PREGABALIN

Indications

Below, we present the therapeutic indications of pregabalin:

1) Pregabalin is recommended as adjunctive therapy in the treatment of refractory partial seizures, whether with or without secondary generalization, in adult patients (AIFA, EMEA, FDA).
2) Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adult patients (AIFA, EMEA). The FDA has approved pregabalin for the treatment of neuropathic pain in diabetic neuropathy and postherpetic neuralgia, which represent the areas of greatest clinical experience with the drug. Pregabalin is eligible for prescription under the National Health Service for patients experiencing severe and persistent pain due to postherpetic neuralgia following Herpes Zoster infection, neuropathy associated with carcinoma, post-stroke pain, or spinal cord injury-related pain, as well as in cases of polyneuropathies, multiple neuropathies, and painful mononeuropathies, including diabetic neuropathy. In the treatment of mono-, multi-, and polyneuropathies, pregabalin should be administered as an alternative to tricyclic antidepressants, which have shown slightly superior efficacy in clinical studies (EFNS Guidelines, European Federation of Neurological Societies) (AIFA Notes, 2009).
3) Pregabalin is indicated for the treatment of generalized anxiety disorder (GAD) in adult patients (AIFA, EMEA).
4) Pregabalin is indicated for the treatment of fibromyalgia (FDA).

Dosage

Monotherapy

Below, we report the dosage of pregabalin in the various therapeutic indications.

Refractory partial seizures

Oral administration.

Adults: 150-600 mg/day of pregabalin divided into 2-3 doses, either on an empty stomach or with a full stomach. If necessary, the pregabalin dose can be increased from 150 mg/day to 300 mg/day and up to 600 mg/day at intervals of at least 1 week. The discontinuation of pregabalin therapy should be gradual, over a period of at least 7 days.

Neuropathic pain

Oral administration.

Adults: 150-600 mg/day of pregabalin, divided into 2-3 daily doses, either on an empty stomach or with a full stomach. The initial dose of 150 mg/day can be doubled after 3-7 days of treatment; if necessary, after another 7 days, the dose can be increased from 300 to 600 mg/day. The discontinuation of pregabalin therapy should be gradual, over a period of at least 7 days. The FDA, which has authorized pregabalin for the treatment of neuropathic pain associated with postherpetic neuralgia and diabetes (peripheral diabetic neuropathy), reports a maximum dosage of 300 mg/day for the former and 600 mg/day for the latter (300 mg twice daily or 200 mg three times daily).

Generalized anxiety disorder

Oral administration.

Adults: 150-600 mg/day of pregabalin to be divided into 2-3 daily doses. Initiate treatment at the lowest dose, which is 150 mg/day, and then increase the dosage weekly until a therapeutic response is achieved, following this schedule: 300 mg/day, 450 mg/day, 600 mg/day. Do not exceed the maximum dose of 600 mg/day. Gradually taper off pregabalin over one week.

Fibromyalgia

Oral administration.

Adults: 300-600 mg/day of pregabalin, divided into 2-3 daily doses (FDA). In clinical trials, the most significant clinical benefits, both qualitatively and quantitatively (duration of therapeutic effect), were achieved with the higher dose of pregabalin (Crofford et al., 2005 and 2008; Mease et al., 2008).

Special populations

Patients with renal insufficiency

In patients with renal insufficiency, reduce the pregabalin dose by 50% for each 50% reduction in CLcr. Since an increase in half-life is observed in patients with renal insufficiency, consider the possibility of increasing the interval between two successive doses of the drug. In case of dialysis, reintroduce the pregabalin dose after each dialysis session (the drug loss during 4-hour dialysis sessions is approximately 50-60%). The additional dose is 25-100 mg/day.

Adults (CLcr ≥60 ml/min): 150 mg/day (initial dose), 600 mg/day (maximum dose), administered 2-3 times daily.

Adults (CLcr ≥30 and < 60 ml/min): 75 mg/day (initial dose), 300 mg/day (maximum dose), administered 2-3 times daily.

Adults (CLcr ≥15 and < 30 ml/min): 25-50 mg/day (initial dose), 150 mg/day (maximum dose), administered 1-2 times daily.

Adults (CLcr <15 ml/min): 25 mg/day (initial dose), 75 mg/day, single administration.

Patients with hepatic insufficiency

Pregabalin does not undergo hepatic metabolism: therefore, the pharmacokinetic profile is not affected by any potential reduction in hepatic function.

Elderly patients

Elderly patients may experience a physiologic reduction in renal function, which may necessitate an adjustment of the pregabalin dose depending on creatinine clearance values.

Pediatric patients

There are no literature data available regarding the efficacy and safety of pregabalin in this patient population.

Contraindications

Contraindications for the use of pregabalin:

1) Hypersensitivity.

Warnings

Discontinuation of therapy: pregabalin should be discontinued gradually, reducing the dosage progressively over at least 7 days.

Withdrawal syndrome: following the cessation of pregabalin treatment, withdrawal syndrome may occur (LYRICA Product Information).

Patients with renal failure: in patients with renal failure, the pregabalin dose should be adjusted based on creatinine clearance. In end-stage renal disease patients undergoing dialysis, pregabalin should be reintroduced after the dialysis session.

Antiepileptic drugs: administering pregabalin to patients with partial seizures who are already on carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, or valproate treatment does not require dosage adjustments for pregabalin or other drugs (no interaction) (Bockbrader et al., 2002). There is no literature data supporting the switching to pregabalin monotherapy after achieving seizure control with adjunctive pregabalin therapy.

Suicidal ideation and behavior: pregabalin treatment has been associated with mood changes, including the development of depression and suicidal ideation and behaviors. A review conducted by the FDA on antiepileptic drugs highlighted a slight risk of suicidal ideation and behavior associated with antiepileptic therapy. The studied drugs included carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. Based on available data, the use of antiepileptic drug increases the risk of suicidal thoughts and behaviors by about 2 times compared to placebo (0.43% vs. 0.22%). This risk can manifest as early as one week into therapy and persists for 24 weeks (FDA, 2008). Monitor for signs or symptoms of mood changes leading to suicidal thoughts or behaviors.

Congestive heart failure: during post-marketing surveillance, pregabalin has been associated with episodes of heart failure in patients with cardiovascular disease receiving the drug for neuropathic pain (Page et al., 2008; De Smedt et al., 2008; Laville et al., 2008). Pregabalin should be administered cautionsly in this patient population.

Central neuropathic pain from spinal cord injury: in patients with central neuropathic pain resulting from spinal cord injury, pregabalin therapy may lead to a higher incidence of adverse effects, especially drowsiness and neurological side effects. This may be partly due to the concurrent administration of antispasmodic drugs used for this condition.

Hepatic toxicity: pregabalin can rarely induce acute liver damage, as evidenced by alterations in transaminase levels, AST and ALT (Crespo Perez et al., 2008; Einarsdottir et al., 2008; Orive Calzada et al., 2008). Therefore, it is advisable to measure these enzymes before starting pregabalin therapy to establish pre-treatment reference values. Drug-induced liver damage is generally an idiosyncratic

reaction but can also result from an immune-mediated reaction or hepatocellular necrosis caused by the drug itself or its metabolites.

Ophthalmic toxicity: both clinical studies and post-marketing surveillance have associated pregabalin therapy with visual disturbances (reduced visual acuity, vision loss, blurred vision). In clinical trials, the incidence of eye-related adverse effects in patients treated with pregabalin was higher compared to placebo. Discontinuation of the drug usually leads to the resolution of this side effect in patients experiencing visual problems during pregabalin therapy.

Diabetic patients: in diabetic patients who experience weight gain with pregabalin therapy, dosage adjustments of hypoglycemic drugs may be necessary.

Elevated creatine phosphokinase levels: pregabalin has been associated with increases in creatine phosphokinase concentration. In controlled clinical trials, the percentage of patients with an increase in creatine phosphokinase levels reaching 3 times the upper limit of normal interval was 1.5% with pregabalin and 0.7% with placebo. Three cases of rhabdomyolysis were reported in patients receiving pregabalin therapy in controlled clinical trials; however, a causal link between myopathy and the antiepileptic drug was not established because these patients had other risk factors that could have contributed to or triggered the condition. In the presence of symptoms such as muscle weakness or muscle pain associated with malaise and/or fever, assess creatine phosphokinase levels, and, if myopathy is confirmed or suspected, discontinue pregabalin.

Thrombocytopenia: in randomized clinical trials, pregabalin induced a significant reduction in platelet count in a limited number of patients, although it did not lead to significant bleeding episodes.

Constipating drugs: co-administration of pregabalin with constipating drugs, such as opioid analgesics, can result in reduced gastrointestinal tract function, including severe cases of constipation, intestinal obstruction, and paralytic ileus. Evaluate whether it is appropriate to adopt measures to reduce the risk of constipation in patients requiring this combination therapy.

Abuse potential: pregabalin is classified as a drug with low abuse potential. However, this dpes not exclude that it can be use as such, especially in patients with a history of substance abuse (Filipetto et al., 2010; Schwan et al., 2010).

Encephalopathy: rare cases of encephalopathy following sudden discontinuation of pregabalin have been reported in the literature, even in non-epileptic patients. The possibility of developing focal vasogenic edema following abrupt withdrawal of antiepileptic therapy is a known event. A similar condition was reported in a non-epileptic patient receiving pregabalin for the treatment of neuropathic pain resulting from postherpetic neuralgia. Sudden pregabalin cessation led to the onset, 30 hours later, of symptoms including nausea, headache, and ataxia, progressing to delirium 8 days later. Magnetic resonance imaging revealed lesions in the splenium of the corpus callosum similar to those observed in high-altitude cerebral edema (Oaklander, Buchbinder, 2005).

Lactose: patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take pregabalin.

Alertness/vigilance: since pregabalin may cause dizziness and drowsiness, caution is advised when engaging in activities that require constant attention and coordination.

Hypersensitivity: during post-marketing surveillance of pregabalin, cases of angioedema have been reported. In the presence of signs or symptoms indicative of facial and/or mouth edema, discontinue drug administration.

Pregnancy: since pregabalin has demonstrated reproductive toxicity in vivo, the use during pregnancy requires careful evaluation of the balance between maternal benefits and potential fetal toxicity. In epileptic patients, pharmacological treatment should continue during pregnancy to reduce the risk of seizures, which are harmful to both the mother and the baby. To minimize the toxicity associated with antiepileptic drugs, monotherapy is recommended over polytherapy (avoiding combinations of antiepileptic drugs), administering the drug at the minimum effective dose, and using divided doses to avoid concentration peaks throughut the day. The FDA has placed pregabalin in Class C. This category includes drugs where animal studies have shown adverse effects on the fetus, and there are no specific human studies available, as well as drugs for which there are no human or animal studies.

Lactation: pregabalin is excreted in breast milk in vivo. Whether this occurs in humans is unknown. As a precaution, breastfeeding is not recommended during pregabalin therapy.

Interactions

Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproate, gabapentin, oral antidiabetics, diuretics, insulin, phenobarbital: no interactions have been reported between these medications and pregabalin (Bockbrader et al., 2002; Blockbrader et al., 2011).

Tiagabine: co-administration with pregabalin led to a 34.9% increase in tiagabine plasma clearance. The clinical relevance of this observation is not well-established (Bockbrader et al., 2011).

Oral Contraceptives: no interactions have been reported between oral contraceptives (norethisterone/ethinylestradiol) and pregabalin when administered for 21 days over 3 consecutive cycles (days 1-29, 29-49, 57-77) alongside pregabalin (200 mg every 8 hours) administered from day 57 to day 78 (Bockbrader et al., 2004).

Oxycodone, lorazepam, ethanol: no interactions have been reported between these medications and pregabalin concerning respiratory effects. Pregabalin appears to have an additive effect on the cognitive and motor impairment caused by oxycodone. Pregabalin can potentiate the effects of lorazepam and ethanol (LYRICA Product Information).

Pioglitazone, rosiglitazone: co-administration of pioglitazone and pregabalin resulted in increased incidence of peripheral edema and weight gain compared to individual drugs administered as monotherapy. In studies conducted on diabetic neuropathy patients, the incidence of peripheral edema was 3% vs 8% vs 19%, respectively, in patients treated with the thiazolidinedione alone, pregabalin alone, and the combination of both drugs. Weight gain was observed in 0% vs 4% vs 7.5% of patients, respectively (LYRICA Product Information).

Side effects

The most common side effects associated with pregabalin are central nervous system-related. The most frequent ones include dizziness and drowsiness, both dose-dependent, peripheral edema, ataxia (progressive loss of motor coordination), headache, blurred vision, and constipation. Most adverse events were mild/moderate and transient. Analysis of adverse reactions collected through the National Pharmacovigilance Network in the years 2005-2006 (pregabalin was introduced to the Italian market in 2005) highlighted that 36% of reported side effects for pregabalin (total reports: 73) occurred on the same day of the first drug intake, leading to drug discontinuation in 86% of cases.

In patients with peripheral diabetic neuropathy, the incidence of dizziness ranged from 2-10% with placebo to 10% with pregabalin 150 mg/day and increased to 27-39% with pregabalin 300-600 mg/day; the incidence of drowsiness ranged from 3-4% with placebo to 5% with pregabalin 150 mg/day and increased to 20-27% with pregabalin 300-600 mg/day; the incidence of peripheral edema ranged from 1-5% with placebo to 4% with pregabalin 150 mg/day and increased to 7-17% with pregabalin 300-600 mg/day.

In epileptic patients, treatment discontinuation due to adverse effects affected 6.8%, 1.2%, 14.4%, 23.6%, and 5% respectively with doses of 50, 150, 300, and 600 mg/day and placebo. Side effects leading to discontinuation were primarily dizziness (4.2%), drowsiness (3.1%), and ataxia (2%).

For peripheral diabetic neuropathy, the percentage of patients discontinuing pregabalin due to side effects was 3-9% with 150 and 600 mg/day and 11% with 300 mg/day, compared to 3-5% in the placebo group. Pregabalin administration did not affect glycemic control in patients treated for peripheral diabetic neuropathy (Rosenstock et al., 2004).

Additing pregabalin to antiepileptic treatment could induce myoclonus, both in patients with refractory focal epilepsy and with complex partial seizures, but in clinical trials it did not lead to treatment discontinuation.

Cardiovascular: (uncommon: >1/1000, <1/100) tachycardia; (rare: <1/1000) hypotension, peripheral coldness sensation, hypertension.

Eye: common (>1/100, < 1/10) blurred vision, diplopia; (uncommon: >1/1000, <1/100) vision disorders, dry eyes, eye swelling, reduced visual acuity, eye pain, asthenopia, increased tear production; rare (<1/1000) photopsia, eye irritation, mydriasis, object oscillation in the visual field (oscillopsia), altered depth perception, peripheral vision loss, strabismus, visual brightness.

Gastrointestinal: (common: >1/100, <1/10) dry mouth, constipation, vomiting, flatulence; (uncommon: >1/1000, <1/100) abdominal distension, increased salivary secretion, gastroesophageal reflux disease, oral hypoesthesia; (rare: <1/1000) ascites, dysphagia, pancreatitis.

General: (common: >1/100, <1/10) increased appetite, weight gain, fatigue, peripheral edema, feeling of intoxication, edema, gait abnormalities; (uncommon: >1/1000, < 1/100) anorexia, asthenia, falls, thirst, chest constriction; (rare: <1/1000) hypoglycemia, worsened pain, anasarca, fever, tremors, weight loss, hypersensitivity reactions (especially angioedema of face, mouth, eyes, tongue, and upper respiratory tract).

Analysis of pregabalin data collected through the Australian pharmacovigilance network until 2007 reported 22 cases of hypersensitivity reactions to the drug, mainly in the form of skin rashes and angioedema with respiratory difficulty (Aust. Adv. Drug Reaction Bull., 2007).

Genitourinary: (common: >1/100, <1/10) erectile dysfunction; (uncommon: >1/1000, <1/100) dysuria, urinary incontinence, delayed ejaculation, sexual dysfunction; (rare: <1/1000) oliguria, renal failure, amenorrhea, breast pain, breast secretion, dysmenorrhea, breast hypertrophy.

Hematological: (uncommon: >1/1000, <1/100) reduced platelet count; (rare: <1/1000) neutropenia.

Liver/biliary: acute liver damage associated with increased AST and ALT transaminases, cholestasis, jaundice (Crespo Perez et al., 2008; Einarsdottir et al., 2008; Orive Calzada et al., 2008).

Metabolic disorders: (uncommon: >1/1000, <1/100) increased ALT and AST, creatine phosphokinase increase; (rare: <1/1000) increased blood glucose, increased creatinine, decreased potassium.

Musculoskeletal: (uncommon: >1/1000, <1/100) muscle contractions, joint swelling, muscle cramps, myalgia, arthralgia, back pain, limb pain, muscle stiffness; (rare: <1/1000) cervical spasm, neck pain, rhabdomyolysis.

Nervous System: (very common: >1/10) dizziness, drowsiness; (common: >1/100, <1/10) ataxia, attention disturbances, altered coordination, impaired memory, tremors, dysarthria, paresthesia, euphoria, confusion, reduced libido, irritability; (uncommon: >1/1000, <1/100) cognitive disorders, hypoesthesia, visual field disturbances, nystagmus, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, postural dizziness, hyperesthesia, ageusia, burning sensation, intentional tremor, stupor, syncope, depersonalization, anorgasmia, restlessness, depression, agitation, mood swings, worsened insomnia, language impairments, hallucinations, altered dreams, increased libido, panic, apathy, suicidal ideation and behavior; (rare: >1/1000) disinhibition, elevated mood tone.

Ototoxicity: (common: >1/1000, <1/10) vertigo; (rare: <1/1000) hyperacusis.

Respiratory: (uncommon: >1/1000, <1/100) rhinopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, throat constriction, severe respiratory impairment (reporting).

Skin: (uncommon: >1/1000, <1/100) sweating, papular rash; (rare: <1/1000) cold sweats, hives.

Toxicity

Overdose: two cases of intentional pregabalin overdose have been reported in the literature. In one of the cases, the ingested dose of the antiepileptic agent was 8.4 g. In both cases, the maximum serum concentration of pregabalin ranged from 13 to 60 mg/L. Symptoms, appearing after a certain time period, were mainly associated with central depression, leading to coma approximately 3 hours after ingestion. Supportive treatment was administered to maintain vital functions, including assisted respiration (endotracheal intubation and mechanical ventilation). There is no antidote for pregabalin overdose. Based on pharmacokinetic characteristics of pregabalin, hemodialysis is a viable practice to reduce the drug concentration in the blood and enhance its elimination (Wood et al., 2010).

Chronic toxicity: in studies of repeated dose toxicity, in vivo hypo/hyperactivity and ataxia were observed; retinal atrophy (in albino rats) for long-term exposures ≥ 5 times the human exposure after administration of the maximum dose.

Mutagenicity, carcinogenicity: pregabalin is not genotoxic (in vitro and in vivo tests). In mice exposed to higher doses than those in humans, an increase in the incidence of hemangiosarcoma (a malignant tumor developing in vascular endothelium) was observed. not of genotoxic origin but likely caused by platelet alterations and endothelial cell proliferation, was observed. These observations were not seen in rats or humans.

Reproductive toxicity: pregabalin was not found to be teratogenic; fetal toxicity was observed at systemic exposures higher than those in human at the maximum recommended dose. In pre/postnatal toxicity studies, developmental alterations in offspring were observed at double the human exposure to the maximum dose. At doses higher than the maximum human dose, reversible toxic effects on sperm motility were observed. In humans, the administration of pregabalin at the maximum dose of 600 mg/day did not affect spermatogenesis (no differences were reported between the drug and placebo in the percentage of sperm with normal motility in healthy volunteers) (Morrell et al., 2004).

The FDA has categorized pregabalin as Class C. This class includes drugs that have shown harmful effects on the fetus in animal studies, and for which there are no specific human studies, as well as drugs for which there are no studies in either humans or animals.

Although in vivo toxicity profiles did not show statistically significant differences between young and adult animals (rats), young animals exhibited greater sensitivity to the drug: hyperactivity, bruxism, and weight gain at exposures similar to therapeutic doses; effects on the menstrual cycle at exposures equal to 5 times the therapeutic exposure in humans; neurobehavioral/cognitive effects at exposures > 2times (response to acoustic stimuli) or >5 times (learning/memory) the therapeutic exposure in humans.

Pharmacology

Pregabalin (3-isobutyl GABA) (INN: pregabalin) is a structural analogue of the neurotransmitter GABA with a pharmacological profile similar, though not identical, to that of gabapentin. It is the S-enantiomer of 3-aminomethyl-5-methylhexanoic acid and possesses anti-convulsant, analgesic, and anxiolytic activities. Its pharmacological effects have been evaluated in the treatment of epilepsy, neuropathic pain (especially diabetic neuropathy and postherpetic neuralgia), generalized anxiety disorder, and fibromyalgia.

Pregabalin does not interact with GABA receptors A and B, nor does it influence neurotransmitter uptake. Its mechanism of action likely depends on its high-affinity binding with the alpha2-delta protein, an auxiliary subunit of voltage-dependent calcium channels. Binding to this protein reduces Ca- and K-dependent noradrenaline release and K-dependent glutamate release in cortical tissue, representing a prerequisite for the molecule's analgesic activity. It is possible that pregabalin acts through inhibitory modulation of neuronal excitability (Dooley et al., 2002; Fink et al., 2002; Taylor, 2004).

Anticonvulsant Activity

Pregabalin does not have a direct effect on sodium channels but reduces Ca- and K-dependent noradrenaline release in cortical tissue. In animal models, pregabalin exhibits its maximal antiepileptic activity in electroshock-induced seizures. It completely or partially prevents seizures induced by pentylenetetrazol, picrotoxin, and bicuculline but not those induced by strychnine. In genetically predisposed animals, pregabalin has not shown efficacy in reducing spontaneous seizures (absences) (Warner, Figgitt, 2005).

The effects of pregabalin (450 mg/day for 3 days) on cognitive and psychomotor functions were lower compared to alprazolam (3 mg/day for 3 days in healthy volunteers). Both drugs reduced the time required to fall asleep and improved its quality (Hindmarch et al., 2002).

Seizures can be classified into partial and generalized. Partial seizures originate in a specific area of the brain, while generalized seizures have a non-specific onset point. Partial seizures can be simple, not causing a loss of consciousness, or complex, involving loss of consciousness. Currently, drug resistance in epilepsy is estimated to be around 30%. The therapeutic efficacy of pregabalin as adjunctive therapy in patients with refractory partial seizures (simple partial, complex partial, or secondary generalized tonic-clonic seizures) was evaluated in a trial in which the drug at various doses (50, 150, 300, and 600 mg/day) was compared with placebo. The study lasted 12 weeks, and the patients' ages ranged from 12 to 75 years, with an average of 10 seizures in a 28-day period despite receiving up to three concurrently administered antiepileptic drugs (49.9% of patients on two drugs and 19.6% on three drugs) (French et al., 2003). Exclusion criteria included Lennox-Gastaut syndrome, absences, non-epileptic seizures, and status epilepticus in the past year, CLcr <60 ml/min, clinically significant comorbidities, and use of gabapentin in the last week.

In this study the primary endpoint was the reduction in seizure frequency, expressed as the RRatio (*response ratio*). RRatio values range from –100 to +100, where –100 represents complete eradication of seizures, zero indicates no change from baseline, +33 indicates a doubling of seizure frequency compared to baseline, and -33 corresponds to a 50% reduction in seizure frequency. The secondary endpoint was the responder rate, defined as the percentage of patients with a reduction of at least 50% in seizure frequency compared to baseline. Pregabalin was more effective than placebo at doses equal to or greater than 150 mg/day (RRatio: -6, -21, -28, -37, -4, respectively, for pregabalin 50, 150, 300, 600 mg/day, and placebo; reduction in seizure frequency compared to baseline: 12%, 34%, 44%, 54%, and 7%, respectively, for pregabalin 50, 150, 300, 600 mg/day, and placebo). Treatment response was dose-dependent, with 31% vs 40% vs 51% vs 14% of patients responding to pregabalin 150, 300, 600 mg/day, and placebo, respectively. The percentage of patients who discontinued therapy due to lack of efficacy was 1.1% vs 1.1% vs 2.2% vs 4.5% vs 5%, respectively, for pregabalin 50, 150, 300, 600 mg/day, and placebo.

Similar results were obtained in another trial where pregabalin was added as adjunctive therapy for the treatment of refractory partial seizures. RRatio was –11.5 vs –31.4 vs +0.9, respectively, with the drug at doses of 150 or 600 mg/day and placebo. The response rate of patients was 14.1% and 43.5% with the two doses of pregabalin and 6.2% with placebo (Arroyo et al., 2004).

In another trial, administration of pregabalin (600 mg/day) to patients inadequately controlled with combined therapies involving up to 3 antiepileptic drugs simultaneously resulted in RRatio values of –28.4 and –36.1 with pregabalin administered 2 or 3 times a day compared to +0.6 in the placebo group. The response rate was 43% and 49% with the two different pregabalin dosing regimens and 9% with placebo. The mean reduction in seizure frequency was –35.6% vs –48.1% vs –0.8%, respectively, with the fixed and flexible pregabalin dosing regimens, and placebo (Beydoun et al., 2005).

Analyzing the efficacy data from the three described trials, the following indications emerged: the 150 mg/day dose demonstrated superior therapeutic efficacy to placebo in the treatment of complex partial seizures; the 600 mg/day dose was superior to placebo in cases of simple partial, complex partial, and secondary generalized tonic-clonic seizures (Greiner et al., 2004).

Pregabalin exhibited a dose-response relationship in 75% of patients treated for refractory partial seizures, with a capability to reduce seizure frequency by 50% at a dose of 186 mg. The antiepileptic showed superiority to placebo both using a fixed dose (600 mg/day) and employing dose flexibility (150 and 300 mg/day, followed by 450 and 600 mg/day). The flexible regimen involved dose reduction based on patient tolerance to a level ensuring a 4-week seizure-free interval. The mean dose administered in the last month of therapy was 588 mg in the fixed-dose group and 508 mg in the flexible-dose group. The reduction in seizure frequency was 49.3% and 35.4%, respectively, with the fixed or flexible dosing regimens, and patient response rates were 45.3% and 31.3% respectively (Guberman et al., 2004).

Neuralgic Activity

Pregabalin has demonstrated anti-hyperalgesic and anti-allodynic activity in various animal models of neuropathic pain. Hyperalgesia refers to the perception of intense pain in response to mild painful stimuli, while allodynia is the perception of pain in response to stimuli that are normally non-painful. Pregabalin has shown analgesic activity in cases of allodynia induced by neural damage, vincristine, or streptozocin, as well as in cases of hyperalgesia caused by thermal damage or substances like formalin, carrageenan, substance P, or NMDA (N-methyl-D-aspartate). Both hyperalgesia and allodynia activity have been observed at doses of pregabalin 2-4 times lower than gabapentin (Lauria-Horner et al., 2003).

Pregabalin has been evaluated in the treatment of pain associated with diabetic neuropathy, diagnosed for at least 6 months or 1-5 years, in controlled clinical trials. Patients, aged ≥18 years, had a baseline pain score of ≥4 (on a scale from 0 to 10 where 10 represents maximum pain) during the week preceding the study initiation; a value of ≥40 mm on the Visual Analog Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ). Exclusion criteria included patients with CLcr <30 ml/min or ≤60 ml/min and non-response to previous gabapentin therapy (≥1200 mg/day). In clinical trials, pregabalin was administered twice daily (bid) for up to 13 weeks or three times daily (tid) for 8 weeks. Pregabalin demonstrated therapeutic efficacy in reducing diabetic neuropathy-associated pain at doses of 300 and 600 mg/day, administered in 3 doses, but not at doses of 75 and 150 mg/day. Considering that the average initial pain score, on a weekly basis, calculated using the least squares method, was approximately 6-7 in all treated patients, the reduction in this value was 4.29 vs 5.55 with pregabalin 600 mg/day and placebo (Sharma et al., 2000); 3.80 and 3.60 vs 5.06 with pregabalin 300 and 600 mg/day and placebo (Lesser et al., 2004); 3.99 vs 5.46 with pregabalin 300 mg/day and placebo (Rosenstock et al., 2004).

The percentage of responders (patients with a reduction in the pain score ≥50% vs baseline) in the group treated with pregabalin 300 and 600 mg/day (tid) was more than twice that observed in the placebo groups (39-48% vs 15-18%). On average, up to 48% of patients with neuropathic pain showed a reduction equal or greater than 50% in pain intensity. Patients treated with pregabalin three times daily demonstrated better sleep quality compared to the placebo group: the score related to sleep disturbances (calculated using the least squares method) was 2.90 vs 4.05 with pregabalin 600 mg/day and placebo (Sharma et al., 2000a); 2.86 and 2.62 vs 4.17 with pregabalin 300 and 600 mg/day and placebo (Sharma et al., 2000); 2.78 vs 4.32 with pregabalin 300 mg/day and placebo (Rosenstock et al., 2004); the initial score for all patients was between 4.5 and 6.

Both the reduction in weekly pain and the improvement in sleep quality were statistically different between pregabalin (300 and 600 mg/day divided into 3 daily administrations) and placebo after just one week of therapy, and this trend persisted throughout the studies (5-8 weeks). Considering daily pain assessment, the therapeutic efficacy of pregabalin was already evident after the first day in studies where the drug was administered as a fixed dose of 300 mg/day; it became apparent

from the second day to the seventh day in studies that titrated the drug dosage starting with 75 or 100 mg/day and reaching a final dose was 600 mg/day (Rowbotham et al., 2003).

Similar results were observed when pregabalin was administered in two daily doses, both in reducing diabetic neuropathy and herpetic neuralgia-associated pain and in improving sleep quality. Statistically significant results compared to placebo were achieved starting from the first week of therapy (fixed dose of 600 mg/day) and were sustained throughout the 12-week study period. The percentage of patients responsive to treatment was significantly higher with the drug (46 vs 30%) (Toelle et al., 2004).

The primary efficacy endpoints for pregabalin, reduction in pain score, and percentage of responsive patients, did not show significant variations whether pregabalin was administered at fixed doses (initial dose of 300 mg/day for 1 week, maintenance dose of 600 mg/day) or flexible doses (dosage titration for the first 4 weeks, starting from 150 mg/day up to 600 mg/day, and then continuing with the selected optimal dose during the titration phase) (Strojek et al., 2004). The weekly pain assessment score was 3.81 vs 3.60 vs 4.98, respectively, with fixed-dose pregabalin, flexible-dose pregabalin, and placebo (baseline score of 6.50-7). The percentage of responder patients, those with a reduction in pain score was equal or greater than 50%, was 52% vs 48% vs 24%, respectively, with fixed-dose pregabalin, flexible-dose pregabalin, and placebo. Statistically significant deviations from placebo, regarding pain, were observed after 1 week with fixed-dose pregabalin and after 2 weeks with flexible-dose pregabalin; regarding sleep quality, improvement was observed after 1 week in both pregabalin-treated groups (Strojek et al., 2004).

In a comparative study with amitriptyline, patients with diabetic neuropathic pain were treated with amitriptyline (10, 25, and 50 mg/day in the evening) and pregabalin (75, 150, and 300 mg twice daily) (dosage adjusted according to therapeutic response); each treatment lasted for 5 weeks, with a 3-week placebo interval between treatments. Pain relief was judged as good, moderate, and minimal in 48%, 13%, and 15% of patients treated with pregabalin, and in 34%, 11%, and 27% of patients treated with amitriptyline, respectively. Various measurement indices (Patient and Physician's Global Assessment, McGill Pain Questionnaire, Likert Pain Scale, Patient Global Impression of Change) showed no differences between the two treatments. The incidence of adverse events was higher with amitriptyline (65.4% of 52 reported adverse events), and drowsiness was the most frequent side effect for both drugs (43% and 20% of patients treated with amitriptyline and pregabalin, respectively) (Bansal et al., 2009).

In another study, while amitriptyline (75 mg/day) was more effective than placebo ($p=0.01$) in reducing painful symptoms in patients with diabetic neuropathy, pregabalin (titrated to 600 mg/day) was not equally effective ($p=0.08$). A similar outcome was observed for the percentage of responder patients (≥50% reduction in pain): statistically significant difference for amitriptyline ($p=0.03$), but not for pregabalin (0.24) (Drug and Therapeutics Bulletin, 2006).

Anxiolytic Activity

In phase II and III studies, pregabalin has demonstrated anxiolytic activity in generalized anxiety disorder, social phobia, and panic disorder (Lauria-Horner et al., 2003).

Pregabalin, at all administered dosages (200, 300, 400, and 600 mg/day), has shown efficacy in improving both psychological and somatic symptoms associated with generalized anxiety disorder. The therapeutic efficacy of pregabalin in controlling somatic symptoms is found to be comparable to benzodiazepines (Hamilton Anxiety Scale score reduction: -9.2 vs -10.3 vs -12 vs -6.8 points, respectively, with pregabalin 150 mg/day vs pregabalin 600 mg/day vs lorazepam 6 mg/day vs placebo) (Pande et al., 2003). Based on tolerability profile and data collected from studies on healthy volunteers, pregabalin appears to offer additional benefits in terms of tolerability compared to both benzodiazepines and venlafaxine (Baldwin, Ajel, 2007).

The administration of pregabalin using therapeutic regimens involving the daily dose division into 2 or 3 administrations showed no differences in efficacy or tolerability (Pohl et al., 2005). In placebo-controlled clinical trials (7 studies), a reduction of ≥50% in the overall Hamilton Anxiety Scale score was achieved in 52% of patients treated with pregabalin compared to 38% in the placebo group.

In patients with an initial Hamilton Anxiety Scale (HAM-A) score ≥20, the improvement in psychological and somatic symptoms with pregabalin was rapid: after 1 week of treatment, the reduction of HAM-A score by ≥30% was observed, and similar or greater improvement was found in a percentage of patients ≥38% of each subsequent assessment. Furthermore, the therapy discontinuation rate due to adverse events was comparable to that observed in the placebo group (9-13% vs 8%, respectively, with pregabalin and placebo) (Pohl et al., 2005).

In a clinical study on the use of pregabalin in the treatment of social phobia, although the reduction in the score of the Liebowitz Social Anxiety Scale (LSAS) was statistically superior to placebo ($p=0.024$), at the maximum recommended dose of pregabalin (600 mg/day) after 11 weeks of therapy, the reduction was not clinically significant as it was less than the minimum required change of 20 points in a range from 0 to 144 (Pande et al., 2004).

Fibromyalgia

Fibromyalgia is a pathological condition whose cause has not yet been definitively determined. The accompanying symptoms, which are nonspecific, include pain, fatigue, and non-restorative sleep. These symptoms may be associated with headache, gastrointestinal disturbances, dysmenorrhea, anxiety, and/or depression. It is more common in women than in men (USA data: 3.4% vs 0.5%) (Wolfe et al., 1995).

The administration of pregabalin to patients with fibromyalgia was more effective than placebo in reducing pain at the dose of 450 mg/day ($p\leq0.001$), but not at doses of 300 mg/day and 150 mg/day (Crofford et al., 2005). In the pregabalin-treated

group, 29% of patients achieved at least a 50% reduction in pain compared to 13% in the placebo group (p=0.003). approximately half of the treated patients experienced dizziness, and slightly less than a third experienced drowsiness.

In another study, pregabalin was administered at doses of 300, 450, and 600 mg/day to patients with fibromyalgia (94% female). The comparison group received placebo. The study lasted for 13 weeks. All three doses tested were more effective than placebo in reducing pain. Although the difference reached statistical significance, the pain reduction with the drug was limited, amounting to approximately 0.5 points on a 10-point scale (0-10) (minimal clinical relevance). This difference remained consistent throughout the study only for the highest dose, 600 mg/day. The percentage of patients who achieved at least a 30% reduction in pain was 43-44% with pregabalin (regardless of the dose) and 35% with placebo (not statistically significant difference). There were no differences between pregabalin and placebo in terms of impact on fatigue and overall Fibromyalgia Impact Questionnaire (FIQ) score (secondary clinical outcomes). The percentage of patients discontinuing the study due to adverse events was 19% vs 22% vs 33% with doses of 300, 450, and 600 mg/day, respectively (Mease et al., 2008).

Analysis of sleep-related data (Medical Outcomes Study (MOS) Sleep Scale and sleep quality assessment through daily diary) obtained from clinical studies vs placebo has shown a statistically significant effect of pregabalin on the following parameters (vs placebo): MOS Sleep Disturbance ($p<0.01$), Sleep Quality Diary ($p<0.001$), MOS Quantity of Sleep ($p<0.003$), MOS Sleep Problems index score ($p<0.02$). By using models, it appears that 40-80% of pregabalin's sleep benefits may be due to a direct effect, while the remaining percentage is due to an indirect effect resulting from the drug's analgesic action (Russell et al., 2009).

The assessment of pregabalin's long-term analgesic effects in fibromyalgia treatment was conducted through a clinical study that enrolled patients previously treated with the drug who had achieved at least a 50% reduction in pain (responder patients). These patients were randomized to receive pregabalin or placebo for 26 weeks, after which the time to therapeutic response loss (defined as a reduction in pain <30% or worsening of fibromyalgia) was evaluated. Approximately 50% of patients in the placebo group experienced therapeutic response loss after 19 days, while in the pregabalin-treated group, 50% still had a therapeutic response at the end of the study. After 26 weeks, the percentage of patients meeting the criteria for "loss of therapeutic response" was 61% vs 32% with placebo and pregabalin, respectively (Crofford et al., 2008). The percentage of patients still showing a therapeutic response after 6 months was 32%; in this group, the average time to response loss was 34 days (Siler et al., 2011).

In a phase III study, the efficacy of controlled-release pregabalin formulation for potential once-daily use was analyzed. The double-blind randomized study demonstrated statistically significant beneficial effects of controlled-release pregabalin compared to placebo. A total of 441 patients were involved, treated with an initial dose of 165 mg/day of pregabalin for three weeks, increased to 495 mg/day for another three weeks. At the end of this period, patients who had achieved a >50%

pain reduction were given either pregabalin or placebo at the optimal dose (330-495 mg/day) (63 patients with pregabalin, 58 with placebo). The evaluated parameter was the mean time to loss of therapeutic response (LTR), which was significantly longer in the pregabalin-treated group (58 days vs 22 days, respectively; p=0.02). Furthermore, the treatment was well-tolerated with modest side effects (Arnold et al., 2014).

Pharmacokinetics

Following oral administration, pregabalin is rapidly absorbed. The pharmacokinetic profile is linear: peak plasma concentration and AUC, after single administration, are dose-dependent. Pharmacokinetics after multiple doses can be predicted from data obtained after a single dose, making periodic monitoring of drug plasma concentrations unnecessary.

Interindividual variability in pharmacokinetic parameters is less than 20%.

Food reduces peak plasma concentration by 25-30% and delays time to peak pasma concentration by 2.5 hours without altering AUC and half-life (Willmore, 2000).

Bioavailability: ≥90%, independent of the dose.

Peak plasma concentration: 0.0383-9.46 mcg/ml (single dose of 1-300 mg).

AUC: 0.233-66.3 mcg/h/ml (single dose of 1-300 mg).

Time to peak plasma concentration: 1.3 hours.

Steady state after repeated administrations is achieved within 24-48 hours.

Pregabalin does not bind to plasma proteins; in vivo, it crosses the blood-brain barrier, placental barrier, and is secreted in breast milk.

Vd: 0.56 L/kg.

Vd is found to be dependent on body weight and gender (Bockbrader et al., 2011a).

Pregabalin does not undergo hepatic metabolism: 98% of the administered dose is excreted unchanged in the urine, with 0.9% attributed to the N-demethylated derivative and 0.4% to unidentified metabolites. Less than 1% of the pregabalin dose is excreted in the urine. Preclinical studies have not indicated racemization of the S-enantiomer into the R-enantiomer.

Half-life: 6 (4.6-6.8) hours. It is dose-independent and does not vary with repeated dosing.

Oral clearance (Cl/F) of pregabalin is directly proportional to creatinine clearance and is not influenced by age, gender, race, menopause, or concurrent administration of other antiepileptic drugs (Corrigan et al., 2002; Bockbrader et al., 2011a).

Oral clearance: approximately 56% of CLcr.

Renal clearance: approximately 58% of CLcr.

Patients with renal failure

In cases of renal failure, there is a prolongation of half-life and an increase in AUC:

1) Patients with CLcr >60 ml/min have an oral clearance of 56.5 ml/min and a half-life of 9.1 hours.

2) Patients with CLcr between 30 and 60 ml/min have an oral clearance of 30.6 ml/min and a half-life of 16.7 hours.
3) Patients with CLcr between 15 and 29 ml/min have an oral clearance of 16.7 ml/min and a half-life of 25 hours.
4) Patients with CLcr <15 ml/min have an oral clearance of 8.3 ml/min and a half-life of 48.7 hours.

In cases of end-stage renal disease, dialysis removes approximately 50-60% of circulating drug over a 4 hours session; therefore, it is pregabalin dose supplementation is necessary after the dialysis session.

Classification

Chemical formula

C8H17NO2

Molecular weight

PM 159.23

Atc code

N03AX16

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