NEURONEWS
The Neurology Portal

EXCLUSIVE INTERVIEW

Current issue, Volume 11, August 2012 www.NeuroNews.eu ISSN 1864-6095

Levetiracetam for the treatment of epilepsy in children

Levetiracetam DESITIN® minitablets*) – small tablets for small patients

The current guidelines of the German Society of Neurology (DGN) explicitly recommend the anticonvulsive agent levetiracetam – in addition to lamotrigine – as the agent of first choice for initial treatment of focal seizures with or without secondary generalisation from the age of 16 years onward. Furthermore, levetiracetam is indicated for additional treatment of myoclonic seizures in adults and adolescents from the age of 12 years onward with juvenile myoclonic epilepsy or primary generalised tonic-clonic seizures with idiopathic generalised epilepsy. However, for a long time the drug was not authorised for use in young children. In 2004 levetiracetam was approved in Germany for additional treatment of focal seizures in children from the age of 4 years onward. In 2010 the agent was approved for additional treatment of focal seizures in children from the age of 1 month onward. Experts unanimously agreed that this therapy option has decisively improved the treatment of epilepsy in very young patients.

Levetiracetam DESITIN minitablets*), containing a new levetiracetam preparation with special galenics, are available from May 2011 onward for the treatment of epilepsy. Levetiracetam DESITIN® is available in different dosage strengths. Each of these is marked on the package in a different colour. The diversity of dosage strengths, the small size of the minitablets, and the corresponding child-friendly packaging of the drug have all helped to improve compliance in epilepsy patients.

? Dr. Bast, together with Prof. Dr. med. Gerhard Kurlemann, president of the convention of this year's GNP meeting in Münster, and the epilepsy expert Prof. Dr. Florian Heinen, you held interesting lectures for the attendees of the congress at the satellite symposium „Epilepsy therapy today – what experts recommend", which was supported by Desitin Company. What opportunities do the GNP meeting and the symposium offer, in your opinion?

! This year's meeting of the Society of Neuropaediatrics is an international German-language convention of incredible diversity. I believe this is a very special advantage. The attendees include, in addition to epilepsy specialists, paediatric neurologists working in various sub-specialities. Therefore, most recent information concerning the evolution of epilepsy treatment, such as that presented at the Desitin symposium, will be received by a wide range of experts.

Gesellschaft für Neuropädiatrie
Die Neurologie des Kindes und Jugendlichen

38th Annual Meeting of the Society of Neuropaediatrics 19 – 22 April 2012, Münster, Germany

Photo: Halle Münsterland GmbH

The Annual Meeting of the Society of Neuropaediatrics was held in the „Messe- und Congress-Centrum" in Münster, Germany, from 19 – 22 April 2012.

Photo: private

Interview with PD Dr. med. Thomas Bast, chief physician at the Clinic for Children and Adolescents, Epilepsy Centre Kork, Kehl-Kork, Germany, about levetiracetam therapy in children and the advantages of Levetiracetam minitablets) from Desitin Arzneimittel in Hamburg, Germany.*

*) minitablet = approved administrative form Levetiracetam DESITIN® film-coated granules in sachets

? For many years now, the anticonvulsive agent levetiracetam has been an effective drug for the treatment of epilepsy. What is the spectrum of indications for levetiracetam in adults and children?

! Levetiracetam is indicated as monotherapy for partial seizures with or without secondary generalisation from the age of 16 years onward, for additional treatment of partial seizures with or without secondary generalisation from the age of 1 month onward in patients with epilepsy, for additional treatment of myoclonic seizures in adults and adolescents from the age of 12 years with juvenile myoclonic epilepsy, and for additional treatment of primary generalised tonic-clonic seizures in adults and adolescents from the age of 12 years with idiopathic generalised epilepsy.

? Are there any special practical aspects that favour the use of levetiracetam in children with epilepsy? In what way does levetiracetam differ from other antiepileptic agents?

! Levetiracetam differs from other antiepileptic agents primarily in terms of its special properties. It is not merely very effective; its efficacy can also be assessed rapidly. Furthermore, levetiracetam is nearly devoid of any interaction, has ideal pharmacokinetics, and is a safe drug. Throughout the world, severe organic side effects were found to occur very rarely under levetiracetam therapy.

? In 2004 levetiracetam was approved in Germany for additional treatment of focal epilepsies in children from the age of 4 years onward. The long awaited approval for additional treatment of focal seizures in children from the age of 1 month onward was issued in 2010. What is your opinion about this decision and the fact that even infants can now be treated with levetiracetam?

! Personally I think it is wonderful that levetiracetam is now approved for the treatment of children from the age of 1 month onward. Especially for this age group of very young patients we need modern and effective therapies with a very low side-effect profile. Levetiracetam is the first of the new antiepileptic agents that has been investigated in infants and has been approved for the youngest of epilepsy patients. This is an enormous step forward for all of us – for young patients and their parents as well as physicians.

? What is your view about the tolerability of levetiracetam in children? Is there a difference compared to adults with epilepsy who are treated with levetiracetam?

! With regard to potential organic side effects, levetiracetam is one of the safest drugs we have for children and adults. Severe organic side effects occur in just isolated cases among adults. We have no reports of such effects in children. As regards the psychotropic effects of levetiracetam therapy, which may well be a problematic aspect, we find a certain difference between adults and children. Patients undergoing treatment with levetiracetam may demonstrate aggressive behaviour. Adults are usually more controlled and sometimes more active in this regard, whereas children express such behaviour immediately. Therefore, aggression is a more relevant side effect in this age group.

? Have you had any experience at your medical office as regards the occurrence of behavioural problems in children undergoing treatment with levetiracetam? If yes, how frequently does this occur and at what age? Is it possible to prevent behavioural problems associated with levetiracetam or to counteract these if necessary?

! Yes, in my own paediatric population about 10 to 15 percent of children react in terms of aggression, agitation, or sleep disorders. Our own experience concurs with published data in this regard. Aggressive behaviour under levetiracetam therapy may occur at any age. Actually younger children appear to tolerate levetiracetam somewhat better than older patients. A special risk group are mentally retarded persons who demonstrate aggressive behaviour, or have other psychiatric comorbidities. In very young children, behavioural problems like aggression are most commonly manifested as sleep disorders, difficulty to ingest fluids, and/or screaming episodes. Parents are able to sense whether their child tolerates a drug or not. It

> ***"Levetiracetam DESITIN® minitablets*) are a really new alternative for the treatment of children with epilepsy."***

is important for us doctors to take parents very seriously and treat them as our partners in the treatment process. Currently, however, we have no effective means of treating such potential aggression. I think the provision of thorough information is the most important aspect. Then, of course, one must observe the children carefully and exactly, especially when they have special risk factors for behavioural problems. The only really effective means of controlling aggression, in my opinion, is to terminate the treatment. I do not think that the occurrence of behavioural problems under levetiracetam is a dose-dependent effect. There are anecdotal reports about the effectiveness of administering vitamin B6. This may be recommended. The body of data on this subject is meagre and insufficient.

? Are there differences between children and adults as regards the pharmacokinetics of levetiracetam?

*) minitablet = approved administrative form Levetiracetam DESITIN® film-coated granules in sachets

! Differences between children and adults exist especially with regard to the elimination of levetiracetam. Renal clearance appears to be markedly more rapid, especially in young children than in adults. Therefore, theoretically one would require other doses to achieve the same levels of the active substance. However, it should be mentioned that blood levels of the active substance are hardly correlated with its efficacy and tolerance. These effects are therefore negligible. The dosage of levetiracetam depends on one's needs in relation to body weight.

? Levetiracetam DESITIN® minitablets*) – a new levetiracetam drug with special galenics – is available since May 2011 for the treatment of epilepsy. What, in your opinion, are the advantages of this pharmaceutical form for the treatment of children with epilepsy?

! The principal advantage is definitely the fact that levetiracetam minitablets*) constitute a further alternative in terms of drug administration because some children are very „unique" as regards the intake of tablets. Some patients are unable to swallow certain tablets whereas others do not wish to take them and/or their parents are looking for new alternatives every now and then. A juice is also not everybody's cup of tea. Besides, one is sometimes a little uncertain as regards the ingested dose of a drug in children. The minitablets constitute a really new alternative in this regard. The minitablets can be easily concealed in a spoon when feeding a child. A further advantage is the fact that levetiracetam minitablets*) are available in various doses so that the individual dose need not be achieved by dividing the tablet in halves or quarters. Summarised briefly one could say: small tablets for small patients.

? Can you provide more exact data about the dosage of, and the speed of dosing Levetiracetam DESITIN® in children? Does an upper dose limit exist?

! How rapidly one can dose levetiracetam depends on the respective situation. In an emergency one may administer 20 to 30 mg of levetiracetam per kilogramme body weight. Higher starting doses, believed to be tolerated well, have been reported in the published literature. Usually, however, we start with 5 to 10 mg per kilogramme body weight per day, and increase the dose every 3 to 4 days by the same gradient until we achieve 30 to 40 mg per kilogramme body weight per day. If necessary, one may then further increase the dose to 60 mg per kilogramme body weight per day. Much higher doses have been reported in the published literature; we also have used these doses. Personally I don't see any problem here as regards tolerance. A few patients appear to benefit from levetiracetam only when it is administered at these unusually high doses.

? How high do you rate compliance – or adherence as one calls it today – in the treatment of children with epilepsy? Do you think Desitin Company has succeeded in achieving best possible compliance in children by manufacturing the special pharmaceutical form of Levetiracetam DESITIN® minitablets*) or Levetiracetam DESITIN® coated granules in sachets?

! Epilepsy therapy does not work without compliance or adherence. After all, we need to implement the doctor's recommendations. I find parents very reliable once they have been informed well and are convinced of the treatment. In contrast to adults, when treating children we always have parents as a controlling factor. However, even consistent continuation of drug therapy must be actually implemented, and may be quite difficult especially in young and/or disabled children. The minitablets provide us with an additional alternative that looks child-friendly and is also perceived as such. In fact, today paediatrics in Germany is not conceivable without another drug of Desitin Company, the antiepileptic agent Orfiril® long, and its small sustained-release minitablets. Orfiril® long is also well accepted. I think our experience in respect of Levetiracetam DESITIN® minitablets*) has been similar so far.

? Levetiracetam DESITIN® is available in different dosage strengths. Each of these is marked on the package in a different colour. What are the advantages of these special features for patients – children and parents?

! Of course the colours help to clearly mark the strengths of the drug so that the risk of error is minimised. The most important advantage, however, is that children become familiar with their drug, are able to identify it, and thus establish a close relationship with it. Identification by means of animals or colours contributes to better compliance as well. Besides, the minitablets protect patients from substitution at the pharmacy.

Dr. Bast, thank you very much for this interview.

The interview was conducted by MD Susanne Schweizer on behalf of NeuroNews at the 38th Annual Meeting of the Society of Neuropaediatrics on April 20, 2012 in Münster, Germany.

*) minitablet = approved administrative form Levetiracetam DESITIN® film-coated granules in sachets

Impressum

The Neurology-Portal
NEURONEWS
www.NeuroNews.eu

Editorship for special publications:
Susanne Schweizer, MD

Publication in the Internet available:
www.NeuroNews.eu/media/doc/Interview_DrBast_eng_2012.pdf

Managing director: Beate Döring

Publishing house:
MedienCompany GmbH
Medizin-Medienverlag
Weitseestr. 5
83242 Reit im Winkl
GERMANY

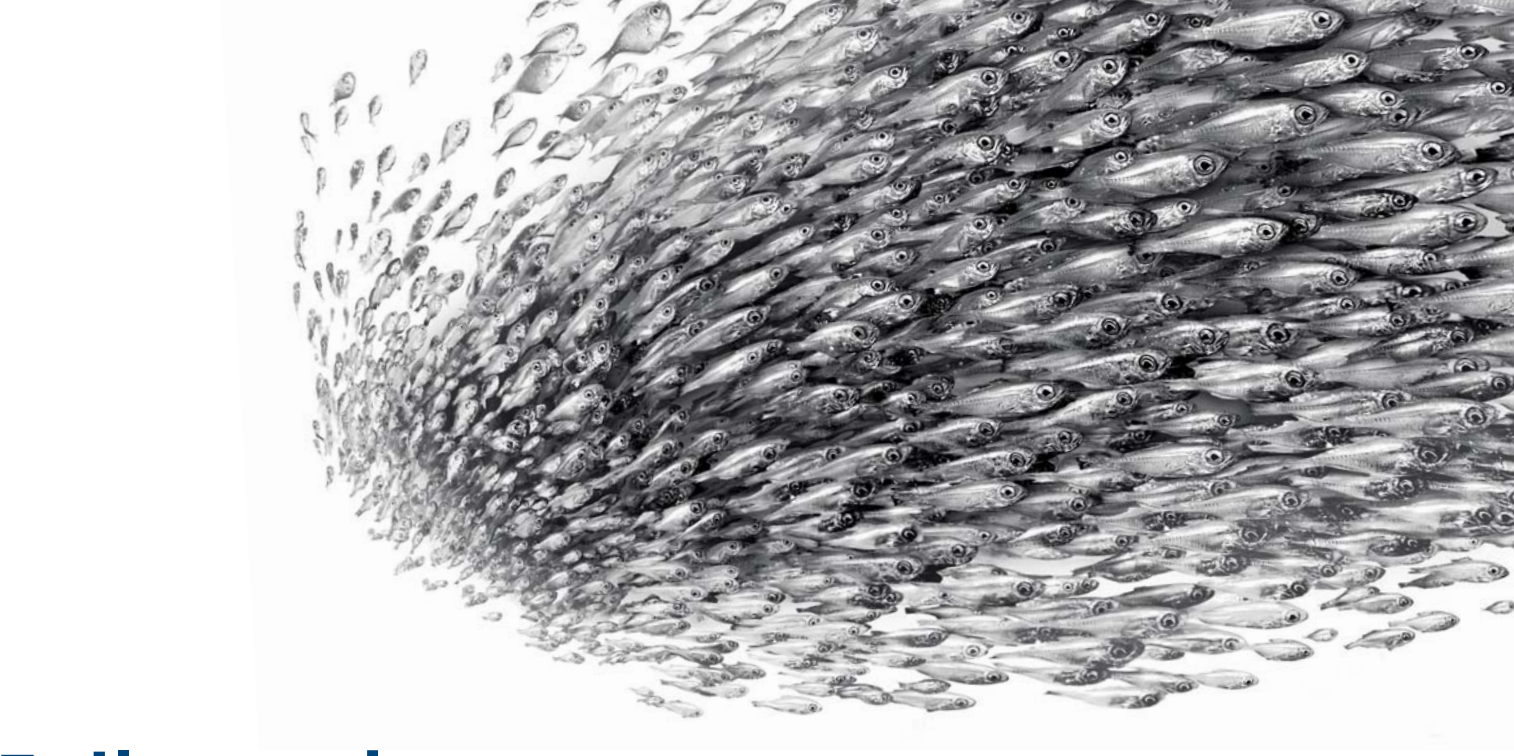
Phone: ++49-(0)8640 – 797 801
Fax: ++49-(0)8640 – 797 804
Internet: www.mediencompany.de
www.medizin-medienverlag.de

E-Mail: info@mediencompany.de

Printed in Germany

© 2012 • Medizin-Medienverlag
Reit im Winkl / Munich

ISSN-Nr. 1864-6095 (Print)



Epilepsy therapy in an intelligent form.

Made in Germany

Levetiracetam minitablets* – it's the small things that make the big difference.

- Innovative preparation
- Intake independent from meals
- Handy even when on the go
- Simple feeding tube application with prior suspension[1]

Levetiracetam DESITIN®

*minitablet = approved administrative form Levetiracetam DESITIN® film-coated granules in sachets

[1] Desitin; Internal Tests on Usability in Feeding Tubes (2010)

Levetiracetam DESITIN® 250 / 500 / 1000 mg coated granules in sachet
Active substance: Levetiracetam. **Legal category: POM.** Please consult your local product information for full details, as prescribing information may vary from country to country. **Qualitative and quantitative composition:** 1 sachet with coated granules contains 250 / 500/ 1000 mg levetiracetam. **Excipients:** povidone K30, cellulose, microcrystalline, silica, colloidal anhydrous, magnesium stearate, poly(vinyl alcohol), titanium dioxide (E 171), macrogol 3350, talc. **Therapeutic indications:** Monotherapy of partial seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy of partial seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy. Adjunctive therapy of myoclonic seizures in patients from 12 years of age with Juvenile Myoclonic Epilepsy. Adjunctive therapy of primary generalised tonic-clonic seizures in patients from 12 years of age with Idiopathic Generalised Epilepsy. **Contraindications:** Hypersensitivity to levetiracetam, to other pyrrolidone derivatives or to any of the excipients. Infants and children under the age of 6 years (levetiracetam oral solution is the preferred formulation for use). **Special warnings and precautions for use:** Patients with renal or severe hepatic dysfunction may require dose adjustment. Discontinue gradually (see SmPC). Although available data in children do not suggest impact on growth and puberty, long term effects remain unknown. The safety and efficacy of levetiracetam has not been thoroughly assessed in infants with epilepsy aged less than 1 year. Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam). A meta-analysis of placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. Patients should be monitored for respective signs and appropriate treatment should be considered. *Ability to drive/reaction:* Reaction time may be impaired. *Pregnancy/lactation:* Use during pregnancy, lactation and in women of childbearing potential without contraception is not recommended unless clearly necessary. Levetiracetam plasma levels decrease during pregnancy, particularly in the third trimester. **Side effects:** *Very common:* Nasopharyngitis, somnolence, headache. *Common:* convulsion, dizziness, vertigo, lethargy, tremor, impaired balance, depression, hostility/aggression, anxiety, insomnia, nervousness/irritability, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, anorexia (increased risk when coadministered with topiramate), rash, cough, asthenia/fatigue. *Uncommon:* thrombozyto-/leucopenia, weight increase or decrease, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour, hallucination, anger, confusion, emotional lability/mood swings, agitation, amnesia, memory impairment, coordination abnormal/ataxia, paraesthesia, disturbance in attention, diplopia, blurred vision, abnormal liver function test, alopecia (in several cases recovery of hair loss was observed after discontinuation of levetiracetam), eczema, pruritus, muscular weakness, myalgia, injury. *Rare:* infection, completed suicide, personality disorder, thinking abnormal, choreoathetosis, dyskinesia, hyperkinesia, pancreatitis, hepatic failure, hepatitis, neutro-, pancytopenia (bone marrow suppression identified in some of the cases), toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme. Side effects occurring more frequently than in other age groups: children and adolescents between 4 and 16 years: *Very common:* vomiting. *Common:* agitation, emotional lability, mood swings, aggression, abnormal behaviour, lethargy. Infants and children between 1 month and 4 years of age: *Very common:* irritability. *Common:* coordination abnormal. **Further details and warnings:** See Information for Healthcare Professionals and Package Leaflet. Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany, www.desitinpharma.com **May 2012**

www.desitinpharma.com

DESITIN
SUCCESS IN CNS

Orfiril® long 150 mg, 300 mg, 500 mg, 1000 mg

Active substance: Sodium valproate.

Legal category: POM.

Please consult your local product information for full details, as prescribing information may vary from country to country.

Qualitative and quantitative composition: 1 prolonged release capsule, hard Orfiril® long 150/300 mg contains 150/300 mg sodium valproate. 1 single dose (sachet) with prolonged-release minitablets Orfiril® long 500/1000 mg contains 500/1000 mg sodium valproate.

Excipients: Orfiril® long 150/300/500/1000 mg: calcium stearate (Eur. Ph.), ethyl cellulose, silicon dioxide (methylated), ammonium methacrylate copolymer (type B), sodium dodecylsulphate, polysorbate 80, oleic acid, dibutyldecandioate; Orfiril® long 150/300 mg also gelatine, indigocarmine (E132), Orfiril® long 300 mg also quinoline yellow (E 104).

Therapeutic indications: Generalised seizures (absence seizures, myoclonic and tonic-clonic seizures), partial and secondary generalised seizures. For combination therapy in other forms of seizure when the latter fail to respond to usual antiepileptic treatment. For treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania. N.B.: In infants, valproate is the medication of choice only in exceptional circumstances (greater caution, strict weighing of benefit-risk ratio; as monotherapy where possible).

Contraindications: Hypersensitivity to valproate or to any of the excipients, liver disease in personal or family medical history, severe current dysfunction of the liver or pancreas, impaired liver function with fatal outcome during valproic acid treatment in siblings, porphyria, blood coagulation disorders.

Special warnings and precautions for use: Use with special care in: infants receiving at the same time treatment with several antiepileptics, children/juveniles with multiple disabilities and severe forms of seizures, bone marrow damage (close monitoring required), kidney failure or hypoproteinemia (may require dose reduction), metabolic disorders, particularly congenital enzyme deficiency diseases, systemic lupus erythematosus. If symptoms of hyperammonaemia occur plasma levels of ammonium and valproate should be determined and the dose reduced if necessary. If non-dose-dependent side effects occur the drug should be discontinued. Prior to surgical or dental procedures and in coadministration with vitamin A antagonists coagulation values should be determined. Patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Regular physical and laboratory examinations required. Patients should be closely monitored for early signs of liver damage and signs requiring immediate discontinuation of sodium valproate. Particularly at the start of treatment liver enzymes may be increased without any liver damage. In case of weight increase suitable measures of weight control should be performed. Discontinuation of treatment or change-over to another antiepileptic treatment must be carried out gradually and with particular caution. Concomitant use of valproate and carbapenems is not recommended. In vitro stimulating effect of valproate on HI virus replication should be considered. *Ability to drive/reaction*: Reaction time may be impaired. *Pregnancy/lactation*: Women of childbearing age should be informed of the need to plan and monitor pregnancies before starting treatment and have to use effective contraception during treatment. Increased rate of mild or moderate deformities. Particularly on exposure during 1st and early 2nd trimester, increased risk of neural tube defects (e.g. spina bifida, meningomyelocele), other midline defects (e.g. hypospadia), deformities of the extremities, cardiovascular deformities and multiple deformities involving various organ systems. Furthermore, bilateral aplasia of the radius and an increase in other malformations (e.g. facial dysmorphia, also associated with mental retardation, digital and nail deformities) have been observed, as well as a foetal antiepileptic syndrome and autistic disorders. Valproate can delay foetal development (particularly of verbal IQ). Administer in the lowest seizure-controlling dose and, wherever possible, as monotherapy. Folic acid supplementation and prenatal diagnostic measures as well as regular monitoring of valproate plasma concentration recommended. Risks in newborn infants: blood coagulation disorders, hypofibrinogenaemia (blood platelets, fibrinogen and coagulation factors must be checked regularly). Withdrawal syndrome possible in newborn infants. Breast-feeding is allowed. Manic episode in bipolar disorder additionally: Valproate should not be used in pregnant women or women of childbearing age unless clearly necessary.

Side effects: *Very common*: moderately marked hyperammonaemia with no change in liver function values. *Common*: thrombopenia and leucopoenia (often reversible while treatment continues, but always reversible after discontinuation), weight gain or weight loss, increased appetite/loss of appetite, drowsiness, sleepiness, tremor, paraesthesia, transient hair loss (regrowing hair may become more curly than previously), hair fading, increased liver enzymes. *Uncommon*: hypersalivation, diarrhoea, peripheral oedema, haemorrhage, headaches, spasticity, ataxia, excitability, hyperactivity, stupor up to transient coma, sometimes associated with increased seizure frequency (usually developing during combination therapy [particularly with phenobarbital] or following a rapid dose increase; reversible after dose reduction/discontinuation), encephalopathy occuring shortly after therapy onset (reversible after discontinuation, in a few cases associated with increased ammonia levels and, on combination with phenobarbital, an increase in phenobarbital levels), non-dose-dependent severe (sometimes fatal) liver dysfunction (markedly increased risk in children, particularly if other antiepileptics are being taken concomitantly). Especially at the start of treatment: nausea, stomachache (usually reversible after a few days), confusion. *Rare*: amenorrhoea, elevated testosterone levels, polycystic ovaries, reversible (after discontinuation) Fanconi's syndrome (metabolic acidosis, phosphaturia, aminoaciduria, glucosuria), hyperinsulinaemia, decreased levels of insulin-like growth factor binding protein (IGFBP), exanthema, multiform erythema, lupus erythematosus, vasculitis, chronic encephalopathies with neurological symptoms and impairment of higher cortical functions (especially at higher dosages or in combination therapy with other anti-epileptics), pancreatic damage (sometimes with a fatal outcome), hypothermia. *Very rare*: hyponatraemia, during long-term therapy with other antiepileptics, especially phenytoin: encephalopathy (increased number of convulsions, lack of drive, stupor, muscular hypotension, choreiform dyskinesias, severe general EEG changes), impaired bone marrow function (may lead to lympho-, neutro- or pancytopenia or anaemia). *Frequency not known*: dementia accompanied by cerebral atrophy (reversible on discontinuation), transient/persistent hearing loss, severe skin reactions (Stevens-Johnson syndrome, Lyell's syndrome), decreased concentration of fibrinogen and/or factor VIII, inhibition of the secondary phase of platelet aggregation (prolonged bleeding time), sedation, reversible extrapyramidal symptoms (e.g. parkinsonism), tinnitus, hallucinations, enuresis in children, allergic reactions, drug rash with eosinophilia and systemic symptoms (DRESS syndrome), change in thyroid function parameters, osteoporosis, eosinophilic pleural effusion, syndrome of inappropriate antidiuretic hormone secretion (SIADH). *Signs of liver and possibly pancreatic damage*: reduced antiepileptic effect (recurrence or increase in epileptic seizures), physical weakness, partial apathy, loss of appetite, nausea or repeated vomiting, upper abdominal symptoms of unclear origin, oedema, impaired consciousness with confusion, unrest or motor disorder. Babies and infants in particular should be closely monitored for these signs. Appropriate laboratory tests must be carried out in addition to a thorough medical examination if any of the afore-mentioned symptoms persist or are severe.

Further details and warnings: See Information for Healthcare Professionals and Package Leaflet.

Desitin Arzneimittel GmbH, Weg beim Jäger 214, 22335 Hamburg, Germany, www.desitinpharma.com

April 2011