpnoea** are very reliable in signalling that the upper therapeutic limit has been reached or exceeded. For identifying the individual reference range, blood level determination can be reasonable.

- Blood levels are only useful and helpful when assessing the measurement data within the framework of the clinical picture. The so-called **therapeutic range** is subject to individual variation.

- Low blood levels, which lead to seizure freedom, are not "subtherapeutic" or ineffective. "Toxic" blood levels generally only require a reduction in dose if there is also a clinical suspicion of intolerance and overdose. There are very few exceptions, such as PHT, which can also have gradually increasing toxic effects in permanent blood levels of more than 20 mg/l total concentration or 2.2 mg/l free fraction.

2.7 Length of treatment

- Freedom from seizures for 2-5 years (depending on the type of epilepsy) is a prerequisite for a careful and gradual attempt at discontinuing the medication; if seizure freedom after epilepsy surgery has been achieved, discontinuation can be attempted after 1 year.

- Depending on the type of epilepsy, the relapse rate during or after discontinuing the medication varies between 2% (relapse rate in adults after benign Rolando epilepsy in children) and 85% (in juvenile epilepsy with grand mal seizures after waking up, depending on lifestyle), and lies on average at 25% in children and 35-40% in adults.

- In generalised idiopathic epilepsy, the treatment should only be discontinued – if at all – prior to the age of 18 years, as the risk-benefit ratio deteriorates significantly in case of recurrent seizures at this point (driver's license, finding a job, need for mobility).

- Long-term prognosis (i.e. freedom from seizures without medication) is best for idiopathic focal forms of epilepsy (e.g. Rolando Epilepsy, Panayiotopoulos Syndrome) and for some generalised idiopathic forms (e.g. childhood absence epilepsy). However, juvenile myoclonic epilepsy and grand mal epilepsy on awakening in particular may require a long-term, possibly even life-long low maintenance therapy due to the high risk of relapse (after discontinuing the antiepileptic medication). Attempt to discon-

tinue medication following comprehensive and well-documented education of the patient about the possible risks of a recurrence of seizures. If the patient is able to drive and in possession of a Class 1 driver's license, inform the patient that a 3-month break from driving is recommended. (In Germany.)

2.8 Drug resistance - problem cases

- If an epilepsy diagnosis is not definite, it is not possible to classify seizures or an epileptic syndrome. In the case of drug resistance or psychiatric and psychosocial problems, refer the patient to a neuropaediatric specialist / neurologist or other relevant specialist, or to an outpatient seizure clinic, a hospital epilepsy department, epilepsy clinic or an epilepsy specialist centre.

- Drug resistance can be accepted if two therapeutic attempts have failed with adequate medication, reasonable dosing and within an adequate period of time. In the case of proven drug resistance, consider surgical epilepsy intervention. Prerequisite: sufficient pre-surgical diagnostics in specialist institutions (hospital epilepsy department, epilepsy specialist centre). If epilepsy surgery is not a viable option, vagus nerve stimulation or similar procedures (e.g. deep brain stimulation) should be considered as well as ketogenic diet as an alternative. Be aware of clinical trials with new antiepileptic drugs and literature concerning new complementary methods of treatment.

2.9 Supporting measures

- Well-regulated lifestyle (particularly important in generalised idiopathic forms of epilepsy):
  - Avoid major lack of sleep and big changes in sleep-wake-rhythm.
  - Avoid excessive consumption of alcohol.

- Medical assistance also in the case of social medical problems (school, work, family, free time, ability to drive, driver's license, military service, insurances, etc.). However, the quality of the treatment must withstand "normal" everyday stresses. Do not overprotect patients or promote social invalidity by imposing an excessively restrictive treatment plan.

2.10 Highlight sources of information to patients and their relatives, for example:

- Opportunities for self-training and self-control (e.g., MOSES, PEPE, Famoses, Diary E [Epilepsy] and Youth Diary E; documentation of long-term treatment courses online)

- International bureau for epilepsy, www.ibe-epilepsy.org

- Epilepsy Network, www.epilepsynetwork.org

3.1 Antiepileptic drugs and drug interactions

Interactions between individual antiepileptic drugs are possible in either direction and cannot always be predicted (importance of monitoring blood levels during combination therapy). The table on page 79 gives you an overview on the most frequent interactions.

- VPA also acts as an inhibitor in combination with PB (note: PB intoxication after adding PB/PRM to VPA, also as a late effect); if given in combination with CBZ, VPA inhibits the breakdown of the metabolite CBZ epoxide and thus results in an overdose of CBZ epoxide, even more so when adding CBZ to VPA than vice-versa. (Note: particularly significant inhibitory [and toxic allergic] effect when combining VPA with LTG; titration of LTG should therefore be particularly slow when administered in combination with VPA. VPA can increase the concentration of RUF.)

- Initially, VPA can displace the protein binding of CBZ and particularly of PHT (note: PHT intoxication via the free fraction of PHT – without increasing the total PHT concentration – when adding VPA.)

- When administered in combination with CBZ, LTG can lead to symptoms of a CBZ overdose (dizziness, nausea, diplopia), possibly as a result of an increase in CBZ epoxide. In these cases, a reduction of the CBZ dose by 10-20% is indicated (possibly even as prophylaxis if the CBZ dose is already in the upper range before adding LTG).

- TPM can occasionally increase the concentration of PHT. When combined with VPA it can lead to an increase in VPA-induced side effects, in particular encephalopathy, especially in young children.

- From a pharmacodynamic viewpoint, antiepileptic drugs with a depressant effect on the central nervous system, such as PB/PRM, MSM, benzodiazepines and bromide (CBR) can mutually intensify CNS side effects (cumulative toxicity when combining these antiepileptic drugs).

- Combining three and more antiepileptic drugs can also result in cumulative toxicity which can further develop to prostration syndrome even with **non-toxic** blood levels in the middle or upper therapeutic range.

- Enzyme inducers (e.g. PHT, CBZ, OXC) reduce PER serum levels.

- BRV increases CBZ-epoxide.

Interactions with non-antiepileptic drugs
(selection of clinically relevant drug interactions)

Antacids
Aluminium and magnesium hydroxides and calcium carbonate can decrease blood levels of PHT, while cimetidine and famotidine increase those of PHT and CBZ. PHT increases the levels of cimetidine and decreases absorption of sucralfate.

Antibacterial drugs
Macrolide antibiotics, erythromycin in particular, increase CBZ levels possibly two- to three-fold (Note: CBZ intoxication following oral and particularly i.v. administration of erythromycin); VPA levels can also be increased by macrolide antibiotics. Meropenem can significantly reduce VPA levels. PB/PRM, PHT and CBZ can halve doxycycline levels, but not those of other tetracyclines. Chloramphenicol and sulphonamides increase PHT levels; isoniazid can significantly increase levels of PHT, CBZ and PRM (risk of intoxication); PB lowers chloramphenicol levels, while PB/ PRM can intensify the toxicity of trimethoprim; rifampicin levels may fall under treatment with PB and PHT.

Antidepressants
Imipramin, trazodone and viloxazine increase PHT and CBZ levels. The side effects of lithium are also intensified by PHT and CBZ. The breakdown of citalopram can also be inhibited by STP. Increased reduction of NaSSA (e.g. mirtazapine) and tricyclic antidepressants (e.g. amitryptiline) under enzyme inducers (e.g. CBZ, PHT).

Antihistamines
The breakdown of antihistamines can be inhibited by STP.

Oral anticoagulants
The addition of CBZ and PB/PRM decreases the anticoagulant effect of coumarin derivatives and of warfarin, while the discontinuation of these antiepileptic drugs may lead to an increased risk of haemorrhaging (prothrombin time should be monitored!). The effect of coumarin derivatives and of warfarin, on the other hand, is intensified by the addition of VPA. The addition of coumarin derivatives / warfarin can increase PHT levels.

Antimycotics
Absorption of griseofulvin is poor under PB; fluconazole increases PHT levels.

Antirheumatics
Phenylbutazone and derivatives can increase PHT levels. Acetylsalicylic acid (ASA) increases VPA levels by displacement from protein binding and increases a latent VPA-induced bleeding tendency (Note: beware of manifest haemorrhagic diathesis, e.g., when taking ASA as an antipyretic agent!). PB, CBZ and PHT can increase toxic paracetamol metabolites by means of enzyme induction (especially at high doses).

Beta-blockers
The breakdown can be inhibited by STP.

Calcium antagonists
Verapamil and diltiazem increase CBZ levels more significantly than flunarizine. (This interaction is not known with nifedipine.)

Disulfiram (Antabus®)
PHT levels are increased significantly by disulfiram.

Immunosuppressants
Tacrolimus, cyclosporin and sirolimus can be increased by STP. Enzyme inducers (e.g. PHT, CBZ) decrease everolimus serum levels.

Cardiac medication
Blood levels of the antiarrhythmic drugs quinidine and disopyramide as well as those of digitoxin can be reduced by PB/PRM, CBZ and PHT (risk of underdosage during treatment with digitalis!). Blood levels of cisapride, halofantrin, pimo-zide, quinidine and bepridil can be increased by STP.

Ergoline
Ergotamine and dihydroergotamine levels can be increased significantly by STP.

Neuroleptics
When administered together with CBZ, haloperidol is broken down more rapidly. The same applies to clozapine and PHT. PHT levels can be increased by neuroleptics. STP increases the centrally depressant effect of chlorpromazine.

Proton pump inhibitors
The breakdown of proton pump inhibitors can be inhibited by STP.

Statins
The breakdown of statins can be inhibited by STP.

Steroids, hormones and vitamins
The breakdown of corticosteroids, oral contraceptives, vitamin D, vitamin B6 (pyridoxine) and folic acid is rapidly accelerated by PB/PRM, PHT, CBZ and OXC, thus reducing their efficacy. STP inhibits the degradation of oral steroids especially contraceptives. On the other hand, folic acid can reduce the plasma concentration of PHT. Adrenocorticotropic hormone (ACTH) reduces the blood levels of PB/PRM, CBZ and PHT, but increases those of VPA. Adding danazol significantly increases CBZ levels (Note: CBZ intoxication!). Contraceptives can reduce serum LTG levels considerably (up to 50%).

Stimulants
Methylphenidate can impair the metabolism of PHT and PB/PRM and thus favour an increase in plasma concentration levels of these substances.

Theophyllin and **derivatives**
Levels of PHT and CBZ are reduced by theophyllin and its derivatives (risk of PHT intoxication upon discontinuation). Conversely, theophyllin levels are decreased by PB/PRM, PHT and CBZ and increased by STP. Drug interactions of STP with theophyllin or caffeine (Cyp 1A2) cannot be ruled out.

Virostatic agents
Aciclovir can decrease VPA serum levels.

Centrally depressant drugs and alcohol
PB/PRM and benzodiazepines as well as all generally sedating anticonvulsants or such that cause dizziness and impaired vision in higher doses, lead to mutually enhancing effects when taken in combination with centrally depressant drugs and alcohol.

Cytostatics
Cisplatine and, in combination with other cytostatics, carmustine lower PHT levels considerably. PB and PHT can increase methotrexate toxicity.

3.2 Contraindications and intolerance

- No **benzodiazepines** in acute narrow-angle glaucoma and myasthenia gravis.
- No **CBZ** in hypersensitivity to tricyclic antidepressants.
- A higher risk for allergic reactions to different anticonvulsants like **CBZ**, **OXC**, **PHT** or **LTG** was reported for the different HLA gene markers HLA 1502, HLA 2402, HLA 3101, HLA 3303 or HLA 3502.
- No **PHT** in high-grade AV block and sino-atrial block.
- No **PB/PRM**, **PHT**, **CBZ**, **VPA** and **clonazepam** in hepatic porphyria (e.g., acute intermittent porphyria or cutaneous hepatic porphyria).
- Extra caution in and strict surveillance of patients with depression or psychosis (actual or in medical history). Especially when using ESM, STM, VGB, TPM, ZNS, LEV and PER.
- Caution with TPM or ZNS in glaucoma.
- For precautionary measures when using **VPA** see p. 57-64 and the use of ACTH or corticosteroids see p. 65 ff.

Generally in epilepsy patients...
(due to a possible induction of epileptic seizures)

■ **Caution should be exercised when using:**
Antihistamines (e.g., also as antiemetics), antidepressants, chloroquine, desmopressin, dopamine antagonists, gadopentetates (gadolinium [incidence of seizure provocation around 1:1000]), indomethacin, interferons, isoniazid, local anaesthetics (lidocaine, procaine), methohexital, neuroleptics, propofol, piracetam, protirelin, prostaglandins, retinoids, stimulating sympathomimetics (fenetylline, methylphenidate, pemoline), vasopressin, virostatics (aciclovir can induce cerebral seizures when administered as an i.v. infusion!) and cytostatics (chlorambucil, ifosfamide). Betalactam antibiotics (penicillins) can trigger seizures only at extremely high doses when administered i.v. or intrathecally.

■ **Extreme caution should be exercised when using:**
Cisapride, sevofluran, theophylline and its derivatives (risk of a grand mal epileptic status with elevated theophylline blood levels).

■ **The following should not be used whenever possible:**
Quinolones (gyrase inhibitors), piperazine-containing antihelminthics, mefloquine.

3.3 Antiepileptic drugs and contraception

Hormonal contraception is less reliable when administered concurrently with CBZ, ESL , OXC, PB/PRM, PHT, TPM (at doses >200 mg/day) and FBM. Using another method of contraception in addition to hormonal contraception or using a non-hormonal contraceptive method is advisable.
This has also been discussed recently for LTG at high doses.

If intermenstrual bleeding occurs when using hormonal contraception (dose of ethinylestradiol not below 50 µg, possibly 80 µg) concurrently with antiepileptic drugs, hormonal protection is for sure inadequate. However, contraceptive reliability is not necessarily reduced if the progestogen component is above the ovulation inhibitory dose in combination preparations (without concomitant administration of oestrogen). As a result, the concomitant intake of a low-dose ovulation inhibitor with a strong progestogen component can be recommended for use as contraception.

Patients are advised to consult their gynaecologist about contraceptive methods that supplement hormonal contraception or are considered an alternative to hormonal contraception.

In general, hormonal contraception does not cause a deterioration of epilepsy (Exception: reduction of LTG plasma concentration under the effect of hormonal contraceptives). In female patients taking LTG, the use of progestogen containing substances might reduce the influence on serum concentration. The interaction free and safe use of an intrauterine system (e.g. Mirena®, Jaydess®), which is usually also an option for young girls, can be a good contraceptive option.

3.4 Desire to have a child and pregnancy
The following points must be taken into account

Before a planned pregnancy

When planning the medical treatment and counsel of epilepsy patients the teratogenicity of VPA plays a major role since the first publications about this issue. For a while now teratogenicity of anticonvulsants is registered in several pregnancy registries. A Danish population study on all-over 837,795 live births revealed a malformation rate (e.g. cleft palate, hypospadias, spina bifida) of 2.4% for the normal population and a rate of 3.2% after prenatal exposition to newer anticonvulsants. The most recent publication of the European pregnancy registry (EURAP) added some essential data about the teratogenicity of monotherapy. The average probability for major malformations for all dose ranges are 2.9% for LTG, 5.5% for CBZ, 10.3% for VPA, 2.8% for LEV, 3.0% for OXC, 6.5% for PB, 3.9% for TPM and 6.4% for PHT. The risk was increasing dose dependently for LTG, CBZ, VPA and PB. For LEV, OXC, TPM and PHT no dose dependency was shown. Additionally the observation that the cognitive development in children from mothers taking VPA during pregnancy was impaired is alarming and definitely relevant for patient education. The IQ of children whose mothers were on VPA therapy during pregnancy was significantly lower than the IQ of the remaining children whose mothers had a therapy with CBZ, PHT or LTG during pregnancy.

Regarding the dose levels it was assumed that only doses of 1000 mg VPA were responsible. However, a Danish popula-

tion study puts the so far postulated dose dependent negative effects of VPA on cognition strongly into question. Children from mothers that had taken VPA during pregnancy performed significantly worse in language tests as well in mathematical performance compared to children from mothers that had not taken any anticonvulsants, but also compared to children from mothers that had been treated with LTG. The results were dose independent! Therefore, on basis of the available data no threshold dose can be deduced below which there is no risk for negative effects of VPA.
The verifiably increased teratogenicity of VPA and its negative impact on the cognitive development of children being exposed to the drug in the womb, prompted the European Medicines Agency (EMA) to give the explicit advice (EMA, 21.11.2014) to limit the use of VPA in female patients to only those who depend on it (also see chapter 3.4.2 Contraindication: Valproate in pregnant women or women of childbearing age). If folic acid levels in the serum are too low this might also have a negative impact leading to neural tube defects. Therefore, prophylactic administration of 5 mg folic acid per day should be started significantly prior to the pregnancy and continued through the 1st trimester.
The indication for continuous prophylaxis with folic acid in women of childbearing age needs further evidence. Minor malformations (e.g. concha anomalies, epicanthus, nail and finger hyperplasia, reduced height) are more frequent than major malformations, but are usually not perceived as disturbing any more until school age is reached.

Special epileptologic counsel needs to be actively provided if the wish to have children persists. Check the need to continue antiepileptic treatment very thoroughly. If possible switch from polytherapy to low dose monotherapy and adhere to pregnancy prevention programme as well as the contraindications of valproate. Divide the daily dose into several doses (usually 3). If VPA is given as grand mal prophylaxis, educate the patient and try to reduce the dose. Maybe it is possible to replace VPA with levetiracetam or lamotrigine (also see chapter 3.4.2 Contraindication: Valproate in pregnant women or women of childbearing age).
To assess the risk of teratogenic side effects it is crucial to keep an eye on the publications of the pregnancy registries. The high teratogenic risk for a combination of VPA with LTG seems assured. Therefore the patient should under no circumstances become pregnant as long as the switch from VPA to LTG is not fully completed.
The risk for malformations grows with dose and number of the administered anticonvulsants.

Special epilepsy consultation if patients wish to have a child: early active discussion of the subject. The indication to continue the antiepileptic medication should be particularly strict, polytherapy should be switched to the lowest possible dose of monotherapy and medication taken in several doses (usually 3 daily doses); the patient should be informed extensively when taking VPA for grand mal protection, and the dose should be reduced, and if necessary replaced by PB or LTG. Consider the pregnancy prevention programme and the contraindications vor VPA.

In order to assess the risk of teratogenic side effects, it is recommended to keep an eye on the current pregnancy register and the resulting publications. The high teratogenic risk of the combination of VPA and LTG appears to be confirmed. Pregnancy should therefore be strictly prevented if the switch has not been fully completed. The teratogenic risk under standard anti-epileptics for LTG in monotherapy up to 200 mg per day is the lowest.

3.4.2 Contraindication: Valproate in pregnant women or women of childbearing age

Monotherapy as well as combination therapy of valproate is associated with a dose dependent risk for anomalies of the newborn. Data suggest that a polytherapy for epilepsy in combination with VPA bears a higher risk for anomalies in the newborn than a therapy with VPA alone.
The risk for congenital malformations is about 10% whereas studies in pre-school children who were exposed to VPA in the womb show a delay in early childhood development in about 30-40%. For instance they start to talk and walk later, have low cognitive abilities, a low language competence and suffer memory problems.

The intelligence quotient (IQ) which was measured in a study with children at the age of 6 who were exposed to VPA in the womb was on average 7-10 points lower than in children exposed to other antiepileptic drugs. Available data show that children who were exposed to VPA in the womb have a higher

risk for autism spectrum disorders (ca. 3x higher) and infantile autism (ca. 5x higher) when compared to the overall study population. Limited data suggest that children exposed to VPA in the womb have a higher probability to develop symptoms of an attention deficit/ hyperactivity disorder (ADHD).

Therefore the following points must be regarded:

- VPA is contraindicated during pregnancy unless no appropriate alternatives are available

- VPA is contraindicated in women of childbearing potential unless the conditions of the valproate pregnancy prevention programme (p. 2) are fulfilled

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy:

- There is no dose threshold considered to be without any risk. However, the risk of birth defects and developmental disorders is higher at greater doses

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day

- The use of a prolonged-release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations

- All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine.

If a woman is already pregnant, switching to another therapy usually does not make sense. However if a switch is favoured in view of possible cognitive damage only antiepileptics with a fast and reliable onset like phenobarbital or levetiracetam are to be considered.

For risk minimisations local competent authorities provide information material for healthcare professionals and patients as well as a risk acknowledgement form.

Once pregnancy has been established
Once an unplanned pregnancy has been established, antiepileptic medication should not be discontinued (discontinuing medication once pregnancy has been confirmed is not sensible, as the risk of impairment of organogenesis is greatest during the first weeks of pregnancy), review the dose, monitor plasma levels (possibly also the free fraction). Divide VPA into at least three doses, where possible switch to a prolonged-release formulation (to prevent plasma level peaks). If the pregnancy is discovered very early on, during the very first weeks, consider switching to e.g. LEV. Inform and advise pregnant patients about the necessity and risks of antiepileptic treatment and the availability of prenatal diagnostics.

Attempt to work together with the attending gynaecologist in consultation with the patient.

Pregnancy rarely causes a deterioration of epilepsy. However, all pregnancies should be monitored by a neurologist/epileptologist.

In pregnant epileptic patients, a grand mal status is a rare complication (0.5-1%).

A fall in plasma concentrations of antiepileptic drugs is usually observed. However, the dose should only be increased in case of recurrent seizures, or in exceptional cases following a significant increase in potentials typical for epilepsy in the EEG (note: overdose after end of pregnancy!).
As the significant decreases in plasma levels of LEV and OXC are usually uncomplicated, LTG remains a special case. The decrease in serum level to up to a quarter from the initial value can lead to significant aggravation of seizures, especially in active epilepsies. Dose increases up to twice the amount of the initial dose can become necessary. To avoid post partum intoxications it is essential to go back to the initial dose in one step right after the delivery.

There is no increased risk of gestosis, premature labour, abnormal foetal presentation, miscarriage or premature birth for pregnant epileptic patients.

Delivery at a hospital is strictly indicated, also with regards to possible neonatal complications. The risk of peripartal seizures is considerably elevated.

In cases of prolonged labour, the oral administration of antiepileptic drugs should be considered. Discuss this possibility before the delivery. The prophylactic administration of 5-10 mg CLB (e.g., Frisium®) every 12 hours during labour has proven successful in preventing seizures without any adverse effect on the course of birth during prolonged labour.
The occasionally recommended prophylactic administration of vitamin K to mothers during the last 2-4 weeks of pregnancy may increase the risk of thrombosis. Manufacturer's recommendation: vitamin K prophylaxis for pregnant patients who are taking (enzyme-inducing) antiepileptic drugs:

10-20 mg vitamin K1 orally or 2-5 mg vitamin K1 i.m. 48 hours to a few hours prior to delivery. However, a significant reduction in the risk of bleeding was not demonstrated in a large-scale Finnish study, so this should only be considered optional.

3.5 Antiepileptic drugs, neonatal period and nursing

Newborn babies whose mothers were treated with PB, PHT or CBZ during pregnancy have an increased risk of bleeding, vitamin K should therefore be given to the newborn (1 mg Konakion® once, exceptionally i.m.). This should also be taken into consideration following administration of newer anticonvulsants which are associated with enzyme induction.

Sedating antiepileptic drugs taken during pregnancy (e.g., CBZ and VPA at high doses, PB/PRM, benzodiazepines and CBR) can lead to temporarily impaired alertness in newborns (monitor by means of blood level determinations in umbilical cord blood) accompanied by feeding difficulties and/or withdrawal symptoms, which can last for 6-7 days (restlessness, crying, hasty feeding and tremor; treatment with PB if necessary).

Even though antiepileptic drugs pass into breast milk, breast-feeding can and should generally be recommended (gentle weaning of the child). In cases of **abnormal drowsiness** and **feeding difficulties** of the newborn, levels of antiepileptic drug in the plasma (child) and possibly breast milk (mother) should be measured (the amount of free, non-protein-bound fraction is also important); discontinue breastfeeding if necessary. Special precautions should be exercised when breastfeeding if the mother is taking high doses of PB/PRM, DZP, ESM or CBR.

Mothers should also take care to avoid sleep deprivation when breastfeeding the baby, as this favours seizures (e.g., feeding using pumped breast milk at night is recommended). This should be discussed with the partner/family support member at an early stage.

The risk to the child as a result of a possible seizure in the mother should be considered (Suggestions include: e.g., feed child while sitting down; nappies changed on a sheet on the floor; presence of another person while child is being cared for).

3.6 Vaccinations, infection prophylaxis and desensitisation for epileptic patients

The presence of epilepsy is not generally a contraindication to routine vaccinations currently recommended by the German STIKO (Standing Committee on Vaccination), even though the vaccine reaction can trigger solitary seizures. Caution must be exercised in cases of newly diagnosed epilepsy (especially in infants) as long as the classification (and possibly also the cause) have not been clarified.

From the "Vaccine recommendations of the German standing committee of vaccinations" (last revised February 2019): As febrile reactions after a vaccination can trigger a seizure, it should be considered whether children with a tendency to epileptic seizures should be treated with antipyretics: e.g., in dead vaccines at the time of vaccination and at 4 and 8 hours after the vaccination, as well as between Day 7 and Day 12 in measles, mumps and rubella (MMR) vaccinations in case of an increase in temperature. In addition, inpatient admission for the time of the expected rise in temperature may be justified in patients with Dravet's syndrome or other forms of epilepsy with a known status tendency.

Homologous immunglobulin preparations and heterologous antisera
Can be used in epilepsy patients without any problems.

Hyposensitisation
Epilepsy per se is not a contraindication to hyposensitisation therapy. It should, however, be performed in close collaboration between the allergologist and epileptologist, and modified as required (lower allergen dosage, longer intervals).

3.7 Taking antiepileptic drugs on long-distance travels

Airlines have very different ways of assessing the ability of epilepsy patients to fly and therefore frequently lay down a wide variety of divergent preconditions. Patients are therefore advised to obtain the appropriate information before starting their journey in order to avoid possible claims for compensation (unscheduled landings).

When travelling westward

- Three times daily dosing:
  continue in an approximately 8-hour rhythm.
- Once or twice daily dosing:
  – day lengthened <3 hours:
    unchanged dose, adjust times.
  – day lengthened 3-6 hours:
    take one quarter of the daily dose upon arrival as additional dose.
  – day lengthened >6 hours:
    half of the daily dose upon arrival as additional dose.

When travelling eastward

- Day shortened <3 hours: unchanged dose, adjust times.
- Day shortened 3-6 hours: halve the dose*
  at time of next dose (local time).
- Day shortened >6 hours: halve the dose*
  at time of next dose (local time).

3.8 Special treatment monitoring for long-term valproate therapy

Based on the 1995 and 2011 revised recommendation of the Königstein Study Group for Epileptology

A. Procedure in children

Due to the risk of a rare yet life-threatening treatment complication with VPA it is necessary to:

- Establish the indication for VPA treatment strictly.
- To be aware of special instructions and recommendations for the first-time use of VPA and for monitoring the treatment.

1. Indications in medical history for particular caution for the first-time use of VPA

Family history
Unexplained deaths in childhood; unexplained critical medical conditions accompanied by fever and impaired consciousness; hepatic diseases in the family; metabolic diseases in the family; clinically relevant bleeding or coagulation disorders.

Direct medical history
Acute or chronic hepatic or (non-endocrine) pancreatic diseases; metabolic diseases with a possible involvement of the liver and/or pancreas; signs of disturbed hepatic and/or pancreatic function or disturbed coagulation.

With regard to the present disease
Multiple disabilities of uncertain aetiology; age <2 years; treatment with more than one other antiepileptic drug (except for VPA); process epilepsy with a suspected metabolic disorder – particularly in the field of beta-oxidation, mitochondriopathy (Alper's syndrome), peroxisomal diseases and urea cycle defects.

Contraindication
Death of a relative under treatment with VPA (direct line).

2. Measures before initiating VPA therapy

Apart from informing the patient generally about the benefits, side effects and risks of treatment with VPA, special instructions should be provided about early clinical symptoms arising from the onset of VPA intolerance: lack of appetite, newly developed aversion to usual foods or against VPA itself, nausea and vomiting, apathy, tendency to develop oedemas, deterioration in the seizure situation, increased bleeding tendency (it is recommended to hand out the appropriate information leaflet to the patient – see Appendix page 75 ff.).

Clinical examination
Comprehensive clinical examination of the child – especially with regard to metabolic disorders, hepatic and pancreatic diseases and coagulation disorders.

Laboratory tests
Blood count and thrombocytes, coagulation parameters (prothrombin time = Quick's test International Normalised Ratio [INR], partial thromboplastin time (PTT), fibrinogen in plasma, alpha-amylase in the blood and liver function parameters (total bilirubin, serum glutamatic oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT], gamma-gluta-myl transferase [γ-GT]). Metabolic defects (e.g. disturbed breakdown of amino, organic and fatty acids, mitochondriopathy, urea cycle defects) should be excluded in children with associated developmental disorders and/ or neurological findings (e.g. ataxia) especially when in progress. If the appropriate tests have not already been carried out in the context of aetiological investigations the following screening tests should be performed as required: lactate, ammonia, uric acid, glucose and blood gas analysis, amino acids, organic acids, acetone levels and pH values in urine.

3. Recommendations for support and monitoring after initiating treatment

Clinical monitoring
Clinical monitoring of the patient should be performed in the first instance in the form of observation by the (informed!) parents or caregiver who then report to the attending physician and by means of medical examinations as secondary monitoring. The less reliable the parents/caregivers are, the more frequently medical examinations should be carried out.

If necessary, close direct contact or contact by telephone between the physician and parents/caregivers may be required during the first weeks and months of treatment.

In case the child develops a fever, monitoring efforts should be intensified (in a large proportion of previously observed serious complications, patients had developed a febrile infection at the time of the first suspicious symptoms).

Physician/patient contact, laboratory tests
Since the first symptoms of VPA intolerance are generally clinical symptoms (laboratory results only come at a later point), the following recommendations apply with regard to clinical and laboratory chemical tests following the initiation of treatment with VPA:

- As the maximum incidence (60-70%) of VPA-induced fatal liver diseases occur between the end of the fourth treatment week and the third treatment month, a clinical examination and laboratory tests, including a determination of blood count as well as of SGOT, SGPT, bilirubin, amylase and coagulation parameters (thrombocytes, PTT, Quick's test [INR], fibrinogen), should be performed no later than 3 months after the start of the treatment.

- If the clinical course continues to be unremarkable, these control examinations should be repeated 6 months after the start of the treatment.

- During the **further course of treatment**, it is sufficient to carry out clinical examinations and laboratory tests at the same intervals as when monitoring treatment with other standard antiepileptic drugs.

- The following procedure is recommended prior to **scheduled elective surgical interventions**: extensive discussion with the parents; thorough clinical examination, particularly with regard to coagulation disorders; determining coagulation parameters including bleeding time as well as specific tests for von-Willebrand-Jürgens syndrome (factor VIII-associated proteins: C, R-AG, ristocetin co-factor).

- **Pre-, peri- or post-surgical** prophylaxis or treatment with desmopressin acetate (e.g., Minirin® or coagulation factors (factor VIII concentrate) as required.

Parents should be advised to contact the physician immediately in case of abnormalities in the clinical course or if unclear/suspicious symptoms occur – irrespective of the planned follow-ups and reporting times*. If the situation is unclear, the patient will have to be admitted for inpatient treatment for a thorough examination and for continuous monitoring;

an EEG recording can be particularly important during this phase. Is the basic activity slowing down? Is epilepsy typical activity increasing?

Even today there is no screening method that can signal the development of dangerous or even fatal complications of VPA treatment early enough and therefore prevent this complication reliably. Detailed information and consultation of the patient (according to the age and understanding) and/or the patients at the beginning of a first-time treatment with VPA as well as close monitoring of the child in their familiar environment is recommended.

B. Approach in adults

The risk of dangerous or fatal complications is considerably lower in adults compared to children, but remains theoretically possible (particularly in patients with multiple disabilities and/or undergoing polytherapy).
Therefore, the same precautionary measures/contraindications apply to adults as in children (see above); in addition, patients must also be asked about their alcohol drinking habits.

As a precaution, adults should also be given specific instructions about early clinical symptoms of an incipient VPA intolerance, and the mentioned laboratory tests (see above) should be carried out prior to starting treatment.

The clinical and laboratory tolerance tests after starting treatment should then be carried out in the same way as for other standard antiepileptic drugs (see p. 66 ff), provided that tolerability is acceptable.

Discontinuation of treatment with valproate
An immediate discontinuation of treatment with VPA should be considered in the event of:

- An inexplicable deterioration in the general condition of the patient.
- Clinical symptoms of hepatic or pancreatic involvement or of a sudden strong bleeding tendency.
- More than 2.5 times increase in transaminases (even in the absence of other abnormal clinical or laboratory results).
- Mild increase (to 1.5 - 2.5 times the upper limit of normal) of hepatic enzymes with concurrent acute febrile infection.
- Marked disorder of coagulation.

If the treatment has to be discontinued suddenly, treatment with antiepileptic drugs can be continued e.g., with benzodiazepines during the acute phase. All potentially hepatotoxic medications should be discontinued at the same time.

If there is sufficient evidence to suspect VPA-induced liver failure, pancreatitis or a marked coagulation disorder, the patient should be urgently admitted for further inpatient diagnostic procedures and also treatment, if necessary.
If there is evidence of liver failure, the patient should be referred to a hepatology centre. Early treatment with high-dose i.v. carnitine substitution (100 mg/kg BW in two daily doses) is indicated. In addition, administration of acetylcysteine (14 mg/kg BW orally), and high-dose glucose (8-15 g/kg/day) are recommended.
Lipid-containing solutions must **not** be infused.

3.9 Special guidelines for treatment monitoring for depot ACTH and corticosteroids*

The indication for this treatment, which is associated with a number of side effects and is generally initiated under inpatient conditions, must be strictly determined. Depot ACTH preparations (e.g., Synacthen® Depot) oral corticosteroids (e.g., prednisolone or dexamethasone) are applied.

Suggested initial daily dose (taken as a single early morning dose) in West-Syndrome:

- Prednisolone 40-60 mg/p.o.:
  Duration for 2 weeks each and 2 weeks stepwise termination
- Depot ACTH (tetracosactide):
  40 IU i.m. for 2 weeks, every 2 days each and 2 weeks stepwise termination via prednisolone p.o.

Corticosteroids in other epilepsy forms

Alternatively to a continuous hormone application the so called high dose pulsatile corticoid therapy is established frequently - e.g. 3 days 20 mg/kg (methyl) prednisolone p.o. once daily followed by 4 days pause (= one week cycle). Apply 4 cycles, then prolong interval to every 2 or 3 weeks if needed. Stop by tapering dose. (Details should be discussed with an epileptologist who is experienced with this therapy.) So far the pulstile treatment seems to be better tolerated than the continuous therapy. As for efficacy no final statement can be made.

* For details on implementing and monitoring steroid treatment for West syndrome we refer to the AWMF guideline (date: 10/2014).

Examinations before starting the treatment:

- Sleep and wake EEG.
- Height, weight and blood pressure.
- Age-dependent: tuberculin test, thoracic X-ray (to rule out florid tuberculosis), X-ray of wrist, ECG, abdominal sonography (pancreas, kidneys), echocardiography.
- Fasting glucose, electrolytes: sodium, potassium, calcium; blood gas analysis if necessary, hepatic enzymes, total protein and electrophoresis, immunoglobulins, and varicella antibody titre if required.
  (Consider active immunisation in case of a negative varicella titre if the seizure situation allows.) Complete all vaccinations before therapy initiation if possible.

Tolerance testing during treatment:

- Blood pressure monitoring, daily to begin with.
- Weekly sleep and wake EEGs during the first 4 weeks, fasting glucose, electrolytes, blood gas analysis if necessary, ECG.
- X-ray of wrist, renal sonography and echocardiography if necessary after several weeks.
- Ophthalmologic examinations (Cataract? Elevated intraocular pressure?)

Ending the treatment

- Discontinue treatment if no clinical effect is observed within 4 weeks of continuous single daily dosing on seizures and if no effect is observed in the wake and sleep EEG: halve the dose every 2-3 days until full discontinuation.

- If treatment is effective, switch to an alternating treatment early on and gradually taper off, or in pulse therapy prolong intervals. Followed by recommendation of hydro cortisol substitution dose (10-14 mg/m^2 body surface/ day) and "stress dose" (at least 3-times higher) in case of infections associated with high fever or status epilepticus.

Consult a paediatric epilepsy specialist for further details on dosing and tolerance testing.

Choice of medication according to epilepsy-syndrome

Note: The recommendations are not always consistent with the corresponding licensing requirements of the medicines and can in some cases be viewed as an individual treatment attempt requiring justification.

For abbreviations of substances see p. 91

Epilepsy with focal seizures	AED of first choice	AED of second choice	AED of third choice[1]	Notes
Cause structural or not known	LTG[6], LEV[3-6], OXC[3]	LCM[3], OXC[3]	BRV[3], ESL[3], GBP[3], KD[7], PB, PER, PGB[3], STM, VGB[2], VPA, ZNS[3]	
Rolando epilepsy (and relatives)	STM, OXC[3]	BRV[3], ESL[3], LEV[3], PER[3], VPA	CLB, TPM, ZNS[3], KD[7]	Review general indication for treatment strictly.
Atypical variants of idiopathic focal epilepsy	STM, CLB	CS[9], ESL[3], ESM, LCM[3], LEV, VOP, TPM	ZNS[3], KD[7]	Early use of CS.
Epilepsy with generalised seizures				
Childhood absence epilepsy	ESM	VPA, LTG[4]	LEV[3], TPM, ZNS[3], STM, KD[7]	
Juvenile myoclonic epilepsy	VPA (male), LTG[4] (female)	LEV, TPM, VPA (female), LTG[4] (male), PER[3] (bilateral tonic-clonic-seizures)	ESM, STM, ZNS[3], PB, PER[3]	LTG can intensify myoclonia and is less effective than VPA. In the treatment of IGE LEV is effective as well but is only licensed as add-on therapy.
Specific epilepsy syndromes				
West syndrome	VGB[2] and/or CS[9]	STM, VPA, TPM	KD[7], LEV[3], LTG, RUF[3], ZNS[3]	Initial trial with pyridoxal phosphate (30 mg/kg/d 3 days).
Dravet syndrome	VPA	+TPM, +CBR, +STP +CLB	CBD, ESM[3], KD[7], LEV[3], MSM[8], PB, PRM, ZNS[3]	Rapid polytherapy. Not: CBZ, OXC, LTG, PHT.
Myoclonic-astatic epilepsy	VPA	ESM, LTG, KD[7]	BR, CLB, CS[9], MSM[8], PB, PRM, TPM, ZNS[3]	
Lennox-Gastaut syndrome	VPA, TPM, LTG[3]	RUF[3], PB, ESM, ZNS[3], CLB	BR, CS[9], FBM[5], KD[7], MSM[8], PHT, PRM, VGB[2], TPM	In principle, every AED can be used depending on the target seizure type. Note: deterioration possible.

[1] Benzodiazepines (CLB, CZP) can also be used in all epilepsy syndromes as alternative medications; however, these usually only have a temporary effect (relapse as a result of tolerance development).

[2] Reduction in field of vision is relatively common with VGB (probably in 30 % or more of all patients treated with VGB!). Note: the significance of possible reduction in visual field as a result of VGB is still unclear in infants!

[3] Specific license restrictions: see p. 90 ff.

[4] Lamotrigine is not officially licensed as monotherapy in children under the age of 12 years with absence epilepsy and myoclonic epilepsy; and can hence only be given with an existing indication at the discretion of the physician's freedom to treat ("individual treatment attempt").

[5] Felbamate is only licensed for (previously refractory) Lennox-Gastaut syndrome as of the age of 4 years (for combination treatment)!

[6] Preferred first-choice treatment for adolescents as of 16 years of age according to the DGN Guidelines.

[7] KD = Ketogenic diet

[8] Mesuximide is licensed for petit mal seizures within the scope of mixed epilepsy and in absences, whose treatment with other antiepileptic drugs did not bring about the desired success.

[9] CS = Corticosteroids. Possibly also consider pulsatile corticosteroid therapy. ACTH or oral steroids (e.g. prednisolone) in West syndrome.

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Acetazolamide[1] (AZA)	ca. 10 mg/kg	750 - 1000 mg	2 - 3 days	10 - 20 mg/l = 45 - 90 µmol/l (4.5)	Enzyme inhibition	Tachypnoea, hyperpnoea, dysgeusia, paraesthesia, drowsiness, nausea, metabolic acidosis, hypokalaemia, hyperglycaemia, in case of liver cirrhosis disorientation (serum concentration of ammoniac in alkalised urine), kidney- and urethra calcifications	Add-on therapy	Anticonvulsant of most distant choice
Brivaracetam[2] (BRV)	2 - 4 mg/kg, highest dose (off-label) ca. 5 mg/kg	50 - 200 mg	2 days	0.2 - 2 mg/l = 1 - 10 µmol/l (5)	Moderate enzyme induction: increase of CBZ-epoxide	Tiredness, dizziness, nausea, irritability	Add-on in focal epilepsies, from 4 years on	Effective dose from day 1; simple substitution of LEV, parenteral form available
Bromide (e.g. Potassium bromide) (BR)	Toddlers: 50 - 70 mg/kg Children: 40 - 60 mg/kg	850 - 2250 mg	60 days	100 - 250 mg/dl = 31.25 mmol/l	None	Common: chronic intoxication with central nervous effects such as tiredness, impaired concentration, overall weakness and anorexia, later: restlessness, headache, sleeplessness, disorientation, depression, impaired memory up to symptoms of dementia, hallucinations, psychosis, impaired coordination, tremor, ataxia, paraesthesia, weakening of reflexes and finally loss of pupillary reflex as well as vasomotoric disturbances. skin alterations: acneiform eruptions in the face and on upper body, bromoderma tuberosum, halogenpanniculitis gastrointestinal: stomach ache, vomiting at start of treatment, in difficult cases: ulcerations up to perforations, in case of high serum levels coated tongue, halitosis, rhinitis, polydipsia, diarrhoea or obstipation Less common: pancreatitis, arthritis, hypothyroidism, renal failure, dysmorphia syndromes in children of mothers who took bromide during pregnancy.	Mono-therapy in epilepsies with bilateral tonic seizures and severe myoclonic syndromes in childhood	Still essential in neuropediatrics (Dravet-Syndrome!). In case of overdose sodium chloride solution (also i.v.) to shorten elimination half-life, note: pseudo-hyperchloraemia!

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Carbamazepine (CBZ)	20 - 25 mg/kg	400 - 2400 mg/kg	24 - 7 days (decreasing in long-term monotherapy due to auto-induction)	CBZ: 3 - 12 mg/l = 13 - 50 µmol/l (4.2) free CBZ: 20 - 30% CBZ-epoxide: 0.6 - 3.0 mg/l = 2.3 - 11.7 µmol/l (3.9)	Massive enzyme induction, several other anticonvulsants elevate epoxide concentration (e.g. OXC, FBM, BRV)	Exanthema (ca. 10%) such as exfoliative dermatitis, rarely Stephens-Johnson-Syndrome, leukopenia (ca. 2%), thrombocytopenia, refractory anaemia, agranulocytosis, tiredness, dizziness, nystagmus, blurred vision, diplopia, dysarthrophonia, conduction- and heart rhythm disturbances, immunoglobulin deficiency, hyponatremia (less common than with OXC and ESL), water retention syndrome, nausea, vomiting, headache, obstipation, hair loss, hyper- and dyskinesia, osteopathy (Vitamin-D deficiency) and other consequences due to the massive enzyme induction, vasculitis, nephritis, myocarditis, interstitial pneumonia, lupus erythematosus, hepatitis, pancreatitis, cholangitis, proteinuria, haematuria, oliguria to anuria, provocation of generalized seizures like absences or myoclonus, EEG-deterioration, encephalopathy	Focal epilepsies	Prolonged release form significantly better to control and more tolerable
Clobazam [3] (CLB)	0.2 - 1.0 mg/kg	5 - 40 mg	3 - 6 days, N-desmethyl-CLB: 14 - 28 days	CLB: 0.03 - 0.3 mg/l = 0.1 - 1.0 µmol/l (3.3), N-desmethyl-CLB: 0.3 - 3.0 mg/l = 1 - 10 µmol/l (3.3)	Few interactions: CBZ-epoxide, PB and PRM can increase, massive increase of CLB-concentration under cannabidiol, decrease of serum concentration if enzyme inducers are applied simultaneously	For all benzodiazepines possible but least distinctive under CLB: sedation, diplopia, dysarthrophonia, ataxia, muscle hypotension, impulse control weakness, dysphoria, depression, loss of libido, hypersecretion of salivary- and bronchial glands, respiratory depression, worsening of tonic seizures, tolerance, acute delirium including seizures during weaning, paradox reaction with agitation and confusion especially in elderly patients and children	Focal and generalized epilepsies	Long-term treatment more popular in Anglo-American countries, suitable PRN medication to bypass e.g. allergic reactions during up-titration of other anticonvulsants or as seizure prophylaxis on special occasions (family celebrations, exams, etc.)

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Clonazepam[3] (CZP)	Toddlers: 0.5 - 1.0 mg Children: 0.5 - 3.0 mg	1 - 6 mg	7 days	0.013 - 0.038 mg/l = 0.04 - 0.12 µmol/l (3.1)	Decrease of serum concentration if enzyme inducers are applied simultaneously	See CLB, but more frequent and more severe	Focal and generalized epilepsies	Also available as parenteral and oral solution, as chronic medication almost exclusively in progressive myoclonus epilepsies
Eslicarbazepineacetat (ESL)	10 - 30 mg/kg	400 - 2400 mg	4 - 5 days	MHD (monohydroxy derivative as active metabolite): 20 - 35 mg/l = 80 - 140 µmol/l (4.0)	Decrease of serum concentration if enzyme inducers are applied simultaneously, neurotoxic adverse events like tiredness and dizziness, intensified when applied together with e.g. CBZ or LCM	Dizziness, sedation, headache, ataxia, attention deficit, tremor, blurred vision, diplopia, nausea, vomiting, diarrhoea, exanthema, hyponatremia, more common than under CBZ and as common as under OXC	Mono-therapy in adults with focal epilepsies and add-on therapy in focal epilepsies from 6 years on	
Ethosuximide (ESM)	20 - 30 mg/kg	750 - 1500 mg	4 - 10 days	40 - 100 mg/l = 280 - 700 µmol/l	No relevant interactions, VPA serum levels can decrease	More common: gastrointestinal symptoms (nausea, anorexia, weight loss, hiccup), headache, sedation, psychotic symptoms Uncommon: depression, dyskinesias, akathisia, exanthema, erythema multiforme, Stevens-Johnson-Syndrome, lupus erythematosus, hematotoxic effects	Generalized epilepsies and absences and/or myoclonic seizures	

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Everolimus (EVR)	Initial dose for children under 10 years 6 mg/m² without additional enzyme inducers, 9 mg/m² if additional enzyme inducers are given, in patients aged 10 - 18 years 5 and 8 mg/m², followed by up-titration according to serum level	Initial dose 3 mg/m² without additional enzyme inducers and 5 mg/m² if additional enzyme inducers are given, followed by up-titration according to serum level	7 days	3 - 15 ng/ml	Significant impact by enzyme inducers and inhibitors, enzyme inducing	Stomatitis, diarrhoea, mouth ulcerations, nasopharyngitis, infections of upper airways, aphthae, fever, cough, vomiting, exanthema, thrombocytopenia, leukopenia, hyperlipidaemia	Add-on therapy in difficult to treat epilepsies based on tuberous sclerosis, from 2 years on	
Felbamate (FBM)	20 - 45 mg/kg	1200 - 3600 mg	4 days	20 - 45 mg/l = 85 - 190 µmol/l (4.2)	Increase of CBZ-epoxide, PHT and VPA serum levels, decrease of CBZ serum levels, the serum concentration of FBM decreases under CBZ, PHT and PBN and rises under VPA	Anorexia, weight loss, dysgeusia, dyspepsia, headache, dizziness, diplopia, sedation, insomnia, refractory anaemia(1:4000), toxic (also fatal) hepatopathy, exanthema, Stevens-Johnson-Syndrome	Last line add-on therapy for Lennox-Gastaut- Syndrome, from 4 years on	Blood count controls before start of therapy and every 2 weeks afterwards

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Gabapentin (GBP)	10 - 60 mg/kg	1200 - 3600 mg	1 - 2 days	3 - 21 mg/l = 20 - 120 µmol/l (6), therapeutic range in question	No relevant interactions	Sedation, drowsiness, dizziness, ataxia	Monotherapy in focal epilepsies from 12 years on, add-on therapy in focal epilepsies from 6 years on	Saturable resorption, therefore relatively low serum concentrations at high doses
Lacosamide (LCM)	2 - 10 mg/kg	200 - 600 mg	3 days	3 - 12 mg/l = 12 - 48 µmol/l (4)	No relevant interactions. Neurotoxic (pharmacodynamical caused) side effects like tiredness and dizziness, intensified when applied together with e.g. CBZ, OXC, ESL, PHT or LTG	Sedation, dizziness, drowsiness, ataxia, potentially conduction disorders (ECG-controls at start of therapy recommended)	Monotherapy and add-on therapy in focal epilepsies from 4 years on	Also available as parenteral solution
Lamotrigine (LTG)	1 - 15 mg/kg	Monotherapy 100 - 700 mg Add-on to VPA 100 - 200 mg add-on to enzyme inductors 400 - 1000 mg	5 - 6 days in monotherapy 9 - 11 days in combination with VPA 2 - 3 days in combination with enzyme inducers	2 - 14 mg/l = 7.8 - 54.6 µmol/l (3.9)	Massive increase in serum concentration by VPA (supra-additive effect?) significant decrease in serum concentration by enzyme inducers, by estrogen containing contraceptives and in pregnancy	Toxic-allergic skin- and mucosa reactions, Stevens-Johnson syndrome, dizziness, blurred vision, diplopia, ataxia, dysarthrophonia, insomnia, irritability, nausea, vomiting, very rarely kidney failure, rhabdomyolysis, multiorgan failure, lymphoproliferative syndrome	Monotherapy in focal and generalized epilepsies from 13 years on, add-on therapy from 2 years on	Extremely low up-titration, especially when patient is already treated with VPA, If necessary dose adjustments during pregnancy and quick restitution of starting dose postpartum

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Levetiracetam (LEV)	20 - 60 mg/kg	1000 - 4000 mg	2 days	5 - 41 mg/l = 30 - 240 µmol/l (6) therapeutic range in question due to dose independence regarding efficacy and tolerability	No relevant interactions	Sedation, irritability, depression, mood swings, psychotic episodes, weakness, mucous irritation of upper airways rarely: dizziness, nausea, vomiting, dyspepsia, diarrhoea, weight loss (very rarely)	Monotherapy in focal epilepsies from 16 years on, add-on therapy in focal epilepsies from 1 month on, add-on therapy in GTCS in juvenile myoclonic epilepsy from 12 years on	Parenteral solution available
Mesuximide (MSM)	10 - 15 mg/kg according to SmPC (up to 20 mg/kg possible)	450 - 1200 mg	8 days N-desmethyl-mesuximide	20 - 35 mg/l = 100 - 175 µmol/l (4.9)	Significant interaction potential due to enzyme inhibition, e.g. massive increase in serum concentrations of PHT and PB	Like ESM, additionally sedation, abdominal pain and borborygmi, weight loss leukopenia, thrombocytopenia, aplastic anaemia, exanthema, allergic reaction		
Oxcarbazepine (OXC)	25 - 35 mg/kg	600 - 3000 mg	4 – 5 days	MHD (monohydroxy-derivative as active metabolite): 20 - 35 mg/l = 80 - 140 µmol/l (4.0)	Decrease of serum concentrations of PHT, PB and CBZ-epoxide, potent enzyme induction resulting in decrease of serum concentrations of e.g. LTG, decrease of serum concentration of MHD by potent enzyme inductors like CBZ, PHT or PB, neurotoxic (pharmaco-dynamic) side effects like tiredness and dizziness increased if applied together with LCM or TPM	Like CBZ and ESL, less sedative than CBZ, hyponatremia as frequent as under ESL and more frequent than under CBZ, allergic reactions, cross allergies after allergic reaction under CBZ ca. 25%.	Monotherapy in adults with focal epilepsies and add-on therapy in focal epilepsies from 6 years on	Prolonged release form significantly better to control and more tolerable

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Perampanel (PER)	4 - 12 mg	4 - 12 mg	14 days	0.1 - 1 mg/l = 0.25 - 2.85 µmol/l (2.8) therapeutic range in question due to dose independence regarding efficacy and tolerability	Decrease in serum concentration if enzyme inducers are applied simultaneously	Sedation, tiredness, dizziness, irritability, ataxia	Add-on therapy in focal and generalized epilepsies from 12 years on	Once daily dose before sleep, if combined with enzyme inducers need for much higher doses possible
Phenobarbital (PB)	2 - 5 mg/kg	Up to 300 mg	14 - 21 days	10 - 40 mg/l = 45 - 170 µmol/l (4.3)	Significant interactions: potent enzyme inducer, concentration of PB is decreased by other enzyme inducers	Sedation, lack of energy, personality changes, concentration attention deficit, depression, loss of libido, blurred vision, ataxia, dysarthrophonia, paradox reaction in children and elderly patients possible: increase in irritability, dysphoria, megaloblastic anaemia, vitamin deficiency, fibromatoses, obstipation, urinary retention, exanthema, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, abstinence phenomena including increase in seizures	Focal and generalized epilepsies	Parenteral solution available, parenteral (i.m. or i.v.) fast uptitration possible
Phenytoin (PHT)	5 - 7 mg/kg	100 - 400 mg	5 - 14 days	5 - 20 mg/l = 20 - 80 µmol/l (4.0) free PHT: < 2.3 mg/l	Significant interactions: potent enzyme inducer, concentration of PHT is decreased by other enzyme inducers, increase e.g. under MSM and STM	Blurred vision, diplopia, ataxia, dizziness, tremor, fasciculations, delirium, psychotic symptoms, encephalopathy, extrapyramidal movement disorders, atrophy of the cerebellum under chronic intoxication, heart rhythm disturbances, hepatitis, liver cell necrosis, blood count changes, lupus erythematosus, albuminuria, kidney failure, megaloblastic anaemia, vitamin deficiency, coarse facial features, gingival hyperplasia, hypertrichosis, exanthema, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, increase in seizures at toxic serum levels, seizure provocation generalized seizures like absences or myoclonus, in case of extravasation: necroses and Purple-Glove syndrome, cardiac arrhythmia up to asystole if given i.v. too fast	Focal epilepsies and primary generalized tonic-clonic seizures	Parenteral solution available, parenteral and oral fast uptitration possible

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Pregabalin (PGB)	No recommendations	150 - 600 mg	1 - 2 days	2 - 6 mg/l = 10 - 35 µmol/l (5), therapeutic range in question	No relevant interactions	Sedation, mood changes, loss of libido, weight gain, dizziness, blurred vision, diplopia, dysarthrophonia, ataxia, obstipation, dry mouth	Add-on therapy in focal epilepsies from 18 years on	
Primidone (PRM)	20 mg/kg	Up to 1250 mg	PB 14 - 21 days (significant metabolite) PRM 1 - 2 days	PB 10 - 40 mg/l = 45 - 170 µmol/l (4.3) PRM 4 - 15 mg/l = 20 - 70 µmol/l (4.6)	Like PB	Like PB, additionally: more nausea and vomiting than under PB during up-titration	Focal and generalized epilepsies	
Rufinamide (RUF)	under 30 kg without VPA: up to 35 mg/kg under 30 kg with VPA: up to max. 600 mg/d above 30 kg: up to max. 600 mg/die	2400 - 3200 mg	2 days	4 - 31 mg/l = 15 - 130 µmol/l (3.9)	Potent enzyme inducer, marked increase in serum concentration if VPA is applied simultaneously	Headache, sedation, dizziness, blurred vision, diplopia, anorexia, vomiting, weight loss, sleep disturbances	Add-on therapy in Lennox-Gastaut-syndrome, from 1 year on	
Stiripentol (STP)	20 - 50 mg/kg in combination with VPA and CLB	2000 - 3000 mg	2 - 3 days	4 - 22 mg/l = 15 - 95 µmol/l (4)	Potent enzyme inhibitor, formation of toxic serum concentrations of other drugs possible	Anorexia, weight loss, disturbance of growth, sleep disturbance, ataxia, muscle hypotension, dystonia	Add-on therapy in combination with VPA and CLB in Dravet-Syndrome	
Sulthiame (STM)	3 - 10 mg/kg	100 - 300 mg	2 - 3 days	1 - 3 mg/l = 3.5 - 10.5 µmol/l (focal epilepsy with centro temporal spikes)5 - 10 mg/l = 17.5 - 35 µmol/l other focal epilepsies (3.5)	Potent enzyme inhibitor, formation of toxic serum concentrations of other drugs possible e.g. marked increase in PHT serum concentrations	Tachypnoea, hyperpnoea, paraesthesia, psychotic symptoms, loss of efficacy in adults possible	Epilepsy with centro-temporal spikes	

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Topiramate (TPM)	3 - 10 mg/kg	50 - 600 mg	4 - 8 days	2 - 10 mg/l = 6 - 30 µmol/l (3)	Increase in serum concentration of PHT Decrease of serum concentration if applied together with enzyme inducers	Dizziness, sleepiness, anorexia, weight loss, kidney stones, paraesthesia, thought disorders, dysphasia, aphasia, glaucoma, psychosis	Mono-therapy in focal and generalized epilepsies from 6 years on, add-on therapy from 2 years on	
Valproate (VPA)	20 - 30 mg/kg	600 - 2000 mg	2 - 4 days	50 - 120 mg/l = 205 - 820 µmol/l (6.9) free VPA < 10%	Potent enzyme inhibitor. Decrease of serum concentration if applied together with enzyme inducers	Anorexia, nausea, vomiting, increase in appetite, weight gain, polycystic ovaries, polycystic ovaries syndrome, coagulation disorder, hepatopathy, liver failure, leukopenia, thrombocytopenia, aplastic anaemia, pancreatitis, oedema, tremor, acute and chronic encephalopathy, hair loss, negative effect on cognition and forms of autism in children that have been exposed to VPA during pregnancy, significantly elevated teratogenicity	Focal and generalized epilepsies	Parenteral solution available, it is imperative to check the necessity of VPA in girls and women of child-bearing age and to educate them about the teratogenic risks and negative effect on cognition in children that are exposed to VPA during pregnancy. This counselling has to be documented. At least one attempt with a different anticonvulsant should be made before using VPA. This should also be documented. Follow pregnancy prevention programme in women of childbearing age

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Currently available and applicable Anticonvulsants

In alphabetical order of generic preparations

Antiepileptic drug (Abbreviation)	**Daily dose** child	**Daily dose** adult	**Time** to constant blood levels (steady state)	**Therapeutic plasma concentrations of total fraction** Conversion factor ()	**Enzyme induction** interactions	**Side effects**	**Authorised indications in Germany (for details in your country refer to SmPC)**	**Specialities**
Vigabatrin (VGB)	50 - 100 mg/kg	2000 - 4000 mg	1 - 3 days	Serum concentration can be measured, no therapeutic range defined or suggested	No relevant interactions	Dizziness, sedation, headache, changes in weight (gain more likely), diplopia, provocation of myoclonia and bilateral tonic-clonic seizures possible, psychotic symptoms, agitation, aggressiveness, in 30% irreversible visual field defects, loss of efficacy, withdrawal seizures when tapering down	Monotherapy West-Syndrome, Add-on therapy as ultima ratio in focal epilepsies	
Zonisamide (ZNS)	4 - 12 mg/kg	200 - 600 mg	13 days	15 - 40 mg/l = 70 - 190 µmol/l (4.7)	No relevant interactions	Dizziness, blurred vision, diplopia, ataxia, attention deficit, nausea, anorexia, weight loss, kidney stones, psychotic symptoms	Monotherapy in adults with focal seizures and add-on treatment in focal epilepsies from 6 years on	

Explanation:

According to clinical efficacy and tolerability in individual cases it is possible that higher or lower doses for reaching the treatment goal than specified above. The dose ranges delineated here refer to clinical experience and are not always in line with the authorized doses. These are in accordance with the doses tested in the authorization studies.

[1] Acetazolamide might not be authorised for treatment of epilepsy in different countries

[2] Brivaracetam is not licensed for children, off-label use

[3] The only mentioned benzodiazepines are clobazam and clonazepam as they should best be used for long-term epilepsy treatment

Tolerability testing for antiepileptic pharmacotherapy*

Before starting treatment:

- General examination with body weight and blood pressure measurement.

- Laboratory tests:
  - Complete blood count, thrombocytes and urine analysis.
  - Liver function: bilirubin, transaminases (γ-GT, GOT, GPT) and alkaline phosphatase.
  - Total protein + electrophoresis (with suspected dysproteinaemia, hepatic and renal diseases).
  - Calcium, potassium (before AZA), sodium (before CBZ, ESL and OXC).
  - Fasting glucose.

After stabilisation:

For the first time after 1-3 months, later in about 6 month intervals and then yearly. (note: special monitoring of treatment with VPA and ACTH/corticoid therapy and with FBM [SmPC]):

- General examination with measurement of body weight, possibly also blood pressure measurement.

- Neuropsychological examination (especially in case of unclear aetiology and if side effects of the antiepileptic drugs affecting the central nervous system are suspected).

* For special monitoring of treatment with valproate, depot ACTH and corticosteroids see p. 57 ff

Tolerability testing for antiepileptic pharmacotherapy*

- EEG control examination.
- Plasma concentrations if necessary.
- Complete blood count including differential blood count, thrombocytes.
- In plasma/serum:
  - Hepatic enzymes γ-GT, GPT, GOT and alkaline phosphatase (AP).
  - Electrolytes: sodium (with CBZ and especially with OXC and ESL) and potassium (with AZA).
  - Calcium if the antiepileptic drugs are suspected of causing osteopathy (under CBZ, PB/PRM, PHT and PNT) together with AP, possibly also calcidiol blood levels (25-OH-D = transport form of vitamin D3 in the blood); in case of elevated AP levels in children and adolescents and concurrent suspicion of osteomalacia induced by antiepileptic drugs possibly also measurements of bone isoenzyme. If evidence arises consider bone density measurement.
  - Possibly blood lipid levels which may increase under treatment with antiepileptic drugs.
- As a rule the occasional control of γ-GT, AP and the blood count is enough with stable therapy and repeated controls.

* For special monitoring of treatment with valproate, depot ACTH and corticosteroids see p. 57 ff

4. Epilepsy surgery

For eligible therapy refractory patients (failure of two adequate therapy attempts) epilepsy surgery is by far the most promising alternative for a medical treatment. Unfortunately, the latency between epilepsy diagnosis and successful surgery on average is still more than 20 years. A pre-surgical epilepsy evaluation at a specialist centre, including a routine MRI scan should be initiated in patients with focal seizures with or without a potential epileptogenic lesion. Diagnostic evaluation is also indicated, particularly in young children, for generalized seizures (e.g. epileptic spasms in the new born), if a unilateral lesion can be identified from a MRI scan. The decision to recommend epilepsy surgery should be based on the individual's chances of success, on the assessment of risks, and on an elaborate diagnostic process. The decision to operate should never be based solely on anamnesis, routine diagnostics and a doctor's own recommendation.

4.2 Vagus Nerve Stimulation (VNS)

VNS is a non-resective surgical procedure which can significantly reduce the number of seizures by between 30-40%. However, seizure-free rates remain low. Therefore, it should only be considered after a definite exclusion of curative resective epilepsy-surgical intervention. Usually it takes many months of treatment following a step wise optimisation of the stimulation parameters before a reduction in seizure frequency is achieved. The overall tolerability is good (swallowing difficulties, cough reported rarely). Some MRI scans (e.g. whole body MRI) are not possible after a VNS device has been implanted. Before having an MRI scan with a head coil, the VNS device must be deactivated.

4.3 Deep-brain stimulation

Deep-brain stimulation is another method authorised in Germany. This stimulation is comparable to the procedure used in Parkinson's patients and is an option for rather desperate situations, as the chances of success in treating epilepsy are relatively low.

4.4 Ketogenic diet

A diet extremely rich in fat leads to production of ketone bodies and other metabolic changes in the brain that have anti-epileptic properties. It is the therapy of choice in glucose-1-transporter deficiency and pyruvate dehydrogenase deficiency. However, it can also be used in other epilepsy forms and aetiologies. The ketogenic diet proved its worth especially in severe myoclonic astatic epilepsy and tuberous sclerosis. Contraindications, due to an impaired fat-metabolism, must be excluded (measurement of acylcarnitine in blood and organic acids in urine). The diet should be started under strict supervision in a hospital with ketogenic diet expertise. Besides the classic ketogenic diet (weight ratio fat:[carbohydrates+protein] of 4:1 [adults] to 2:1 [infants] – if necessary as formula - for each meal) there are other therapeutic options such as the "low glycaemic index diet" (favoured in Germany) and the modified Atkins diet (reduction of the daily carbohydrate amount to 10-15 g/day with protein and fat supply distributed over the day); the latter being important for children above 3 years of age. As this is an unphysiological diet, calorie uptake has to be balanced and micronutrients and vitamins should be supplemented and controlled. Efficacy of the diet can usually be assessed after about three months. Similar to treatment with drugs the diet should be continued for 1 to 3 years (rarely longer) and in accordance with the epilepsy syndrome. Possible side effects are growth disturbances, nephrocalcinosis, liver function impairment, and cardiac problems (e.g. long-QT syndrome).

Antiepileptic drugs

In alphabetical order of trade names*

(date: February 2019)

Commercial preparation[1]	Active substance	Abbreviation	Form of administration	Dosage strengths
Antelepsin®	Clonazepam	CZP	Tablets	0.5 mg, 2 mg
Apydan®** Apydan® extent	Oxcarbazepine	OXC	Tablets Tablets with a sustained release formulation	300 mg, 600 mg 150 mg, 300 mg, 600 mg
Briviact®	Brivaracetam	BRV	Film-coated tablets Solution for injection Solution	10 mg, 25 mg, 50 mg, 74 mg, 100 mg 10 mg/ml 10 mg/ml
Buccolam®	Midazolam	MDZ	Solution for use in the oral cavity	2.5 mg/0.5 ml, 5 mg/1 ml, 7.5 mg/1.5 ml, 10 mg/2 ml
Convulex®	Valproic acid	VPA	Capsules	300 mg, 500 m
Diacomit® powder Diacomit® capsules	Stiripentol	STP	Powder Capsules	250 mg, 500 mg 250 mg, 500 mg
Diazepam DESITIN® rectal tube Diazepam ratiopharm®	Diazepam	DZP	Mini-enema Solution for injection (ampoule) Tablets Drops Suppository	5 mg/2.5 ml, 10 mg/2.5 ml 10 mg/2 ml 2 mg, 5 mg, 10 mg 10 mg/ml (1ml=20 drops) 10 mg
DIBRO-BE® mono	Potassium bromide	BR	Tablets	850 mg
Dormicum®	Midazolam	MDZ	Film-coated tablets Solution for injection (ampoule)	7.5 mg 5 mg/1 ml, 15 mg/3 ml, 50 mg/10ml

* Tradenames can differ from country to country
** Trade name in Denmark, Estonia and Finland.

Antiepileptic drugs

In alphabetical order of trade names*

(date: February 2019)

Commercial preparation[1]	Active substance	Abbreviation	Form of administration	Dosage strengths
Ergenyl® Ergenyl® chrono Ergenyl® solution Ergenyl® intravenous	Valproate sodium Valproate sodium/ Valproic acid Valproate sodium Valproate sodium	VPA	Film-coated tablets Prolonged-release tablets Solution Solution for injection (ampoule)	150 mg, 300 mg, 500 mg 300 mg, 500 mg 300 mg/ml 400 mg/4 ml (100 mg/ml)
Frisium®	Clobazam	CLB	Tablets	10 mg, 20 mg
Fycompa®	Perampanel	PER	Tablets	2 mg, 4 mg, 6 mg 8 mg, 10 mg, 12 mg
Gabitril®	Tiagabin	TGB	Film-coated tablets	5 mg, 10 mg, 15 mg
Inovelon®	Rufinamide	RUF	Film-coated tablets Oral solution	200 mg, 400 mg 40 mg/ml
Keppra® Keppra® solution Keppra® concentrate	Levetiracetam	LEV	Film-coated tablets Oral solution Infusion concentrate (vial)	250 mg, 500 mg, 750 mg, 1000 mg 100 mg/ml 100 mg/ml
Lamictal®	Lamotrigine	LTG	Tablets/chewing tablets	2 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg
Lamotrigin DESITIN®/ Plexxo®**	Lamotrigine	LTG	Tablets	50 mg, 100 mg, 100 mg quadro (quartered), 200 mg
Levetiracetam DESITIN®/ Desitrend®*** Levetiracetam DESITIN® solution Levetiracetam DESITIN® concentrate	Levetiracetam	LEV	Minitablets**** Oral solution Infusion concentrate (ampoule)	250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg 100 mg/ml 500 mg/5 ml (100 mg/ml)

* Tradenames can differ from country to country
** Trade name in Czech Republic an Slovakia
*** Trade name in the UK.
**** Minitablet = approved administrative form of Levetiracetam DESITIN® film-coated granules in sachets.

Antiepileptic drugs

In alphabetical order of trade names*

(date: February 2019)

Commercial preparation[1]	Active substance	Abbreviation	Form of administration	Dosage strengths
Liskantin® Liskantin® syrup	Primidone	PRM	Tablets Syrup	250 mg 25 mg/ml (5 ml=125 mg)
Luminal®/Phenaemal®** Luminal® solution for injection Luminaletten®/Phenaemaletten®**	Phenobarbital Phenobarbital-sodium	PB PB	Tablets Solution for injection (ampoule) Tablets	100 mg, 15 mg 200 mg/ml 15 mg
Lyrica®	Pregabalin	PGB	Hard capsules Oral solution	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg 20 mg/ml
Mylepsinum®	Primidone	PRM	Tablets	250 mg
Neurontin®	Gabapentin	GBP	Hard capsules Film-coated tablets	100 mg, 300 mg, 400 mg 600 mg, 800 mg
Orfiril® long Episenta®***	Sodium valproate	VPA	Capsules with prolonged-release, minitablets; sachet with prolonged release minitablets****	150 mg, 300 mg 500 mg, 1000 mg
Orfiril® Orfiril® syrup Orfiril® solution for injection	Sodium valproate	VPA	Sugar-coated tablets Syrup Solution for injection (ampoule)	150 mg, 300 mg, 600 mg 60 mg/ml 300 mg/3 ml, 1000 mg/10 ml (each 100 mg/ml)
Ospolot®	Sulthiame	STM	Film-coated tablets	50 mg, 200 mg
Petinutin®	Mesuximide	MSM	Hard capsules	150 mg, 300 mg
Petnidan® Petnidan® syrup	Ethosuximide	ESM	Soft capsules Syrup	250 mg 50 mg/ml (5 ml=250 mg)

* Tradenames can differ from country to country
** Trade name in Czech Republic, Estonia and Slovakia.
*** Trade name in UK.
**** Minitablet = approved administrative form of Orfiril® long / Episenta® film-coated granules in sachets.

Antiepileptic drugs

In alphabetical order of trade names*

(date: February 2019)

Commercial preparation[1]	Active substance	Abbreviation	Form of administration	Dosage strengths
Phenhydan® Phenhydan® solution for injection	Phenytoin Phenytoin-sodium	PHT PHT	Tablets Solution for injection (ampoule)	100 mg 250 mg phenytoin/5 ml
Rivotril® Rivotril® concentrate	Clonazepam	CZP	Tablets Drops Solution for injection and solvent (ampoule)	0.5 mg, 2 mg 2.5 mg/ml (25 drops=1 ml, 1 drop=0.1 mg) 1 mg/ml
Sabril® Sabril® sachet	Vigabatrine	VGB	Film-coated tablets Granulate	500 mg 500 mg
Stesolid® emulsion for injection Stesolid® rectal tube	Diazepam	DCP	Emulsion for injection (ampoule) Micro-enema	10 mg/2 ml (5 mg/ml) 5 mg/2.5 ml, 10 mg/2.5 ml
Suxilep®	Ethosuximide	ESM	Hard capsules	250 mg
Synacthen® depot	Tetracosactid	ACTH	Suspension for solution (ampoule)	1.1 mg tetracosactide hexaacetate/1 ml, 1 mg=100 I.E. ACTH
Taloxa® Taloxa® syrup	Felbamate	FBM	Tablets Suspension	600 mg 600 mg/5 ml
Tavor® Tavor® expidet Tavor® for injection	Lorazepam	LZP	Tablets Wafers Solution for injection (ampoule)	0.5 mg, 1 mg, 2 mg, 2.5 mg 1 mg, 2.5 mg 2 mg/ml
Tegretal® Tegretal® suspension	Carbamazepine	CBZ	Tablets Prolonged-release tablets Suspension	200 mg 200 mg, 400 mg 100 mg/5 ml

* Tradenames can differ from country to country

Antiepileptic drugs

In alphabetical order of trade names*

(date: February 2019)

Commercial preparation[1]	Active substance	Abbreviation	Form of administration	Dosage strengths
Timonil® Timonil® syrup Timonil® retard/Trimonil® retard[2]	Carbamazepine	CBZ	Tablets Syrup Prolonged-release tablets	200 mg 20 mg/ml (100 mg/5 ml) 150 mg, 200 mg, 300 mg, 400 mg, 600 mg
Timox® extent Timox® suspension	Oxcarbazepine	OXC	Tablets with sustained release formulation Suspension	150 mg, 300 mg, 600 mg 60 mg/ml
Topamax®	Topiramate	TPM	Film-coated tablets Hard capsules	25 mg, 50 mg, 100 mg, 200 mg 25 mg, 50 mg
Trileptal® Trileptal® Suspension	Oxcarbazepine	OXC	Film-coated tablets Suspension	150 mg, 300 mg, 600 mg 60 mg/ml
Valproat chrono DESITIN®	Sodium valproate, valproic acid	VPA	Prolonged-release tablets	300 mg, 500 mg
Vimpat® Vimpat® syrup Vimpat® solution for infusion	Lacosamide	LCM	Film-coated tablets Syrup Solution for infusion (vial)	50 mg, 100 mg, 150 mg, 200 mg 10 mg/ml (2000 mg/200 ml, 4650 mg/465 ml) 10 mg/ml (200 mg/20 ml)
Zebinix®	Eslicarbazepine acetat	ESL	Tablets Oral suspension	800 mg 50 mg/ml
Zonegran®	Zonisamide	ZNS	Hard capsules	25 mg, 50 mg, 100 mg

* Tradenames can differ from country to country

[1] The above compilation does not list all finished products available in Germany for antiepileptic therapy for reasons of comprehensibility. In the case of substances for which several commercial preparations are available, only those used most frequently are listed.

[2] Tradename in Denmark, Sweden and Norway.

Appendix 1

Interactions of antiepileptic drugs

(Modified according to Krämer)

Addition of	Effect on persistent therapy												Effect on persistent therapy												
	BRV	CBD	CBZ	CLB	ESL	ESM	EVR	FBM	GBP	LCM	LTG	LEV	MSM	OXC	PER	PB	PHT	PGB	PRM	RUF	STP	STM	TGB	TPM	VPA	VGB	ZNS
Brivaracetam (BRV)	x		E+	O							O	O		O			O/(+)	O						O	O		
Cannabidiol (CBD)		x		++																							
Carbamazepine (CBZ)	(-)		x	-	-		--	--	(+)/O	-	--	-		-	-	(+)/-	+/-	-	-(PB+)	-		-		--	--	O/(-)	--
Clobazam (CLB)		++	+/-(E+)	x					O	O	O	O		O	O	(+)/O	+	O	(+)/O			O		+			O
Eslicarbazepine (ESL)			O/(-)	O/(-)	x		--		O	O	-	O		O	-	(+)/O	+	O	(+)/O	-		-		-	O/-		O/-
Ethosuximide (ESM)						x					O					O			O						--		
Everolimus (EVR)							x																				
Felbamate (FBM)			--(E+)					x			O			O		++	++								++	O	
Gabapentin (GBP)			O	O	O				x		O	O	O	O		O	(+)/O	O/(-)				O		O	O		+
Lacosamide (LCM)			O		O	O		O		x			O	O	O/(-)			O					O		O	O	O
Lamotrigine (LTG)	O		O/(-)	O	(-)			O	O	O	x			+/-	O	O	O	O	O			O		(+)/O	O/-		+/O
Levetiracetam (LEV)	O		O	O	O				O	O	O	x		O	O	O	O	O	O	O	O	O	O	O	O	O	O
Mesuximide (MSM)			+		+						--		x	+		++	++					+		--	--		
Oxcarbazepine (OXC)	O		O/(-)	-	O		--		O	O	--	-		x		+	+	-	O	-		-		-	O/-		O/-
Perampanel (PER)			O		+			--				O		+	x		O/(-)					O	--	O	O		O
Phenobarbital (PB)	(-)		--(E+)	--	-		--	--	O/(-)	-	--	-	+	-	-	x	+/-	O	-(PB+)	-		--	--	--	--		--
Phenytoin (PHT)	(-)		--	--	-		--	--	O/(-)	-	--	-	+	-	-	+	x		-(PB+)			--		--	--	O	--
Pregabalin (PGB)			O	O	O				O/(-)		O/-	O/(+)	O	O		O	O	x				O	--	O	O		O
Primidone (PRM)			--(E+)	-	--			--	O/(-)	-	--	-		-	--	(+)/O	+/-		x			--		--	--	O	--
Rufinamide (RUF)											O					O	+			x				O	O		
Stiripentol (STP)			+	++	+						+		+	+	+	++	++		++	+	x			+			
Tiagabine (TGB)			O													O	O		O			x		O			
Sultiam (STM)			+		+						+			+		+	++		+/-				x				
Topiramate (TPM)	O		O/(+)		-						(+)/-	O		-	-	O	+	O	O			--		x			
Valproate (VPA)	O		(+)/-(E+)	O	O/(-)			(+)/O	O/(-)	O	++	+		O/(-)	(+)	++	+/-(fA+)	O	+/-(PB+)	+		+	O	-	x		+/-
Vigabatrine (VGB)			(+)/O													--	--		O/(-)							x	
Zonisamide (ZNS)			O/-(E+)		O				O	O	O			O	O	O	O/(+)	O	O			--			O		x

E = Epoxide
fA = free fraction
O = no influence on serum concentration
(-) resp. (+) = mild decrease/ increase in serum concentration
- resp. + = moderate decrease/ increase in serum concentration
-- resp. ++ = strong decrease/ increase in serum concentration

O/(-) resp. O/(+) = no influence as well as mild decrease/increase of serum concentration possible
O/- resp. O/+ = no influence as well as decrease/ increase of serum concentration possible
-/+ = decrease as well as increase of serum concentration possible
Empty field = no interactions

Appendix 2

Approvals of antiepileptic drugs

1) Plus monotherapy in typic absences.
2) Licensed in combination with VPA and CBZ.
3) After failure of other medication.
4) Licensed for generalised tonic-klonic seizures in idiopthic generalised epilepsy and myoclonic seizures in juvenile myoklonic epilepsy.
5) Add-on therapy in refractory focal seizures with or without secondary generalisation.

Drug	Abbr.	Approved Indications: Focal and secondary generalised seizures		Approved Indications: Generalised seizures		Special syndromes or seizures	Interaction potential
		Mono-therapy	Combination therapy	Mono-therapy	Combination therapy		
Bromide	BR	No	No	No	No	GTCS, severe myoclonic syndromes	(-)
Carbamazepine	CBZ	Yes	Yes			GTCS	+
Clobazam	CLB	No	Yes	No	Yes		-
Brivaracetam	BRV	No	As of 4 Y	No	No		
Eslicarbazepine	ESL	No	As of 6 Y	No	No		(+)
Ethosuximide	ESM	No	No	yes	Yes	Absences, myoclonic seizures	(-)
Everolimus	EVR	No	No	No	No	Refractory seizures in TSC as of 2 Y 5)	+
Felbamate	FBM	No	No	No	No	LGS as 4 Y 3)	+
Gabapentin	GBP	As of 12 Y	As of 6 Y	No	No		-
Lacosamide	LCM	As of 4 Y	As of 4 Y	No	No		(-)
Lamotrigine	LTG	As of 12 Y	As of 2 Y	As of 12 Y 1)	As of 2 Y	LGS as of 2	(-)
Levetiracetam	LEV	As of 16 Y	As of 1 M	No	As of 12 Y 4)	IGE and JME as of 12 Y	-
Mesuximide	MSM	No	No	No	No	Absence	+
Oxcarbazepine	OXC	As of 6 Y	As of 6 Y	No	No		(+)
Phenobarbital	PB	Yes	Yes	Yes	Yes	GTCS	+
Primidone	PRM	Yes	Yes	Yes	Yes		+
Perampanel	PER	No	As of 12 Y	No	No	Add-on in GTCS	(+)
Phenytoin	PHT	Yes	Yes	Yes	Yes		+
Pregabalin	PGB	No	As of 18 Y	No	No		-
Rufinamide 3)	RUF	No	No	No	No	LGS as of 4 Y	+
Stiripentol	STP	No	No	No	No	Dravet Syndrom 2)	+
Sulthiam	STM	No	No	No	No	Rolandic Epilepsiy	+
Tiagabine	TGB	No	As of 12 Y	No	No		-
Topiramate	TPM	As of 6 Y	As of 2 Y	As of 6 Y	As of 2 Y	LGS as of 2Y	(-)
Valproate	VPA	Yes	Yes	Yes	Yes		+
Vigabatrine	VGB	No	Yes 3)	No	As of 1 Y	West Syndrome	+
Zonisamide	ZNS	As of 18 Y	As of 16 Y	No	No		-

- no interaction potential (-) low interaction potential (+) medium interaction potential + strong interaction potential

Antiepileptic drug abbtreviations

Acetazolamide	=	AZA
Brivaracetam	=	BRV
Bromide	=	CBR
Cannabidiol	=	CBD
Carbamazepine	=	CBZ
Clobazam	=	CLB
Eslicarbazepine acetate	=	ESL
Ethosuximide	=	ESM
Everolimus	=	EVR
Felbamate	=	FBM
Gabapentin	=	GBP
Lacosamide	=	LCM
Lamotrigine	=	LTG
Levetiracetam	=	LEV
Mesuximide	=	MSM
Oxcarbazepine	=	OXC
Perampanel	=	PER
Pheneturide	=	PNT
Phenobarbital	=	PB
Phenytoin	=	PHT
Pregabalin	=	PGB
Primidone	=	PRM
Rufinamide	=	RUF
Stiripentol	=	STP
Sulthiam	=	STM
Tiagabine	=	TGB
Topiramate	=	TPM
Valproate	=	VPA
Vigabatrine	=	VGB
Zonisamide	=	ZNS