Dexcel® pharma

Regadex® Capsules

(Pregabalin)

1. NAME OF THE MEDICINAL PRODUCT

Regadex

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg, 50 mg, 75 mg, 150 mg or 300 mg of pregabalin.

3. PHARMACEUTICAL FORM

25 mg: Size 4, hard gelatin capsule, white cap and white body. "DP25" imprinted on body in black.

50 mg: Size 3, hard gelatin capsule, grey cap and white body. "DP50" imprinted on body in black.

75 mg: Size 4, hard gelatin capsule, brown cap and white body. "DP75" imprinted on body in black.

150 mg: Size 2, hard gelatin capsule, white cap and white body. "DP150" imprinted on body in black.

300 mg: Size 0, hard gelatin capsule, brown cap and white body. "DP300" imprinted on body in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Pregabalin is indicated for the treatment of neuropathic pain, which includes diabetic peripheral neuropathy and post-herpetic neuralgia, in adults.

Epilepsy

Pregabalin is indicated as adjunctive therapy of partial seizures, with or without secondary generalisation, in adults.

Generalised anxiety disorder

Pregabalin is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Fibromyalgia

Pregabalin is indicated for the management of fibromyalgia.

4.2 Posology and method of administration

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Pregabalin may be taken with or without food.

Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage 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. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage of 600 mg per day may be achieved after an additional week.

Generalised anxiety disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week, the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

Fibromyalgia

The recommended dose of pregabalin is 300 to 450 mg per day. Dosing should begin at 75 mg two times a day (150 mg per day) and may be increased to 150 mg two times a day (300 mg per day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg per day may be further increased to 225 mg two times a day (450 mg per day). Although pregabalin was also studied at 600 mg per day, there is no evidence that this dose confers additional benefit and that this dose was less tolerated.

In view of the dose-dependent adverse reactions, treatment with doses above 450 mg per day is not recommended.

Discontinuation of pregabalin

If pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Patients with renal impairment

Dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}) (see Section **5.2 Pharmacokinetic properties**, Pharmacokinetics in special patient groups, Renal impairment), as indicated in Table 1 determined using the following formula:

$$CL_{cr}\ (mL/min) = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} (\times 0.85 \text{ for female patients})$$

For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

	Total Pregabalin Daily Dose*		
Creatinine Clearance (CLcr) (mL/min)	**Starting Dose (mg/day)**	**Maximum Dose (mg/day)**	**Dose Regimen**
≥60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	QD or BID
<15	25	75	QD
Supplementary Dosage Following Haemodialysis (mg)			
	25	100	Single dose+

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

Use in patients with hepatic impairment

No dosage adjustment is required for patients with hepatic impairment (see Section **5.2 Pharmacokinetic properties**, Pharmacokinetics in special patient groups, Hepatic impairment).

Use in children and adolescents (12 to 17 years of age)

The safety and effectiveness of pregabalin in paediatric patients below the age of 12 years and adolescents have not been established. The use in children and adolescents is not recommended (see Section **5.3 Preclinical safety data**).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to decreased renal function (see Section **5.2 Pharmacokinetic properties**, Pharmacokinetics in special patient groups, Elderly (over 65 years of age)).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Regadex 50 mg capsules contain Allura red AC (E129) which may cause allergic reactions.

Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications.

There have been reports in the post-marketing 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.

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 medication.

In the post-marketing experience, transient visual blurring and other changes in visual acuity have been reported in patients treated with pregabalin. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

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.

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, hyperhidrosis, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. Cases of misuse, abuse and dependence have been reported in the post-marketing database. As with any central nervous system (CNS) active drug, carefully evaluate patients for history of drug abuse and/or psychiatric disorders. Patients should be observed for signs of pregabalin misuse, abuse or dependence (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

Concerning discontinuation of long-term treatment of pregabalin, there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal function following discontinuation or dose reduction of pregabalin has been reported.

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. Because there are limited data on severe congestive heart failure patients, pregabalin should be used with caution in these patients (see Section **4.8 Undesirable effects**).

Treatment with pregabalin was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum values were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated patients had events reported as rhabdomyolysis in pre-marketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Regadex (pregabalin) should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur in the context of symptoms of myopathy.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials 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.

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. In an observational 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 to 2.36]).

There is evidence from case reports, human studies, and animal studies associating pregabalin with serious, life-threatening, or fatal respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment. When the decision is made to co-prescribe pregabalin with another CNS depressant, particularly an opioid, or to prescribe pregabalin to patients with underlying respiratory impairment, monitor patients for symptoms of respiratory depression and sedation, and consider initiating pregabalin at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including pregabalin).

There is more limited evidence from case reports, animal studies, and human studies associating pregabalin with serious respiratory depression, without co-administered CNS depressants or without underlying respiratory impairment. Patients with renal impairment might be at higher risk of experiencing this severe adverse reaction.

Women of child-bearing potential/Contraception

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of child-bearing potential must use effective contraception during treatment (see Section **4.6 Fertility, pregnancy and lactation**).

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.

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.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either substance. Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

In the post-marketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and other CNS depressant medications, including in patients who are substance abusers. 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.

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of pregabalin in pregnant women.

Data from an observational study, which included more than 2,700 pregnancies exposed to pregabalin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, is as follows:

Major congenital malformations (MCM)

The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01-1.65)) or to duloxetine (1.39 (1.07-1.82)).

Birth and post-natal neurodevelopmental outcomes

There were no statistically significant findings for stillbirth, low birth weight, preterm birth, small for gestational age (SGA), low Apgar score at 5 minutes, and microcephaly. Adjusted prevalence ratios (aPRs, and 95% confidence intervals) results for the meta-analysis for stillbirth, low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed to antiepileptic drugs (AEDs) of 1.72 (1.02-2.91), 1.05 (0.91-1.21), 1.13 (0.99-1.29), 1.21 (1.01-1.44), 1.18 (0.95-1.48), and 1.09 (0.88-1.36) respectively.

In paediatric population exposed *in utero*, the study did not provide evidence of an increased risk for attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities (ID). In the meta-analyses of the neurodevelopmental outcomes (ADHD, ASD, and ID), results for ADHD, ASD, and ID for pregabalin-exposed compared to unexposed to AEDs were 1.32 (1.04-1.67), 1.00 (0.68-1.47), and 1.03 (0.80-1.32) respectively.

Studies in animals have shown reproductive toxicity (see Section **5.3 Preclinical safety data**). Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of child-bearing potential.

Lactation

Pregabalin is excreted in the milk of lactating women (see Section **5.2 Pharmacokinetic properties**). As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Pregabalin 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 medication affects their ability to perform these activities.

4.8 Undesirable effects

The pregabalin clinical program involved over 12,000 patients who were exposed to pregabalin, of whom over 7,000 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 14% 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.

Selected adverse drug reactions that were treatment related in the pooled analysis of clinical trials, are listed in the table below by System Organ Class (SOC). The frequency of these terms has been based on all-causality adverse drug reactions in the clinical trial data set (very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100) and rare (<1/1000)).

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medications.

Table 2. Adverse Drug Reactions from Clinical Trial Experience

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, depression, disorientation, insomnia, libido decreased
Uncommon	Hallucination, restlessness, agitation, depressed mood, elevated mood, mood swings, depersonalization, abnormal dreams, word finding difficulty, libido increased, anorgasmia
Rare	Panic attack, disinhibition, apathy

Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, co-ordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, myoclonus, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hyperaesthesia, burning sensation
Rare	Stupor, parosmia, hypokinesia, ageusia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	Oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia
Rare	Sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring
Rare	Throat tightness, nasal dryness
Gastrointestinal disorders	
Common	Vomiting, constipation, flatulence, abdominal distension, dry mouth
Uncommon	Gastro-oesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, sweating
Rare	Cold sweat
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Uncommon	Erectile dysfunction, sexual dysfunction, ejaculation delayed, dysmenorrhoea
Rare	Breast pain, amenorrhoea, breast discharge, breast enlargement
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased, blood creatinine increased

The following adverse drug reactions were reported during POST-MARKETING SURVEILLANCE:

Immune system disorder: Uncommon: Hypersensitivity; Rare: Angioedema, allergic reaction

Nervous system disorders: Very Common: Headache; Uncommon: Loss of consciousness, mental impairment

Eye disorders: Rare: Keratitis§

Cardiac disorders: Rare: Congestive heart failure

Respiratory, thoracic and mediastinal disorders: Rare: Pulmonary oedema§

Gastrointestinal disorders: Common: Nausea, diarrhoea; Rare: Swollen tongue

Skin and subcutaneous tissue disorders: Uncommon: Face swelling, pruritus; Rare: Stevens-Johnson syndrome

Renal and urinary disorders: Rare: Urinary retention

Reproductive system and breast disorders: Rare: Gynaecomastia§

General disorders and administration site conditions: Uncommon: Malaise

§ Adverse drug reaction frequency estimated using "The Rule of 3".

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were reported.

In the post-marketing experience, the most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation, and restlessness. Seizures were also reported.
Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see Section **4.2 Posology and method of administration**, Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03A (proposed).
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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system.

Evidence from animal models with nerve damage has shown that pregabalin reduces calcium dependent release of pronociceptive neurotransmitters in the spinal cord possibly by disrupting calcium trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage suggests the antinociceptive activities of pregabalin may also be mediated through interactions with the descending noradrenergic and serotonergic pathways.

Clinical experience

Neuropathic pain

Efficacy has been shown in studies in diabetic neuropathy and post-herpetic neuralgia. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 9 controlled clinical studies of up to 13 weeks with twice a day dosing and up to 8 weeks with three times a day dosing. Overall, the safety and efficacy profiles for twice a day and three times a day dosing regimens were similar.

In clinical trials up to 13 weeks, a reduction in pain was seen by Week 1 and was maintained throughout the treatment period.

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

Epilepsy

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

A reduction in seizure frequency was observed by Week 1.

Generalised anxiety disorder

Pregabalin has been studied in 6 controlled studies of 4 to 6 weeks duration, an elderly study of 8 weeks 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 weeks 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.

Fibromyalgia

Pregabalin as monotherapy has been studied in 5 placebo-controlled studies, three of 12 weeks fixed-dose duration, one of 7 weeks fixed-dose duration, and a 6-month study demonstrating long-term efficacy. Pregabalin treatment in all fixed-dose studies produced a significant reduction in pain associated with fibromyalgia at doses from 300 to 600 mg per day (BID).

In the three 12-week fixed-dose studies, 40% of pregabalin-treated patients experienced a 30% or more improvement in pain score versus 28% of the patients on placebo; 23% of treated patients experienced a 50% or more improvement in pain score versus 15% of the patients on placebo.

Pregabalin produced significantly superior global assessment scores via the Patient Global Impression of Change (PGIC) in the three 12-week fixed-dose studies as compared to placebo treatment (41% patients feeling very much or much improved on pregabalin versus 29% on placebo). As measured by Fibromyalgia Impact Questionnaire (FIQ), pregabalin produced a statistically significant improvement in function versus placebo treatment in 2 out of the 3 fixed-dose studies in which it was evaluated.

Pregabalin treatment produced significant improvements in patient-reported sleep outcomes in the 4 fixed-dose studies as measured by Medical Outcomes Study Sleep Scale (MOS-SS) Sleep disturbance subscale, MOS-SS overall sleep problem index, and the daily sleep quality diary.

In the 6-month study, improvement in pain, global assessment (PGIC), function (FIQ total score) and sleep (MOS-SS Sleep disturbance subscale) were maintained for pregabalin-treated patients for a significantly longer period compared to placebo.

Pregabalin 600 mg per day showed an additional improvement in patient-reported sleep outcomes as compared to 300 and 450 mg per day; mean effects on pain, global assessment, and FIQ were similar at 450 and 600 mg per day, although the 600 mg per day dose was less well tolerated.

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.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25%-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

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.

Metabolism

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 Pharmacokinetic properties**, Pharmacokinetics in special patient groups, Renal impairment).

Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see Section **4.2 Posology and method of administration**, 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.

Pharmacokinetics in special patient groups

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, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see Section **4.2 Posology and method of administration**, 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.

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 Posology and method of administration**, 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 post-partum. 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 average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose.

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.

Teratogenicity

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

Mutagenicity

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

Carcinogenicity

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 per 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. Neurobehavioral/cognitive effects were observed in juvenile rats 1-2 weeks after exposure >2 times (acoustic startle response) or >5 times (learning/memory) 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

For 25 mg:
Capsule content: Strach, pregelatinized, Mannitol, Magnesium stearate
Capsule shell: Gelatin, Titanium dioxide (E171)
Black ink: Shellac, Propylene glycol (E1520), Strong ammonia solution (E527), Potassium Hydroxide, Black iron oxide (E172)

For 50 mg:
Capsule content: Strach, pregelatinized, Mannitol, Magnesium stearate
Capsule shell: Gelatin, Titanium dioxide (E171) , Allura red AC (E129) and Brilliant blue FCF (E133)
Black ink: Shellac, Propylene glycol (E1520), Strong ammonia solution (E527), Potassium Hydroxide, Black iron oxide (E172)

For 75 mg:
Capsule content: Strach, pregelatinized, Magnesium stearate
Capsule shell: Gelatin, Titanium dioxide (E171), Red Iron oxide (E172), Yellow iron oxide (E172), Black iron oxide (E172)
Black ink: Shellac, Propylene glycol (E1520), Strong ammonia solution (E527), Potassium Hydroxide, Black iron oxide (E172)

For 150 mg:
Capsule content: Strach, pregelatinized, Magnesium stearate
Capsule shell: Gelatin, Titanium dioxide (E171)
Black ink: Shellac, Propylene glycol (E1520), Strong ammonia solution (E527), Potassium Hydroxide, Black iron oxide (E172)

For 300 mg:
Capsule content: Strach, pregelatinized, Magnesium stearate
Capsule shell: Gelatin, Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Black iron oxide (E172)
Black ink: Shellac, Propylene glycol (E1520), Strong ammonia solution (E527), Potassium Hydroxide, Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

The hard capsules are packed in 7 capsules/ Alu-Alu blister x 8.

6.6 Instructions for use and handling

No special requirements.

7. PRODUCT OWNER / MANUFACTURER

Product owner: AmediusTec Ltd., 4 Loyang Way 1, Singapore 508708.

Manufacturer: Dexcel Ltd., 1 Dexcel Street, Or-Akiva 3060000, Israel.

8. DATE OF REVISION OF THE TEXT

Date of last revision: September 2022

V-000746/1

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