SUMMARY OF THE PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neurogil® 75 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg of pregabalin

List of excipients : Caramel gelatin capsule, Microcrystalline cellulose, Colloidal silicon dioxide

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL DATA

4.1 Therapeutic indications

Neuropathic pain

Neurogil ® 75 is indicated for the treatment of peripheral and central neuropathic pain in the adult.

Epilepsy

Neurogil ® 75 is indicated in adults in combination for the treatment of epileptic seizures partial with or without secondary generalization.

Generalized anxiety disorder

Neurogil ® 75 is indicated for the treatment of Generalized Anxiety Disorder (GAD) in adults.

Patients with renal insufficiency

Pregabalin is eliminated from the systemic circulation, mainly renally, in the unchanged form. The clearance of pregabalin is directly proportional to the clearance of creatinine (see section 5.2), in patients with renal impairment a reduction in dose should be established individually taking into account the clearance of creatinine (CLcr),

Pregabalin is effectively removed from the plasma by hemodialysis (50% of the drug in 4 hours). In hemodialysis patients, the daily dose of pregabalin should be adjusted on the basis of renal function. In addition to the daily dose, an additional dose must be administered immediately after each 4-hour hemodialysis (see Table 1).

Creatinine clearance (ClCr)	Total daily dose of pregabalin		Posology
	Initial dose(mg/day)	Maximal dose(mg/day)	
$\geqslant 60$	150	600	BID or TID
$\geqslant 30 - < 60$	75	300	BID or TID
$\geqslant 15 - < 30$	25-50**	150	Once per day or BID
<15	25**	75	Once per day

Supplementary dose after hemodialysis (mg)			
	25**	100	Unique dose

TID: Three times a day

BID: Two times a day

* The total daily dose (mg / day) should be divided by the number of shots indicated to obtain the number of mg per dose.

The additional dose is a complementary dose given as a single dose.

Patients with hepatic insufficiency

No dose adjustment is necessary in patients with hepatic impairment (see section 4.2). 5.2).

Pediatric population

The safety and effectiveness of pregabalin in children under 12 years of age and in teenager (12-17 years old) have not been established.

The currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on dosage may be given.

Older population (over 65 years old)

In view of the decrease in renal function, a reduction in the dose of pregabalin may older patients (see "Patients with renal impairment").

Administration mode

Neurogil® 75 can be taken with or without food.
Neurogil® 75 is exclusively administered orally

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic patients

In line with current clinical practice, treatment adaptation hypoglycemic therapy may be necessary in some diabetic patients who have taken weight under pregabalin.

Hypersensitivity reactions

Cases of hypersensitivity reactions, including cases of Quincke's edema, have been reported in during post-marketing surveillance. The occurrence of Quincke's edema symptoms such swelling of the face, perioral swelling or upper airway requires immediate discontinuation of pregabalin.

Dizziness, drowsiness, unconsciousness, confusion and impaired mental function
Treatment with pregabalin has been associated with dizziness and somnolence to increase the occurrence of accidental injuries (falls) in the elderly population. After putting on market, the following cases have been reported: loss of consciousness, confusion and alteration of the mental function, patients should be advised to be cautious until they become accustomed to potential effects of the drug.

Visual troubles

In controlled clinical trials, the proportion of patients reporting blurred vision was important in patients treated with pregabalin than in those treated with placebo; in the majority cases, these disorders disappeared despite continued treatment.

In clinical studies, ophthalmological examinations, the incidence of decreased visual acuity and Visual field changes were greater in patients in the pregabalin group compared to placebo group; the incidence of fundus abnormalities was higher with placebo (see 5.1).

During post-marketing surveillance, visual adverse effects, including vision, blurred vision or other changes in visual acuity, have also been reported, most of which are transient in nature. Stopping pregabalin may result in the disappearance of these visual symptoms or their improvement.

Renal failure

Cases of renal failure have been reported and discontinuation of treatment has reversibility of this adverse reaction in some cases.

Suppression of concomitant antiepileptic drugs

There are no sufficient data to suppress anti-epileptic drugs concomitant with the goal of introducing monotherapy, when seizure control is achieved with pregabalin used in combination.

Withdrawal symptoms

After discontinuation of short or long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients. The following events have been reported, suggesting a physical dependence: insomnia, headache, nausea, anxiety, diarrhea, flu syndrome, nervousness, depression, pain, convulsions, hyperhidrosis and dizziness; the patient must be informed in start of treatment.

Convulsions including states of epilepticus and states of great harm may appear during or shortly after stopping treatment with pregabalin.

Regarding the interruption of prolonged treatment with pregabalin, the data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Congestive heart failure

Cases of congestive heart failure have been reported during postmarketing surveillance in some patients treated with pregabalin. These effects have been observed mainly during treatment with pregabalin for an indication of neuropathic pain in elderly patients whose cardiovascular function was impaired, pregabalin should be used with caution in these patients, and this side effect may disappear after stopping pregabalin.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury, the incidence of adverse reactions in general, adverse reactions to the system; Central nervous system, and drowsiness in particular, has been increased. This increase can be attributed to an additive effect due to concomitant medicinal products (eg anti-spastics) necessary for the treatment of this type of affection. This information must be taken into account when prescribing the pregabalin for this condition.

Suicidal ideation and behavior

Suicidal ideation and behavior has been reported in patients treated with antiepileptic drugs in several indications. A meta-analysis of randomized controlled trials against placebo evaluating antiepileptic drugs also highlighted a slightly increased risk increased suicidal ideation and behavior. The mechanism underlying this risk is not known and the available data do not exclude the possibility of a higher risk for pregabalin; Patients should therefore be monitored for signs of ideas and behavior suicidal, and appropriate treatment should be considered,therefore; it should be advised to patients (and their carers) to seek medical advice if signs of suicidal ones appear.

Slow transit of the gastrointestinal tract

Notifications of adverse effects related to a slowing of transit of the gastrointestinal tract (eg intestinal obstruction, paralytic ileus, constipation) have been reported during post-marketing surveillance when pregabalin was administered in combination with drugs likely to induce constipation, such as opioid analgesics.
When the Pregabalin is used in combination with opioids, there is a need to consider prevention of constipation (especially in women and the elderly).

Misuse, risk of abuse or addiction

Cases of misuse, abuse and dependence have been reported. Caution should be exercised patients with a history of substance abuse. Symptoms of misuse, abuse or Pregabalin dependence should be monitored in these patients (cases of development of tolerance, dose-escalation and drug-seeking behavior have been reported).

Encephalopathy

Cases of encephalopathy have been reported, mainly in patients with underlying conditions that may lead to encephalopathy.

4.5 Interaction with other medicinal products and other forms and other forms of interactions

Since pregabalin is essentially eliminated unchanged in the urine, that it is only weakly metabolized in humans (less than 2% of the dose is found in the urine as metabolites), that it does not inhibit the metabolism of drugs in vitro and does not bind to plasma proteins, it is unlikely to induce or pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis

Therefore, no clinically significant pharmacokinetic interaction was observed in vivo studies between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Pharmacokinetic analyzes populations have shown that oral antidiabetic agents, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on the clearance of pregabalin.

Oral contraceptives, norethisterone and / or ethinylestradiol

Concomitant administration of pregabalin with oral contraceptives such as norethisterone and / or ethinyl estradiol does not influence the steady-state pharmacokinetic parameters of either either of these substances.

Drugs influencing the central nervous system

Pregabalin may potentiate the effects of ethanol and lorazepam. In clinical trials controlled, multiple oral doses of pregabalin concomitantly administered with oxycodone, lorazepam or ethanol did not result in clinically important effects on function respiratory.

During post-marketing surveillance, cases of respiratory failure and coma have been reported in patients receiving pregabalin and other depressant CNS. The effect of pregabalin seems to add to that of oxycodone on the alteration of overall cognitive and motor function.

Interactions and elderly

No specific pharmacodynamic interaction studies were conducted in elderly subjects volunteers, Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing age / Contraception in men and women

Since the risk to humans is unknown, women of childbearing potential must use a effective contraception.

Pregnancy

There are no sufficiently relevant data concerning the use of pregabalin in pregnant woman. The potential risk in clinic is not known.
Pregabalin should not be used during pregnancy unless absolutely necessary (if benefits for the mother clearly outweigh the potential risks to the fetus).

Breast-feeding

Pregabalin is excreted in breast milk (see section 5.2). The effect of pregabalin on newborns / infants is not known. A decision must be made to stop breastfeeding to discontinue treatment with pregabalin taking into account the benefit of breastfeeding for the child with regard to the benefit of the treatment for the woman.

Fertility

No clinical data are available on the effects of pregabalin on fertility in wife.

4.7 Effects on ability to drive and use machines

Neurogil® 75 may have minor or moderate influence on the ability to drive and to use machines, Neurogil® 75 may induce dizziness and drowsiness and may therefore have an influence on the ability to drive or use machines. It is therefore advisable to patients not to drive, not to use complex machinery or to undertake other potentially dangerous activities before evaluating the possible impact of this drug on their ability to perform these activities.

4.8 Undesirable effects

The clinical evaluation program for pregabalin was conducted in more than 8,900 exposed patients, Pregabalin, more than 5,600 were in double-blind controlled trials against placebo. The most commonly reported adverse reactions were dizziness and drowsiness; these effects were generally of mild to moderate intensity.

In all studies monitored, treatment interruptions related to adverse events amounted to 12% patients receiving pregabalin and 5% of those receiving placebo; the most serious side effects.

The frequent discontinuation of pregabalin was dizziness and drowsiness.

Table 2 below lists, by type and frequency, all adverse events occurring at a higher incidence than placebo and more than one patient (very common (≥ 1/10); (≥ 1/100, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥ 1/10 000, <1/1000); very rare (<1/10000); indeterminate frequency (can not be estimated based on available data).

Within each frequency group, adverse effects are presented in order of decreasing severity
The adverse reactions mentioned may also be associated with the underlying disease and / or Concomitant medications.

In the treatment of central neuropathic pain due to spinal cord injury, the incidence of adverse reactions in general, CNS adverse reactions and drowsiness in particular has been increased (see section 4.4).

Additional reactions reported during post-marketing surveillance in the list below in italics.

Organ system class	Side effects
Infections and infestations Frequent	Rhinopharyngitis
Blood and lymphatic system disorders Less frequent	Neutropenia
Immune system disorders Less frequent Rare	 Hypersensibility Quincke edema , Allergic reactions
Metabolism and nutrition disorders Frequent Less frequent	 Increase of appetite Anorexia , Hypoglycemia
Psychiatric disorders Frequent Less frequent Rare	 Euphoric mood, confusion, irritability, disorientation, insomnia, decreased libido Hallucinations, panic disorders, nervousness , agitation, depression, depressive mood, exalted mood, aggressiveness , mood swings, loss of personality, nightmares, increase of the libido, anorgasmia , apathy . Disinhibition
Nervous system disorders Very frequent Frequent Less frequent	 Sleepness, drowsiness, headaches Ataxia, coordination disorders, tremors, dysartria, amnesia , trouble with memory , Attention disorders , paresthesia, hypoaesthesia , sedation , lethargy. Syncope, panic , myoclonia , psychomotor hyperactivity, dyskinesia , orthostatic dizziness , nystagmus, cognitive disorder , impairement of mental function , hyporeflexia, burning sensation, discomfort.

Rare	Convulsions, parosmia , hypokinesia , dysgraphia
Eye disorders	
Frequent	Vision trouble, diplopia
Less frequent	Loss of peripheral vision, visual troubles, eye swellings, visual field defects, decreased visual acuity , eye pain, eye strain, eye dryness , eye irritation
Rare	Visual loss , keratitis, oscillopsia , impairement of stereoscopic vision , mydriasis , strabismus , visual halo
Affection of the ear and the labyrinth	
Frequent	Dizziness
Less frequent	hyperacusis
Heart diseases	
Less frequent	Tachycardia, first degree atrioventricular block, sinusal bradycardia, flushing , congestive heart failure
Rare	Lengthening of the interval QT, sinusal tachycardia , sinusal arrythmia.
Vascular disorders	
Less frequent	Hypotension, Hypertension, flushing, feeling cold at the extremities
Respiratory affection, thoracic and mediestinal	
Less frequent	Dyspnea, epistaxis, cough, Nasal congestion, Rhinitis, snoring, nasal dryness.
Rare	Pulmonary edema, constriction of the pharynx.
Gastro-intestinal disorders	
Frequent	Emesis, Nausea, constipation, Diarrhea, flatulences, abdominal distension, oral dryness.
Less frequent	Gastroesophageal reflux, oral hypoaesthesia .
Rare	Ascites, pancreatitis, swelling of the tongue, dysphagia.

Skin and subcutaneous tissue disorders	
Less frequent	Papular rash, urticaria, hyperhidrosis, pruritus
Rare	Stevens-Johnson syndrome, cold sweat
Musculoskeletal and systemic disorders	
Frequent	Muscular cramps, arthralgia , back pain ; limb pain , cervical spasm
Less frequent	Articular swellings, myalgia , muscular contractions, cervical pain, muscular rigidity
Rare	Rhabdomyolsis
Kidney and urinary tract	
Less frequent	Urinary incontinence , dysuria
Rare	Kidney failure, oliguria, urinary retention
Reproduction organ and breast	
Frequent	Erectile dysfunction.
Less frequent	Erectile dysfunction, delayed ejaculation, dysmenorrhea, breast pain .
Rare	Amenorrhea, breast flow, breast hypertrophy, gynecomastia.
General disorders and abnormalities at the site of administration	
Frequent	Peripheral edema, edema, gait disturbances, falls, tiredness.
Less frequent	Generalised edema, edema of the face, chest tightness, pain, pyrexia, thirst, chills, asthenia.
Investigations	
Frequent	Weight gain
Less frequent	Increase of creatine phosphokinase in the blood, increase of alanine aminotransferase, increase of aspartate aminotransferase, increase of the glycemia, decrease of the platelets numbers, increase of creatinenine, decrease of kalemia , weight loss

Rare	Decrease of white blood cells.

After discontinuation of short or long-term treatment with pregabalin, withdrawal symptoms have been observed in some patients, the following reactions have been reported, suggesting a physical dependence: insomnia, headache, nausea, anxiety, diarrhea, flu syndrome, seizures, nervousness, depression, pain, hyperhidrosis and dizziness.

The patient must be informed in start of treatment. Regarding the interruption of prolonged treatment with pregabalin, the data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization of the drug is important. She allows continuous monitoring of the benefit / risk ratio of the drug.

4.9 Overdose

The most commonly reported adverse reactions in case of overdose with pregabalin were: drowsiness, confusion, agitation and nervousness; Rare cases of coma have been reported.
Treatment of an overdose of pregabalin should include general measures of support and possibly hemodialysis, if necessary (see section 4.2 Table 1).

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

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

Mechanism of Action

Pregabalin binds to an auxiliary subunit (α2-δ protein) of calcium channels voltage-dependent in the central nervous system.

4.2 Pharmacokinetic properties

The pharmacokinetic characteristics at steady state of pregabalin are similar in patients with volunteers in epileptic patients treated with antiepileptic drugs and in patients with chronic pain.

Absorption

Pregabalin is rapidly absorbed when administered on an empty stomach, with peak plasma levels occurring within one hour after single or multiple doses. The
Oral bioavailability of pregabalin is estimated to be ≥ 90% and is dose independent.

After repeated administration of the drug, the steady state is reached within 24 to 48 hours Hours, the absorption rate of pregabalin decreases when the drug is administered with foods, resulting in a decrease in Cmax of approximately 25-30% and a delay of tmax of approximately 2.5 hours. However, administration of pregabalin in combination with food does not result in clinically significant effect on its absorption rate.

Distribution

In humans, the apparent volume of distribution of pregabalin after oral administration is about 0.56 l / kg, pregabalin does not bind to plasma proteins.

Biotransformation

Pregabalin is very weakly metabolized in humans, after administration of a dose of radioactively labeled pregabalin, about 98% of the radioactivity found in the urine corresponds to pregabalin in unchanged form. The N-methylated derivative of pregabalin, the major metabolite of Pregabalin, found in the urine, accounted for 0.9% of the dose.

Elimination

Pregabalin is mainly eliminated from the general renal circulation, in the form of unchanged, the average elimination half-life of pregabalin is 6.3 hours. Clearance Plasma and renal clearance of pregabalin are directly proportional to the clearance of creatinine (see section 5.2 Renal insufficiency), dose adjustment is required in patients with patients who have reduced renal function or are treated with hemodialysis.

Linearity / non-linearity

At the recommended daily doses, pregabalin has linear pharmacokinetics, the inter-individual pharmacokinetic variability observed with pregabalin is low (<20%), the pharmacokinetics of repeated pregabalin can be extrapolated on the basis of obtained during single-dose administration. It is therefore not necessary to carry out checks of routine plasma concentrations of pregabalin.

Sex

Clinical studies show that plasma concentrations of pregabalin are not significantly different clinically between men and women.

Renal failure

The clearance of pregabalin is directly proportional to the clearance of creatinine. Furthermore, pregabalin is removed from the plasma by hemodialysis (after a 4-hour hemodialysis)
Plasma concentrations of pregabalin are reduced by approximately 50%), Given that renal elimination is the main route of elimination, a dose reduction in renal insufficiency and additional dose after hemodialysis are necessary.

Hepatic insufficiency

No specific pharmacokinetic studies have been conducted in patients with hepatic impairment, being given that pregabalin does not undergo significant metabolism and is essentially excreted unchanged in the urine, liver failure should not affect significantly the plasma concentrations of pregabalin.

Pediatric population

The pharmacokinetics of pregabalin have been evaluated in pediatric epileptic patients (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) has dose levels of 2.5; 5, 10 and 15 mg / kg / day in a pharmacokinetics and tolerance study.

After oral administration of pregabalin in fasted pediatric patients, the time required

Peak plasma levels were generally similar in all age groups and were 0.5 at 2 hours after dosing.

Parameters of Cmax and AUC of pregabalin increased linearly with respect to the increase in the dose in each age group, AUC was 30% lower in patients pediatric patients weighing less than 30 kg due to increased clearance adjusted to body weight of 43 % in these patients compared to patients whose weight was ≥ 30 kg.

The mean half-life of pregabalin was approximately 3 to 4 hours in patients pediatric patients until the age of 6 years and 4 to 6 hours in pediatric patients from the age of 7 years.

The pharmacokinetic analysis of the population showed that creatinine clearance was a significant covariate of oral clearance of pregabalin, that body weight was a significant covariate of the apparent oral distribution volume of pregabalin and that these correlations were similar in pediatric and adult patients.

The pharmacokinetics of pregabalin have not been studied in patients less than 3 months of age .

Elderly patients (over 65 years old)

The clearance of pregabalin tends to decrease with age, this decrease in oral clearance of pregabalin is the decrease in age-related clearance of creatinine. A reduction of dose of pregabalin may be necessary in patients with decreased renal function related to age .

Breastfeeding mothers

The pharmacokinetics of pregabalin 150 mg administered every 12 hours (300 mg daily) was evaluated in 10 lactating women after at least 12 weeks postpartum.
Breastfeeding had no influence on the pharmacokinetic parameters of pregabalin, pregabalin was excreted in breast milk, steady-state concentrations about 76% of those found in maternal plasma.

The estimated dose ingested by infants through breast milk (assuming average milk consumption of 150 ml / kg / day) of mothers receiving 300 mg / day or the maximum dose of 600 mg / day 0.31 or 0.62 mg / kg / day, respectively.

These estimated doses correspond to approximately 7% of the dose maternal daily total on a mg / kg basis.

4.3 Preclinical safety data

Not applicable

5. PHARMACEUTICAL DATA

5.1 List of excipients

Caramel gelatin capsule
Microcrystalline cellulose
Colloidal silicon dioxide

5.2 Incompatibilities

Not applicable.

5.3 Shelf life

3 years

5.4 Special precautions for storage

Store at a temperature not exceeding 30 ° C.

5.5 Nature and contents of container

2 aluminum pads each containing 10 capsules with a leaflet

5.6 Special precautions for disposal and other handling

No special requirements for disposal.

6. HOLDER OF THE MARKETING AUTHORIZATION

BEKRA PHARMA UK LTD
13 Lavington
London, UNITED KINGDOM

7. MARKETING AUTHORIZATION NUMBERS

8. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

9. DATE OF APPROVAL / UPDATE OF THE TEXT

Date of text approval: 01/2016.