# AAAN9350-PRE C ACT 50/75/150-MY/L

## BRIEKA
### capsules

**Product Name**
BRIEKA capsules 50mg
BRIEKA capsules 75mg
BRIEKA capsules 150mg

**Composition**
*Name and Strength of Active Substance(s)*
50mg: Each capsule contains Pregabalin 50mg
75mg: Each capsule contains Pregabalin 75mg
150mg: Each capsule contains Pregabalin 150mg

**Product Description**
50mg: White cap and white body, hard gelatine capsules size 3. Markings in black ink on body: "PGB 50" with a black band.
75mg: Orange cap and white body, hard gelatine capsules size 4. Markings in black ink on body: "PGB 75".
150mg: White cap and white body, hard gelatine capsules size 2. Markings in black ink on body: "PGB 150".

**Pharmacology**
Pharmacotherapeutic group: Antiepileptics, other antiepileptics
ATC code: N03AX16
The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid].

Mechanism of action
Pregabalin binds to an auxiliary subunit ($\alpha_2$-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [$^3$H]-gabapentin.

**Pharmacokinetics**
Pregabalin steady-state pharmacokinetics is similar in healthy volunteers, patients with epilepsy receiving antiepileptic drugs and patients with chronic pain.
Absorption
Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in $C_{max}$ by approximately 25-30% and a delay in $t_{max}$ to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.
Distribution
The apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.
Biotransformation
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. There was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.
Elimination
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.
Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance. Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.
Linearity / non-linearity
Pregabalin pharmacokinetics is linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20%). Multiple dose pharmacokinetics is predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.
Gender
Gender does not have a clinically significant influence on the plasma concentrations of pregabalin.
Renal impairment
Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4-hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary.
Hepatic impairment
No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.
Elderly (over 65 years of age)
Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.

**Indications**
*Neuropathic pain*
Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults.
*Epilepsy*
Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
*Generalised Anxiety Disorder*
Pregabalin is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.
*Fibromyalgia*
Management of fibromyalgia.

**Dosage and Administration**
Posology
The dose range is 150 to 600 mg per day given in either two or three divided doses.
*Neuropathic pain*
Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.
*Epilepsy*
Pregabalin treatment can be started with a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.
*Generalised Anxiety Disorder*
The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.
Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.
*Fibromyalgia*
The dose range is 300 to 450 mg per day given as two or three divided doses. Dosing should begin at 75mg two times a day (150mg/day) and may be increased to 150mg two times a day (300mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300mg/day may be further increased to 225mg two times a day (450mg/day). In view of dose-dependent adverse reactions, treatment with doses >450mg/day is not recommended. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (creatinine clearance <60mL/min).
*Discontinuation of pregabalin*
In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.
*Patients with renal impairment*
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance, dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$CL_{cr}\ (ml/min) = \frac{1.23 \times [140 - age\ (years)] \times weight\ (kg)}{Serum\ creatinine\ (\mu mol/l)} \times (0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

**Table 1. Pregabalin dose adjustment based on renal function**

| **Creatinine clearance ($CL_{cr}$) (ml/min)** | **Total pregabalin daily dose *** | | **Dose regimen** |
|---|---|---|---|
| | Starting dose (mg/day) | Maximum dose (mg/day) | |
| ≥ 60 | 150 | 600 | BID or TID |
| ≥ 30 - < 60 | 75 | 300 | BID or TID |
| ≥ 15 - < 30 | 25 - 50 | 150 | Once Daily or BID |
| < 15 | 25 | 75 | Once Daily |
| Supplementary dosage following haemodialysis (mg) | | | |
| | 25 | 100 | Single dose[+] |

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose
[+] Supplementary dose is a single additional dose

*Patients with hepatic impairment*
No dose adjustment is required for patients with hepatic impairment.
*Paediatric population*
The safety and efficacy of pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established.
*Elderly (over 65 years of age) population*
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).
Method of administration
Pregabalin may be taken with or without food.
Pregabalin is for oral use only.

**Contraindications**
Patients with known hypersensitivity to any component of Brieka capsules.

**Warnings and Precautions**
Potential for an increase in risk of suicidal thoughts or behaviors.
*Angioedema*
Caution should be exercised when prescribing pregabalin to patients who have had previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (eg. angiotensin converting enzyme inhibitor [ACE-inhibitors]) may be at increased risk of developing angioedema. Specific symptoms include swelling of the face, mouth (tongue, lips and gums), and neck (throat and larynx), as well as life-threatening angioedema with respiratory compromise requiring emergency treatment. Pregabalin should be discontinued immediately in patients with these symptoms.
*Hypersensitivity reactions*
There have been reports of hypersensitivity reactions, shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea and wheezing. Pregabalin should be discontinued immediately if these symptoms occur.
*Peripheral edema*
Pregabalin treatment may cause peripheral edema. Peripheral edema was not associated with laboratory changes suggested of deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering pregabalin and these agents.
*Dizziness and somnolence*
Pregabalin treatment has been associated with dizziness and somnolence, which may impair the patient's ability to perform tasks such as driving or operating machinery and could increase the occurrence of accidental injury (fall) in the elderly population. There have also been reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product
*Weight gain*
Pregabalin treatment may cause weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender or age. Weight gain was not limited to patients with edema.
In accordance to current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications.
*Withdrawal of concomitant antiepileptic medicinal products*
There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.
*Withdrawal symptoms*
After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.


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Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin.
Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.
*Ophthalmological effects*
Visual adverse reactions have also been reported, including visual blurring or other changes of visual acuity. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.
*Creatine kinase elevations*
Pregabalin treatment was associated with creatine kinase elevations. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.
*Decreased platelet count*
Pregabalin treatment was associated with a decrease in platelet count.
*PR interval prolongation*
Pregabalin treatment was associated with PR interval prolongation.
*Others*
*Renal failure*
Cases of renal failure have been reported and in some cases, discontinuation of pregabalin did show reversibility of this adverse reaction. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.
*Effects on the ability to drive or operate machinery*
Pregabalin may cause dizziness and somnolence and therefore may influence the ability to drive or use machines.

**Use in Pregnancy and Lactation**
*Pregnancy*
There are no adequate data from the use of pregabalin in pregnant women.
The potential risk for humans is unknown. Therefore, pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). Effective contraception must be used in women of childbearing potential.
*Lactation*
Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breastfeeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breastfeeding or to discontinue from pregabalin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

**Drug Interactions**
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (< 2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.
*In vivo studies and population pharmacokinetic analysis*
Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.
*Oral contraceptives, norethisterone and/or ethinyloestradiol*
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyloestradiol does not influence the steady-state pharmacokinetics of either substance.
*Central nervous system influencing medical products*
Pregabalin may potentiate the effects of ethanol and lorazepam. There are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.
*Incompatibilities*
Not applicable

**Adverse Effects**
The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased.
Additional reactions reported are included in the list below.

**Table 2. Pregabalin Adverse Drug Reactions**

| System Organ Class | Adverse drug reactions |
|---|---|
| **Infections and infestations** | |
| Common | Nasopharyngitis |
| **Blood and lymphatic system disorders** | |
| Uncommon | Neutropaenia |
| **Immune system disorders** | |
| Uncommon | Hypersensitivity |
| Rare | Angioedema, allergic reaction |
| **Metabolism and nutrition disorders** | |
| Common | Appetite increased |
| Uncommon | Anorexia, hypoglycaemia |
| **Psychiatric disorders** | |
| Common | Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased |
| Uncommon | Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression,* mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy |
| Rare | Disinhibition |
| **Nervous system disorders** | |
| Very Common | Dizziness, somnolence, headache |
| Common | Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy |
| Uncommon | Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise |
| Rare | Convulsions, parosmia, hypokinesia, dysgraphia |
| **Eye disorders** | |
| Common | Vision blurred, diplopia |
| Uncommon | Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation |
| Rare | Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness |
| **Ear and labyrinth disorders** | |
| Common | Vertigo |
| Uncommon | Hyperacusis |
| **Cardiac disorders** | |
| Uncommon | Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure |
| Rare | QT prolongation, sinus tachycardia, sinus arrhythmia |
| **Vascular disorders** | |
| Uncommon | Hypotension, hypertension, hot flushes, flushing, peripheral coldness |
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon | Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness |
| Rare | Pulmonary oedema, throat tightness |
| **Gastrointestinal disorders** | |
| Common | Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth |
| Uncommon | Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral |
| Rare | Ascites, pancreatitis, swollen tongue, dysphagia |
| **Skin and subcutaneous tissue disorders** | |
| Uncommon | Rash papular, urticaria, hyperhidrosis, pruritus |
| Rare | Stevens Johnson syndrome, cold sweat |
| **Musculoskeletal and connective tissue disorders** | |
| Common | Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm |
| Uncommon | Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness |
| Rare | Rhabdomyolysis |
| **Renal and urinary disorders** | |
| Uncommon | Urinary incontinence, dysuria |
| Rare | Renal failure, oliguria, urinary retention |
| **Reproductive system and breast disorders** | |
| Common | Erectile dysfunction |
| Uncommon | Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain |
| Rare | Amenorrhoea, breast discharge, breast enlargement, gynaecomastia |
| **General disorders and administration site conditions** | |
| Common | Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue |
| Uncommon | Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia |
| **Investigations** | |
| Common | Weight increased |
| Uncommon | Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased |
| Rare | White blood cell count decreased |

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.
Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

**Overdose and Treatment**
In overdoses up to 15g, no unexpected adverse events were reported. The most commonly reported adverse reactions observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation, and restlessness.
In rare occasions, cases of coma have been reported.
Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

**Storage**
Store below 30°C.

**Availability**
50mg: Blister pack of 6x10's
75mg: Blister pack of 6x10's
150mg: Blister pack of 6x10's

***For further information, please consult your physician or pharmacist.***

**Manufactured by**
**Balkanpharma-Dupnitsa AD**
3 Samokovsko Shosse Str.
Dupnitza 2600, Bulgaria

**DATE OF REVISION:** December 2021

Actavis
AAAN9350

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