תאריך: 11.2020

רופא /ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלונים לרופא ולצרכן של התכשירים:

Gabapentin Teva 600 & 800 mg Tablets

גאבאפנטין טבע 600 ו- 800 מ״ג טבליות

Contains: Gabapentin 600 mg/ 800 mg

עדכונים בעלונים לרופא ולצרכן

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Epilepsy :
- Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents (age 12 and up) with epilepsy.
- Treatment of neuropathic pain
- Gabapentin is indicated for the treatment of neuropathic pain in diabetic neuropathy or postherpetic neuropathy (neuralgia) in adults.

<u>ברצוננו להודיע שהעלון לרופא עודכן. בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):</u>

הושמטה התייחסות לכמוסות גאבאפנטין טבע בחוזקים של 300 ו- 400 מ״ג.

<u>4.1 Therapeutic Indications</u>

Epilepsy

Gabapentin Teva is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents (age 12 and up) with epilepsy.

Neuropathic Pain

Gabapentin Teva is ~~also~~ indicated for the treatment of neuropathic pain in diabetic neuropathy or post herpetic neuropathy (neuralgia) in adults.

<u>4.2 Posology and method of administration</u>
<u>~~Dosage and Administration~~</u>

~~Gabapentin is given orally with or without food.~~

<u>Posology</u>

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above.

Table 1		
DOSING CHART - INITIAL TITRATION		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Epilepsy

~~Gabapentin Teva is recommended for add-on therapy in patients over 12 years of age. Evidence bearing on its safety and effectiveness in children is not available.~~

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.

When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution with an alternative medication, this should be done gradually over a minimum of one week.

Adults and ~~pediatric patients over 12 years of age~~ adolescents:

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1~~, or by titrating the dose as described in the Table~~. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days ~~three equally divided doses~~ up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies, the maximum time interval between doses ~~in the three times a day (TID) schedule~~ should not exceed 12 hours to prevent breakthrough convulsions.

~~Dosing Chart - Initial Titration~~			
~~Dose~~	~~Day 1~~	~~Day 2~~	~~Day 3~~
~~900mg~~	~~300 mg QDa~~	~~300 mgBID b~~	~~300 mg TID c~~

~~a QD = once a day~~

~~b BID = two times a day~~

~~c TID = three times a day~~

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic drugs without concern for alteration of the plasma concentrations of ~~gabapentin or serum concentrations of~~ other antiepileptic drugs.

Neuropathic Pain

~~Peripheral neuropathic pain~~

Adults ~~(over the age of 18)~~

~~Gabapentin should be titrated to a maximum dose of 1800 mg per day.~~

~~Titration~~

~~to an effective dose can progress rapidly and can be accomplished over a few days by administering 300 mg once a day on day 1, 300mg twice a day on day 2 and 300 mg three times a day on day 3, as described in the following table.~~

~~DOSING CHART - INITIAL TITRATION~~			
~~Dose~~	~~Day 1~~	~~Day 2~~	~~Day 3~~
~~900mg~~	~~300mg~~ ~~once a day~~	~~300mg~~ ~~two times a day~~	~~300mg~~ ~~three times a day~~

~~Thereafter, the dose can be increased using increments of 300 mg per day given in three divided doses to a maximum of 1800 mg per day. It is not necessary to divide the doses equally when titrating gabapentin.~~

~~It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy.~~

~~The maximum time between doses in a three times daily schedule should not exceed 12 hours. Gabapentin may be given orally with or without food.~~

~~If gabapentin is discontinued, or the dose reduced or substituted with an alternative medication, this should be done gradually over a minimum of one week.~~

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and postherpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age. (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

~~Dosage adjustment in impaired renal function for patients with epilepsy:~~ Use in patients with renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing hemodialysis.

Table 2

Dosage of Gabapentin in Adults Based on Renal Function

Creatinine Clearance (mL/min)	Total Daily Dose[a] (mg/day)
~~≥~~ >80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b]-600
< 15 [c]	150[b]-300

a Total daily dose should be administered ~~as a TID regimen~~ as three divided doses. ~~Doses used to treat patients with normal renal function (creatinine clearance >80 mL/min) range from 900 to 3600 mg/day.~~ Reduced dosages are for patients with renal impairment (creatinine clearance < 79 mL/min).

b To be administered as 300 mg every other day.

c For patients with creatinine clearance <15 mL/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

~~Dosage adjustment~~ Use in patients undergoing hemodialysis:

For patients undergoing hemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg ~~is recommended~~, then 200 to 300 mg of gabapentin following each 4 hours of hemodialysis is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

~~Dosage and~~ Method of Administration

~~Gabapentin is given orally~~

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid-intake (e.g. a glass of water).

4.4 Special warnings and precautions for use

~~General~~ Seizures

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other antiepileptics, attempts to withdraw concomitant antiepileptics in treatment refractive patients on more than one antiepileptic, in order to reach gabapentin monotherapy have a low success rate.

~~When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.~~

Gabapentin is not ~~generally~~ considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients ~~in the treatment of absence seizures and may exacerbate these seizures in some patients~~. Consequently, gabapentin should be used with caution in patients who have mixed seizure ~~disorders that~~ including absences ~~seizures~~.

~~Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately (see Drug Interactions).~~

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been post-marketing reports of confusion, loss of consciousness and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

Suicidal ideation and behaviour

…

~~Pooled analyses of 199 placebo-controlled clinical trials of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients~~

~~randomized to placebo. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed.~~

~~The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years)in the clinical trials analyzed.~~

Concomitant use with opioids

Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or opioids should be reduced appropriately (see section 4.5).

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Elderly (over 65 years of age)

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

~~Diagnostic Interference~~

~~Because false positive readings were reported with the Ames N-Multistix SG, dipstick test when gabapentin or placebo was added to other anticonvulsant drugs, the more specific sulphosalicylic acid precipitation procedure is recommended to determine urine protein.~~

Laboratory Tests

~~Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of gabapentin. The value of monitoring blood concentrations has not been established..~~

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to gabapentin

Gabapentin crosses the human placenta.
There are no ~~adequate data~~ or limited amount of data from the use of gabapentin in pregnant women.

Breast-feeding

Gabapentin is ~~secreted~~ ~~into~~ excreted in human milk ~~following oral administration~~. ~~A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin.~~ Because the effect on the ~~nursing~~ breast-fed infant is unknown caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in ~~women who are nursing~~ breast-feeding mothers only if the benefits clearly outweigh the risks.

~~Effect on~~ Fertility ~~and Reproduction~~

There is no effect on fertility in animal studies (see section 5.3).

4.8 Undesirable effects

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in italics in the list below.

System organ class	**Adverse drug reactions**
Infections and infestations	
Very Common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	
Common	leucopenia
Not known	*thrombocytopenia*
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria)
Not known	*hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4)*
Metabolism and nutrition disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycaemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	*hyponatraemia*
Psychiatric disorders	

Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	agitation
Not known	*hallucinations*
Nervous system disorders	
Very Common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	*other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)*
Eye disorders	
Common	visual disturbances such as amblyopia, diplopia
Ear and labyrinth disorders	
Common	vertigo
Not known	*tinnitus*
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	

Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	respiratory depression
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	dysphagia
Not known	*pancreatitis*
Hepatobiliary disorders	
Not known	*hepatitis, jaundice*
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	*Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)*
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	*rhabdomyolysis, myoclonus*
Renal and urinary disorder	
Not known	*acute renal failure, incontinence*
Reproductive system and breast disorders	
Common	impotence
Not known	*breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)*
General disorders and administration site conditions	
Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema
Not known	*withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.*

Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	*blood creatine phosphokinase increased*
Injury, poisoning and procedural complications	
Common	accidental injury, fracture, abrasion
Uncommon	fall

~~Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.~~

4.9 Overdosage

~~A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg.~~

~~Manifestations~~

~~Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation.~~

Acute, life-threatening toxicity has not been observed with ~~oral overdose of~~ gabapentin overdoses up to 49 ~~grams~~. ~~have been reported~~. ~~In these cases~~ Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhea. ~~were observed~~. All patients recovered with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

~~Treatment~~

Although gabapentin can be removed by hemodialysis~~. Although hemodialysis has not been performed in the few overdose cases reported~~, based on prior experience it is usually not required .~~It may be indicated by the patient's clinical state or~~ However, in patients with ~~significant~~ severe renal impairment, hemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, hypoactivity, or excitation.

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics ATC code: N03AX12

Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy.

~~Gabapentin is an oral anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter gama-amino-butyric acid (GABA). Although Gabapentin was developed as a structural analog of GABA, it does not interact with GABA receptors, it is not metabolized to GABA or to GABA agonists, and it is not an inhibitor of GABA uptake or degradation,~~ Gabapentin does not ~~exhibit~~ possess affinity ~~for a number of other common receptor sites. In vitro studies have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. The identity and function of this binding site remain to be elucidated.~~ for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the $\alpha 2\delta$ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the $\alpha 2\delta$ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than $\alpha 2\delta$.

~~The mechanism by which gabapentin exerts its anticonvulsant action is unknown but in animals it has properties in common with other anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy). The relevance of these models to human epilepsy is not known.~~
~~Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.~~
~~All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized.~~

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to $\alpha 2\delta$ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the $\alpha 2\delta$ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

5.2 Pharmacokinetic properties

Absorption

~~Gabapentin bioavailability is not dose-proportional (i.e., as dose in increased, bioavailability decreases). A 400-mg dose, for example, is about 25% less bioavailable than a 100-mg dose. Over the recommended dose range of 300 to 600 mg 3 times daily, however, the differences in bioavailability are not large, and bioavailability is about 60%. Food has no effect on the rate and extent of absorption.~~

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.
Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 μg/mL and 20 μg/mL in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3
Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (µg/mL)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg·hr/mL)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

Cmax = Maximum steady state plasma concentration
tmax = Time for Cmax
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution

~~Gabapentin circulates largely unbound (less than 3%) to plasma protein.~~

~~The apparent volume of distribution after 1 mg I.V. administration is 58±6L. In patients with epilepsy, steady-state pre-dose (Cmin) concentrations of gabapentin in cerebrospinal fluid (CSF) were approximately equal to 20% of the corresponding plasma concentrations.~~

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

~~Metabolism/Excretion~~

~~Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug; it is not appreciably metabolized.~~

~~Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Elimination rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance (Ccr). In elderly patients and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.~~

~~Pharmacokinetics in Patients with Renal Insufficiency~~

~~When subjects with renal insufficiency were administered single 400 mg oral doses, the mean half-life ranged from about 6.5 hours (patients with Ccr less than 60 ml/min) to 52 hours (Ccr less than 30 ml/min) and renal clearance from about 90 ml/min to about 10 ml/min. Mean plasma clearance decreased from about 190 to 20 ml/min. Therefore dosage adjustment is necessary in patients with compromised renal function (see Dosage and Administration).~~

Biotransformation

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of

gabapentin is independent of dose and averages 5 to 7 hours.
In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.
Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).
Linearity/non-linearity
Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

Linearity/non-linearity
Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

~~Carcinogenicity~~ Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell ~~adenomas and carcinomas~~ tumors was found only in male rats at the highest dose; ~~the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day.~~ Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day, ~~and in rats receiving 1000 mg//kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day.~~ The pancreatic acinar cell ~~carcinomas~~ tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. ~~Studies to attempt to define a mechanism by which this relatively rare tumor type is occurring are in progress.~~ The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

~~Mutagenicity~~ Mutagenesis

~~Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 in vitro and 2 in vivo assays. It was negative in the Ames test and the in vitro HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the in vitro Chinese hamster lung cell assay; it was negative in the in vivo chromosomal aberration assay and in the in vivo micronucleus test in Chinese hamster bone marrow.~~

Gabapentin demonstrated no genotoxic potential. It was not mutagenic in vitro in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation in the bone marrow of hamsters.

~~Teratogenicity~~ Teratogenesis

~~- Gabapentin is fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day.~~

~~- When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to approximately to 1 to 5 times the maximum human dose. There was an increased incidence of hydroureter or hydronephrosis in rats. The doses at which the effects occurred are approximately equal to1 to 5 times the maximum human dose of 3600 mg/day.~~
~~- In rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300 and 1500 mg/kg/day, or less than approximately equal to ¼ to 8 times the maximum human dose.~~

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m2 basis).
Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.
No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m2 basis).
An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.
In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in pregnant rabbits given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 0.3 to 8 times the daily human dose of 3600 mg on a mg/m2 basis. The margins of safety are insufficient to rule out the risk of these effects in humans.

כמו כן, עודכן גם העלון לצרכן. בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):

אזהרות מיוחדות הנוגעות לשימוש בתרופה לפני הטיפול גאבאפנטין טבע, ספר לרופא אם:

- אם יש לך הפרעות במערכת העצבים, הפרעות בנשימה, או שהנך מעל גיל 65, יתכן והרופא ירשום לך משטר מינון שונה.

<u>תרופות אחרות וגאבאפנטין טבע</u>

אם אתה לוקח, או לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

במיוחד אם אתה לוקח או לקחת לאחרונה:

- תרופות לפרכוסים, הפרעות שינה, דיכאון, חרדה או בעיות נוירולוגיות או פסיכיאטריות כלשהן.

~~שימוש בתרופה וצריכת אלכוהול:~~

~~אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם התרופה.~~

<u>הריון, הנקה ופוריות</u>

<u>הריון</u>

~~לא מומלץ ליטול~~ אין ליטול ~~את התרופה~~ גאבאפנטין טבע במהלך ההריון, ~~אלא אם כן רופאך קבע שנית לקחתה~~ נאמר לך אחרת על ידי הרופא שלך. ~~על~~ נשים בגיל הפוריות חייבות להשתמש באמצעי מניעה יעילים בעת הטיפול בתרופה.

<u>פוריות</u>

במחקרים בחיות לא נמצאה השפעה על פוריות.

<u>נהיגה ושימוש במכונות</u>

השימוש בתרופה זו עלול ~~לפגום בעירנות~~ ולגרום לסחרחורת, נמנום ולעייפות.

~~ועל כן אין לנהוג ברכב~~ עליך להימנע מנהיגה, מהפעלת מכונות או מלעסוק בפעילויות אחרות שיכולות להיות מסוכנות עד שתדע כיצד התרופה משפיעה עליך ועל יכולתך לבצע פעולות אלו.

יש לפנות מיד לרופא אם אתה חווה אחד או יותר מהתסמינים הבאים לאחר נטילת התרופה כיוון שהם עלולים להיות חמורים:

- בעיות נשימה, אשר אם חמורות יתכן ותזדקק לטיפול חרום בכדי להמשיך לנשום רגיל.

- גאבאפנטין טבע עלולה לגרום לתגובה אלרגית חמורה או מסכנת חיים שעלולה להשפיע על העור או על חלקי גוף אחרים, כגון הכבד או תאי הדם. פריחה יכולה להופיע, או לא להופיע, כחלק מתגובה זו. יתכן שכתוצאה מתגובה זו תיאלץ להתאשפז או להפסיק ליטול גאבאפנטין טבע. פנה לרופא שלך מיד אם אתה סובל מאחד מהתסמינים הבאים:
  - פריחה בעור
  - חרלת
  - חום
  - נפיחות בבלוטות שאינה נעלמת
  - התנפחות השפתיים והלשון
  - הצהבת העור או לובן העיניים
  - הופעת חבורות או דימום יוצאי דופן
  - עייפות או חולשה חמורות
  - כאב שרירים בלתי צפוי
  - דלקות תכופות

תסמינים אלה עלולים להיות סימנים ראשונים של תגובה חמורה. רופא צריך לבדוק אותך ולהחליט אם אתה יכול להמשיך ליטול את התרופה.

~~**<u>תופעות לוואי המחייבות התייחסות מיוחדת, במידה והתופעות הבאות מתרחשות פנה מיד לרופא:</u>**~~

- ~~חולשת שרירים, רגישות או כאב במיוחד אם מלווה בהרגשה לא טובה או בחום ייתכן שהינם סימנים של פירוק שריר בלתי רגיל שעלול לסכן חיים ולהוביל לבעיות בכליה. ייתכן שבנוסף השתן שלך יהיה חסר צבע ויהיו שינויים בתוצאות בדיקת דם (עליה ברמות קראטין פוספוקינאז בדם)- פנה לרופא מיד!~~

- ~~החמרה בעוויתות – פנה לרופא מיד;~~
- ~~תנועות לא רצוניות בעיקר של הפנים, הלשון או הגפיים- יש לפנות לרופא מיד;~~

תופעות לוואי ~~נפוצות~~ שכיחות (מופיעות ב עד- 1 מכל 10 אנשים ~~עלולות להופיע ביותר מ- 1 מתוך 100 מטופלים~~):
~~שכחה, רגישות מופחתת למגע (קהות)~~
~~בנוסף במחקרים קליניים בילדים היו נפוצים דיווחים בדבר התנהגות אגרסיבית ותנועות עוויתיות.~~

תופעות לוואי ~~לא נפוצות~~ שאינן שכיחות (מופיעות ב- עד 1 מכל 100 אנשים ~~עלולות להופיע ביותר מ- 1 מתוך 1000 מטופלים~~):
- אי שקט (מצב של חוסר מנוחה כרוני ותנועות לא מכוונות וחסרות מטרה)
- קושי בבליעה
- התנפחות העלולה לכלול את הפנים, הגוף והגפיים

תופעות לוואי נדירות (מופיעות ב- עד 1 מכל 1,000 אנשים ~~עלולות להופיע ביותר מ- 1 מתוך 10000 מטופלים~~):

- קושי בנשימה, נשימות שטוחות (דיכוי נשימתי)

תופעות לוואי שדווחו לאחר שיווק התרופה ושכיחותן אינה ידועה ~~מאז תחילת שיווק גאבאפנטין דווחו תופעות הלוואי הבאות~~ :

- ~~תנודות ברמת הסוכר בדם בחולי סוכרת~~
- ~~סינדרום Stevens – Johnson (עלול להתבטא בשלפוחיות, קילוף או דימום של העור מסביב לשפתיים, עיניים, פה, אף ואברי המין, סימנים דמויי שפעת וחום גבוה)- יש לפנות לרופא מיד;~~
- אנפילקסיס (תגובה אלרגית חמורה ומסכנת חיים, כולל קשיי נשימה, נפיחות של השפתיים, הגרון והלשון, ולחץ דם נמוך המחייב טיפול חירום)

העלון לצרכן נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות http://www.health.gov.il,

וניתן לקבלו מודפס ע"י פניה לחברת טבע.