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.

The use of Valproate during pregnancy can lead to severe developmental disorders and malformations in the unborn child.

In above mentioned patients regularly perform a risk benefit assessment on the Valproate treatment. Explain potential risks as well as the necessity of an effective contraceptive method to your patients.

Information material as well as an informed consent form can be found on the homepage of the European Medicines Agency (www.ema.europa.eu/ema/).
COMPENDIUM
ANTIEPILEPTIC DRUGS
2017/2018

Pharmacotherapy of epilepsy
8th revised international edition

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PD Dr. T. Bast

(initiated by Prof. Dr. A. Matthes, continued
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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

Neither the authors nor the company DESITIN Arzneimittel GmbH assume any liability for information regarding the use of medications, licensing or restrictions concerning licensing, dosage recommendations, interactions, side effects and forms of administration. Users are required to thoroughly check the packaging leaflet supplied with the medication and, if necessary, to consult a specialist in order to determine whether the recommendations there deviate from those provided in this Compendium.

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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Acute and emergency treatment of epileptic seizures

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.
- 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 2 minutes, then administer drug therapy:

  **Rectal diazepam (rectal tubes 5 mg and 10 mg)**
  onset of action usually after 2-3 min.

| 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), **buccal 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
Acute and emergency treatment of epileptic seizures

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.

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

* If the medication shows no effect after 5-10 minutes, an additional dose of 2.5 mg can be administered if necessary following prior consultation with the attending physician.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &gt; 4 months</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Toddlers &gt;15 kg</td>
<td>1 mg</td>
</tr>
<tr>
<td>School children</td>
<td>1-2.5 mg</td>
</tr>
<tr>
<td>Adults</td>
<td>2.5 (5 mg)</td>
</tr>
</tbody>
</table>

**Buccal clonazepam (e.g., Rivotril® drops)**

*Highest authorized dose in children: 1 mg*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Initial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &gt; 4 months</td>
<td>2-5 drops</td>
</tr>
<tr>
<td>Toddlers &gt;15 kg</td>
<td>5-10 drops</td>
</tr>
<tr>
<td>School children</td>
<td>10-15 drops</td>
</tr>
<tr>
<td>Adults</td>
<td>10-30 drops</td>
</tr>
</tbody>
</table>
Acute and emergency treatment of epileptic seizures

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

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months - &lt; 1 year</td>
<td>2.5 mg*</td>
</tr>
<tr>
<td>1 year - &lt; 5 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>5 years - &lt; 10 years</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>10 years - &lt; 18 years</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

* 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 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.
- Cardiac massage; mouth-to-mouth resuscitation.
- Restraining the patient in case of impulsive restlessness (calming support instead).

1.2 Treatment recommendations for general practitioners/emergency physicians

A situation is considered to be an emergency if generalised tonic-clonic seizures (grand mal) or hemi-seizures threaten to
Acute and emergency treatment of epileptic seizures

Develop into status epilepticus or if this is already present, prolonged or there are rapidly succeeding seizures. 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®), 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). For generalised non-convulsive seizures (absence status) valproate (VPA) i.v. (e.g., Orfiril®/Episenta® solution for injection) as an alternative.

- Treatment of second choice:
  Phenobarbital (PB) ampoules i.v. (e.g., Luminal®/Phenaemal®). For phenytoin (PHT) i.v. (e.g., Phenhydan®) see p. 15-16. VPA i.v. (e.g., Orfiril®/Episenta® solution for injection) as treatment of second choice for convulsive and non-convulsive simple and complex focal seizures.

- 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 and lacosamide (LCM, e.g., Vimpat®) are not officially licensed for the treatment of status epilepticus. There is anecdotal evidence from studies of the efficacy of LEV and LCM.

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.
## Acute and emergency treatment of epileptic seizures

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage recommendations for general practitioners or emergency physicians</th>
<th>Infants</th>
<th>Toddlers and school children</th>
<th>Adults****</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorazepam</strong></td>
<td>If possible i.v.<strong>, otherwise i.m. (1 ampoule 1 ml = 2 mg), alternative with delayed onset of action: swallowing-independent absorption (Tavor® Expidet)</strong></td>
<td>0.05 - 0.1 mg/kg</td>
<td>0.05 - 0.1 mg/kg repeat if needed after 10-15 min.</td>
<td>4 mg repeat after 10-15 min. if needed; max. dose in 12 h: 8 mg</td>
</tr>
<tr>
<td><strong>Clonazepam</strong> (e.g., Rivotril®)</td>
<td>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</td>
<td>0.01-0.05 mg/kg up to 0.5 mg</td>
<td>0.01-0.05 mg/kg equals 1-2 mg</td>
<td>1-2 mg</td>
</tr>
<tr>
<td><strong>Diazepam</strong></td>
<td>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)</td>
<td>0.3-0.5 mg/kg up to 5 mg*</td>
<td>0.2-0.4 mg/kg equals 10-20 mg*</td>
<td>10-30 mg</td>
</tr>
<tr>
<td><strong>Midazolam</strong></td>
<td>(1 ampoule 5 ml = 5 mg - 10 mg i.m. or oral (Buccolam®)</td>
<td>0.15-0.2 mg/kg i.m. or 0.15 mg/kg i.v. bolus</td>
<td>Infants, toddlers 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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infants, toddlers 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valproate</strong> (e.g., Orfiri®/Episenta® solution for injection)</td>
<td>Only i.v. (3 ml ampoule = 300 mg, 10 ml ampoule = 1000 mg)</td>
<td>Infants and toddlers: Use with special caution only</td>
<td>School children and adults: 10-20 mg/kg within the space of 5-10 min., followed by continuous infusion with max. rate of 6 mg/kg/h******</td>
<td></td>
</tr>
<tr>
<td><strong>Phenobarbital</strong> (e.g., Luminal® solution for injection)</td>
<td>If possible i.v.**, otherwise i.m. (1 ampoule = 1 ml = 200 mg)</td>
<td>4-10 mg/kg up to 100 mg</td>
<td>5-6 mg/kg up to 200 mg</td>
<td>200-400 mg</td>
</tr>
</tbody>
</table>

* Not for infants under 4 months
** i.v. injection very slowly: 1 ampoule in 10 min.
*** 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
- AV-block / sino-atrial block: no phenytoin
- Hepatic porphyria: no benzodiazepines, no phenobarbital, no phenytoin and no valproate; use rectal chloral hydrate instead; (possible alternative in exceptions: magnesium i.v.).
Acute and emergency treatment of epileptic seizures

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".

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.

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. 12, 15). Given their low rate of interactions, 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 a good
Acute and emergency treatment of epileptic seizures

alternative. PHT (e.g., Phenhydan® solution for injection) is administered undiluted and at a very slow rate (i.v. 0.5 ml/minute) via a one-way safe i.v. access or as a concentrated infusion (e.g., Phenhydan® concentrated infusion) via an external cannula (see p. 15-16). 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 O₂, 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 of epileptic seizures

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Infants</th>
<th>Toddlers and school children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorazepam</strong></td>
<td>0.05-0.3 mg/kg</td>
<td>0.05-0.1 mg/kg repeat after 10-15 min. if necessary</td>
<td>4 mg repeat after 10-15 min. if necessary; max. dose within 12 h 8 mg</td>
</tr>
<tr>
<td>(1 ampoule 1 ml = 2 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clonazepam (e.g., Rivotril®)</strong></td>
<td>0.01-0.05 mg/kg</td>
<td>0.01-0.05 mg/kg</td>
<td>1-3 mg</td>
</tr>
<tr>
<td>(mixed ampoule 2 ml = 1 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diazepam</strong></td>
<td>0.5 mg/kg</td>
<td>0.3-0.5 mg/kg</td>
<td>10-30 mg</td>
</tr>
<tr>
<td>(1 ampoule = 2 ml = 10 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Midazolam</strong></td>
<td>0.15-0.2 mg/kg i.m. or 0.15 mg/kg i.v. bolus</td>
<td>1-3 mg</td>
<td>5-10 mg i.m. or i.v.</td>
</tr>
<tr>
<td>(1 ampoule 5 ml = 5 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenobarbital</strong> (e.g., Luminal®/Phenaemal® solution for injection) i.v., in emergency i.m. (1 ampoule = 1 ml = 200 mg)</td>
<td>6-15 mg/kg</td>
<td>6-10 mg/kg</td>
<td>200-400 mg</td>
</tr>
<tr>
<td><strong>Phenytoin (e.g., Phenydan®)</strong></td>
<td></td>
<td>10-15 mg/kg</td>
<td></td>
</tr>
<tr>
<td>i.v., (cannot be dosed according to effect), (1 ampoule = 5 ml = 250 mg [Phenydan®]) or concentrate for infusion (1 ampoule = 50 ml = 750 mg)</td>
<td></td>
<td>250-500 mg</td>
<td>500-750 mg</td>
</tr>
<tr>
<td><strong>Valproic acid (e.g., Orfiril®/Episenta® solution for injection)</strong> (3 ml ampoule = 300 mg; 10 ml ampoule = 1000 mg)</td>
<td></td>
<td>Authors recommendations: 900-1500 mg within the space of 30 min. 2400-5100 mg in 24 h (2-4 mg/kg/h) School children and adults: according to Sm PC: 10-20 mg/kg within the space of 5-10 min., followed by continuous infusion with max. rate of 6 mg/kg/h***</td>
<td></td>
</tr>
<tr>
<td><strong>Levetiracetam (e.g., Levetiracetam Desitin®)</strong> (1 ampoule = 5 ml = 500 mg)</td>
<td></td>
<td>Authors recommendation: Single dose of 30 mg/kg; repeat if necessary</td>
<td></td>
</tr>
</tbody>
</table>

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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.
Acute and emergency treatment of epileptic seizures

* 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.

** Because of better tissue tolerance, the concentrate for infusion is preferable to the solution. Infusion treatment with Phenhydan®: dilute 1 ampoule concentrate for infusion (50 ml = 750 mg phenytoin) with NaCl 0.9% to 500 ml; drip rate between approx. 10/min (= 0.5 ml/min = 0.75 mg phenytoin/min) and 50/min (= 2.5 ml/min = 3.75 mg phenytoin/min; 1 mg phenytoin/min = approx. 13 drops/min).

– For children (up to 12 years) the maximum infusion rate is 1.0 mg/kg/min; maximum Daily dose: on Day one 30 mg/kg, on Day two 20 mg/kg, on Day three 10 mg/kg.

– In adults only "status infusion" if needed: infuse 750 mg concentrate for infusion within 15-30 min. Cardiac monitoring necessary during the infusion: pulse, blood pressure, electrocardiogram (ECG); special caution in patients with cor pulmonale, cardiac arrhythmia and cerebral circulatory disorders. Maximum daily dose 1500 mg.

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

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

**** Levetiracetam is not licensed for the treatment of status epilepticus. The dosage recommendations stem from the German guideline of treatment of status epilepticus (Georg Thieme Verlag 2012, p 48-57)
Acute and emergency treatment of epileptic seizures

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

If the situation is not an emergency (see p. 11-16), 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). In our experience, the rate of allergic exanthema is increased by rapid titration with PHT.
Acute and emergency treatment of epileptic seizures

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 (the bioavailability has not been sufficiently systematically assessed for this dosage) or PB i.m./i.v. or PHT i.v..

- Instead of clonazepam orally (or other benzodiazepines): clonazepam or diazepam i.m./i.v. or diazepam rectally.

- Instead of ethosuximide (ESM) orally: diazepam rectally.

- Instead of PHT orally: PHT i.v. (not i.m.).

- Instead of primidone (PRM) orally: PB i.m./i.v. (250 mg PRM is equivalent to 50 mg phenobarbital).

- Instead of VPA orally: VPA solution for injection; or PB i.m./i.v. as replacement where necessary (for grand mal seizures) or diazepam rectally (for petit mal seizures).*

* If necessary, valproate suppositories can be prepared by the pharmacist.
Acute and emergency treatment of epileptic seizures

- Instead of LEV orally: LEV i.v.: dissolve a 5 ml vial, corresponding to 100 mg/ml, in at least 100 ml of a compatible diluent (sodium chloride, NaCl [0.9%], Ringer's lactate solution, dextrose 5% for injection) before the infusion, do not mix the solution for infusion with other products, ideally apply immediately after preparation; however, the solution can be stored for 24 hours at 2 to 8°C.

- Instead of LCM orally: LCM i.v.: dissolve 20 ml solution for infusion, corresponding to 10 mg/ml, in 250 ml NaCl 0.9% solution and infuse slowly for a period of 15 - 60 minutes.

In addition, all oral antiepileptic drugs can be replaced in the short term by rectal diazepam (as a suppository or rectal solution), i.m. or i.v.

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 already be resumed within less than 24 hours after surgery, the brief interruption of tablets on the day of the surgery can be compensated for additional administration of a single oral dose in the evening before or after surgery.
Acute and emergency treatment of epileptic seizures

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.
Long-term drug therapy
2. General treatment guidelines

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 [particularly important in children: Romano-Ward syndrome], narcoleptic seizures, pavor nocturnus, dissociative seizures).

In the case of epileptic seizures be aware of:
– Occasional spasms, e.g., febrile seizures, or seizures within the scope of correctable metabolic derailments, e.g., hypocalcaemia and hypoglycaemia.
– Local or diffuse cerebral processes, e.g., brain tumour, metabolic genetic diseases.

If an epilepsy disposing constellation is present during acute symptomatic seizures, therapy for approximately 6 months is recommended.

Only treat clinically manifest forms of epilepsy. Electroencephalography (EEG) patterns typical of epilepsy without manifest seizures are normally not a clear indication for long-term drug therapy. (Important exceptions: continuous spike wave status during sleep [CSWS], Landau-Kleffner syndrome).

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.
Long-term drug therapy
2. General treatment guidelines

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.
- Integration at school, at work and socially.

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. 61 ff.); if the effect is inadequate, wait for a possible late onset of action (can occur after 4-6 weeks, especially when administering VPA), provided the seizure frequency allows this.
Long-term drug therapy

2. General treatment guidelines

- 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 seizure freedom under polytherapy persists, combination therapy can be continued.

- Gradually discontinue medications that have proved to be ineffective.

- Do not change 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.

- Ask patients to keep a seizure diary.

- Ask patients to use a dosing box.
Long-term drug therapy
2. General treatment guidelines

- 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. 68-69).

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. 29-34 as well as p. 82), to identify blood level fluctuations (e.g., selfinduction 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).

- As a general rule, blood samples should only be drawn once the steady state is reached (see p. 61 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.
Long-term drug therapy
2. General treatment guidelines

- 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), tiagabine (TGB), topiramate (TPM), vigabatrine (VCB), retigabine (RTG), rufinamide (RUF), stiripentol (STP), perampanel (PER) and LCM 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.

- 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 seizures 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 e.g. PHT, which can also have gradually increasing toxic effects in
Long-term drug therapy
2. General treatment guidelines

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 with rolandic spikes and for some generalised idiopathic forms of epilepsy. However, juvenile myoclonic epilepsy and grand mal epilepsy on awakening in particular may require a long-term, possibly even life-long low mainte-
Long-term drug therapy
2. General treatment guidelines

nance therapy due to the high risk of relapse (after discontinuing the antiepileptic medication). Attempt to discontinue medication in generalised epilepsy only once the EEG has normalised and 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. Be aware of clinical trials with new antiepileptic drugs and literature concerning new complementary methods of treatment.
Long-term drug therapy
2. General treatment guidelines

2.9 Supporting measures
- Well-regulated lifestyle (particularly important in generalised idiopathic forms of epilepsy):
  - Regular sleep-wake rhythm.
  - Avoid lack of sleep.
  - 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 longterm treatment courses online)

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

- Epilepsy Network, www.epilepsynetwork.org
Long-term drug therapy
3. Special treatment situations

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 [see S. 62]. 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 [see p. 24]).

- 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).
Long-term drug therapy
3. Special treatment situations

- 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.

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);
Long-term drug therapy

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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.

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.
Long-term drug therapy
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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.

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, pimozide, quinidine and bepridil can be increased by STP.
Long-term drug therapy
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**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, OXC and STP, thus reducing their efficacy. 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%).
**Long-term drug therapy**

3. Special treatment situations

**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**
When administered in combination with centrally depressant drugs and alcohol, PB/PRM and benzodiazepines result in a mutually enhancing effect.

**Cytostatics**
Cisplatine and, in combination with other cytostatics, carmustine lower PHT levels considerably. PB and PHT can increase methotrexate toxicity.
Long-term drug therapy

3. Special treatment situations

3.2 Contraindications and intolerance

- No benzodiazepines in acute narrow-angle glaucoma and myasthenia gravis.
- No CBZ in atrioventricular block and hypersensitivity to tricyclic antidepressants.
- CBZ has increasingly been associated with an increased risk of severe skin reactions (Steven-Johnson-Syndrome, Toxic-Epidermal-Necrolysis, DRESS-Syndrome, acute generalized exanthemic pustulosis and makuopapular rash) correlated with the gene marker HLA-B*1502 in Han Chinese, Thais and other Asian populations. In Europeans and Japanese the same risk applies to the gene marker HLA-A*3101. A risk for the severe skin reactions in association with the gene marker HLA-B*1502 has been observed in structurally related drugs such as OXC. For the allele HLA-A*3101 a correlation has been suggested.
- No PHT in high-grade AV block and sino-atrial block.
- No LCM or RTG in second-degree and third-degree AV block.
- No PB/PRM, PHT, CBZ, VPA and clonazepam in hepatic porphyria (e.g., acute intermittent porphyria or cutaneous hepatic porphyria), use CBR instead.
- Caution in patients at risk of psychosis (direct and family medical history!) particularly when using ESM, RTG, STM, VGB, and ZNS.
Long-term drug therapy
3. Special treatment situations

- Caution with TPM or ZNS in glaucoma

- For precautionary measures when using VPA see p. 47-55 and the use of ACTH or corticosteroids see p. 56 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), mefloquine, methohexitol, 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). Beta-lactam 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.
Long-term drug therapy
3. Special treatment situations

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 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.
Long-term drug therapy
3. Special treatment situations

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

Before a planned pregnancy
The risk of foetal malformations is slightly increased in children of epileptic parents. When taking antiepileptic drugs (mother), the risk of major malformations (e.g., cleft lip face palate, cardiac defects, skeletal abnormalities) is around twice as high as in the general population. The risk of a neural tube defect is increased under treatment with VPA. Insufficient folic acid serum concentrations may also have an adverse effect on the development of neural tube defects. Prophylactic administration of folic acid should therefore, if possible, be initiated 4 weeks prior to the start of pregnancy and continued during the 1st trimester with a dose of 5 mg folic acid per day. The indication for continuous prophylaxis with folic acid in women of childbearing age requires further investigation. Minor malformations are more common than major malformations (so-called minor anomalies, e.g., anomalies affecting the external ear, epicanthus, hypoplasia of the nails and terminal phalanges, reduced body mass), but are not generally considered to be more than an inconvenience by the time the child starts school.

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
Long-term therapy
3. Special treatment situations

dose should be reduced, and if necessary replaced by PB or LTG. 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 antiepileptics for LTG in monotherapy up to 200 mg per day is the lowest. Under VPA therapy during pregnancy, cognitive impairment in offspring was reported. Cognitive impairment in children was described when VPA was given during pregnancy. Children whose mothers took VPA doses of at least 1000 mg during pregnancy suffer from autistic disorders more often. Furthermore there are signs that they may also have a higher risk for developing ADHD (for more information on VPA see also p 47).

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 necessary, switch from VPA to a benzodiazepine or, in case of major seizures, consider PB. 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!).

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.
Long-term drug therapy
3. Special treatment situations

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 that 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 new-born (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).
Long-term drug therapy
3. Special treatment situations

Even though antiepileptic drugs pass into breast milk, breastfeeding 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).
Long-term drug therapy

3. Special treatment situations

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 January 2017):
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.
Contraindications

- No parenteral vaccination against typhoid, paratyphoid and cholera.

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

Malariaprophylaxis
Epileptic seizures have been observed in isolated cases when using chloroquine (e.g., Resochin®) (this also applies to hydroxychloroquine sulphate [e.g., Quensyl®]); toxic effects may occur in addition to those of antiepileptic drugs after taking sulfonamides and pyrimethamine (e.g., Daraprim®). Mefloquin (e.g., Lariam®) can occasionally provoke seizures (higher risk compared to chloroquine)! It can also accelerate the metabolism of VPA. No contraindications are currently known for epilepsy patients when using the more recent antimalarial drugs proguanil (e.g., Paludrine®, malaria prophylaxis), halofantrin (e.g., Halfan®, malaria treatment) and atovaquon (e.g., Malarone®, malaria treatment).
Long-term drug therapy
3. Special treatment situations

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).
Long-term drug therapy
3. Special treatment situations

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).

* Irrespective of the number of doses
Long-term drug therapy
3. Special treatment situations

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

On recommendation of the EMA in November 2014 in patients of childbearing potential, VPA may only be used if other drugs failed. This is in the background of the dose dependent higher risk for malformations and developmental disorders in children after intrauterine exposure. Especially in doses above 800 mg or in combination therapy, e.g. with LTG, the risk increases. This is especially important with regards to the treatment of generalized seizures as numerous alternative drugs for treating focal seizures are available. In generalized seizures VPA for sure is one of the most effective substances and there are only few alternatives so in that case VPA has to be used nevertheless. In epilepsy syndromes in children it has to be pondered whether there is a chance of cure until childbearing age is reached. Even if this is not the case VPA is to be considered to be used in serious epilepsies such as the Dravet-syndrome or myoclonic-astatic epilepsy. Women who are treated with VPA should choose a safe form of contraception. If a pregnancy is planned the VPA dose should be below 800 mg or the patient should be switched to an alternative drug. The patient should take 5 mg of folic acid. If the pregnancy is already ongoing switching to an alternative drug is usually not reasonable. If, with regards to a possible cognitive decline, the medication should be switched anyhow only antiepileptics with a fast and reliable response such as PB or LEV should
be used. For risk minimization the EMA and local authorities in the EU provide educational material for health care professionals and patients as well as a form for confirmation of education.

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.
**Long-term drug therapy**  
3. Special treatment situations

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

**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, mitochondrialopathy (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 of a starting 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 (pro-thrombin time = Quick’s test International Normalised Ratio [INR], partial thromboplastin time (PTT), fibrinogen in plasma, factor VIII-associated factors – due to the incidence of VPA-induced von-Willebrand-Jürgens type I disease, namely in 20-30% of all patients treated with valproate, compared to a prevalence of 1-2% in the general population), 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]). In retarded children (risk group), metabolic defects (such as e.g., disturbed breakdown of amino, organic and fatty acids, mitochondriopathy, urea cycle defects) should be ruled out as far as possible. 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 physi-
Long-term drug therapy

3. Special treatment situations

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

cian 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.
Long-term drug therapy

3. Special treatment situations

- 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® - Note: possible induction of seizures, see p. 38) 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 hypersynchronous 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 (see leaflet p. 75 ff.).

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 and family history of spina bifida.

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.

* see Appendix page 76 ff.
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. 68 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 bleeding tendency.

- Marked increase in transaminases to two or three times the upper limit of normal (even in the absence of other abnormal clinical or laboratory results).

- Mild increase (to 1.5 to two times the upper limit of normal) of hepatic enzymes with concurrent acute febrile infection.

- Marked disorder of coagulation.
Long-term drug therapy
3. Special treatment situations

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 of crucial importance for the outcome. 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. A depot ACTH preparation (e.g., Synacthen® Depot) is the preferred therapy, or alternatively oral corticosteroids (e.g., prednisolone or dexamethasone).

**Suggested initial daily dose (taken as a single early morning dose):**

- 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.

* For details on implementing and monitoring steroid treatment for West syndrome we refer to the AWMF guideline (date: March 2009).
Long-term drug therapy
3. Special treatment situations

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).

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.
**Long-term drug therapy**

3. Special treatment situations

**Ending the treatment**

- Discontinue treatment if no clinical effect is observed within 4 weeks of continuous single daily dosing (see p. 56) 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: only give single daily dose every second day, after 2 weeks only every third day or three times weekly, after a further 2 weeks only twice weekly, etc.

Consult a paediatric epilepsy specialist for further details on dosing and tolerance testing.
Long-term drug therapy
3. Special treatment situations

Note
So-called high-dose pulsatile corticosteroid therapy has recently been proposed as an alternative to continuous hormone administration, e.g.,: 20 mg/kg methylprednisone orally once daily for 3 days, followed by a 4-day break (= 1 weekly cycle). Continue this treatment for 4 cycles, then extend the interval to 2 and later to 3 weeks with a gradual discontinuation of treatment.
(Details should be discussed with an epileptologist with experience of this therapy).

Previous experience suggests a better tolerability of pulsatile therapy compared to continuous administration. No definite statements can be made yet about its efficacy.
## 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. 86

### Epilepsy with focal seizures

<table>
<thead>
<tr>
<th>Cause structural or not known</th>
<th>AED of first choice</th>
<th>AED of second choice</th>
<th>AED of third choice</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTG&lt;sup&gt;6&lt;/sup&gt;, LEV&lt;sup&gt;6&lt;/sup&gt;, OXC&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CBZ, VPA, PHT, TPM, ZNS</td>
<td>LCM&lt;sup&gt;1&lt;/sup&gt;, VGB&lt;sup&gt;2&lt;/sup&gt;, ZNS&lt;sup&gt;3&lt;/sup&gt;, TGB&lt;sup&gt;1&lt;/sup&gt;, GB&lt;sup&gt;1&lt;/sup&gt;, PGB&lt;sup&gt;1&lt;/sup&gt;, ESL&lt;sup&gt;1&lt;/sup&gt;, PB&lt;sup&gt;1&lt;/sup&gt;, KD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Authorised as add-on therapy in adults: LCM, ZNS, PGB, ESL age 12 and older: PER</td>
<td></td>
</tr>
</tbody>
</table>

### Rolando epilepsy (and relatives)

| STM<sup>3</sup>, OXC<sup>3</sup> | LEV<sup>2</sup>, VPA | CLB, TPM, ZNS<sup>3</sup>, KD<sup>2</sup> | Review general indication for treatment strictly. |

### Atypical variants of idiopathic focal epilepsy

| STM<sup>3</sup>, CLB | CS<sup>9</sup>, LEV, VPA, ESM, TPM | ZNS<sup>3</sup>, KD<sup>2</sup> | Early use of CS. |

### Epilepsy with generalised seizures

| Childhood absence epilepsy | ESM | VPA, LTG<sup>4</sup> | LEV<sup>3</sup>, TPM, ZNS<sup>3</sup>, STM<sup>3</sup>, KD<sup>2</sup> |

### Juvenile myoclonic epilepsy

| VPA (male) LTG<sup>1</sup> (female) | LEV, TPM, VPA (male), LTG<sup>1</sup> (male) | ESM, STM<sup>3</sup>, ZNS<sup>1</sup>, PB | 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<sup>2</sup> or CS<sup>9</sup> | STM<sup>3</sup>, VPA, TPM | LEV<sup>3</sup>, ZNS<sup>3</sup>, RUF<sup>3</sup>, LTG, KD<sup>7</sup> | Initial trial with pyridoxal phosphate (30 mg/kg/d 3 days). |
| Dravet syndrome | VPA | +TPM, +CBR, +STP +CLB | ESM<sup>1</sup>, MSM<sup>8</sup>, LEV<sup>1</sup>, PB, PRM, ZNS<sup>3</sup>, KD<sup>2</sup> | Rapid polytherapy. Not: CBZ, OXC, LTG, PHT. |
| Myoclonic-astatic epilepsy | VPA | ESM, LTG, KD<sup>2</sup> | TPM, CBR, MSM<sup>8</sup>, PB, PRM, CLB, ZNS<sup>3</sup>, CS<sup>9</sup> |
| Lennox-Gastaut syndrome | VPA, TPM, LTG<sup>1</sup> | RUF<sup>3</sup>, PB, ESM, ZNS<sup>3</sup>, CLB | FBM<sup>3</sup>, MSM<sup>8</sup>, PRM, CBR, PHT, CS<sup>9</sup>, VGB<sup>1</sup>, KD<sup>7</sup> | In principle, every AED can be used depending on the target seizure type. Note: deterioration possible. |

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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. 79 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 Valproate 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 DGZGN ZNS2 Guidelines.
7 KD = Ketogenic diet
8 Mesuximide is licensed for petit mal seizures within the scope of mixed epilepsy and in absence, 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.
Antiepileptic drugs for long-term treatment
In alphabetical order

<table>
<thead>
<tr>
<th>Antiepileptic drug</th>
<th>Abbreviation/ commercial preparation</th>
<th>Child</th>
<th>Adults</th>
<th>Time to constant blood levels (steady state)</th>
<th>Therap. plasma concentrations of total fraction ( = conversion factor)</th>
<th>Side effects(^a), overdose, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide (AZA)</td>
<td>e.g. Diamox(^c)</td>
<td>~ 10 mg/kg</td>
<td>3 x 250 mg</td>
<td>2-3 days</td>
<td>10-20 mg/l [45-50 \mu mol/l (4.5)]</td>
<td>As for sulthione (milder dyspnoea), also: hypokalaemia (potassium substitution may be necessary), hyperglycaemia, renal calculi.</td>
</tr>
<tr>
<td>Brivaracetam (BRV)</td>
<td>Briviact(^d)</td>
<td>no recommendations</td>
<td>50-200 mg</td>
<td>2 days</td>
<td>not known</td>
<td>Tiredness, dizziness, nausea, irritability</td>
</tr>
<tr>
<td>Bromide (CBR)</td>
<td>e.g. potassium bromide Dibo-Be mono (BR)</td>
<td>Infants: 50-70 mg/kg</td>
<td>850-2550 mg</td>
<td>60 days</td>
<td>100-250 mg/dl [12.5-31.25 mmol/l]</td>
<td>Bromide acne, bromoderma, bromide panniculitis, loss of appetite, gastritis, ulcers, polydipsia, rhinitis, bronchitis (also asthmoid), somnolence, psychosis (rare).</td>
</tr>
<tr>
<td>Carbamazepine(^e)</td>
<td>e.g. Finlepsin(^a), Fokalepsin(^a), Sirtal(^b), Tegretal(^b), Timonil(^b)</td>
<td>~ 20-25 mg/kg</td>
<td>400-2400 mg</td>
<td>4-7 days (in longterm monotherapy sinking due to autoinduction)</td>
<td>CBZ: 3-12 mg/l [13-50 \mu mol/l (4.2)] [CBZ-Epoxid: 0.6-3.0 mg/l [2-3.17 \mu mol/l (3.9)] ]</td>
<td>Exantheme ~ 10%, leucopenia (&lt; 2500 mm(^3)) ~ 2%; tiredness (esp. at start of th.), dizziness, visual disorders; stimulus conduction and heart rhythm disorders; immunoglobulin deficiency, hyponatraemia, water retention syndrome; headache, constipation, alopecia; extrapyramidal hyper- or dyskinesia, osteopathy (vitamin D deficiency); seizure induction (esp. petit mal), deterioration of EEG. Specific to CBZ epoxide: nausea, vomiting, drowsiness.</td>
</tr>
<tr>
<td>Clobazam(^f)</td>
<td>e.g. Frisium(^m)</td>
<td>~ 0.2-1.0 mg/kg</td>
<td>540 mg</td>
<td>3-6 days</td>
<td>0.1-0.6 mg/l [N-Desmethyl-CLB: 0.5-4 mg/l]</td>
<td>Possible with all benzodiazepines, but least pronounced with clobazam: decreased muscle tone, ataxia, impaired emotional control, dysphoria, hyper-secretion of salivary and bronchial glands, increase in tonic seizures, greatest tolerance development, withdrawal syndrome possible on discontinuation.</td>
</tr>
<tr>
<td>Eslicarbazepine acetate (ESL)</td>
<td>e.g. Zebinix(^a)</td>
<td>no recommendations</td>
<td>400-2400 mg</td>
<td>4-5 days</td>
<td>MHD: 20-35 mg/l [80-140 \mu mol/l (4.0)]</td>
<td>Dizziness, drowsiness, tiredness, headache, coordination disorder, attention disorder, tremor, diplopia, blurred vision, nausia, vomiting, diarrhoea, skin rash, hyponatraemia; interactions with other AEDs: PHT (increase in ESL dosage necessary); LTG (?), TPM (?), CBZ (decrease in visual acuity, coordination disorder and tiredness increased); VPA and LEV: no interactions.</td>
</tr>
</tbody>
</table>

\(^a\) For more details have a look at the specific SmPC.
\(^b\) 1-13 Explanations on page 66-67
Antiepileptic drugs for long-term treatment
In alphabetical order of generic preparations

<table>
<thead>
<tr>
<th>Generic preparation</th>
<th>Abbreviation/commercial preparation</th>
<th>Daily dose(^a)</th>
<th>Time to constant blood levels(^b) (steady state)</th>
<th>Therap. plasma concentrations of total fraction ((f) = \text{conversion factor})</th>
<th>Side effects(^c), overdose, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethosuximide (ESM)</td>
<td>E.g. Petnidan(^d); Suxilep(^e)</td>
<td>(~ 30 \text{ mg/kg})</td>
<td>(~ 30 \text{ mg/kg})</td>
<td>(~ 4-10 \text{ days})</td>
<td>40-100 mg/l = 280-700 (\mu\text{mol/l}) (7.1)</td>
</tr>
<tr>
<td>Felbamate(^f) (FBM)</td>
<td>E.g. Taloxa(^g)</td>
<td>(~ 20-45 \text{ mg/kg})</td>
<td>(~ 1200-3600 \text{ mg})</td>
<td>(~ 4 \text{ days})</td>
<td>20-45 mg/l = 85-190 (\mu\text{mol/l}) (4.2)</td>
</tr>
<tr>
<td>Gabapentin(^h) (GBP)</td>
<td>E.g. Neurontin(^i); Gabapentin DESITIN(^n)</td>
<td>(~ 10-60 \text{ mg/kg})</td>
<td>(~ 1200-3600 \text{ mg})</td>
<td>(~ 1-2 \text{ days})</td>
<td>2-10 (20) mg/l = 11.6-58.0 (\mu\text{mol/l}) (5.8)</td>
</tr>
<tr>
<td>Lamotrigine(^j) (LTG)</td>
<td>E.g. Lamictal(^k); Lamotrigin DESITIN(^o) quadro; Plexxo(^q) quarto</td>
<td>(~ 1-15 \text{ mg/kg})</td>
<td>(~ 100-700 \text{ mg})</td>
<td>(~ 5-6 \text{ days} \text{ in monotherapy})</td>
<td>2-10 (~14%) mg/l = 7.8-39 (54.8%) (\mu\text{mol/l}) (3.9)</td>
</tr>
<tr>
<td>Lacosamide(^l) (LCM)</td>
<td>E.g. Vimpat(^p)</td>
<td>no recommendations</td>
<td>200-400 mg</td>
<td>3 days</td>
<td>Measurement of plasma concentration possible; no therapeutic range defined</td>
</tr>
<tr>
<td>Levetiracetam(^m) (LEV)</td>
<td>E.g. Keppra(^s); Levetiracetam DESITIN(^n); Desitrend(^t)</td>
<td>According to SmPC</td>
<td>(~ 1000-4000 \text{ mg})</td>
<td>(~ 2 \text{ days})</td>
<td>Measurement of plasma concentration possible; no therapeutic range defined</td>
</tr>
<tr>
<td>Mesuximide (MSM)</td>
<td>E.g. Petinutin(^e)</td>
<td>(~ 20 \text{ mg/kg})</td>
<td>(~ 450-1200 \text{ mg})</td>
<td>(~ 8 \text{ days})</td>
<td>N-desmethyl-mesuximide: 20-35 mg/l = 100-175 (\mu\text{mol/l}) (4.9)</td>
</tr>
</tbody>
</table>

\(^{a}\) Child: \(~ 30 \text{ mg/kg}\) to \(~ 60 \text{ mg/kg}\); Adults: \(~ 600 \text{ mg}\) to \(~ 3600 \text{ mg}\). \(^{b}\) Measurement of plasma concentration possible; no therapeutic range defined. \(^{c}\) \(^{d}\) \(^{e}\) \(^{f}\) \(^{g}\) \(^{h}\) \(^{i}\) \(^{j}\) \(^{k}\) \(^{l}\) \(^{m}\) \(^{n}\) \(^{o}\) \(^{p}\) \(^{q}\) \(^{r}\) \(^{s}\) \(^{t}\) \(^{u}\) \(^{v}\) \(^{w}\) \(^{x}\) \(^{y}\) \(^{z}\)
# Antiepileptic drugs for long-term treatment

In alphabetical order of generic preparations

<table>
<thead>
<tr>
<th>Generic preparation</th>
<th>Abbreviation/ commercial preparation</th>
<th>Child</th>
<th>Adults</th>
<th>Time to constant blood levels(^\text{a}) (steady state)</th>
<th>Therap. plasma concentrations of total fraction ((\cdot)) = conversion factor</th>
<th>Side effects(^\text{b}), overdose, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine(^1) (OXC)</td>
<td>e.g. Apydan(^a) (extent); Timox(^a); Trileptal(^a)(^1)</td>
<td>~ 25-35 mg/kg</td>
<td>600-2400 mg</td>
<td>2-3 days</td>
<td>Monohydroxy-derivative (MHD)</td>
<td>MHD: 20-35 mg/l = 80-140 µmol/l (4.0)</td>
</tr>
<tr>
<td>Perampanel (PER)(^3)</td>
<td>e.g. Fycompa(^a)</td>
<td>not authorized</td>
<td>4-12 mg(^a)</td>
<td>14 days</td>
<td>Measurement of plasma concentration possible; no therapeutic range defined</td>
<td>Tiredness, vertigo, CBZ, OXC, PHT may decrease PER plasma levels.</td>
</tr>
<tr>
<td>Pheneturide(^2) (PNT)</td>
<td>e.g. Laburide(^a)</td>
<td>~ 25 mg/kg</td>
<td>750-1500 mg</td>
<td>8-10 days</td>
<td>10-20 mg/l = 40-80 µmol/l (4.0)</td>
<td>Hearing disorder, thrombocytopenia, psychotic syndrome, do not combine with STMI!</td>
</tr>
<tr>
<td>Phenobarbital (PB)</td>
<td>e.g. Luminal(^a); Phenaemall(^a); Luminaletten(^a) / Phenaemaletten(^a)</td>
<td>~ 4 mg/kg</td>
<td>up to 300 mg</td>
<td>14-21 days</td>
<td>10-40 mg/l = 45-170 µmol/l (4.3)</td>
<td>Osteopathy (vitamin D deficiency), increased bleeding tendency (vitamin K deficiency) in newborns of PB-treated mothers, megaloblastic anemia (folic acid deficiency); depressive syndrome; especially in children and in the elderly: increased irritability, dysphoria. Fibromatosis, constipation, urinary retention; barbexacne: appetite, weight ↓, hypertension.</td>
</tr>
<tr>
<td>Phenytoin (PHT)</td>
<td>e.g. Epanutin(^a); Phenhydan(^a); Zentropil(^a)</td>
<td>~ 5-7 mg/kg</td>
<td>100-400 mg</td>
<td>5-14 days</td>
<td>5-20 mg/l = 20-80 µmol/l (4.0)</td>
<td>Free fraction &lt; 2.3 mg/l</td>
</tr>
<tr>
<td>Pregabalin(^1) (PGB)</td>
<td>e.g. Lyrica(^a)(^1)</td>
<td>no recommendation</td>
<td>150-600 mg(^a)</td>
<td>1-2 days</td>
<td>(\text{——})</td>
<td>Light-headedness and sleepiness (very common), mood swings, reduced libido, concentration and memory disorder; tremor, dystonia, diplopia, co-ordination disorders, dizziness; constipation, dry mouth, increased appetite, weight gain (common), anorexia (occasionally). No known interaction with other drugs to date.</td>
</tr>
</tbody>
</table>

\(^{a}\) Licensed for adults and adolescents from 12 years of age. Treat adolescents like adult patients. 

1-13 Explanations on page 66-67
# Antiepileptic drugs for long-term treatment

In alphabetical order of generic preparations

<table>
<thead>
<tr>
<th>Generic preparation</th>
<th>Abbreviation/ commercial preparation</th>
<th>Child</th>
<th>Daily dose</th>
<th>Time to constant blood levels(^{11}) (steady state)</th>
<th>Therap. plasma concentrations of total fraction (1 = conversion factor)</th>
<th>Side effects(^{1},) overdose, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primidone (PRM)</td>
<td>e.g. Liskantin®; Mylepsinum®</td>
<td>~ 20 mg/kg</td>
<td>up to 1250 mg</td>
<td>Phenobarbital: 14-21 days Primidone: 1-2 days</td>
<td>Phenobarbital: 10-40 mg/l = 45-170 µmol/l (4.3) Primidone: 4-15 mg/l = 20-70 µmol/l (4.6)</td>
<td>Like PB, also: at start of therapy dizziness, vomiting, sleepiness (also possible at low doses).</td>
</tr>
<tr>
<td>Rufinamide(^{4}) (RU F)</td>
<td>e.g. Inovelon®</td>
<td>Below 30 kg without VPA: up to 35 mg/kg Below 30 kg with VPA: up to max. 600 mg/d Above 30 kg up to max. 60 mg/kg</td>
<td>2400-3200 mg</td>
<td>2 days</td>
<td>not known</td>
<td>Headache, tiredness, dizziness, diplopia, sleepiness, vomiting, loss of appetite, sleep disturbance.</td>
</tr>
<tr>
<td>Stiripentol(^{4}) (STP)</td>
<td>e.g. Diacomit®</td>
<td>Up to 50 mg/kg BW in combination with CLB and VPA</td>
<td>2000-3000 mg</td>
<td>not known</td>
<td>not known</td>
<td>Loss of appetite, weight loss, growth disturbance, sleep disturbance, ataxia, decreased muscle tone, dystonia, due to inhibition of the CYP 450 enzyme system the breakdown of other concomitant medication may be inhibited, resulting in toxic plasma concentrations (antiepileptic drugs, cardiac medication, theophylline etc. see SPC).</td>
</tr>
<tr>
<td>Sulthiamine (STM)</td>
<td>e.g. Ospolot®</td>
<td>3-10 mg/kg</td>
<td>100-300 mg</td>
<td>2-3 days</td>
<td>1-3 mg/l (Rolandic epilepsy) = 3.5-10.5 µmol/l 5-10 mg/l (symptom. epilepsy) = 17.5-35 µmol/l (3.5)</td>
<td>Tachypnoea, hyperpnoea, paraesthesia, psychotic symptoms (therefore do not combine with PNT); enzyme inhibitor, e.g. PHT + STM. PHT ↑.</td>
</tr>
<tr>
<td>Tiagabine(^{4}) (TGB)</td>
<td>e.g. Gabitril®</td>
<td>~ 0.25-1.5 mg/kg (dose not established exactly yet)</td>
<td>Combination without enzyme inducers: 15-30 mg Combination with enzyme inducers: 30-50 mg</td>
<td>1-2 days</td>
<td>13</td>
<td>Tiredness, dizziness, “nervousness”; induction of non-convulsive status, TGB + enzyme-inducing antiepileptic drugs: TGB ↓.</td>
</tr>
</tbody>
</table>

1-13 Explanations on page 66-67
## Antiepileptic drugs for long-term treatment

In alphabetical order of generic preparations

<table>
<thead>
<tr>
<th>Generic preparation</th>
<th>Abbreviation/commercial preparation</th>
<th>Child Daily dose&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Adults</th>
<th>Time to constant blood levels&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Therap. plasma concentrations of total fraction&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Side effects&lt;sup&gt;i&lt;/sup&gt;, overdose, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topiramate</strong>&lt;sup&gt;5&lt;/sup&gt; (TPM)</td>
<td>e.g. Topamax®; Topiramat DESITIN&lt;sup&gt;®&lt;/sup&gt;</td>
<td>3-9 (-15) mg/kg</td>
<td>50-600 mg</td>
<td>4-8 days</td>
<td>Measurement of plasma concentration possible; no therapeutic range defined</td>
<td>Dizziness, tiredness, weight loss (can be excessive!), renal calculi, thought disorders, psychosis, speech disorders; TPM + PHT: PHT ↑. TPM + enzym-inducing antiepileptic drugs: TPM ↓. TPM reduces effect of hormonal contraceptives (at doses &gt;200 mg/day).</td>
</tr>
<tr>
<td><strong>Valproate</strong> (VPA)</td>
<td>e.g. Convulex®; Convulsofin®; Leptilan®; Orfiri&lt;sup&gt;a&lt;/sup&gt; long; Ergenyl®; Valproat chrono DESITIN&lt;sup&gt;®&lt;/sup&gt;</td>
<td>~ 20-30 mg/kg</td>
<td>600-3600 mg</td>
<td>2-4 days</td>
<td>50-120 mg/l = 205-820 µmol/l (6.9)</td>
<td>Lack of appetite (usually initially and temporarily); nausea, vomiting; increased appetite; weight gain; coagulation disorders; hepatopathy&lt;sup&gt;5&lt;/sup&gt;; pancreatitis&lt;sup&gt;5&lt;/sup&gt;; oedema; tremor; acute encephalopathy (apathy syndrome), chronic encephalopathy; alopecia (usually transient); teratogenic effect: negative impact on IQ and cognition, autism, neural tube defects, radial aplasia.</td>
</tr>
<tr>
<td><strong>Vigabatrine</strong>&lt;sup&gt;5&lt;/sup&gt; (VGB)</td>
<td>e.g. Sabril&lt;sup&gt;a&lt;/sup&gt;</td>
<td>~ 60-100 mg/kg</td>
<td>2000-4000 mg</td>
<td>1-3 days</td>
<td>Measurement of plasma concentration possible; no therapeutic range defined</td>
<td>Dizziness, tiredness, headache, weight change (more common: gain), diplopia, induction of myoclonic and grand mal seizures; psychotic syndromes; agitation, aggression (esp. in multihandicapped patients with organic brain disorder), particularly common and important: (irreversible) reduced field of vision (probably in 30% or more of all VGB-treated patients!).</td>
</tr>
<tr>
<td><strong>Zonisamide</strong>&lt;sup&gt;5&lt;/sup&gt; (ZNS)</td>
<td>e.g. Zonegran®</td>
<td>4-12 mg/kg</td>
<td>300-600 mg</td>
<td>ca. 13 days</td>
<td>15-40 mg/l = 70-190 µmol/l (4.71)</td>
<td>Anorexia, ataxia, dizziness, diplopia; rarely: attention disorders, nausea, weight loss, very rarely: renal calculi, psychotic symptoms.</td>
</tr>
</tbody>
</table>

<sup>i</sup>Explanations on page 66-67
Antiepileptic drugs for long-term treatment

Explanations

1. The substance is available in various strengths (see p. 70 ff.).
2. As an example for all antiepileptic benzodiazepines.
3. Not commercially available in Germany (international pharmacy – where applicable, obtain information of reimbursability by German health insurer beforehand).
4. Licensing restrictions: see p. 79 ff.
5. In principle, prescribe lower doses to patients with renal impairment!
6. Guidelines for titration of LTG in adults and children aged 12 years and over:
   - in monotherapy: 25 mg daily in the first 2 weeks, then 50 mg per day for a further 2 weeks; then increase by max. 50-100 mg every 1-2 weeks.
   - in combination with enzyme-inducing antiepileptic drugs (e.g., CBZ, PB, PRM, PHT): start with 25 mg twice daily, if tolerated well by patient increase to between 50 mg twice daily and 100 – 200 mg twice daily (possibly up to 300 mg twice daily) every 2 weeks; possibly continue increasing titration according to clinical presentation (seizure freedom/side effects).
   - in combination with enzyme-inhibiting antiepileptic drugs (e.g., VPA): start with 25 mg = one 25 mg tab. every second day for 2 weeks, then increase to 25 mg = one 25 mg tab. every day for a further 2 weeks; after week 4 of treatment (subject to good tolerability) the subsequent titration can be done more rapidly (e.g., by max. 25-50 mg every 1-2 weeks) – the final maintenance dose is based on the clinical presentation (freedom seizure freedom/side effects).

Guidelines for titration of LTG in children aged 2-12 years (add-on therapy):

- in combination with enzyme-inducing antiepileptic drugs: start with 0.6 mg/kg BW/day (2 single doses), after 2 weeks double the dose (for 2 weeks); the dose should then be increased every 1-2 weeks by 1.2 mg/kg to max. 400 mg/day until the maintenance dose is reached (5-15 mg/kg BW/day).
- in comb. with VPA: start with 0.15 mg/kg BW (once daily) for two weeks; for the following 2 weeks 0.3 mg/kg BW (once daily). The dose should be increased every 1-2 weeks by 0.3 mg/kg BW to max. 200 mg/day until the maintenance dose is reached (1-5 mg/kg BW, once or twice daily).
Antiepileptic drugs for long-term treatment

7 FBM (e.g., Taloxa®) may only be used after an extremely careful benefit-risk assessment – particularly with regard to a possible blood disease (especially aplastic anaemia) and serious and potentially fatal liver damage. Contraindications and special precautionary measures for use should be observed particularly carefully (Summary of Product Characteristics [SmPC], specialist literature).

8 Special treatment monitoring. See page 47 ff.

9 Daily dosing range according to the authors’ recommendations: in some cases the daily doses are above the authorised range according to the SmPC. Higher doses may be necessary for combination therapy with enzyme-inducing antiepileptic drugs, while lower doses may be required with enzyme-inhibiting antiepileptic drugs.

10 The time to steady state is frequently equal to five times the half-life (HL) of the drug. Shorter half-lives: in children, following self-induction, or in combination with enzyme-inducing antiepileptic drugs.

11 Now used almost exclusively as a prolonged-release formulation.

12 Hypersensitivity reactions are possible with all antiepileptic drugs, but very rare. The following usually occur within the first 10-20 days of treatment: exanthema (often urticarial or morbilliform); Stevens-Johnson syndrome; exfoliative bullous dermatitis; fever, swelling of lymph nodes (pseudolymphoma); mononucleosis-like syndrome with hepatosplenomegaly. Later appearance: leucopenia; very rarely agranulocytosis; aplastic anaemia; thrombocytopenia; panmyelopathy. Even more rarely: visceral lupus erythematosus, granulomatous vasculitis.

13 Blood level measurements may be omitted because of the lack of or (still) unknown dose-effect/side effect correlation.
Tolerability testing for antiepileptic pharmacotherapy*

Before starting treatment:

- General examination with body weight and blood pressure measurement.

- Laboratory tests:
  - Complete blood count, thrombocytes and urin 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 (before PHT).
  - Triglycerides, cholesterol (especially in adults).

After stabilisation:
For the first time after 1-3 months, later in 4- to 6-month intervals (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).
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 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.
  - 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. 47 ff
## Antiepileptic drugs

In alphabetical order of trade names.  
(date: January 2017)

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

* Trade name in Denmark, Estonia and Finland.
# Antiepileptic drugs

In alphabetical order of trade names

(date: January 2017)

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

---

* 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: January 2017)

<table>
<thead>
<tr>
<th>Commercial preparation¹</th>
<th>Active substance</th>
<th>Abbreviation</th>
<th>Form of administration</th>
<th>Dosage strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liskantin®</td>
<td>Primidone</td>
<td>PRM</td>
<td>Tablets</td>
<td>250 mg, 25 mg/ml (5 ml=125 mg)</td>
</tr>
<tr>
<td>Liskantin® syrup</td>
<td></td>
<td></td>
<td>Syrup</td>
<td></td>
</tr>
<tr>
<td>Luminal®/Phenaemal®</td>
<td>Phenobarbital</td>
<td>PB</td>
<td>Tablets</td>
<td>100 mg, 15 mg</td>
</tr>
<tr>
<td>Luminal®/solution for injection</td>
<td>Phenobarbital-sodium</td>
<td>PB</td>
<td>Solution for injection (ampoule)</td>
<td>200 mg/ml</td>
</tr>
<tr>
<td>Luminaletten®/Phenaemaletten®</td>
<td></td>
<td></td>
<td>Tablets</td>
<td>15 mg</td>
</tr>
<tr>
<td>Lyrica®</td>
<td>Pregabalin</td>
<td>PGB</td>
<td>Hard capsules</td>
<td>25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg</td>
</tr>
<tr>
<td>Mylepsinum®</td>
<td>Primidone</td>
<td>PRM</td>
<td>Tablets</td>
<td>250 mg</td>
</tr>
<tr>
<td>Neurontin®</td>
<td>Gabapentin</td>
<td>GBP</td>
<td>Hard capsules</td>
<td>100 mg, 300 mg, 400 mg</td>
</tr>
<tr>
<td>Neurotin®</td>
<td></td>
<td></td>
<td>Film-coated tablets</td>
<td>600 mg, 800 mg</td>
</tr>
<tr>
<td>Orfiriil® long</td>
<td>Sodium valproate</td>
<td>VPA</td>
<td>Capsules with prolonged-release, minitablets; sachet with prolonged release minitablets***</td>
<td>150 mg, 300 mg</td>
</tr>
<tr>
<td>Episenta®</td>
<td></td>
<td></td>
<td></td>
<td>500 mg, 1000 mg</td>
</tr>
<tr>
<td>Orfiriil®</td>
<td>Sodium valproate</td>
<td>VPA</td>
<td>Sugar-coated tablets</td>
<td>150 mg, 300 mg, 600 mg</td>
</tr>
<tr>
<td>Orfiriil® syrup</td>
<td></td>
<td></td>
<td>Syrup</td>
<td>60 mg/ml</td>
</tr>
<tr>
<td>Orfiriil® solution for injection</td>
<td></td>
<td></td>
<td>Solution for injection (ampoule)</td>
<td>300 mg/3 ml, 1000 mg/10 ml</td>
</tr>
<tr>
<td>(each 100 mg/ml)</td>
<td></td>
<td></td>
<td></td>
<td>(each 100 mg/ml)</td>
</tr>
<tr>
<td>Ospolot®</td>
<td>Sulthiame</td>
<td>STM</td>
<td>Film-coated tablets</td>
<td>50 mg, 200 mg</td>
</tr>
<tr>
<td>Petinutin®</td>
<td>Mesuximide</td>
<td>MSM</td>
<td>Hard capsules</td>
<td>150 mg, 300 mg</td>
</tr>
<tr>
<td>Petnidan®</td>
<td>Ethosuximide</td>
<td>ESM</td>
<td>Soft capsules</td>
<td>250 mg</td>
</tr>
<tr>
<td>Petnidan® syrup</td>
<td></td>
<td></td>
<td>Syrup</td>
<td>50 mg/ml (5 ml=250 mg)</td>
</tr>
</tbody>
</table>

¹ Trade name in Czech Republic, Estonia and Slovakia.
² Trade name in UK.
³ Minitablet = approved administrative form of Orfiriil® long/Episenta® film-coated granules in sachets.
# Antiepileptic drugs

In alphabetical order of trade names  
(date: January 2017)

<table>
<thead>
<tr>
<th>Commercial preparation</th>
<th>Active substance</th>
<th>Abbreviation</th>
<th>Form of administration</th>
<th>Dosage strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenhydan®</td>
<td>Phenytoin</td>
<td>PHT</td>
<td>Tablets</td>
<td>100 mg</td>
</tr>
<tr>
<td>Phenhydan® solution for injection</td>
<td>Phenytoin-sodium</td>
<td>PHT</td>
<td>Solution for injection (ampoule)</td>
<td>250 mg phenytoin/5 ml</td>
</tr>
<tr>
<td>Phenhydan® solution for concentrate</td>
<td>Phenytoin-sodium</td>
<td>PHT</td>
<td>Infusion concentrate (ampoule)</td>
<td>750 mg phenytoin/50 ml</td>
</tr>
<tr>
<td>Sabril®</td>
<td>Vigabatrine</td>
<td>VGB</td>
<td>Film-coated tablets</td>
<td>500 mg</td>
</tr>
<tr>
<td>Sabril® sachet</td>
<td>Vigabatrine</td>
<td>VGB</td>
<td>Granulate</td>
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</tr>
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<td>Felbamate</td>
<td>FBM</td>
<td>Tablets</td>
<td>400 mg, 600 mg</td>
</tr>
<tr>
<td>Taloxa® syrup</td>
<td>Felbamate</td>
<td>FBM</td>
<td>Suspension</td>
<td>600 mg/5 ml</td>
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<tr>
<td>Tavor®</td>
<td>Lorazepam</td>
<td>LZP</td>
<td>Tablets</td>
<td>0.5 mg, 1 mg, 2 mg, 2.5 mg</td>
</tr>
<tr>
<td>Tavor® expidet</td>
<td>Lorazepam</td>
<td>LZP</td>
<td>Wafers</td>
<td>1 mg, 2.5 mg, 2 mg/ml</td>
</tr>
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<td>Tavor® for injection</td>
<td>Lorazepam</td>
<td>LZP</td>
<td>Solution for injection (ampoule)</td>
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<tr>
<td>Tegretal®</td>
<td>Carbamazepine</td>
<td>CBZ</td>
<td>Tablets</td>
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</tr>
<tr>
<td>Tegretal® suspension</td>
<td>Carbamazepine</td>
<td>CBZ</td>
<td>Prolonged-release tablets</td>
<td>200 mg, 400 mg, 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suspension</td>
<td>200 mg/5 ml</td>
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### Antiepileptic drugs

In alphabetical order of trade names

(date: January 2017)

<table>
<thead>
<tr>
<th>Commercial preparation</th>
<th>Active substance</th>
<th>Abbreviation</th>
<th>Form of administration</th>
<th>Dosage strengths</th>
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<tbody>
<tr>
<td><strong>Timonil®</strong></td>
<td>Carbamazepine</td>
<td>CBZ</td>
<td>Tablets</td>
<td>200 mg, 400 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Syrup</td>
<td>20 mg/ml (100 mg/5 ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged-release tablets</td>
<td>150 mg, 200 mg, 300 mg, 400 mg, 600 mg</td>
</tr>
<tr>
<td><strong>Topamax®</strong></td>
<td>Topiramate</td>
<td>TPM</td>
<td>Film-coated tablets</td>
<td>25 mg, 50 mg, 100 mg, 200 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hard capsules</td>
<td>25 mg, 50 mg</td>
</tr>
<tr>
<td><strong>Vimpat®</strong></td>
<td>Lacosamide</td>
<td>LCM</td>
<td>Tablets with sustained release formulation</td>
<td>150 mg, 300 mg, 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suspension</td>
<td>60 mg/ml</td>
</tr>
<tr>
<td><strong>Vimpat® syrup</strong></td>
<td></td>
<td></td>
<td>Syrup</td>
<td>20 mg/ml (2000 mg/200 ml, 4650 mg/465 ml)</td>
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<tr>
<td><strong>Vimpat® solution for infusion</strong></td>
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<td></td>
<td>Solution for infusion (vial)</td>
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</tr>
<tr>
<td><strong>Trileptal®</strong></td>
<td>Oxcarbazepine</td>
<td>OXC</td>
<td>Tablets</td>
<td>150 mg, 300 mg, 600 mg</td>
</tr>
<tr>
<td><strong>Trileptal® Suspension</strong></td>
<td>Oxcarbazepine</td>
<td>OXC</td>
<td>Film-coated tablets</td>
<td>60 mg/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suspension</td>
<td></td>
</tr>
<tr>
<td><strong>Valiquid® 0.3</strong></td>
<td>Diazepam</td>
<td>DZP</td>
<td>Oral solution</td>
<td>10 mg/ml (30 drops=1 ml=10 mg)</td>
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<tr>
<td><strong>Valium®</strong></td>
<td>Diazepam</td>
<td>DZP</td>
<td>Tablets</td>
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<tr>
<td><strong>Valproat chrono DESITIN®</strong></td>
<td>Sodium valproate, valproic acid</td>
<td>VPA</td>
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<tr>
<td><strong>Timox® extent</strong></td>
<td>Oxcarbazepine</td>
<td>OXC</td>
<td>Tablets</td>
<td>200 mg quadro (quartered)</td>
</tr>
<tr>
<td><strong>Timox® suspension</strong></td>
<td>Oxcarbazepine</td>
<td>OXC</td>
<td>Tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Film-coated tablets</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Suspensión</td>
<td></td>
</tr>
<tr>
<td><strong>Zebinix®</strong></td>
<td>Eslicarbazepine acetate</td>
<td>ESL</td>
<td>Tablets</td>
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<tr>
<td><strong>Zentropil®</strong></td>
<td>Phenytoin</td>
<td>PHT</td>
<td>Tablets</td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Zonegran®</strong></td>
<td>Zonisamide</td>
<td>ZNS</td>
<td>Hard capsules</td>
<td>25 mg, 50 mg, 100 mg</td>
</tr>
</tbody>
</table>

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

Part 1
Information for parents whose children are being treated with valproate for the first time due to epilepsy
(Adapted from the recommendations of the Königsstein Study Group for Epileptology, March 2011)

Your doctor has prescribed valproate

(trade name: ____________________________)

to treat your child’s epilepsy. Valproate is generally well tolerated and severe side effects seldom occur. Your doctor has, however, informed you that severe side effects may appear during the first 6 months of valproate treatment in extremely rare cases. These side effects may affect the liver in particular and the pancreas or coagulation system less frequently. Your doctor has provided you with this information leaflet in order to recognise such side effects as early as possible. You are requested to contact your doctor if you have the least suspicion of medication-related intolerance, regardless of appointment dates. (After the first 6 months of treatment, severe valproate-induced side effects occur only in exceptional cases).
Appendix 1

Part 2

Obviously, such severe side effects will not occur in most cases. However, in those exceptional cases in which they do appear, they generally begin with non-characteristic clinical (visible) signs, i.e. you may notice changes in your child, which were not apparent prior to treatment. It is very important that you inform your doctor, as they do not see your child on a daily basis. If you are unclear as to the nature, extent and cause of the change in your child, please do not hesitate to telephone your doctor to pass on your observations and, if needed, to arrange an appointment in the near future.
Appendix 1

Part 3
Please pay particular attention to the following potential changes in your child over the next 6 months:

- Loss of appetite, nausea, vomiting and stomach ache
- Fatigue/lethargy
- Increase in the incidence or severity of the epileptic seizures
- Tendency to haemorrhage (bruise, nose bleeds)
- Swelling (legs and eyelids)
- Yellow colouration of the skin
Appendix 1

If you notice one or more of these changes in your child, they are not always indicative of intolerance towards valproate. Numerous, transient, healthrelated disorders occur that are associated with these or similar clinical signs.

However, as the changes may be the first signs of valproate intolerance, you must contact your treating doctor immediately. They will then discuss the next key step with you. Contact to your doctor (test for blood coagulation) is also advisable if your child is about to undergo surgery (e.g., removal of the tonsils, appendectomy).
### Appendix 2
Interactions of antiepileptic drugs
(Modified according to Krämer)

<table>
<thead>
<tr>
<th>Addition of</th>
<th>Effect on persistent therapy</th>
<th>Effect on persistent therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRV</td>
<td>CBZ</td>
</tr>
<tr>
<td>Brivaracetam (BRV)</td>
<td>x</td>
<td>E+</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>(+)</td>
<td>x</td>
</tr>
<tr>
<td>Clobazam (CLB)</td>
<td>+/-(E+)</td>
<td>x</td>
</tr>
<tr>
<td>Eslicarbazepine (ESL)</td>
<td>O/(+)</td>
<td>O/(−)</td>
</tr>
<tr>
<td>Ethosuximide (ESM)</td>
<td>x</td>
<td>O</td>
</tr>
<tr>
<td>Feltbamate (FBM)</td>
<td>-(E+)</td>
<td>x</td>
</tr>
<tr>
<td>Gabapentin (GBP)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lamotrigine (LTG)</td>
<td>O</td>
<td>O/(+)</td>
</tr>
<tr>
<td>Levetiracetam (LEV)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Mesuximide (MSM)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oxicarbazepine (OXC)</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Perampanel (PER)</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Phenobarbital (PB)</td>
<td>(E+)</td>
<td>x</td>
</tr>
<tr>
<td>Phenytoin (PHT)</td>
<td>(E+)</td>
<td>x</td>
</tr>
<tr>
<td>Pregabalin (PGB)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primidone (PRM)</td>
<td>-(E+)</td>
<td>x</td>
</tr>
<tr>
<td>Rufinamide (RUF)</td>
<td>x</td>
<td>O</td>
</tr>
<tr>
<td>Stiripentol (STP)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Tiagabine (TGB)</td>
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<td>0</td>
</tr>
<tr>
<td>Sulthiam (STM)</td>
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<td>+</td>
</tr>
<tr>
<td>Topiramate (TPM)</td>
<td>0</td>
<td>O/(−)</td>
</tr>
<tr>
<td>Vigabatrine (VGB)</td>
<td>(+)</td>
<td>O/(−)</td>
</tr>
<tr>
<td>Zonisamide (ZNS)</td>
<td>O/(−)</td>
<td>O</td>
</tr>
</tbody>
</table>

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.Licensed for generalized tonic-clonic seizures in idiopathic generalized epilepsy and myoclonic seizures in juvenile myoclonic epilepsy.
2.Licensed in combination with VPA and CBZ.
3. After failure of other medication.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbr.</th>
<th>Approved Indications</th>
<th>Approved Indications</th>
<th>Interaction potential</th>
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<tr>
<td></td>
<td></td>
<td>Focal and secondary</td>
<td>Generalized seizures</td>
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<td></td>
<td>seizures</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Monotherapy</td>
<td>Combination therapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Monotherapy</td>
<td>Combination therapy</td>
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</tr>
<tr>
<td>Bromide</td>
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<td>Yes</td>
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<td>CBZ</td>
<td>Yes</td>
<td>Yes</td>
<td>GTCS</td>
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<tr>
<td>Clobazam</td>
<td>CLB</td>
<td>No</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Brivaracetam</td>
<td>BRV</td>
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<td>As of 16 Y</td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>ESL</td>
<td>No</td>
<td>As of 16 Y</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>ESM</td>
<td>No</td>
<td>Yes</td>
<td>Absences, myoclonic seizures (-)</td>
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<td>FBM</td>
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<td>No</td>
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<td>Gabapentin</td>
<td>GBP</td>
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<td>No</td>
<td>As of 12 Y</td>
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<td>LCM</td>
<td>As of 16 Y</td>
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<td>As of 2 Y</td>
<td>LGS as of 2</td>
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<td>As of 1 M</td>
<td>JME as of 12 Y</td>
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<td>As of 12 Y 4</td>
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<td>PRM</td>
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</tr>
<tr>
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<td>OXC</td>
<td>As of 6 Y</td>
<td>As of 6 Y</td>
<td></td>
</tr>
<tr>
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<td>No</td>
<td>As of 12 Y</td>
<td></td>
</tr>
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<td>Phenytoin</td>
<td>PHT</td>
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<td>Yes</td>
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<td>Pregabalin</td>
<td>PGB</td>
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<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Rufinamide 3</td>
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<td>No</td>
<td>LGS as of 4 Y</td>
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<td>Stipirventol</td>
<td>STP</td>
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<td>No</td>
<td>Dravet Syndrome 2</td>
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<td>Sulthiam</td>
<td>STM</td>
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<td>TPM</td>
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<td>VPA</td>
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<td>ZNS</td>
<td>No</td>
<td>As of 16 Y</td>
<td></td>
</tr>
</tbody>
</table>

- no interaction potential

(-) low interaction potential

(+) medium interaction potential

(+) strong interaction potential
Appendix 2

Special license requirements in Germany
Date: January 2017

Brivaracetam
Add-on treatment in patients aged 16 years and older with focal epileptic seizures with or without secondary generalisation.

Eslicarbazepine acetate
Add-on treatment in patients aged 6 years and older with partial epileptic seizures with or without secondary generalisation.

Felbamate
For combination treatment of adults and children aged 4 years and older with LGS with inadequate treatment response to all relevant currently available antiepileptic drugs. (FBM is not the treatment of first choice in epilepsy.) Contraindication: elderly patients (over 65 years of age), children under 4 years of age. Licensed from the age of 4 years.

Gabapentin
Monotherapy (including first-line therapy) or add-on therapy in patients over 12 years of age with simple and complex partial seizures with and without secondary generalisation. Add-on treatment in patients aged 6 years and older with partial seizures with and without secondary generalisation. Licensed from the age of 12 years (film-coated tablets)/as of 3 years (capsules).
Appendix 2

**Lamotrigine**
Monotherapy for adults and children as of 12 years. Add-on treatment in drug-resistant epilepsy in adults and children aged 12 years and older. Add-on treatment in drug-resistant epilepsy as well as in LGS in children aged 2-11 years refractory to treatment.

**Lacosamide**
Monotherapy and add-on treatment of focal seizures with or without secondary generalisation in epileptic patients from the age of 16 years. I.v. administration of LCM is approved for patients who are temporarily unable to take LCM orally.

**Levetiracetam**
Monotherapy: partial seizures with or without secondary generalisation in patients aged 16 years and older with recently diagnosed epilepsy. As add-on treatment for partial seizures with or without secondary generalisation in adults and children as well as infants aged 1 month and older, as well as for myoclonic seizures in adults and adolescents aged 12 years and older with juvenile myoclonic epilepsy.
In Austria licensed as "Levebon" for monotherapy of focal seizures in patients aged 1 month and older as well as for idiopathic generalized epilepsy for patients aged 12 years and older.
Appendix 2

Oxcarbazepine
Epilepsy: focal seizures with or without secondary generalised tonic-clonic seizures in mono- and combination therapy in adults and children aged 6 years and older. In Switzerland, OXC has also been licensed for use in infants aged 1 month and older since 1st February 2006.

Perampanel
Add-on treatment for focal and secondary generalized seizures from 12 years of age.

Tiagabine
As add-on treatment of partial seizures with and without secondary generalisation in patients in whom treatment with other antiepileptic drugs has proved inadequate. Contraindication: Children under 12 years of age. Licensed from the age of 12 years.

Topiramate
As monotherapy in adults and children aged 2 years and older with recently diagnosed epilepsy or when switching to monotherapy. As add-on treatment in adults and children with focal epileptic seizures with and without secondary generalisation, primary generalised tonic-clonic seizures, and epileptic seizures in LGS. Contraindication: Children under 2 years of age (insufficient clinical experience).
Appendix 2

Vigabatrine
In combination with other antiepileptic drugs for the treatment of patients with drug-resistant focal seizures with and without secondary generalisation for whom all other adequate drug combinations have proven insufficiently effective or intolerable. As monotherapy for the treatment of infantile spasms (West syndrome).

Zonisamide
For monotherapy of epilepsy with partial seizures with and without secondary generalisation in newly diagnosed epilepsy in adults. As add-on treatment of partial seizures with and without secondary generalisation in patients of 6 years and older.
Appendix 2

Note

In a large proportion of cases, antiepileptic drugs are used outside of their indication (so-called "off-label" use). It is therefore urgently recommended that parents/caregivers are given detailed information about the risks of treatment, that this is documented in writing and that they are asked to confirm this with their signature.

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### Antiepileptic drug abbreviations

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>AZA</td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>BRV</td>
</tr>
<tr>
<td>Bromide</td>
<td>CBR</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>CBZ</td>
</tr>
<tr>
<td>Clobazam</td>
<td>CLB</td>
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<td>Eslicarbazepine acetate</td>
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<td>Ethosuximide</td>
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<td>Felbamate</td>
<td>FBM</td>
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<td>PER</td>
</tr>
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<td>Phenobarbital</td>
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</tr>
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</tr>
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<td>Pregabalin</td>
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<td>Primidone</td>
<td>PRM</td>
</tr>
<tr>
<td>Rufinamide</td>
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<td>Stiripentol</td>
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<td>Sulthiam</td>
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<td>Tiagabine</td>
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<td>Topiramate</td>
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