

PACKAGE LEAFLET
for medical use of medicinal product

PREGABALIN-DARNITSA

Qualitative and quantitative composition:

Active substance: pregabalin;

1 capsule contains pregabalin 75 mg or 150 mg;

Excipients: lactose monohydrate, corn starch, talc; hard gelatin capsules: gelatin, titanium dioxide (E171).

Pharmaceutical form. Capsules.

Basic physical and chemical properties: solid gelatin capsules with white or almost white body and cap containing white or almost white powder.

Pharmacotherapeutic group. Anti-epileptic medicinal products, other anti-epileptic medicinal products. Code ATC N03A X16.

Pharmacological properties.

Pharmacodynamic properties.

Active substance: pregabalin being an analogue of gamma-aminobutyric acid ((S)-3-(aminomethyl) -5-methylhexanoic acid).

Action mechanism.

Pregabalin binds to an additional subunit ($\alpha_2\text{-}\delta$ protein) of potential-depending calcium channels in the central nervous system (CNS).

Pharmacokinetics properties.

Pharmacokinetics indices of pregabalin in its equilibrium state were shown to be similar in healthy volunteers, patients with epilepsy taking anti-epileptic medicinal products, and in patients with chronic pain.

Absorption.

Pregabalin is quickly absorbed if it is taken fasting and reaches its maximal concentration in the blood plasma (C_{\max}) during 1h following single or multiple dose intake. The pregabalin bioavailability following its peroral administration reaches 90 % and more being dose independent.

In cases of multiple dose intake, this medicinal product equilibrium state becomes reached in 24 – 48 h.

The rate of pregabalin absorption decreases if the medicinal product is used simultaneously with food; in these case C_{\max} value becomes lower approximately by 25 – 30 %, t_{\max} values becoming longer up to 2.5 h. However, the pregabalin intake together with food has no clinically relevant influence on its absorption degree.

Distribution.

Preclinical investigations demonstrate pregabalin penetrate through the blood-brain barrier of mice, rats, and monkeys. Pregabalin is also shown to penetrate through rat placenta and to appear in milk during the lactation period. In humans, an apparent volume of pregabalin distribution following its peroral intake reaches approximately 0.56 l/kg. Pregabalin does not bind to blood plasma proteins.

Metabolism.

In human organism the pregabalin metabolism is insignificant. Following administration of isotope-labeled pregabalin dose about 98 % of the label was excreted as unchanged pregabalin. The part of N-methylated pregabalin derivative being the main metabolite of this medicinal product was found in urine, the quantity being as low as 0.9 % comparing to the dose administrated. The preclinical studies show no pregabalin S-enantiomer racemization to its R-enantiomer.

Excretion.

Pregabalin is excreted from the systemic blood stream without changes, the excretion being mostly realized by kidneys. The mean pregabalin demi-excretion period reaches 6.3 h. Values of pregabalin clearance by plasma and kidneys are directly proportional to creatinine clearance (see “*Pharmacokinetics properties. Renal insufficiency*”).

Dose correction for this medicinal product use is necessary for patients with impaired renal functions and patients treated by hemodialysis (see the chapter “*Posology and method of administration*”).

Linearity/non-linearity.

Pregabalin pharmacokinetics is linear for the whole recommended dose diapason. Pregabalin pharmacokinetics variability in patients is low (< 20 %). In cases of multiple use, pharmacokinetics can be predicted from the data obtained following a single dose administration. That is why there is no need to carry out the planned checking of pregabalin levels in blood plasma.

Sex.

The results of clinical studies show no clinically relevant influence of patient's sex on the pregabalin levels in blood plasma.

Renal insufficiency.

Pregabalin clearance is directly proportional to creatinine clearance. Besides, pregabalin is effectively excreted from the blood plasma by hemodialysis (following 4 h of hemodialysis, the blood plasma pregabalin level becomes lower by 50 %). The medicinal product being mostly excreted by kidneys, it is necessary to decrease pregabalin doses for patients with renal insufficiency and to give an additional dose after dialysis (see “*Posology and method of administration*”).

Hepatic failure.

No special pharmacokinetic studies have been carried out concerning patients with hepatic failure. As pregabalin shows no significant metabolism and is excreted with urine mostly as unchanged compound, it seems not very likely the damage of hepatic function to be of great importance for pregabalin concentration in blood plasma.

Children.

During the study of pregabalin pharmacokinetics and tolerance, this medicinal product pharmacokinetics has been investigated in children with epilepsy (age groups were the following: 1 - 23 months old, 2 – 6 years old, 7 - 11 years old and 12 - 16 years old); the doses used were 2.5 mg/kg/daily, 5 mg/kg/daily, 10 mg/kg/daily, and 15 mg/kg/daily.

Following fasting peroral pregabalin use by children, the time durations necessary for achieving of C_{max} in blood plasma were similar in all age groups (from 0.5 up to 2 h after administration).

The values of C_{max} and area under the curve (AUC) for pregabalin concentration/time dependence increase linearly to the dose increase in each age group. In children with body mass below 30 kg the UAC values were lower by 30 %; this fact is due to the clearance increase by 43 % having been corrected according to the body mass of these patients comparing to patients whose body mass was ≥ 30 kg.

The mean final period of pregabalin half-excretion reaches about 3 – 4 h in children below 6 years and 4 – 6 h in children above 7 years old.

Population pharmacokinetic analysis demonstrates the creatinine clearance to be a relevant co-variate for pregabalin perorally administrated. The body mass being a relevant co-variate for apparent volume for pregabalin distribution after peroral intake, this association is similar in children and adult patients.

Pregabalin pharmacokinetics in children below 3 months has not been investigated.

Elderly patients (above 65).

Pregabalin clearance tends to become decreased in elderly age comparing to younger people. Such decreased pregabalin clearance following its peroral use is conformed with decreased age-associated creatinine clearance. Patients with age-associated renal function insufficiency may need pregabalin doses to be decreased (see “*Posology and method of administration*”).

Brest feeding period.

Pregabalin pharmacokinetics was evaluated in 10 women of breast feeding period; at least 12 weeks passed post labor; the medicinal product (150 mg/dose, daily dose was 300 mg) was given once per 12 h. Brest feeding had no influence on the pregabalin pharmacokinetics or this influence was not significant. Pregabalin penetration into breast milk, its mean levels in the equilibrium state being about 76 % comparing to mother's blood plasma level. The calculated medicinal product dose received by baby with the breast milk (mean daily milk consumption is 150 ml/kg) from a pregabalin-treated woman (the daily medicinal product dose is 300 mg or even 600 mg in case of the maximal dose) reaches 0.31 or 0.62 mg/kg/daily, respectively. These calculated data put together about 7 % of total daily mother's dose in terms of mg/kg.

Clinical particulars.***Therapeutic indications.*****Neuropathic pain.**

Treatment of neuropathic pain of peripheral or central origin in adults.

Epilepsy.

Additional therapy in cases of partial spastic attacks with secondary generalization or without it in adults.

Generalized anxious disorder.

Treatment of generalized anxious disorder in adults.

Fibromyalgia.***Contraindications.***

Hypersensitivity to the active substance or to any accessory substance contained by the medicinal product.

Interactions with other medicinal products and other forms of interactions.

Pregabalin is mostly excreted by urine as an unchanged compound, its metabolism in humans being insignificant ($\leq 2\%$ of the dose administered is excreted in urine as metabolites); the medicinal product does not inhibit *in vitro* metabolism of other medicinal product compounds and does not bind to blood plasma proteins; therefore, it can scarcely cause any pharmacokinetic interactions or become an object of such interactions

In vitro investigations and population pharmacokinetic analysis.

Therefore, during any *in vivo* studies no relevant pharmacokinetic interactions were seen between pregabalin and the following medicinal products: phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis demonstrates that peroral anti-diabetic medicinal products, diuretics, insulin, Phenobarbital, tiagabine and topiramate have no clinically relevant influence on pregabalin clearance.

Peroral contraceptive medicinal products, norethisteron and (or) ethinylestradiol.

Simultaneous use of pregabalin with peroral contraceptives, norethisteron and (or) ethinylestradiol does not influence on pharmacokinetics of equilibrium state in case of any from these medicinal products.

Medicinal products with the influence on the CNS.

Pregabalin may intensify the effects of ethanol and lorazepam. In controlled clinical studies simultaneous multiple peroral pregabalin use together with oxycodone, lorazepam or ethanol does not lead to clinically relevant influence on the respiratory function. In the post-marketing surveillance period there were reports on respiratory failure and coma in patients having used pregabalin together with other medicinal products inhibiting the CNS function. Pregabalin intensifies probably the damage of cognitive and leading motor functions due to oxycodone.

Interactions in elderly patients (above 65).

There are no special studies concerning pharmacodynamic interactions with participation of elderly persons.

Special warnings and precautions for use.**Patients with diabetes mellitus.**

According to the current clinical practice, some diabetic patients whose body mass has increased during the pregabalin therapy may need correction of sugar-decreasing medicinal product doses.

Hypersensitivity reaction.

There are reports concerning the development of hypersensitivity reactions also angioneurotic edema. If angioneurotic edema symptoms appear, such as face edema, perioral edema or high respiratory tract edema, the pregabalin therapy should be immediately stopped.

Dizziness, sleepiness, loss of consciousness, mental confusion, and psychic disorders.

The pregabalin use was reported to be accompanied by the development of vertigo and sleepiness increasing the risk of traumatic events (falling) for elderly patients.

There are data concerning loss of consciousness, mental confusion, and psychic disorders. In these cases the patients should be advised to be cautious until all the possible effects of this new medicinal product would become known.

Vision disorders.

During examination, pregabalin-treated patients informed about vision disorders more frequently comparing to placebo-receiving ones. In most cases this phenomenon disappeared in the course of permanent medicinal product use. During ophthalmologic studies, the frequency of vision acuity worsening and of vision field changes were higher in pregabalin-treated patients comparing to patients of the placebo group; the frequency of fundus of eye changes was, however, higher in placebo patient group.

There are also reports concerning adverse reactions on the part of organs of vision including loss of sight, blurring of vision or other changes of vision acuity; many of them were temporary. Following the pregabalin withdrawal these symptoms on the part of organs of vision may disappear or become weaker.

Renal insufficiency.

There are reports concerning renal failure being sometimes reverse after the pregabalin withdrawal.

Withdrawal of accompanying anti-epileptic medicinal products.

We have not yet a necessary body of information concerning the possibility of accompanying anti-epileptic medicinal product withdrawal in a moment when convulsion control will be reached as a result of pregabalin use and when it will become possible to carry put only pregabalin monotherapy.

Withdrawal symptoms.

Symptoms of medicinal product withdrawal were observed in some patients following short or protracted pregabalin therapy. There are reports concerning: sleeplessness, headache, nausea, anxiety, diarrhea, influenza-like syndrome, nervousness, hyperhidrosis, depression, pain, spasms, and dizziness; they indicate on the physical dependence. This information should be given to patients before the beginning of therapy.

Spasms, in particular epileptic status and major epilepsy may develop during pregabalin therapy or shortly after its withdrawal.

The data on pregabalin withdrawal following its use during a long time indicate that the frequency of symptom development and their severity degree may be dose dependent.

Backward heart failure.

Backward heart failure is registered in some pregabalin-treated patients. Such reaction is mostly seen in cases of pregabalin-treated neuropathic pain in elderly patients with pre-existed cardiovascular disorders. Such patients are to use pregabalin with caution. This phenomenon may disappear following the medicinal product withdrawal.

Treatment of neuropathic pain of central origin due to spinal cord impair.

During the treatment of neuropathic pain of central origin caused by spinal cord impair total frequency of side reaction became higher; the frequency of adverse reactions on the CNS part, especially sleepiness was also increased. It may be due to additive action of accompanying medicinal products (e.g. anti-spastic ones) necessary for therapy of such a state. This situation should be taken into account if pregabalin is prescribed for such patients.

Suicidal thinking and behavior.

There are reports on cases of suicidal thinking and behavior in patients receiving anti-epileptic medicinal products according to some indications. Meta-analysis results obtained in randomized placebo-controlled studies of anti-epileptic medicinal products demonstrate some increase of suicidal thinking and behavior risk. The mechanism of such risk appearance is not known, the data available do not exclude the possibility of increased risk existence in cases of pregabalin use.

Therefore, it is necessary to observe carefully the patients to detect in good time any symptoms of suicidal thinking and behavior and to think over the expedient therapeutic approach. In cases of development of suicidal thinking or behavior the patients and nursing persons are to seek medical advice.

Function worsening of lower gastrointestinal tract parts.

There are facts concerning the functional worsening of lower gastrointestinal tract parts (e.g. intestinal obstruction, paralytic intestinal obstruction, constipation) in cases of pregabalin use together with medicinal products which may cause constipation, e.g. with opioid analgesics. In cases of simultaneous

pregabalin and opioid use, measures are to be taken for constipation prophylaxis (especially in women and elderly patients).

Incorrect use, abuse or dependence.

There are reports on incorrect pregabalin use as well as on this medicinal product abuse and dependence. The medicinal product should be used with caution by patients whose anamneses inform about their abuse with different medicinal products use; it is necessary to observe carefully these persons and to detect any symptoms of incorrect pregabalin use, of abuse or dependence (there are cases of acquired tolerance, exceeding of doses prescribed, behavior having the aim to receive the medicinal product).

Encephalopathy.

There are reports on encephalopathy cases developing mostly in patients with accompanying diseases which are able to provoke encephalopathy.

Excipients.

This therapeutic agent contains lactose monohydrate (58.25/116.5 mg), therefore it could be taken with caution by diabetes patients. The medicinal product Pregabalin-Darnitsa is not recommended for use by patients with a rare hereditary disease (galactose intolerance disease), with glucose-galactose malabsorption syndrome and Lapp syndrome with lactase insufficiency.

Fertility, pregnancy and lactation

Females being able to become pregnant /contraceptive means for females and males.

Any possible risk for humans being unknown, females being able to become pregnant are to use effective contraceptive means.

Pregnancy.

There are no proper data concerning pregabalin use by pregnant women.

The medicinal product reproductive toxicity has been demonstrated using animal models. Possible medicinal product reproductive toxicity for humans is not known.

This medicinal product is used during the pregnancy only in cases when the medicinal product usefulness for mother is clearly higher comparing to its risk for fetus.

Period of breast feeding.

Small pregabalin quantities were found in breast feeding women. Therefore, breast feeding is not recommended to women being treated by pregabalin.

Fertility.

There are no data on the pregabalin effect on female fertility.

During clinical investigation of pregabalin effect on spermatozoid motility, health volunteers-males used pregabalin in doses 600 mg daily. Following this medicinal product use no effect concerning its influence on spermatozoid motility was found during 3 months.

The examination of the medicinal product effect on female rat fertility detected undesirable effect on these animals' reproductive function and development. Clinical relevance of these results is unknown.

Effects on ability to drive and use machines.

The medicinal product may exert insignificant or moderate influence on the ability to drive transport means and to work with other mechanisms. It may cause vertigo and exert in such a way its influence on the ability to drive transport means and to work with other mechanisms. Because of such circumstances, patients are recommended to abstain from transport means driving or other activities which may be dangerous until patients will understand if the medicinal product exerts any influence on their ability for such activities.

Posology and method of administration

Administration.

The medicinal product is taken independently on the food.

This medicinal product is intended only for peroral use.

Doses.

The dose diapason of this medicinal product may be changed in limits of 150 – 600 mg daily. A daily dose may be divided for 2 – 3 times.

Neuropathic pain.

Pregabalin therapy may be begun from a dose 150 mg daily; a daily dose may be divided for 2 – 3 intakes. Depending on individual organism reaction and this medicinal product tolerance, the dose may be increased in 3 - 7 days up to 300 mg daily; if necessary, pregabalin intake may become (in 7 days more) 600 mg daily.

Epilepsy.

Pregabalin therapy may be begun from a dose 150 mg daily; a daily dose may be divided for 2 – 3 intakes. Depending on individual organism reaction and this medicinal product tolerance, the dose may be increased up to 300 mg daily after the first week of therapy. In a week the dose may be increased up to the maximal one – 600 mg daily.

Generalized anxious disorder.

Dose divided for 2 – 3 intakes may be changed in limits of 150 – 600 mg daily. From time to time it is necessary to reconsider the necessity of further therapy.

The pregabalin therapy may be begun from a dose 150 mg daily. Depending on individual organism reaction and this medicinal product tolerance, the dose may be increased in a week up to 300 mg daily. After a week later, the dose may become as high as 450 mg daily. Later, in a week after such therapy, the dose may be increased to the maximal one – 600 mg daily.

Fibromyalgia.

Recommended medicinal product doses for fibromyalgia therapy are from 300 up to 450 mg daily. The treatment should be begun from a dose 75 mg administrated twice per day (150 mg daily). Depending on the medicinal product effects and its tolerance, the dose may be increased up to 150 mg twice per day (300 mg daily) during a week. If the dose 300 mg daily is not effective for some patients, it is possible to increase it to 225 mg are given twice per day (450 mg daily). Although there are studies concerning the use of 600 mg dose daily, we have no evidence of this dose advantages; this dose tolerance is also worse. Taking into consideration different dose-depending adverse reactions, the use of doses above 450 mg daily is not recommended. Pregabalin being mostly excreted by kidneys, the dose taken by patients with kidney function failure should be corrected.

Pregabalin withdrawal.

According to the current clinical practice, the cessation of pregabalin therapy is recommended to be realized gradually, during a week or longer, independently on indications (see chapters “*Special warnings and precautions for use*” and “*Undesirable effects*”).

Kidney function damage.

Pregabalin is excreted from systemic blood stream without changes, mostly by kidneys. The pregabalin clearance being directly proportional to creatinine clearance (see “*Pharmacokinetics properties*”), the dose decrease for patients with impaired kidney function should be individual (see the Table below) according to the creatinine clearance (CL_{cr}) value determined from the formula:

$$CL_{cr}(ml/min) = \left[\frac{1,23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{creatinine level in blood plasma (mmole/l)}} \right] \times 0.85 \text{ for women}$$

Pregabalin is effectively removed from blood due to hemodialysis (50 % of this medicinal product is removed during 4 h). For patients treated by hemodialysis, a daily pregabalin dose should be corrected according to kidney function. Besides the daily dose, after each hemodialysis manipulation being carried out during 4 h it is necessary to administrate an additional medicinal product dose (see the Table).

Table

Pregabalin dose correction according to renal function

Creatinine clearance according to the renal function (CL_{cr}), (ml/min)	Total daily pregabalin dose *		Dosing regime
	Initial dose (mg daily)	Maximal dose (mg daily)	
≥ 60	150	600	2 — 3 times daily
$\geq 30 - < 60$	75	300	2 — 3 times daily
$\geq 15 - < 30$	25 – 50	150	1 – 2 times daily

< 15	25	75	once daily
Additional dose following hemodialysis (mg)			
	25	100	Single dose ⁺

* Cumulative daily dose (mg daily) should be divided into several parts (single doses, mg/dose) to be taken several times according to the dosing regimen.

⁺ Additional dose is an additional single dose.

Patients with hepatic insufficiency.

There is no necessity for dose corrections for patients with damaged hepatic function (see “*Pharmacokinetics properties*”).

Elderly patients (above 65).

Elderly patients may need sometimes decrease of pregabalin dose because of their kidney function aggravation (see the chapter “*Special warnings and precautions for use*”).

Children

Safety and efficacy of the medicinal product Pregabalin-Darnitsa in cases of its use for persons below 18 years are not determined. All the available information is given in chapters “*Pharmacokinetics properties*” and “*Undesirable effects*”; however, the medicinal product safety and dosing in cases of its use are unknown.

Overdose.

The most frequent side effects following the pregabalin overdosing are sleepiness, mental confusion, excitement, and anxiety.

There are also reports on convulsions.

Reports about coma cases are rare.

The treatment of pregabalin overdosing includes usual maintaining measures; if necessary, hemodialysis may be carried out (see the chapter “*Posology and method of administration*”).

Undesirable effects.

Vertigo and sleepiness are rather frequent registered side reactions. Such reactions are usually of slight or moderate degree. During studies, the index of the medicinal product withdrawal due to side reactions was 12 % among pregabalin-treated patients, this index reaching 5 % among patients receiving placebo. The investigations show the most frequent side reactions leading to the medicinal product withdrawal in the pregabalin group are vertigo and sleepiness.

All the side reactions developing more frequently than in cases of placebo use and found more than in a single patient are given below. These side reactions are listed according to systems of organs and these reactions frequency: very frequent ($\geq 1/10$); frequent (from $\geq 1/100$ up to $< 1/10$); not frequent (from $\geq 1/1000$ up to $< 1/100$); rarely (from $\geq 1/10000$ up to $< 1/1000$); very rarely ($< 1/10000$); the frequency is unknown (it cannot be evaluated from the data available). In each group reflecting any side effect development frequency, the data are presented in order of side effect severity decrease.

The indicated side reactions may be associated with underlying disease course and (or) with simultaneous use of other medicinal products.

During the treatment of neuropathic pain of central origin caused by spinal cord damage, the frequency of side reactions on the part of the CNS becomes in generally higher, especially sleepiness (see the chapter “*Special warnings and precautions for use*”).

Additional side reactions having been detected in cases of pregabalin use are given below and distinguished by italics.

Eye disorders:

Frequently: blurred vision, diplopia, conjunctivitis.

Not frequently: loss of peripheral vision, disturbances of vision, eye edema, vision field defects, decreased vision acuity, pain of eyes, asthenopia, photopsia, xerophthalmia, increased lacrimation, eye irritation, blepharitis, accommodation disorders, bleeding into eye, photophobia, retinal edema.

Rarely: *loss of vision, keratitis*, oscillopsia, changes of visual depth appreciation, mydriasis, strabismus, brightness of vision, anisocoria, corneal ulcer, exophthalmus, paralysis of ocular muscle, iritis,

keratoconjunctivitis, moisis, night blindness, ophthalmoplegia, visual nerve atrophy, optic nerve disk edema, blepharoptosis, uveitis.

Ear and labyrinth disorders

Frequently: vertigo.

Not-frequently: hyperacusia.

Respiratory, thoracic and mediastinal disorders

Frequently: pharyngolaryngeal pain.

Not frequently: dyspnea, nosebleed, cough, stuffiness in nose, rhinitis, snoring, xeromycteria.

Rarely: *lung edema*, constriction in throat, laryngospasm, apnoea, atelectasis, bronchiolitis, hiccup, lung fibrosis, yawning.

Gastrointestinal disorders:

Frequently: vomiting, *nausea*, constipation, *diarrhea*, tympanism, abdominal swelling, dry mouth, gastroenteritis.

Not-frequently: gastroesophageal reflux disease, hypersecretion of saliva, oral cavity hypoesthesia, cholecystitis, cholelithiasis, colitis, gastrointestinal bleeding, melena, tongue edema, rectal bleeding.

Rarely: ascites, pancreatitis, *tongue edema*, dysphagia, aphthous stomatitis, esophagus ulcer, periodontal abscess.

Renal and urinary disorders:

Not-frequently: urinary incontinence, dysuria, albuminuria, hematuria, stone formation in kidneys, nephritis.

Rarely: renal insufficiency, oliguria, *urine retention*, acute renal insufficiency, glomerulonephritis, pyelonephritis.

Metabolism and nutrition disorders:

Frequently: increased appetite.

Not-frequently: loss of memory, hypoglycemia.

Nervous system disorders

Very frequently: vertigo, sleepiness, headache.

Frequently: ataxia, disturbance of coordination, tremor, dysarthria, amnesia, worsening of memory, disturbance of attention, paresthesia, hypoesthesia, sedative effect, disturbance of equilibrium, lethargy.

Not-frequently: syncope, stupor, myoclonia, *loss of consciousness*, psychomotor hyperactivity, dyskinesia, postural vertigo, intention tremor, nystagmus, disturbance of cognitive functions, *psychics disturbance*, speech disturbance, hyporeflexia, hyperesthesia, feeling of burning, ageusia, *general malaise*, apathy, perioral paresthesia, myoclonus.

Rarely: *convulsions*, parosmia, hypokinesia, dysphagia, hypalgesia, dependence, cerebellar syndrome, gear-wheel syndrome (cog-wheel syndrome), coma, delirium, encephalopathy, extra-pyramidal symptom, Guillain-Barre syndrome, intracranial hypertension, maniacal reactions, paranoid reactions, dream disorder.

Psychiatric disorders:

Frequently: euphoria, mental confusion, irritability, disorientation, sleeplessness, libido decrease.

Not frequently: hallucinations, attacks of panic, anxiety, excitement, depression, suppressed mood, good mood, *aggression*, changes of mood, depersonalization, difficulties with word choice, pathological dreams, increased libido, anorgasmia, apathy.

Rarely: disinhibition.

Cardiac disorders:

Not frequently: tachycardia, 1st degree atrioventricular blockade, sinus bradycardia, *backward heart failure*.

Rarely: *QT interval prolongation*, sinus tachycardia, sinus arrhythmia.

Vascular disorders

Not-frequently: arterial hypertension, arterial hypotension, flashes, hyperemia, cold feeling in extremities.

Blood and lymphatic system disorders:

Not-frequently: granulocytopenia.

Immune system disorders:

Not frequent: *hypersensitivity*.

Rarely: *angioneurotic edema, allergic reactions, anaphylactoid reactions.*

Skin and subcutaneous tissue disorders:

Frequently: decubitus ulcers.

Not-frequently: papular rash, urticaria, hyperhidrosis, *pruritis*, alopecia, dry skin, eczema, hirsutism, skin ulcers, vasculo-bullous rash.

Rarely: *Stevens-Johnson syndrome*, cold sweat, exfoliative dermatitis, lichen dermatitis, melanosis, nail damages, petechial skin rash, purpura, pustular rash, skin atrophy, skin necrosis, skin and hypodermal nodes.

Musculoskeletal and connective tissue disorders

Frequently: muscle convulsions, arthralgia, back pain, pains in extremities, neck muscle spasms.

Not-frequently: edema of joints, myalgia, muscular twitching, neck pain, muscle stiffness.

Rarely: rhabdomyolysis.

Reproductive system and breast disorders:

Frequently: erectile dysfunction, impotence.

Not-frequently: sex dysfunction, retention of ejaculation, dysmenorrhea, pain in mammary glands, leukorrhea, menorrhagia, metrorrhagia.

Rarely: amenorrhea, discharge from mammary glands, enlargement of mammary glands, *gynecomastia*, cervicitis, balanitis, epididymitis.

General disorders and administration site conditions

Frequently: peripheral edema, edema, gait disturbance, fallings, feeling of drunkenness, unusual feelings, increased fatigability.

Not-frequently: generalized edema, *face edema*, stiffness in chest, pain, fever, thirst, shiver, general weakness, malaise, abscess, fat tissue inflammation, photosensitization.

Rarely: granuloma, intentional damage actions, retroperitoneal fibrosis, shock.

Infections and invasions.

Frequently: nasopharyngitis.

Investigations:

Frequently: increase of body mass.

Not-frequently: increase of blood creatinine phosphatase level, increase of blood aspartate aminotransferase level, increase of blood glucose level, decrease of blood platelets quantity, increase of blood creatinine level, decrease of blood potassium level, body mass decrease.

Rarely: decrease of blood leukocyte level.

In some patients, symptoms of the medicinal product withdrawal were seen following termination of short or long pregabalin therapy. There are reports on the following reactions: sleeplessness, headache, nausea, anxiety, diarrhea, influenza-like syndrome, convulsions, nervousness, depression, pain, hyperhidrosis, and vertigo. They indicate on the physical dependence. This information should be told to patients before the beginning of therapy.

The data on the pregabalin withdrawal after its long use confirm the frequency of symptom development and their severity degree may be dose-dependent

Children. Pregabalin safety profile which has been studied during two investigations with children participation (studies of the medicinal product pharmacokinetics and tolerance, n = 65; open study for safety examination, its duration being 1 h, n = 54) is similar to the profile seen in studies with adult patient's participation (see chapters "*Pharmacokinetics properties*" and "*Posology and method of administration*").

Reporting of suspected adverse reactions.

Reports concerning suspected side reactions after the medicinal product therapy are important. They permit to carry continuously out the monitoring of profit/risk ratio during the medicinal product use.

Shelf life 3 years.

Storage conditions.

Store in the original package at temperature not above 30 °C.

Keep out of reach of children.

Special precautions for storage.

Capsules containing 75 or 150 mg, 7 capsules in a blister; 2 blisters in a pack.

Category of release.

Prescription-only medicine.

Manufacturer.

PrJSC "Pharmaceutical firm "Darnitsa".

Location of the manufacturer and address of manufacturing facilities.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

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