ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White hard capsule, marked "Pfizer" on the cap and "PGN 25" on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14, 21, 56, 84 or 112 (2 x 56) hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/001-005
EU/1/04/279/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 50 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White hard capsule, marked "Pfizer" on the cap and "PGN 50" on the body with black ink. The body is also marked with a black band.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14, 21, 56 or 84 hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/006-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White and orange hard capsule, marked “Pfizer” on the cap and “PGN 75” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water
Red Iron Oxide (E172)

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14, 56 or 112 (2 x 56) hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
HDPE bottle containing 200 hard capsules.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/011-013
EU/1/04/279/027
EU/1/04/279/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 100 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
Orange hard capsule, marked “Pfizer” on the cap and “PGN 100” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 – 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water
Red Iron Oxide (E172)

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 21or 84 hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/014-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White hard capsule, marked “Pfizer” on the cap and “PGN 150” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 – 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14,56 or 112 (2 x 56) hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
HDPE bottle containing 200 hard capsules.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/017-019
EU/1/04/279/028
EU/1/04/279/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
Light orange hard capsule, marked “Pfizer” on the cap and “PGN 200” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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.

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 – 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

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

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water
Red Iron Oxide (E172)

Printing Ink:
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 21or 84 hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/020 - 022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 300 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White and orange hard capsule, marked “Pfizer” on the cap and “PGN 300” on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

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

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.

Lyrica 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 (see section 4.8).

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 section 4.8).

Patients with renal impairment

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

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

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

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (mL/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose[+]

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

Use in patients with hepatic impairment

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

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 – 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 oestradiol does not influence the steady-state pharmacokinetics of either substance.

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. Pregabalin may potentiate the effects of ethanol and lorazepam.

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

4.6 Pregnancy and lactation

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

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica 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 programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 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 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table 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 (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)). 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 medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia

Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia,
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Vomiting, dry mouth, constipation, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain**,** sweating and dizziness. The patient should be informed about this at the start of the treatment.

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.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were 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, 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

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 (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 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 (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.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies 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.

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 Renal impairment).
Dosage 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.

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 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 Table 1).

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.

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. Neurobehavioural/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch
Talc

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Sodium Laurilsulphate
Silica, colloidal anhydrous
Purified water
Red Iron Oxide (E172)

Printing Ink :
Shellac
Black Iron Oxide (E172)
Propylene Glycol
Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14,56 or 112 (2 x 56) hard capsules.
100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.
HDPE bottle containing 200 hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/023 – 025
EU/1/04/279/029
EU/1/04/279/032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/07/2004
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer GmbH Arzneimittelwerk,
Gödecke,
Mooswaldallee 1,
D-79090 Freiburg,
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management Systems for medicinal products for human use.

ANNEX III

LABELLING AND PACKAGING LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (2X56 HARD CAPSULES) WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 25 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

112 (2 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of blister pack (14, 21, 56,84 and 56 (part of multipack)) and perforated unit dose blister pack (100) for 25mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 25 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 25 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
21 hard capsules
56 hard capsules
84 hard capsules
56 hard capsules (part of multipack)
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/001-005
EU/1/04/279/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (14, 21, 56 and 84) and perforated unit dose blister pack (100) for 25mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 25 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister pack (14, 21, 56 and 84) and perforated unit dose blister pack (100) for 50 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 50 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
21 hard capsules
56 hard capsules84 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/006-010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (14, 21, 56 and 84) and perforated unit dose blister pack (100) for 50 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 50 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (2X56 HARD CAPSULES) WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 75 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

112 (2 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/027

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of blister pack (14,56 and 56 (part of multipack)) and perforated unit dose blister pack (100) for 75 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 75 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
56 hard capsules
56 hard capsules (part of multipack)
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/011-013
EU/1/04/279/027

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (14 or 56) and perforated unit dose blister pack (100) for 75 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 75 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle immediate packaging for 75 mg hard capsules – pack of 200

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 75 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

200 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister pack (21 or 84) and perforated unit dose blister pack (100) for 100 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 100 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules
84 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/014 - 016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (21 or 84) and perforated unit dose blister pack (100) for 100 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 100 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (2X56 HARD CAPSULES) WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 150 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

112 (2 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of blister pack (14, 56 and 56 (part of multipack)) and perforated unit dose blister pack (100) for 150 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 150 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
56 hard capsules
56 hard capsules (part of multipack)
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/017 – 019
EU/1/04/279/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (14 or 56) and perforated unit dose blister pack (100) for 150 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 150 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle immediate packaging for 150 mg hard capsules – pack of 200

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 150 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

200 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister pack (21 or 84) and perforated unit dose blister pack (100) for 200 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 200 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules
84 hard capsules
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/020 - 022

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (21 or 84) and perforated unit dose blister pack (100) for 200 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 200 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (2X56 HARD CAPSULES) WRAPPED IN FOIL (INCLUDING THE BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 300mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

112 (2 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton of blister pack (14,56 and 56 (part of multipack)) and perforated unit dose blister pack (100) for 300 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 300 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules
56 hard capsules
56 hard capsules (part of multipack)
100 x 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/023-025
EU/1/04/279/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister pack (14 or 56) and perforated unit dose blister pack (100) for 300 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 300 mg hard capsules
Pregabalin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle immediate packaging for 300 mg hard capsules – pack of 200

1. NAME OF THE MEDICINAL PRODUCT

LYRICA 300 mg hard capsules
Pregabalin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 300 mg pregabalin

3. LIST OF EXCIPIENTS

This product contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

200 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

LYRICA 25, 50, 75, 100, 150, 200 and 300mg hard capsules
(Pregabalin)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT LYRICA IS AND WHAT IT IS USED FOR

LYRICA belongs to a group of medicines used to treat epilepsy, neuropathic pain and Generalised Anxiety Disorder (GAD).

The safety and effectiveness of pregabalin in patients below the age of 18 years with peripheral neuropathic pain, epilepsy and Generalised Anxiety Disorder has not been established.

Peripheral neuropathic pain: LYRICA is used to treat long lasting pain caused by damage to the nerves. A variety of diseases can cause peripheral neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles. Peripheral neuropathic pain may also be associated with mood changes, sleep disturbance, fatigue, and can have an impact on physical and social functioning and overall quality of life.

Epilepsy: LYRICA is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation) in adults. Your doctor will prescribe LYRICA for you to help treat your epilepsy when your current treatment is not controlling your condition. You should take LYRICA in addition to your current treatment. LYRICA is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder: LYRICA is used to treat Generalised Anxiety Disorder (GAD). The symptoms of GAD are prolonged excessive anxiety and worry that are difficult to control. GAD can also cause restlessness or feeling keyed up or on edge, being easily fatigued, having difficulty concentrating or mind going blank, feeling irritable, having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.

2. BEFORE YOU TAKE LYRICA

Do not take LYRICA
- if you are allergic (hypersensitive) to pregabalin or any of the other ingredients of Lyrica.

Take special care with LYRICA
LYRICA has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. Therefore, you should be careful until you are used to any effect the medication might have.

Some patients with diabetes who gain weight while taking pregabalin may need an alteration in their diabetic medicines.

Taking other medicines
Before taking any new medication with LYRICA you should talk to your doctor. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

LYRICA and certain other medicines may influence each other (interaction). The degree of dizziness, sleepiness and decreased concentration may be increased if LYRICA is taken together with medicinal products containing:

Oxycodone – (used as a pain-killer)
Lorazepam – (used for treating anxiety)

LYRICA may be taken with oral contraceptives.

Taking LYRICA with food and drink
LYRICA capsules may be taken with or without food.

It is advised not to drink alcohol while taking LYRICA

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
LYRICA should not be taken during pregnancy, unless you are told otherwise by your doctor.
Effective contraception must be used by women of child-bearing potential. Contact your doctor immediately if you become pregnant, think you might be pregnant or are planning to become pregnant while taking LYRICA.
It is not recommended to breast-feed your baby while using LYRICA as it is not known if LYRICA is excreted in the breast milk. Ask your doctor or pharmacist for advice before taking any medicine while breast-feeding.

Driving and using machines
LYRICA may produce dizziness, sleepiness and decreased concentration. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medication affects your ability to perform these activities.

Important information about some of the ingredients of LYRICA:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LYRICA

Always take LYRICA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

Peripheral neuropathic pain, epilepsy or Generalised Anxiety Disorder: Take the number of capsules as instructed by your doctor. The dose, which has been adjusted for you and your condition, will generally be between 150 mg and 600 mg each day. Your doctor will tell you to take LYRICA

either twice or three times a day. For twice a day take LYRICA once in the morning and once in the evening, at about the same time each day. For three times a day take LYRICA once in the morning, once in the afternoon and once in the evening, at about the same time each day.

If you have the impression that the effect of LYRICA is too strong or too weak, talk to your doctor or pharmacist.

If you are an elderly patient (over 65 years of age), you should take LYRICA normally except if you have problems with your kidneys.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Swallow the capsule whole with water.

Continue taking LYRICA until your doctor tells you to stop.

The safety and efficacy in children and adolescents (under 18 years of age) has not been established and therefore, pregabalin should not be used in this age group.

If you take more LYRICA than you should
Call your doctor or go to the nearest hospital emergency unit immediately. Take your box or bottle of LYRICA capsules with you.

If you forget to take LYRICA
It is important to take your LYRICA capsules regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking LYRICA
Do not stop taking LYRICA unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, LYRICA can have side effects, although not everyone gets them.

Very common side-effects which may affect more than 1 person in 10 are listed below:

- Dizziness, tiredness

Common side-effects which may affect more than 1 person in 100 are listed below:

- Increased appetite
- Feeling of elation, confusion, changes in sexual interest, irritability
- Disturbance in attention, clumsiness, memory impairment, tremor, difficulty with speaking, tingling feeling
- Blurred vision, double vision
- Vertigo
- Dry mouth, constipation, vomiting, flatulence
- Difficulties with erection
- Swelling of the extremities, feeling drunk, abnormal style of walking
- Weight gain

Uncommon side-effects which may affect more than 1 person in 1000 are listed below:

- Loss of appetite
- Change in perception of self, restlessness, depression, agitation, mood swings, insomnia worsened, difficulty finding words, hallucinations, abnormal dreams, panic attacks, apathy
- Difficulty with thinking, numbness, unusual eye movement, jerky movements, reduced reflexes, increased activity, dizziness on standing, sensitive skin, loss of taste, burning sensation, tremor on movement, decreased consciousness, fainting
- Dry eyes, eye swelling, eye pain, weak eyes, watery eyes
- Increased heart rate
- Flushing, hot flushes
- Difficulty breathing, dry nose
- Swollen abdomen, increased saliva production, heartburn, numb around mouth
- Sweating, rash
- Muscle twitching, joint swelling, muscle cramp, muscle pain, joint pain, back pain, pain in limb, muscle stiffness
- Difficulty with or painful urination, incontinence, reduced urine volume
- Weakness, fall, thirst, chest tightness

Rare side-effects which may affect less than 1 person in 1000 are listed below:

- Low blood pressure, coldness of hands and feet, high blood pressure
- Cough, nasal congestion
- Muscle damage
- Breast pain, interruption in menstruation
- High blood sugar
- Increased sensitivity to noise
- Heart rhythm disturbances
- Swollen face
- Swollen tongue

If you experience swollen face or tongue you should seek immediate medical advice.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LYRICA

This medicinal product does not require any special storage conditions.

Keep LYRICA out of the reach and sight of children.

Do not use LYRICA after the expiry date which is stated on the carton or bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What LYRICA contains

- The active substance is pregabalin. Each hard capsule contains either 25 mg**,** 50 mg, 75 mg, 100 mg, 150 mg, 200 mg or 300 mg pregabalin.

- The other ingredients are: lactose monohydrate, maize starch, talc, gelatine, titanium dioxide (E171), sodium laurilsulphate, anhydrous colloidal silica, black ink, (which contains shellac, black iron oxide (E172), propylene glycol, potassium hydroxide) and water. The 75, 100, 200 and 300 mg capsules also contain red iron oxide (E172).

What LYRICA looks like and contents of the pack

- LYRICA 25 mg capsules are hard white gelatine capsules, with “Pfizer” marked on the cap and “PGN 25” on the body.
- LYRICA 50 mg capsules are hard white gelatine capsules, with “Pfizer” marked on the cap and “PGN 50”on the body. The capsule body is marked with a black band.
- LYRICA 75 mg capsules are hard white and orange gelatine capsules with “Pfizer” marked on the cap and “PGN 75” on the body.
- LYRICA 100 mg capsules are hard orange gelatine capsules, with “Pfizer” marked on the cap and “PGN 100” on the body.
- LYRICA 150 mg capsules are hard white gelatine capsules, with “Pfizer” marked on the cap and “PGN 150” on the body.
- LYRICA 200 mg capsules are hard light orange gelatine capsules, with “Pfizer” marked on the cap and “PGN 200” on the body.
- LYRICA 300 mg capsules are hard white and orange gelatine capsules, with “Pfizer” marked on the cap and “PGN 300” on the body.

LYRICA is available in six pack sizes made of PVC with an aluminium foil backing: a 14 capsule pack containing 1 blister strip, a 21 capsule pack containing 1 blister strip, a 56 capsule pack containing 4 blister strips, a 84 capsule pack containing 4 blister strips, a 112 (2 x 56) capsule pack and 100 x 1 capsules as perforated unit dose blisters.
In addition, LYRICA is available in an HDPE bottle containing 200 capsules for the 75, 150 and 300 mg strengths**.**

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, UK.

Manufacturer:
Pfizer GmbH Arzneimittelwerk, Gödecke, Mooswaldallee 1, D-79090 Freiburg, Germany.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder

België/Belgique/Belgien
Pfizer S.A. / N.V.
17 Boulevard de la Plaine / Pleinlaan 17
B-1050 Bruxelles / Brussel / Brüssel
Tél/Tel: +32 (0)2 554 62 11

Česká republika
Pfizer spol s.r.o.
Stroupežnického 17
150 00 Praha 5
Tel: +420-283-004-111

Danmark
Pfizer ApS

Luxembourg/Luxemburg
Pfizer S.A.
17 Boulevard de la Plaine
B-1050 Bruxelles / Brüssel
Belgique / Belgien
Tél/Tel: +32 (0)2 554 62 11

Magyarország
PFIZER Kft.
Alkotás u. 53. MOM Park "F" Épület.
H-1123 Budapest
Tel. + 36 1 488 37 00

Malta
V.J. Salomone Pharma Ltd.,

Lautrupvang 8
DK-2750 Ballerup
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Pfizerstraße 1
D-76139 Karlsruhe
Tel: +49 (0)721 6101 9000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Pirita tee 20
10127 Tallinn
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Λ. Μεσογείων 243,
GR-154 51 N. Ψυχικό
Τηλ.: +30 210 67 85 800

España
Pfizer S.A.
Avenida de Europa 20-B
Parque Empresarial La Moraleja
E-28108 Alcobendas (Madrid)
Tel: +34 91 490 99 00

France
Pfizer
23-25, Av. du Dr. Lannelongue
F-75014 Paris
Tél: +33 (0)1 58 07 34 40

Ireland
Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Tel: +353 1800 633 363

Ísland
Vistor hf.
Hörgatún 2
IS-210 Garðabær
Sími: +354 535 7000

Italia
Pfizer Italia S.r.l.
Via Valbondione, 113
I-00188 Roma
Tel: +39 06 33 18 21

Κύπρος
79, Simpson Street,
Marsa HMR 14,
Malta
Tel :+356 21220174

Nederland
Pfizer bv
Rivium Westlaan 142
NL-2909 LD Capelle aan den IJssel
Tel: +31 (0)10 406 42 00

Norge
Pfizer AS
Strandveien 55
N-1366 Lysaker
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Floridsdorfer Hauptstrasse 1
A-1210 Wien
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
ul. Rzymowskiego 28,
PL – 02-697 Warszawa
Tel.: +48 22 549 38 00

Portugal
Laboratórios Pfizer, Lda.
Lagoas Park, Edifício 10
P-2740-271 Porto Salvo
Tel: +351 21 423 5500

Slovenija
Pfizer Luxembourg SARL,
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Letališka cesta 3c, 1000 Ljubljana
Tel: + 386/1/52 11 400

Slovenská republika
Pfizer Luxembourg SARL,
Dúbravská cesta 2
841 04 Bratislava
Tel: +421–2–5941 8500

Suomi/Finland
Pfizer Oy
Tietokuja 4/Datagränden 4
FI-00330 Helsinki/Helsingfors
Puh./Tel: +358 (0)9 43 00 40

Sverige

GEO. PAVLIDES & ARAOUZOS LTD,
Λεωφ. Δημοσθένη Σεβέρη 25-27,
CY-1080 Λευκωσία
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
pārstāvniecība Latvijas Republikā
J.Alunāna ielā 2
LV-1010 Rīga
Tel: +371 70 35 775

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje,
Goštauto 40a, LT-2001 Vilnius
Tel. +3705 2514000

Pfizer AB
Box 501
SE-183 25 Täby
Tel: +46 (0)8 519 062 00

United Kingdom
Pfizer Limited,
Walton Oaks,
Dorking Road,
Tadworth,
Surrey
KT20 7NS- UK
Tel: +44 (0) 1737 331111

This leaflet was last approved in {date}