

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{Invented name} 25 mg capsule, hard
{Invented name} 50 mg capsule, hard
{Invented name} 75 mg capsule, hard
{Invented name} 100 mg capsule, hard
{Invented name} 150 mg capsule, hard
{Invented name} 200 mg capsule, hard
{Invented name} 225 mg capsule, hard
{Invented name} 300 mg capsule, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[{Invented name} 25 mg capsule, hard](#)

Each hard capsule contains 25 mg of pregabalin.

[{Invented name} 50 mg capsule, hard](#)

Each hard capsule contains 50 mg of pregabalin

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[{Invented name} 75 mg capsule, hard](#)

Each hard capsule contains 75 mg of pregabalin

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[{Invented name} 100 mg capsule, hard](#)

Each hard capsule contains 100 mg of pregabalin

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[{Invented name} 150 mg capsule, hard](#)

Each hard capsule contains 150 mg of pregabalin

[{Invented name} 200 mg capsule, hard](#)

Each hard capsule contains 200 mg of pregabalin

[{Invented name} 225 mg capsule, hard](#)

Each hard capsule contains 225 mg of pregabalin

[{Invented name} 300 mg capsule, hard](#)

Each hard capsule contains 300 mg of pregabalin

Excipients:

[{Invented name} 25 mg capsule, hard](#)

Each hard capsule 25 mg also contains 33,00 mg lactose monohydrate.

[{Invented name} 50 mg capsule, hard](#)

Each hard capsule 50 mg also contains 66,00 mg lactose monohydrate.

[{Invented name} 75 mg capsule, hard](#)

Each hard capsule 75 mg also contains 8,00 mg lactose monohydrate.

[{Invented name} 100 mg capsule, hard](#)

Each hard capsule 100 mg also contains 10,667 mg lactose monohydrate.

[{Invented name} 150 mg capsule, hard](#)

Each hard capsule 150 mg also contains 16,00 mg lactose monohydrate.

{Invented name} 200 mg capsule, hard

Each hard capsule 200 mg also contains 21,333 mg lactose monohydrate.

{Invented name} 225 mg capsule, hard

Each hard capsule 225 mg also contains 24,00 mg lactose monohydrate.

{Invented name} 300 mg capsule, hard

Each hard capsule 300 mg also contains 32,00 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

{Invented name} 25 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 4, cap: opaque grey colour, body: opaque grey colour. Content of capsules: white to off-white powder.

{Invented name} 50 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 3, cap: opaque ivory colour, body: opaque ivory colour. Content of capsules: white to off-white powder.

{Invented name} 75 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 4, cap: opaque red-brown colour, body: opaque white with black imprint "75 mg". Content of capsules: white to off-white powder.

{Invented name} 100 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 3, cap: opaque red-brown colour, body: opaque red-brown with black imprint "100 mg". Content of capsules: white to off-white powder.

{Invented name} 150 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 2, cap: opaque white colour, body: opaque white colour. Content of capsules: white to off-white powder.

{Invented name} 200 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 1, cap: opaque caramel colour, body: opaque caramel colour. Content of capsules: white to off-white powder.

{Invented name} 225 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 0, cap: opaque caramel colour, body: opaque white with black imprint "225 mg". Content of capsules: white to off-white powder.

{Invented name} 300 mg ~~hard~~ capsule, hard:

hard gelatin capsules, size no. 0, cap: opaque red-brown colour, body: opaque white. Content of capsules: white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

{Invented name} is indicated for the treatment of peripheral and central neuropathic pain in adults.

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Epilepsy

{Invented name} is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

{Invented name} is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

4.2 Posology and method of 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.

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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.

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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 (see sections 4.4 and 4.8).

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Patients with renal impairment

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

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Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance (see section 5.2), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 determined using the following formula:

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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 [†]

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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

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Patients with hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2).

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Paediatric population

The safety and efficacy of {Invented name} in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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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 section 5.2](#)).

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Method of administration

{Invented name} may be taken with or without food.

{Invented name} is for oral use only.

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 accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

Hypersensitivity reactions

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion, and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing

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.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section 5.1).

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

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.

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.

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

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, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate

treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case-control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19–2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04–2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24–5.06]).

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Lactose intolerance

{Invented name} contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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 ethinyl oestradiol

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol 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.

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Kommentiert [JN2]: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or 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.

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Kommentiert [JN3]: In Lyrica

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Interactions and the elderly

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

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Pregnancy

There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. {Invented name} should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

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Breast-feeding

Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman

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Fertility

There are no clinical data on the effects of pregabalin on female fertility.

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In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

{Invented name} may have minor or moderate influence on the ability to drive and use machines. {Invented name} may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

The pregabalin clinical programme involved over 8,900 patients who were exposed to pregabalin, of whom over 5,600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse

reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In ~~the~~ table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 (see section 4.4).

Additional reactions reported from post-marketing experience are included in italics in the list below.

Table 2. Pregabalin Adverse Drug Reactions

System Organ Class	Adverse drug reactions				
	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Nasopharyngitis			
Blood and lymphatic system disorders			Neutropenia		
Immune system disorders			<i>Hypersensitivity</i>	<i>Angioedema, allergic reaction</i>	
Metabolism and nutrition disorders		Appetite increased	Anorexia, hypoglycaemia		
Psychiatric disorders		Euphoric mood, confusion, irritability, libido decreased , disorientation, insomnia, libido decreased	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, <i>aggression</i> , mood swings, depersonalisation, word finding, difficulty, abnormal dreams, libido increased, anorgasmia, apathy	Disinhibition	
Nervous system disorders	Dizziness, somnolence, headache	Ataxia, coordination abnormal, tremor, dysarthria,	Syncope, stupor, myoclonus, <i>loss of consciousness</i> , psychomotor hyperactivity,	<i>Convulsions</i> , parosmia, hypokinesia, dysgraphia	

		amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy	dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, <i>mental impairment</i> , speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, <i>malaise</i>		
Eye disorders		Visio blurred, diplopia	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation	<i>Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness</i>	
Ear and labyrinth disorders		Vertigo	Hyperacusis		
Cardiac disorders			Tachycardia, atrioventricular block first degree, sinus bradycardia, <i>congestive heart failure</i>	<i>QT prolongation, sinus tachycardia, sinus arrhythmia</i>	
Vascular disorders			Hypotension, hypertension, hot flushes, flushing, peripheral coldness		
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness	<i>Pulmonary oedema, throat tightness</i>	
Gastrointestinal disorders		Vomiting, <i>nausea</i> , constipation, <i>diarrhoea</i> , flatulence, abdominal distension, dry mouth	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral	Ascites, pancreatitis, <i>swollen tongue</i> , dysphagia	
Hepatobiliary disorders			Elevated liver enzymes*	Jaundice	Hepatic failure, hepatitis

Skin and subcutaneous tissue disorders			Rash papular, urticaria, hyperhidrosis, <i>pruritus</i>	<i>Stevens Johnson syndrome</i> , cold sweat	
Musculoskeletal and connective tissue disorders		Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness	Rhabdomyolysis	
Renal and urinary disorders			Urinary incontinence, dysuria	Renal failure, oliguria, <i>urinary retention</i>	
Reproductive system and breast disorders		Erectile dysfunction	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain	Amenorrhoea, breast discharge, breast enlargement, <i>gynaecomastia</i>	
General disorders and administration site conditions		Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue	Generalised oedema, <i>face oedema</i> , chest tightness, pain, pyrexia, thirst, chills, asthenia		
Investigations		Weight increased	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased	White blood cell count decreased	

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

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.

Paediatric population

The pregabalin safety profile observed in ~~three~~four paediatric studies in patients with partial seizures with

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or without secondary generalization (12-week efficacy and safety study in patients 4 to 16 years of age, ~~with partial onset~~
The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the post-marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 ($\alpha_2\text{-}\delta$ protein) of voltage-gated calcium channels in the central nervous system.

Clinical efficacy and safety

Neuropathic pain

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing

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somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

In the controlled clinical trial in central neuropathic pain 22% of the pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

Epilepsy

Adjunctive Treatment

Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by week 1.

Paediatric population

The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) with partial onset seizures were similar to those observed in adults. Results of a 12-week

In the 12-week placebo-controlled study, paediatric patients (4 to 16 years of age) were assigned to pregabalin

In the 14-day placebo-controlled study, paediatric patients (1 month to younger than 4 years of age)

Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with twice a day dosing (BID). Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated fundoscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Fundoscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

5.2 Pharmacokinetic properties

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

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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 $\geq 90\%$ 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.

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Distribution

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, 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. In preclinical studies, 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 (see section 5.2 Renal impairment). Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

Linearity/non-linearity

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low ($<20\%$). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Gender

Clinical trials indicate that 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 (see section 4.2 Table 1).

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.

Paediatric population

Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Pregabalin C_{max} and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥ 30 kg.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

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 (see section 4.2 Table 1).

Breast-feeding mothers

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures > 2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Formatiert: Tiefgestellt

Pregabalin is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content:
Lactose monohydrate
Maize starch
Talc

[\[Invented name\] 25 mg capsule, hard:](#)
[Capsule shell \(25 mg\)](#)
Iron oxide black (E172)
Titanium dioxide (E171)
Gelatin

[\[Invented name\] 50 mg capsule, hard:](#)
[Capsule shell \(50 mg\)](#)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Gelatin

[\[Invented name\] 75 mg capsule, hard:](#)
[Capsule shell \(75 mg\)](#)
Iron oxide red (E172)
Titanium dioxide (E171)
Gelatin

[\[Invented name\] 100 mg capsule, hard:](#)
[Capsule shell \(100 mg\)](#)
Iron oxide red (E172)
Titanium dioxide (E171)
Gelatin

Formatiert: Schriftart: Nicht Kursiv

[Invented name] 150 mg capsule, hard

Capsule shell ~~(150 mg)~~

Titanium dioxide (E171)

Gelatin

[Invented name] 200 mg capsule, hard

Capsule shell ~~(200 mg)~~

Iron oxide red (E172)

Iron oxide yellow (E172)

Titanium dioxide (E171)

Gelatin

[Invented name] 225 mg capsule, hard

Capsule shell ~~(225 mg)~~

Iron oxide red (E172)

Iron oxide yellow (E172)

Titanium dioxide (E171)

Gelatin

[Invented name] 300 mg capsule, hard

Capsule shell ~~(300 mg)~~

Iron oxide red (E172)

Titanium dioxide (E171)

Gelatin

Printing Ink (75 mg, 100 mg, 225 mg):

Shellac (E 904)

Iron oxide black (E172)

Propylene glycol

Ammonia solution, concentrated 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters placed into cardboard boxes containing: 14, 20, 28, 50, 56, 96 capsules, hard

Not all pack sizes may be marketed.

Formatiert: Schriftart: Nicht Kursiv

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

{To be completed nationally}

8. MARKETING AUTHORISATION NUMBER(S)

{To be completed nationally}

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT