SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Lyrica. For information on changes after approval please refer to module 8.

Introduction

The active substance of Lyrica is pregabalin. The original claimed indication was the treatment of neuropathic pain in adults and as adjunctive therapy for patients 12 years of age and older with partial seizures with or without secondary generalisation. The dose range is 150 to 600 mg per day. Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). Although its precise mechanism of action is still unclear, pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α_2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system. Pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. This application concerns a complete application concerning a new active substance according to article 8.3 (i) of Directive 2001/83/EC.

Neuropathic pain

Neuropathic pain is defined as "Pain initiated or caused by a primary lesion or dysfunction in the nervous system". Neuropathic pains are divided into peripheral neuropathic pain due to lesion of the peripheral nervous system and central pain following lesions of the central nervous system. Neuropathic pain commonly is described as hot burning, throbbing, shooting, lancinating, stabbing, sharp, cramping, gnawing, aching, heavy, tender, splitting, tiring, exhausting, sickening, fearful, punishing, cruel, icy cold, tingling, pins and needles, intense and itch like. Medical descriptors are allodynia (pain due to a stimulus which does not normally provoke pain), hyperalgesia (an increased response to a stimulus which is normally painful), hyperaesthesia (increased sensitivity to stimulation, excluding the special senses), dysaesthesia (an unpleasant abnormal sensation, whether spontaneous or evoked), hyperpathia (a painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold) and neuralgia (pain in the distribution of a nerve or nerves not necessarily of paroxysmal quality). Neuropathic pain may be associated with mood changes, sleep disturbance, fatigue and may have an impact on physical and social functioning. The prevalence of neuropathic pain is estimated to be about 1%.

The relationship between aetiology, pathophysiology and symptoms in neuropathic pain is complex. After a nerve injury, stimulus independent pain may be evoked by an accumulation of sodium channels in the injured neurons, the expression of α-adrenoreceptors on injured axons, sprouting of sympathic axons into the dorsal root ganglion and disinhibition of dorsal horn neurons. This disinhibition is thought to be due to a reduction in GABA, down regulation of GABA and Opioid receptors at dorsal horn neurons and loss of inhibition by interneurons of the dorsal horn. Stimulus dependent pain is thought to be due to sensitisation of dorsal horn neurons mediated by glutamate and stimulation of NMDA receptor. These mechanisms offer a framework for pharmacotherapy of neuropathic pain.

Well-known neuropathic pain syndromes are diabetic neuropathy and post-herpetic neuralgia.

Diabetic neuropathy causing pain is present in 10% of the cases at the time of diagnosis of diabetes and is more than 50% after 25 years of the diabetic disease. Painful diabetic neuropathy is mostly associated with chronic distal diabetic sensory-motor polyneuropathy. Persistent burning pains affecting the feet, ankles and lower leg is the most common symptom. The pain may cause disturbance of sleep and psychological distress. Painful neuropathy in diabetics however, is not limited to polyneuropathy. Proximal mononeuropathies, truncal neuropathy and cranial mononeuropathies also often occur.

Postherpetic neuralgia may be considered a complication of herpes zoster. If pain persists for more than a few months, it is unlikely to resolve spontaneously. It is estimated that about 9-14% of patients with herpes zoster develops postherpetic neuralgia. The incidence increases rapidly with high age.

Other neuropathic syndromes are trigeminal neuralgia, pain following amputation, and central pain. A variety of pain conditions may have a neuropathic component, e.g. cancer neuropathic pain.

Neuropathic pain has been shown to be therapy resistant. Usually a list of possible effective agents is tried until an agent and dose is found that provides satisfactory control of the pain for that individual patient. However, the treatment effect of conventional agents is disappointing and if an effect is observed it is usually transient. A number of agents have been used in neuropathic pain including NSAID's, opioids, antidepressants, anticonvulsants, excitatory amino acid antagonists, GABA-ergic agonists, Substance P antagonists etc. Low doses of carbamazepine and amitriptyline have been recommended for neuropathic pain in general. However, there is no acknowledged standard treatment for the neuropathic pain in the EU. In several European countries carbamazepine and amitriptyline are used off-label for this indication. In some Member states gabapentin has been approved for the treatment of neuropathic pain.

Epilepsy

Epilepsy is a common neurological disorder, with a worldwide estimated prevalence of 50 million. Epilepsy may be defined as a continuing tendency to experience epileptic seizures. For epidemiological purposes, the definition is that of more than one non-febrile seizure of any type. The two peaks in incidence are in early childhood and in the elderly (> 65 years). Although patients with epilepsy may recover spontaneously over time, about 20-30% of all patients will have life-long epilepsy.

The classification of epileptic seizures according to the International Classification of Epileptic Seizures (ILAE) depends upon clinical symptoms and signs during the seizure, and the age of the patient at onset. Both aetiology (idiopathic, symptomatic and cryptogenic) and localization (partial vs generalised) are considered crucial prerequisites for an adequate approach of epileptic disorders. The debate on these topics is still ongoing. In the case of partial seizures, there is always a focus, and this type of epilepsy is limited to one part of one hemisphere. Partial seizures can be further sub-divided into simple partial (without impairment of consciousness), complex partial (with impairment of consciousness with or following a simple partial onset) and secondarily generalised (i.e. partial seizures, either simple or complex, which evolve to generalised tonic-clonic seizures). Simple partial seizures, depending on the anatomical site of origin of the seizure discharge, may be motor, sensory, aphasic, cognitive, affective, dysmnesic, illusional, olfactory or psychic. Primary generalized seizures do not have a focus and are classified as absence, tonic, atonic, myoclonic and tonic-clonic seizures. The complex partial and tonic-clonic types account for the majority (60%) of seizure types.

The burden of epilepsy is high to the patients themselves, their families and society. Patients with epilepsy have a mortality risk approximately two to three times that of the general population, with Sudden Unexplained Death in Epilepsy (SUDEP) a well-recognised complication of the condition itself. Many patients have additional behavioural, neurological and/or intellectual disturbances.

The pathophysiology of most forms of epilepsy remains poorly understood, but it is known that epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurones. The feature common to all epileptic syndromes is a persistent increase in neuronal excitability. Established antiepileptic drugs decrease neuronal membrane excitability by interacting with ion channels (e.g. sodium, potassium or calcium channels) or neurotransmitter receptor complexes (mostly promotion of inhibitory GABA-ergic neurotransmission, or interference with the glutamate system).

The treatment of an individual patient with partial seizures relies on diagnosing the seizure type and epilepsy syndrome, and is focussed on the reduction of seizure frequency, with seizure freedom as the ultimate goal. Usually, treatment consists of daily anticonvulsant medication. Antiepileptic drugs share their activity at the central nervous system, and therefore have similar side effects, i.e. sedation, somnolence, lethargy and ataxia. Product specific side effects and individual differences in tolerability require a treatment regime that is adjusted to the individual patient. In approximately 70% of patients, monotherapy will satisfy, whereas in another 10% of patients treatment with more than one compound is necessary. Still, up to 30% of patients remain refractory to conventional treatment. For this reason, over the past decade, several new antiepileptic drugs were developed and marketed (a/o. felbamate, gabapentin, lamotrigine, topiramate, levetiracetam), in order to optimise the therapeutic spectrum and risk/benefit profile.

Quality aspects

Introduction

Lyrica is presented as hard capsules containing 25, 50, 75, 100, 150, 200 or 300 mg of pregabalin as active substance. The different strengths can be distinguished by the imprinting, colour and size of the capsules.

The other ingredients include lactose monohydrate, maize starch, talc, hard gelatin capsule shell and imprinting ink.

Lyrica is supplied in PVC/Aluminium blister (14, 21, 56 and 84 pack size) and PVC/Aluminium perforated unit dose blister (100x1 pack size).

Drug Substance

Pregabalin is the *S* enantiomer of 3-(aminoethyl)-5-methylhexanoic acid, an analogue of the gamma-aminobutyric acid (GABA) mammalian neurotransmitter.

It is a white to off-white, highly crystalline, non-hygroscopic and water soluble (freely soluble below pH 3.7) powder. It contains one chiral centre, but is synthesised as the single enantiomer *S*. The absolute configuration has been confirmed by X-ray crystallographic analysis. Pregabalin exists as a single anhydrous and not solvated crystal form. Polymorph screening performed during development did not indicate any possible solid-state form transition events.

- Manufacture

Pregabalin is prepared at three different sites through a two-step chemical synthesis. The first step consists of the synthesis of pregabalin racemate from commercially available starting materials. The undesired R enantiomer is subsequently removed by a classical resolution method. Pregabalin crude is terminally purified by recrystallisation from isopropyl alcohol and water to give pregabalin.

Some identified non-clinical and clinical batches have been produced by a different synthetic route, but with essentially the same specification (no major differences in impurity profile).

Satisfactory specifications and associated methods have been provided for the starting materials, key intermediate (pregabalin racemate), reagents and solvents.

- Specification

The drug substance specification includes test for appearance, identity (IR and chiral HPLC), assay (HPLC), impurities, water content (PhEur), heavy metals (PhEur), residue on ignition (PhEur), residual solvents, bulk density and particle size.

The formation of the desired enantiomer of pregabalin is ensured through the route of synthesis and confirmed by a chiral identity test. In addition, the R enantiomer is controlled as part of the specified impurities.

Particle size is part of the specification, but is not expected to be a critical parameter with regards to the bioavailability of the capsules, taking into account the water solubility of pregabalin. This has been confirmed by the broad range particle size distribution of drug substance lots used in clinical studies (see pharmaceutical development).

Specification limits have been adequately justified by analytical, stability and toxicity data. The analytical methods used in routine controls have been suitably described and validated.

Batch analysis data provided for 95 lots prepared using the commercial (n=91) and the development synthesis routes have shown no major differences, especially in term of impurity profiles. These data confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Stability data have been provided for 3 batches synthesized by the commercial process. 3-year data under long term conditions (25°C/60% RH – intended packaging) and 6-month data under accelerated conditions (40°C/75% RH– intended packaging) have been provided. A photostability study has been performed and indicates that the drug substance is not light sensitive. No racemisation of pregabalin was shown during stress stability studies.

A 3-year retest period is supported by the presented data when the substance is stored in sealed doubled low density polyethylene bags placed in drums with secure fitting lids.

Drug Product

- Pharmaceutical Development

Pregabalin being a highly soluble and highly permeable compound, the oral dosage form developed is of standard formulation. The excipients selected are of PhEur quality, commonly used for this type of dosage form and were selected based on compatibility studies with the drug substance.

Particle size distribution of the drug substance has been shown not to adversely impact drug product manufacture and performance (see drug substance).

Regarding the TSE risk, satisfactory certificates of suitability have been provided for the gelatine capsule shells. The lactose derived from milk of bovine origin has been considered in compliance with the current TSE requirements.

The PVC/aluminium blister selected meet the PhEur requirements for packaging material and is in compliance with European regulation on plastic materials and articles intended to come into contact with foodstuffs.

With the exception of an aqueous oral solution used in low-dose phase 1 study, powder-filled hard gelatine capsules of similar qualitative composition, ranging in dose from 5 to 300 mg, and prepared from powder blend formulation series A (25% pregabalin w/w), B (44.44% pregabalin w/w) or C (75% pregabalin w/w) have been used throughout clinical development.

Representative formulations from each series have shown to have similar dissolution profiles as defined by the *Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)* at pH 1.2, 4.5 and 6.8. Based on this result and taking into account the characteristics of the drug substance and of the drug product, it is acceptable not to perform a bioequivalence study between clinical and commercial formulations.

- Manufacture of the Product

The method of manufacture involves the following operations: delumping of pregabalin and of the excipients, blending and encapsulation. In order to accommodate the range of dosage strengths, 2 powder blends formulation are used for commercial manufacturing. Formulation series A containing 25% w/w pregabalin is used to produce 25 and 50 mg capsules and formulation series C containing 75% w/w pregabalin is used to produce the other strengths.

Satisfactory validation data have been provided for 1 of each full-scale powder blend and the corresponding capsules. No change of formulation or process has been necessary during scale-up, confirming the robustness of the formulation and of the process.

- Product Specification

The product specification includes tests controlled by validated methods for appearance, identity (HPLC, IR), assay (HPLC), impurity content (HPLC), dissolution, uniformity of mass (PhEur), identification of colourants (non routine test) and microorganism count (PhEur non routine test).

Batch analysis data have been provided for 45 batches from both formulation series. All data comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the Product

Stability data under long-term conditions (25°C/60% RH – intended packaging) are available for 24 months and 36 months for respectively 9 lots and 1 lot packed in clear PVC blister. 6 months accelerated stability data (40°C/75% RH– intended packaging) are available for 22 batches. A photostability study showed that the drug product is non-light sensitive.

The data provided support the proposed shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taken into account the properties and stability of the water-soluble drug substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing processes were developed and optimized to obtain reproducible

finished product batches. Stability tests under ICH conditions indicate that the products are stable for the proposed shelf life.

Non-clinical aspects

Introduction

Lyrica contains pregabalin as drug substance. Pregabalin is a new active substance known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid and is structurally related to the naturally occurring amino acids L-leucine and γ-aminobutyric acid (GABA). Pregabalin has been developed for the treatment of neuropathic pain and as adjunctive therapy in the treatment of partial seizures.

The maximal recommended dose in humans is 600 mg/day, with an associated mean AUC (0-24) of around 123 μg·hr/mL.

Pregabalin was assessed in nonclinical models of analgesia in rats and monkeys, and seizure models in mice and rats. The (R)-enantiomer of pregabalin and positive control agents were included in many of these studies. Pharmacokinetics were studied in mouse, rat, rabbit, dog and monkey. A standard nonclinical safety evaluation program was conducted to support oral therapy with pregabalin.

Pregabalin is structurally and pharmacologically related to gabapentin, an anti-epileptic drug approved in most European countries, registered for the adjunctive treatment of refractory partial epilepsy with or without secondary generalised seizures. In addition gabapentin has been approved in some Member states for the treatment of neuropathic pain.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). However, pregabalin does not mediate its effects specifically though an effect upon GABA-ergic transmission.

Pregabalin displaces [3H]gabapentin and both *in vitro* and *in vivo* studies with animal models further indicate that binding of pregabalin to the alpha$_2$-delta auxiliary subunit protein of voltage-gated calcium channels affinity with high affinity (IC_{50} = 37 nM) is required for its pharmacology. The (R)-enantiomer of pregabalin was 10-fold less potent than pregabalin (S—enantiomer) in binding at these sites, consistent with the general lack of effect in efficacy models. As determined by either radioligand binding or functional assays, pregabalin is inactive against 41 common neurotransmitter receptors and ion channels. Pregabalin partially reduces neurotransmitter release in several *in vitro* systems at concentrations near 10 μM (1.6 ng/mL). Inhibition is most pronounced with prior activation of neuronal tissues (from prior peripheral inflammation *in vivo*, *in vitro* application of sensory neuropeptides or cellular second messengers, or by depolarization lasting for 120 seconds or more). In vitro, pregabalin reduces the release of glutamate, norepinephrine, Substance P, and calcitonin gene-related peptide from certain brain tissues and also reduces calcium influx in synaptosomes. These findings indicate that pregabalin inhibits calcium channel function in a subtle manner. Pregabalin also is a substrate for the System L amino acid transporter of cell membranes that contribute to the permeation of pregabalin across membrane barriers. Pregabalin does not change the concentration of GABA in rat brain and does not alter binding or responses at GABA-A or GABA-B receptors and is not a substrate or blocker of GABA transport, nor an inhibitor of GABA-transaminase.

Pregabalin reduces both sensory and motor spinal reflexes induced by toe pinch in rats, and this effect was pronounced only in rats that were previously inflamed by injection of an immune antigen or in rats with neuropathic pain from chronic constriction injury to the sciatic nerve. Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain.

Pregabalin is also active in animal models of seizures, including maximal electroshock tonic extensor seizures in mice or rats, threshold clonic seizures from pentylenetetrazol, behavioural and electrographic seizures in hippocampal kindled rats, and tonic and clonic seizures in

DBA/2 audiogenic mice. Pregabalin does not reduce the incidence of spontaneous absence seizures in Genetic Absence Epilepsy in Rats from Strasbourg (GAERS).

- Secondary pharmacodynamics

Pregabalin was also investigated in animal models predictive of anxiolytic-like activity and inflammatory pain.

- Safety pharmacology

Potential CNS effects of pregabalin were evaluated in 10 studies. The predominant findings in these studies were reduced spontaneous locomotor activity and/or ataxia in rats given oral doses ≥25 mg/kg and in mice given IV or IP doses ≥300 mg/kg or oral doses of 1000 mg/kg. In the Sidman Avoidance test in squirrel monkeys, pregabalin dose-dependently reduced activity and motor coordination at 30 and 100 mg/kg. Pregabalin induced dose-related increases in non-rapid eye movement sleep (non-REM sleep) at ≥3 mg/kg and decreased REM sleep at ≥30 mg/kg without affecting latency to onset of non-REM sleep or overall sleep cycle length. The effects of pregabalin resemble effects of sleep deprivation on subsequent sleep, suggesting pregabalin induces a physiological-like sleep without significantly affecting total sleep duration.

No significant effects on cardiovascular parameters were observed in rats given escalating oral doses from 10 to 300 mg/kg, in rats given single IV doses of 15 and 150 mg/kg, in dogs given a single oral dose of 50 mg/kg, or in monkeys given single IV doses of 10 or 40 mg/kg. Although ECG was only evaluated visually for rate and rhythm abnormalities in safety pharmacology studies, a comprehensive evaluation, including measurement of QT interval, was conducted in monkeys given pregabalin for up to 69 weeks. Daily oral administration of pregabalin for 65 to 69 weeks at doses up to 500 mg/kg produced no cardiac changes attributable to drug treatment. No statistically significant differences occurred between treated and control groups in echocardiographic parameters except for increases in aortic diameter in males at 100, 250 and 500 mg/kg at Week 13 (29%, 19%, and 14%, respectively) and increased left ventricular internal dimension (systole) in males at 500 mg/kg at Week 39 (52%). The latter was only seen in males at an 8-fold therapeutic exposure.

No significant effects on renal function were observed in rats given single IV doses of 15 and 150 mg/kg.

Pulmonary function in anesthetized dogs given a cumulative IV dose of pregabalin of 200 mg/kg was unaffected.

Pregabalin given orally decreased gastric emptying and intestinal transit of a liquid meal in rats given 100 or 300 mg/kg (4- to 8-times mean human exposure at the maximum recommended dose) but not at 30 mg/kg (equivalent to mean human exposure), by a non-opiate mechanism. Nevertheless, obstipation events were reviewed in clinical trials and no specific safety concerns were identified, although a slightly higher incidence in pregabalin-treated subjects vs placebo was observed.

Pregabalin was inactive at binding sites associated with drugs of abuse. Pregabalin did not cause conditioned place preference in rats, suggesting that pregabalin does not share morphine's rewarding properties. Pregabalin did not produce opiate-like or benzodiazepine-like discriminative stimulus effects and did not maintain I.V. self-administration responses in rhesus monkeys. Pregabalin induced only modest and mostly statistically insignificant withdrawal signs in rats upon discontinuation of treatment.

- Pharmacodynamic drug interactions

Non-clinical pharmacodynamic drug-drug interaction studies were not conducted.

- Summary of salient findings

In vitro studies show that pregabalin interacts with an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system. Binding to this subunit is probably required for its analgesic and anticonvulsant activity. Pregabalin does not interact with either GABAA or GABAB receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation. Although its precise mechanism of action is still unclear, pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin induces modest ataxia and reduced spontaneous locomotor activity in rats given ≥ 25 mg/kg P.O., but has no effect on cardiovascular parameters. A detailed evaluation of cardiovascular safety was performed in a repeated dose toxicity study in monkeys. The analgesic and anticonvulsant actions of pregabalin occur at doses that lack obvious behavioral side effects. Pregabalin has a low potential for drug abuse or physical dependence.

Pharmacokinetics

The absorption, distribution, metabolism, and elimination of pregabalin were investigated in the species used in pharmacology and/or toxicology studies (mouse, rat, and monkey), using similar or identical formulations. The metabolism was also studied in dogs. Dose proportionality and accumulation were assessed using multiple-dose pregabalin toxicokinetic data in mouse, rat, rabbit, and monkey.

Plasma pregabalin concentrations in mouse, rat, rabbit and monkey were determined using validated high-performance liquid chromatography (HPLC) assays. The limit of quantification was 0.1 ug/ml in all species. Pregabalin concentrations were quantified in dog plasma using a similar HPLC assay.

No *in vitro* or *in vivo* racemization of pregabalin (S-enantioner) to PD 144550 (R-enantiomer) was observed.

- Absorption- Bioavailability

Pregabalin is well absorbed following oral administration. Absolute bioavailability of pregabalin is high (>80%) in mice and rats at a 50-mg/kg dose and in monkeys at a 10-mg/kg dose. In general, pregabalin exposure is dose-proportional up to 2500 mg/kg in mice and rats (except for gravid and lactating rats), and up to 50 mg/kg in monkeys.

- Distribution

[14C]Pregabalin is widely distributed in most tissues and crosses the blood-brain barrier in mouse, rat, and monkey after oral administration. Radioequivalents concentrate in the pancreas of mice and rats, but not in primates. Distribution in pancreas may be related to affinity to branched-chain amino acid aminotransferase (BCAT), an enzyme found in high concentrations in rodent pancreas. Pregabalin does not bind to mouse, rat, monkey, or human plasma proteins. [14C]Pregabalin red blood cell (RBC)/plasma partition coefficients range from 0.69 to 0.80 for all species tested.

- Metabolism (*in vitro/in vivo*)

Pregabalin undergoes minimal metabolism in mouse, rat, and monkey with unchanged parent representing the majority (≥90%) of drug-derived material in urine. A minor metabolite representing 2% to 3% of the urinary radioactivity in mouse and rat is identified as the N-methyl metabolite (PD 0155083). In monkey, only 1 minor (<1%) unidentified component is detected in the urine. In dog, approximately 45% of the pregabalin dose is excreted in urine as N-methyl metabolite (PD 0155083).

No significant inhibition of major cytochrome CYP450 isoforms is observed up to a pregabalin concentration of 1 mM. The potential for metabolism related drug-drug interaction is low at therapeutic concentrations of pregabalin.

- Excretion

Urine is the principal route of 14C excretion following [14C]pregabalin administration. In mouse, rat, and dog, ≥80% of the [14C] pregabalin oral dose is present in the 0- to 24-hour urine sample, while 71% to 75% is excreted by monkey during the same interval. Higher than 90% of the dose was recovered in 0-96 hour urine in rat and monkey.

- Summary of pharmacokinetic parameters (in different species)

Pregabalin is well absorbed after oral administration (exposure is dose-proportional at doses up to 2500 mg/kg in rats and up to 50 mg/kg in monkeys), widely distributed in most tissues (and readily crosses the blood-brain barrier in mice, rats, and monkeys), does not bind plasma proteins (in mouse, rat, monkey and human), undergoes minimal metabolism in mouse, rat, and monkey with unchanged parent representing ≥90% of drug-derived material in urine. In contrast to other animal species and humans, approximately 45% of the pregabalin dose is excreted in urine as N-methyl metabolite in dogs. These data also confirm selection of the rat and monkey as appropriate species for toxicology studies. No significant inhibition of major cytochrome CYP450 isoforms was observed at pregabalin concentrations up to 1 mM.

Toxicology

- Single dose toxicity

The acute oral and IV toxicity of pregabalin was assessed in adult mice and rats. The four single dose toxicity studies are summarised in the table below.

Species/ Sex/Number/group	Dose/Route (mg/kg)	Observed max non-lethal dose	Major findings
Mouse 3-5/sex/gp	Oral: 0, 5000	5000	Mild hypo-activity in males
Rat 3-5/sex/gp	Oral: 0, 5000	5000	Mild hypo-activity, diarrhoea, urine staining
Mouse 3-5/sex/gp	IV: 0, 300	300	None
Rat 3-5/sex/gp	IV: 0, 300	300	Hypo-activity, ataxia, urine staining

No mortality was observed after single oral administration of 5000 mg/kg and single IV administration of 300 mg/kg to mice and rats. Observed effects were hypo-activity in mice and rats and diarrhoea, ataxia, and urine staining in rats.

- Repeat dose toxicity

Repeated-dose oral and IV toxicity was evaluated in rats and monkeys. Twelve oral GLP repeat dose toxicity studies were conducted in rats (14 days, two assays of 1 month, 3 months and 6 month/1 year) and cynomolgus monkeys (escalating dose study, 14 days, two assays of 1 month, 4-day toxicokinetic study, 3 months, 65-69 weeks). Pivotal studies are summarised in the table below.

Pivotal repeated dose toxicity studies.

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL/ NOAEL	Major findings
Rat					
250-01730	Rat 18-21/sex/gp	Oral (diet): 0, 50, 100, 250	4 weeks	NOEL M: 50 F: 100	**≥100**: M: weight pancreas and prostate ↓ **250**: tail dermatopathy, platelets ↓
250-01722	Rat 18-21/sex/gp	Oral (diet): 0, 500, 1250, 2500, 5000	4 weeks	< 500	**≥500**: Ataxia, hypo-activity and hyperreactivity in wk 1, platelets ↓, tail dermatopathy, urine staining. M: body wt gain ↓, RBC + Hb + Ht ↑, urinary bladder dilatation, hypospermia epididymides **≥1250**: cyt p450 ↑. F: body wt gain ↓ **≥2500**: F: RBC ↑, pancreas wt ↓ **5000**: bone marrow megakaryocytes ↓, pancreas atrophy + single cell necrosis, histopathologic changes in urinary system resulting in death. M: pancreas wt ↓, prostate atrophy + wt ↓
745-02570	Rat 10-22/sex/gp	Oral (diet): 0, 50, 250, 500, 1250	13 weeks	NOEL: 50	**≥250**: RBC ↑, platelets ↓. M: Ht ↑, body wt gain ↓, pancreas decreased acinar cell granules. F: bone marrow hypocellularity, MCH ↓ **≥500**: food cons. ↓. M: bone marrow hypocellularity, MCH ↓ **1250**: tail dermatopathy, urinary bladder oedema + hemorrhage + hyperplasia, thymus hemorrhage + mild lymphoid depletion. M: testis degeneration spermatogenic epithelium. F: hypo-activity, urine staining, body wt gain ↓, pyelonephritis

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg)	Duration	NOEL/ NOAEL	Major findings
Rat					
745-02683	Rat 25/sex/gp	Oral (diet): 0, 50, 250, 500	26-52 weeks	M: NOAEL: 50 F: < 50	**≥50**: M: RBC ↑, MCV ↓, platelets ↓. F: pyelonephritis **≥250**: tail dermatopathy, bone marrow hypocellularity and salivary gland secretion ↓. M: food cons. ↓, platelet volume ↓, macrophages in lungs. F: urine staining, RBC ↑, MCV ↓, platelets ↓ **500**: macrophages in lungs, M: urinary bladder hemorrhage + oedema: body wt gain ↓, F: food cons. ↓.
Monkey					
745-02329	Monkey 4/sex/gp	Oral (gavage): 0, 25, 50, 100, 500, 500 BID	4 weeks	NOEL: 25	**≥50**: heart weight ↑, mild focal myocardialde generation/fibrosis **≥100**: nasal cavity inflammation **≥500**: diarrhoea, ataxia, tail dermatopathy, tail/extremities inflammation **500 BID**: reproductive organ weight ↓ (reversible), minimal to mild necrosis and lymphocytolysis in lymphoid organs, kidney dilatation
745-02559	Monkey 3-4/sex/gp	Oral (gavage): 0, 10, 25, 100, 500	13 weeks	NOEL:> 10	**≥25**: M: tail dermatopathy **≥100**: F: tail dermatopathy **500**: soft faeces, diarrhea. M: RBC + Hb + Ht ↓
745-02646	Monkey 3/sex/gp	Oral (gavage): 0, 10, 25, 100, 250/500	65-69 weeks	< 10	**≥10**: M: thymus lymphoid involution **≥25**: prostate lymphocytic infiltrate, F: tail dermatopathy **≥100**: slight erythrocyte autoagglutination **250/500**: diarrhoea. F: lymphocytic infiltrate ventricle. M: tail dermatopathy,

Both in rats and in monkeys, mortality occurred at exposures 7-9 times the maximal daily human exposure; in rats, mortality occurred sporadically at this exposure multiple, associated with pyelonephritis and/or cystitis.

In rats, generally, body weight gain and food consumption were decreased. However, in the rat carcinogenicity study body weight and food consumption increased in the low dose group. In monkeys, decreased food consumption was only observed in one study.

CNS effects such as ataxia and hypoactivity, but also hyperactivity were observed in rats and monkeys.

In some intravenous studies in monkeys, tremors and convulsions were seen as well. In rats, urine staining was observed frequently.

In both rats and monkeys, dermatopathy and vasculopathy were observed, primarily on the tail, but also on the extremities, and, in IV studies in monkeys, also on mucous membranes. In IV studies in monkeys, the lesions were more widespread. The primary alteration involved damage to endothelial cells of superficial blood vessels (vasculopathy) in skin and mucous membrane. Temperature measurements of the tail of monkeys did not indicate changes in blood perfusion. A local lymphe node assay in rats gave no indication for allergic dermatitis.

Effects on haematology were not consistent. In rats, increases were observed in red blood cells, haemoglobin and hematocrit, whereas in monkeys these parameters were decreased. In rats, platelets were decreased and there was a decrease in bone marrow megakaryocytes and total nucleated cells. In monkeys, platelets were decreased in one study, but otherwise there were no relevant effects on platelets. Haematological changes in mice are described below when carcinogenicity is discussed.

Effects on the urogenital tissues were observed, consisting of dilatation of urinary bladder (in one study accompanied by oedema, haemorrhage and hyperplasia) and renal pelvis in rats and kidney

dilatation in monkeys. Pyelonephritis was observed occasionally in rats and occurred dose-related in males in the rat carcinogenicity study at all doses. In the same study, distension of the uterine horn was observed in the high dose females. In repeat dose toxicity studies, there were effects on male reproductive organs: hypospermia, interstitial fibrosis in epididymides, prostatic atrophy and degeneration of spermatogenic epithelium in the testes of rats and, in one study only, hypospermia in monkeys. On retrospective examination, no significant effects were observed on spermatogenesis in the testes of rats. In the rat carcinogenicity study, epididymal and testicular weight decreased 18% at the high dose and the incidence of small testes increased at all doses and correlated with tubular atrophy observed histopathologically and there was a dose-related increase in the incidence of aspermia in the epididymides. The increased incidence of bilateral tubular atrophy was not dose-related. The incidence of small seminal vesicles was increased at the high dose, but there were no histopathologic changes. Lesions in the male reproductive tract generally were observed in debilitated animals or were consistent with spontaneous or age-related changes commonly found in rats.

Some signs of immunotoxicity were observed, generally only at very high exposures, consisting in haemorrhage and mild lymphoid depletion in the thymus of rats and thymus involution, minimal to mild lymphoid necrosis and lymphocytolysis in spleen, thymus, lymph nodes and tonsils in monkeys.

There were some effects on the eyes of rats. Corneal degeneration and mineralization attributed to anaesthesia and chromodacryorrhea were observed in IV studies and a dose-related increase in retinal atrophy, which was more pronounced in females, in the carcinogenicity study was seen.

In a few treated monkeys from the 4-week pivotal study, some cardiac effects were observed. In these monkeys, increased relative heart weights and minimal to mild focal myocardial necrosis or fibrosis of the left ventricular wall and/or interventricular septum as well as atrium fibrosis were observed at 3-4 times human exposure. These histopathological studies were not confirmed in a 13-week follow-up study. Extensive monitoring, including ECG, blood pressure and echocardiography did not reveal abnormalities, except for increases in aortic diameter in males at ≥100 mg/kg. Aortas were considered normal upon gross and microscopic examination, and consequently the increased diameter was not considered significant. From the available data, the daily oral administration of pregabalin for 65 to 69 weeks at doses up to 500 mg/kg, and exposures up to approximately 8 times human exposure, produced no cardiac changes attributable to drug treatment.

In the 52-week rat study, 4 rats died of malignant tumours (mesenchymal tumours, mesothelioma, and hemangiosarcoma) in week 32 (2 animals), and weeks 48 and 52 (each 1 animal).

In one rat study, atrophy and single cell necrosis was observed in the pancreas, but only at very high exposures.

- Genotoxicity *in vitro* and *in vivo*

Pregabalin was not genotoxic based on results of a battery of *in vitro* and *in vivo* tests:

- *in vitro*: AMES test performed in the presence and absence of various metabolic activation systems and point mutation and structural chromosome aberration assays in Chinese hamster ovary cells.
- *in vivo*: micronucleus test in mouse and rat bone marrow, and, unscheduled DNA synthesis test in rat and mouse hepatocytes.

- Carcinogenicity (with toxicokinetics)

Two-year carcinogenicity studies were performed in mice and rats, at the following doses.

Dose/Route	Species/number of animals
0, 200, 1000 and 5000 mg/kg Oral/diet	B6C3F1 mice/ 65 animals/sex/group
0, 200, 1000 and 5000 mg/kg Oral/diet	CD-1 mice/ 65 animals/sex/group
Male: 0, 50, 150 and 450 mg/kg; Female: 0, 100, 300 and 900 mg/kg	Wistar rats/ 65 animals/sex/group
Male: 0, 50, 150 and 450 mg/kg; Female: 0, 100, 300 and 900 mg/kg	Wistar rats/ 65 animals/sex/group

Pregabalin induced an increase in hemangiosarcoma in male and female B6C3F1 mice at 1000 and 5000 mg/kg, i.e. at exposures ≥5 times the mean human exposure at the maximum recommended dose. The NOAEL was seen at exposures equivalent to the mean human exposure. In CD-1 mice, an increased incidence of hemangiosarcoma was observed at an exposure 28 times the mean human exposure at the maximum recommended dose. The NOAEL in this study was seen at exposures up to 5 times mean human exposure. Pregabalin was not carcinogenic in rats at up to 14 and 24 times the mean human exposure at the maximum recommended dose in males and females, respectively.

See "Discussion on the non-clinical aspects".

- Reproductive and developmental studies

Studies to assess effects of pregabalin on fertility and general reproduction and prenatal-postnatal development were conducted in rats, and embryo-foetal development studies were conducted in mice, rats, and rabbits. Additional *in vitro* and *in vivo* studies assessed male reproductive toxicity, a series of studies examined skull development in rats, and a study evaluated the period of drug exposure during prenatal-postnatal development that affected foetal and prenatal survival.

In the fertility studies effects were observed in treated male rats. At high doses (several tenfold human exposure), epididymides were affected, as well as the sperm cells: sperm count, motility and the number of sperm cells with normal morphology were dose-relatedly decreased. At about 77 times human exposure, the males were infertile. This appeared to be a reversible effect: after 6 weeks of recovery, all fertility parameters returned to vehicle control values. The NOAEL is 250 mg/kg (10 times human exposure). Pregabalin did not produce detrimental effects on reproductive function of healthy male subjects given 600 mg/day for 3 months, based on semen analysis and other secondary parameters, when compared to placebo (see clinical section). Although some effects in testis and epididymides seen in the rat carcinogenicity study suggest long-term exposure may exacerbate spontaneous degenerative processes in male reproductive organs in the rat, the negative findings in the clinical study and the high doses used in the fertility studies in rats and the reversibility of the effects seen at high doses suggest that the findings seen at those high doses in the rat fertility studies and the findings in the rat carcinogenicity study are of little or no clinical relevance. The applicant stated that female fertility was not affected, however, various parameters pointed to a reduced fertility index and prolonged oestrous cycles in females at doses resulting in an exposure 54-77 times the human exposure.

No maternal toxicity was observed in mice given pregabalin up to 2500 mg/kg during the period of organogenesis. At doses ≥ 1250 mg/kg (14-31 times human exposure), ossification was reduced but not in a dose-related manner. Studies in female rats dosed with pregabalin up to 2500 mg/kg showed maternal toxicity at all doses, and fetal body weight was decreased at 2500 mg/kg. At high doses (≥ 1250 mg/kg; 54-77 times human exposure), advanced ossification was observed, resulting in e.g. earlier closure of the suture between the jugal bone to maxilla, and of the suture between the nasal bones. At the same high doses, also reduced ossification was observed in rats. In rabbits, maternal toxicity was seen at all doses, and abortion, decreased foetal and placental weights, and decreased ossification indicative of developmental toxicity were observed at 1250 mg/kg (39 times human exposure). Overall, developmental toxicity was not observed at clinically relevant doses. Variable ossification is observed in the animals at high doses. Due to the high exposure multiple the deviant skull bone ossification is considered not clinically relevant.

In a pre/postnatal study in rats, pregabalin induced maternal toxicity at ≥50 mg/kg (twice human exposure) and offspring developmental toxicity at ≥100 mg/kg (5 times human exposure). Fetal and neonatal survival were decreased at ≥250 mg/kg (11 times human exposure), with total litter death at 2500 mg/kg (exposure multiple is >70). In a subsequent time-course study, it was shown that drug-related prenatal mortality resulted primarily from exposure during late gestation (gestation day 17 through parturition).

Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of child bearing potential.

- Local tolerance

In rabbits there was no significant irritation after intravenous administration of pregabalin in the ear for 5 days, although at the site of injection, the incidence of haemorrhage and oedema seem to have

been slightly increased in treated animals. Mild irritation occurred on rat ear skin in a local lymph node assay. There was no evidence of contact sensitization in guinea pigs when the racemic mixture of pregabalin was tested.

- Other toxicity studies

In view of a possible paediatric indication, the applicant studied juvenile toxicity in single and repeated dose studies, reproductive toxicity and neurotoxicity in juvenile rats which were 7 days at study initiation. Toxicity as observed in the juvenile rats does not differ qualitatively from that observed in adult rats. However, relative to adult rats juvenile rats are similarly sensitive with respect to CNS effects and decreased body weight gain and more sensitive with respect to female and male reproductive effects. In addition, neurobehavioural/cognitive effects were observed in juvenile rats 1-2 weeks after the exposure period.

Most effects were observed at clinically relevant exposures (CNS, body weight gain) or above the mean therapeutic exposure at the maximum recommended dose (female reproductive effects).

Alterations in acoustic startle response and impaired performance in learning and memory tests were not pharmacological but signs of developmental toxicity, since they were observed in the drug free period after exposure. The fact that no behavioural/cognitive effects were observed in adult humans is not sufficiently reassuring, since these effects may be related to the developing state of the brain. Therefore the reversibility of these effects should be further addressed in non-clinical study. See discussion on non-clinical aspects.

It has been demonstrated sufficiently that no increased risk is to be expected from the impurities PD 0144550 and PD 0147804 at the maximum expected daily human dosage.

- Summary of salient findings

In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. In rats an increased incidence of retinal atrophy was observed after long-term exposure.

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.

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. See discussion below.

In juvenile rats, at therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and decreased body weight gain. Oestrous cycle effects in female rats occurred at ≥5 times human exposure. Neurobehavioural effects were also observed in juvenile rats. See discussion below.

Discussion on the non-clinical aspects

In vitro studies show that pregabalin interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system. Although its precise mechanism of action is still unclear, pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α_2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known. Pregabalin is well absorbed, widely distributed, undergoes minimal metabolism with unchanged parent representing ≥90% of drug-derived material in urine (except in dog). No significant inhibition of major cytochrome CYP450 isoforms was observed.

Pregabalin was shown to induce haemangiosarcoma in mice. An association between platelet and bone marrow changes and increased hemangiosarcoma incidence was observed at carcinogenic doses of pregabalin. Such changes were not seen in rats. Given the role of bone marrow and platelets in endothelial homeostasis and the endothelial origin of haemangiosarcoma, the Applicant considered the exposure of endothelial cells to elevated levels of growth factors resulting from increased

megakaryopoiesis and increased activation of platelets as the most plausible mode of action of pregabalin-induced stimulation of endothelial cell proliferation in mice, a species predisposed to developing hemangiosarcoma. The relationship between increases in platelet activation, bone marrow and splenic megakaryopoiesis, circulating and tissue levels of endothelial growth factors (PDGF and VEGF, respectively), endothelial cell proliferation, and incidence of haemangiosarcoma was shown in investigational studies in mice at carcinogenic and noncarcinogenic doses of pregabalin. The temporal relationship between these changes and increased endothelial cell proliferation and haemangiosarcoma formation is consistent with a causal association. The lack of similar changes in platelet activation and related endothelial proliferation in rats and monkeys demonstrates that the same mechanism is not active in these species. Subsequent studies in mice showed that pregabalin-induced respiratory depression resulted in increased plasma bicarbonate, pCO2, and blood pH (overcompensated relative metabolic alkalosis). Increased pH was shown to increase ADP-dependent platelet activation and aggregation in vitro. Although similar changes in respiration, bicarbonate, and pCO2 were seen in rats, there were no changes in pH as a result of appropriate compensation and therefore, no subsequent alterations in platelet function. Thus, the Applicant concludes that the alterations in platelet function in mice result from disturbances in acid-base balance due to pregabalin-induced changes in respiratory function and overcompensation to these changes resulting in chronic relative metabolic alkalosis.

Thus far there are no clear indications that increased platelet activation and the related sequelae leading to haemangiosarcoma formation occur when pregabalin is administered to humans. However, additional long term human data may be needed to understand if increased platelet activation by pregabalin is mild in humans and without relevance. Therefore it was agreed that the applicant will provide additional long-term clinical data concerning assessment of platelet morphology, a surrogate marker of platelet activation, in humans receiving pregabalin.

In view of the pre-clinical toxicological finding of myocardial lesions in monkeys (at exposures 3-4 times the therapeutic exposure), its relevance to humans was initially questioned. Clinically, no cardiac concerns were raised with pregabalin in terms of arrhythmias that might possibly be related to the pre-clinical finding. In addition, a subsequent 13-week chronic study with pregabalin in monkeys, with an elaborate follow-up of animals with regular ECG and echocardiography, did not show drug-induced arrhythmia's or changes in blood pressure. No echocardiographic differences were found between pregabalin- and placebo-treated animals, except for an increased aortic diameter in males at >100 mg/kg pregabalin. Aortas were considered normal upon gross and microscopic examination, and consequently the increased diameter was not considered of significance. This was not associated with other concurrent echocardiographic, or blood pressure effects. As a consequence, follow-up of patients with echocardiography does not appear meaningful.

There were some effects on the eyes of rats. 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. (See clinical part).

Compared to adult rats, juvenile rats are similarly sensitive, notably with respect to CNS effects and decreased body weight gain. Female and male reproductive effects occurred at ≥5 times human exposure. In addition, neurobehavioural/cognitive effects were observed in juvenile rats 1-2 weeks after the exposure period at exposures ≥5 times human exposure. The reversibility of these effects has not been studied. In view of further pediatric development, it may therefore be questioned whether monitoring in pediatric studies is sufficient. Upon CPMP's request, the applicant agreed to conduct an additional study in juvenile rats to assess reversibility of alterations in acoustic startle response and impaired performance in learning and memory as a post-approval commitment.

Clinical aspects

Introduction

The active substance of Lyrica is pregabalin, an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). Lyrica is indicated for the treatment of peripheral neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation. The dose range is 150 to 600 mg per day.

The clinical programme included 21 pharmacokinetic studies, 3 pharmacodynamic interactions studies. The clinical programme to support the claimed indications are described below. Other studies

have been performed to investigate the effect of pregabalin in psychiatric diseases and in additional pain models.

In February 2001, a partial clinical hold of pregabalin was imposed by the FDA for safety reasons; increased incidence of haemangiosarcoma formation was reported in mice. Therefore several studies were terminated prematurely, or were amended with respect to the inclusion of patients.

Neuropathic pain:
Twelve randomised placebo controlled studies in neuropathy were submitted:
- Six studies evaluated the efficacy in diabetic neuropathy (DPN-014, DPN-029, DPN-040, DPN-131, DPN-149 and DPN-173),
- Five studies (PHN-030, PHN-045, PHN-127, PHN-132 and -196) were performed in postherpetic neuropathy,
- One study in both diabetic and post herpetic neuropathy (Study 155).

Studies DPN-173 and PHN-132 were terminated prematurely due to the report of increased haemangiosarcoma formation in mice; almost none of the patients completed the study.

There were several extension studies (open label, long term studies) which enrolled patients from the DPN studies, PHN studies or studies investigating the efficacy of pregabalin in other (non-neuropathic) chronic pain states.

Epilepsy:
For efficacy in patients with refractory partial seizures 3 controlled (009, 011, 034), and 4 uncontrolled (008, 010, 012, 035) studies were submitted. Additionally, a proof of concept study (007) was performed and a controlled titration study (145) was terminated prematurely due to the report of increased hemangiosarcoma formation in mice. These two studies were not considered pivotal, but to provide additional information.

It is stated in the Applicant's clinical overview that the trials were conducted in accordance with "good clinical practice" (GCP).

Pharmacokinetics

To support the application of Lyrica, the following pharmacokinetic studies were submitted:
- 3 single dose studies (1008-001, - 002, -005),
- 2 multiple dose studies (1008-002, -023),
- 2 studies in patients with an impaired renal function (studies 1008-049, -121),
- 7 interaction studies (1008-018/126, -019, -020, -075, -140, -077, -144),
- 3 pharmacokinetic/pharmacodynamic interaction studies (1008-076, -078, -079),
- 2 bioequivalence/bioavailability studies (1008-003, -128),
- 2 single dose studies conducted in Japan (studies 1008-1J, -2J)

In all studies, healthy volunteers were included, except for study 1008-018/126, -019, -020, and –140, which included epileptic patients.

- Absorption – Bioavailability

The pharmacokinetics of pregabalin is straightforward and uncomplicated. The absolute bioavailability is estimated to be more than 90%. Pregabalin AUC and Cmax values increased linearly with dose after single dose administration over the dose range of 1 – 300 mg and after multiple dose administration over the dose range of 25 – 300 mg q8h and at 300 mg q12h. Peak plasma concentrations were reached 0.5 – 1.5 h after administration. Steady state was achieved within 2 days, and no unexpected accumulation occurred. In line with the linear pharmacokinetics, the total daily exposure is similar whether the total daily dose was divided q12h or q8h, with almost comparable Cmax values, but with around 20% lower trough levels for the q12h treatment.

- Bioequivalence

The capsule formulations used in the clinical trial program are comparable: identical excipients are used, although not in the same quantity. In addition, the to be marketed capsule formulations are similar to the formulations used in the clinical trial program. No bioequivalence studies are submitted to compare the different formulations used. Instead a biowaiver was requested, taking into account the criteria mentioned in the CPMP Note for Guidance on the investigation of Bioavailability and

Bioequivalence. Pregabalin can be considered highly soluble and rapidly dissolving at the pH 1.2, 4.5 and 6.8, and is highly permeable. The excipients used were lactose monohydrate, corn starch and talc and are well known, and considered not critical with regard to dissolution, solubility and absorption. In addition, pregabalin is rapidly absorbed, the pharmacokinetics are linear over the intended dose range after single dose as well as after multiple dose, and pregabalin is not hepatically metabolised and renally excreted almost completely as intact drug. Taking into account these data, pregabalin can be considered to fulfil the criteria for applying a biowaiver as mentioned in the guidance, and the waiver from performing in vivo bioavailability-/bioequivalence studies on pregabalin has been granted.

- Distribution

In vitro protein binding studies using human plasma indicate that pregabalin does not bind to plasma protein at clinically relevant plasma concentrations of 0.1 – 20 µg/ml. The volume of distribution was estimated to be about 0.56 l/kg (about 42 l), similar to that of total body water.

- Metabolism and excretion

In vitro studies using human liver cytosolic and microsomal preparations indicate that pregabalin is not (or negligibly) metabolised. In vivo, renal clearance covered 88% of the total clearance, which was indicated by the excretion of more than 90% of the dose as intact pregabalin in the urine. The elimination half-life of about 6.3 h was independent of dose and not affected by repeat administration. The total body clearance is about 80 ml/min.

- Special populations

Pharmacokinetics in patients on concurrent anti-epileptic therapy were comparable with the pharmacokinetics in healthy volunteers.
As can be expected from a product that is completely intact excreted in urine, an impaired renal function results in a lower elimination of pregabalin from the body resulting in an increased exposure. Therefore a dose reduction is proposed, based upon the relationship between the patients creatinine clearance and pregabalin plasma clearance. During haemodialysis, pregabalin is adequately eliminated from the body. To compensate for this loss of drug, an additional dose should be given after haemodialysis.

With regard to male and female patients, the elderly and patients with an impaired liver function (which have not been specifically studied) the pharmacokinetics have not been seen to be, nor are expected to be, clinically significantly altered in these patient groups.

- Interaction studies

The *in vitro and in vivo* metabolism studies indicate that pregabalin is not a substrate for cytochrome P450 isozymes, does not inhibit cytochrome P450 isozymes and does not bind to plasma proteins. Pregabalin pharmacokinetics were not clinically significantly affected by concomitant treatment with sodium valproate, carbamazepine, lamotrigine, ethinyl estradiol/ norethindrone, gabapentin, ethanol, phenytoin, lorazepam and oxycodone. In addition, pregabalin did not clinically significantly affect the pharmacokinetics of these drugs.

Population pharmacokinetic analysis indicated that the 3 commonly used drug classes, oral antidiabetics, diuretics and insulin, and the 7 most commonly used anti-epileptic drugs, carbamazepine, lamotrignine, phenobarbital, phenytoin, tiagabine, topiramate and valproate, had no clinically significant effect on pregabalin clearance.

Pharmacodynamics

- Mechanism of action

Although its precise mechanism of action is still unclear, pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α_2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

There is no specific human pharmacodynamic model for studying anti-epileptic products.

- Primary and Secondary pharmacology

Three studies were submitted, in which the pharmacodynamic interaction of pregabalin was studied in healthy volunteers in relation to other drugs that interfere with the central nervous system, i.e.

lorazepam (076), oxycodone (078), and ethanol (079). Their effect was studied at the level of the respiratory system and CNS function. No overall mean data were presented in the dossier, therefore the results are of descriptive nature only. In none of the studies an effect was observed with respect to respiratory suppression, nor was there any correlation between plasma levels of the tested drugs and their effects on cognition.

Lorazepam and pregabalin produced consistent impairments in cognitive performance (mainly reaction time and alertness). Their combination potentiated these effects.

The opiate oxycodone administered by itself resulted in few decrements of task performance. Pregabalin alone impaired cognitive function (mainly reaction time). When administered in combination, the detrimental effects on cognition and motor performance appeared additive rather than synergistic.

Cognitive function (mainly reaction time) was affected by ethanol alone, but not by pregabalin alone. The combination, however, showed a potentiation of pregabalin on the alcohol related impairment of cognitive and gross motor function.

From these limited number of pharmacodynamic studies no conclusion can be drawn with regard to the impact of pregabalin on cognition.

Clinical efficacy

- Dose response study(ies)

The selection of doses (150-600 mg/day of pregabalin) for the different studies was based on pharmacokinetic, safety and tolerability data for pregabalin in healthy volunteers (001, 002, 003, and 023), while taking into consideration the relative potencies of pregabalin and gabapentin in animal seizure models and the dose/plasma concentrations achieved in humans. Hence, no formal Phase 2 dose finding studies in patients were conducted.

- Main studies

Peripheral Neuropathy

Twelve randomised placebo controlled studies in peripheral neuropathic pain were submitted. Six studies concerned diabetic peripheral neuropathy, five postherpetic neuralgia and one both diabetic peripheral neuropathy and postherpetic neuralgia. Studies DPN-173 and PHN-132 were terminated prematurely.

The table below presents main features of the pivotal studies in neuropathy.

DIABETIC PERIPHERAL NEUROPATHY			
	Design	**Study arms**	**Assessment**
DPN-014 USA 1998-1999	RD Db Plac PA Db: 2 + 4 weeks[a] Baseline: 1 week	[TID] Placebo Pregabalin 150 mg Pregabalin 600 mg	Primary: Endpoint mean painscore Secondary: SF-MPQ , Sleepscore, CGIC, PGIC, SF-36 QoL, POMS
DPN-029 USA 1998-1999	RD Db Plac PA Db: 1 + 4 weeks[a] Baseline: 1 week	[TID] Placebo Pregabalin 75 mg Pregabalin 150 mg Pregabalin 600 mg	Primary: Endpoint mean painscore Secondary: SF-MPQ , Sleepscore, CGIC, PGIC, SF-36 QoL, POMS
DPN-040 EU/S-Africa /Australia 1999-2000	RD Db Plac Amit. PA Baseline: 1 week Db: 2 + 6 weeks[a]	[TID] Placebo Pregabalin 600 mg Amitriptyline 75 mg	Primary: Endpoint mean painscore Secondary: SF-MPQ , Sleepscore, CGIC, PGIC, SF-36 QoL, HADS
DPN-131 USA 1999-2000	RD Db Plac. PA Baseline: 1 week Db: 0 + 8 weeks	[TID] Placebo Pregabalin 300 mg	Primary: Endpoint mean painscore Secondary SF-MPQ , Sleepscore, CGIC, PGIC, SF-36 QoL , POMS

DIABETIC PERIPHERAL NEUROPATHY			
	Design	**Study arms**	**Assessment**
DPN-149 EU S-Africa Australia 2000-2002	RD Db Plac. PA Baseline: 1 week Db: 1 + 11 weeks[a]	[BID] Placebo Pregabalin 150 mg Pregabalin 300 mg Pregabalin 300/600 mg	Primary: Endpoint mean painscore Secondary: SF-MPQ, Sleep score, CGIC, PGIC, SF-36 QoL, MOS ,EurQoL
DPN-173 *USA* *2000-2001*	*RD Db Plac. PA* *Baseline: 1 week* *Db: 1 + 11 weeks[a]* ***stopped prematurely***	*[BID]* *Placebo* *Pregabalin 150 mg* *Pregabalin 300 mg* *Pregabalin 300/600 mg*	Primary: Endpoint mean pain score Secondary: SF-MPQ, Sleep score, MOS, CGIC, PGIC, SF-36 QoL, EurQoL
POSTHERPETIC NEURALGIA			
	Design	**Study arms**	**Assessment**
PHN-030 USA 1998-1999	Rd Db Plac PA Baseline: 1 week Db: 5 weeks	[TID] Placebo Pregabalin 75 mg Pregabalin 150 mg	Primary: Endpoint mean painscore Secondary: SF-MPQ, Sleep score, CGIC, PGIC, SF-36 QoL, POMS
PHN-045 EU/AU 1999-2000	Rd Db Plac PA Baseline: 1 week Db: 1 +7 weeks[a]	[TID] Placebo Pregabalin 150 mg Pregabalin 300 mg	Primary: Endpoint mean pain score Secondary: SF-MPQ ,Sleep score, CGIC, PGIC, SF-36 QoL, ZUNG
PHN-127 USA/Can. 1999-2000	Rd Db Plac PA Baseline: 1 week Db 1+ 7 weeks[a]	[TID] Placebo Pregabalin 300/600 mg	Primary: Endpoint mean pain score Secondary: SF-MPQ, Sleep score, CGIC, PGIC, SF-36 QoL, MOS , POMS
PHN-132 *USA* *2000-2001*	*Rd Db Plac PA* *Baseline: 1 week* *Db: 1+11 weeks[a]* ***stopped prematurely***	*[BID]* *Placebo* *Pregabalin 150* *Pregabalin 300* *Pregabalin 300/600 mg*	*Primary: Endpoint mean pain score* *Secondary: SF-MPQ, Sleep score, CGIC, PGIC, SF-36 QoL, MOS, EurQoL*
PHN-196 EU/Australia 2001-2002	Rd Db Plac. PA Baseline: 1 week Db: 1 week titration and 12 weeks maintenance	[BID] Placebo Pregabalin 150 mg Pregabalin 300 mg Pregabalin 300/600mg	Primary: Endpoint mean pain score Secondary: SF-MPQ , Sleep scores, CGIC PGIC, SF-36 QoL MOS, EuroQoL
Diabetic Neuropathy and Postherpetic Neuralgia			
Study 155 EU 2001-2002	Rd Db Plac. PA Baseline: 1 week Db: Titr. / Maint. - Flexible dose; 1-3 / 9-11 weeks - Fixed dose: 1/11 w. - Placebo ; 0/12 w.	[BID] Placebo Flexible dose arm 150-600 mg/day Fixed dose arm 600 mg/day	Primary: Endpoint mean pain score Secondary: SF-MPQ , Sleep scores, MOS, PGIC, SF-36 QoL

[a] Db: 2 + 4 weeks indicates 2 week titration, 4 weeks fixed dose.

Legend: **BID**: Twice a day, **CGIC**: Clinician's Global Impression of Change, **Db**: Double-blind, **DPN**: Diabetic Peripheral Neuropathy, **EurQoL**: European Quality of life Questionnaire, **HADS**: Hospital Anxiety and Depression Scale, **MOS**: Medical Outcome Sleep scale, **PA**: Parallel, **PHN**: Post Herpetic Neuralgia, **Plac**: Placebo, **PGIC**: Patient's Global Impression of Change, **POMS**: Profile of Mood States, **Rd**: Randomised, **SF-MPQ**: Short-Form McGill Pain Questionnaire, **SF-36 QoL**: SF-36 Health Survey, **TID**: Three times daily.

In all studies the primary aim was to evaluate the efficacy of pregabalin on the neuropathic pain versus placebo. The clinical studies in peripheral neuropathic pain were fairly similar. Each study consisted of two phases. Baseline was a one week phase during which patients were screened for eligibility to enter the double-blind phase. The subsequent double-blind phase encompassed a titration period of 0 to 2 weeks followed by a fixed-dose period (4 to 12 weeks). Outcome scales and the statistical analyses of these studies were almost identical. The main differences concerned the dosage and duration of double-blind period (from 5-13 weeks). In study DPN 040 an amitriptyline arm was incorporated as a positive control. Study 155 includes both DPN and PHN and a flexible dose arm.

Study Participants
The diagnosis of polyneuropathy was based on the neurological history and examination. The main inclusion and exclusion criteria for the diabetic neuropathy were a diagnosis of diabetes mellitus with a painful distal, symmetrical, sensorimotor polyneuropathy for at least 1 year (with an upper limit of 5 years in studies 14, 29 and 131) and HbA_{1C} level ≤11%. Patients were required to have a score of ≥ 40 mm on the VAS (visual analogue pain scale) of SF-MPQ at screening and randomisation; and an average daily pain score of ≥4 points over the baseline phase. Additional inclusion/exclusion criteria included the absence of other conditions that might explain the polyneuropathy; mononeuropathy; the absence of other pain syndromes and the use of concurrent medication that may affect the assessments. Antidiabetic medication should be stable and constant during the study.

In the postherpetic neuralgia studies patients suffered from pain for more than 3 months, (more than 6 months for PHN-040) after healing of the herpes zoster skin rash. The main inclusion and exclusion criteria were, a score of ≥ 40 mm VAS of SF-MPQ at screening and randomisation and an average daily pain score of ≥ 4 points over the baseline phase.

Treatments
In most studies pregabalin was titrated to the fixed doses over 1-2 weeks. The daily pregabalin dose ranged from 75 to 600 mg daily divided over three or two doses. In studies DPN-149, DPN-173, PHN-127, PHN-132 and PHN-196 randomisation was stratified according creatinine clearance status. Patients randomised to the 300/600 mg/day arm received a dose of 300 mg/day if their estimated creatinine clearance (CLcr) was 30 to 60 mL/min, or a dose of 600 mg/day if their CLcr was >60 mL/min. The 300 mg dose in patients with a low creatinine clearance was considered equivalent to a dose of 600 mg in patients with a normal renal function. Hence, this study arm referred to as the 300/600 mg arm. Originally, pregabalin was developed with a three times daily (TID) regimen, later a two times daily (BID) programme was considered based on the similarity of the BID and TID pharmacokinetic profiles and to increase compliance.

In study 155, there were 3 arms besides the placebo arm, there was a flexible dose arm and a fixed dose arm. Patients in the flexible dose arm received escalating doses of pregabalin 150-300-450-600 mg/day titrated at weekly dose intervals. Based upon patient's response the dose was increased or kept stable. If intolerance occurred, a single dose reduction to the previous level was allowed. Patients in the fixed dose arm started with pregabalin 300 mg which was increased to 600 mg daily the second week. The daily doses were given in a BID regime.

Antidepressants were allowed as a co-medication in pain studies if the medication was stable for 30 days prior to study start.. Aspirin was allowed for prevention of myocardial infarction and/or TIA (transient ischemic attack). In some studies lorazepam was allowed as a hypnotic. The agents should have been used before study start and kept stable for the duration of the study. Paracetamol was allowed in all studies up to 3-4 gram daily on an "as needed" basis.

In the studies in diabetic neuropathy the anti-diabetic medication had to remain stable throughout the course of the studies.

Outcomes/endpoints
Primary efficacy assessment was based upon an 11 point Numerical Rating Pain Scale with 0 = no pain and 10 = worst possible pain. The pain was assessed by the patient in their daily pain score diary. The patients scored their pain during the last 24 hours at awakening. The primary endpoint in all studies was the weekly mean pain score at endpoint (=endpoint mean score) defined as the mean pain score for the last 7 available pain diary entries while on study medication. Responder rates defined as a 50% reduction in pain score as compared to baseline were part of a secondary analysis.

Numerous secondary efficacy measurement scales were used. Almost all studies included the Short-Form McGill Pain Questionnaire (SF-MPQ), a Sleep interference scale, the global impression of change by clinician (CGIC), the global impression of change by patient (PGIC), the SF-36 Quality of life Questionnaire and a mood assessment (profile of mood states [POMS], Hospital anxiety and depression scale [HADS] or Zung).

Statistical methods
In all studies, except study DPN-149, the primary analysis concerned the ITT population defined as subject randomised receiving at least one medication. In study DPN-149 the primary dataset was the modified ITT population defined as all randomised patients with at least one study medication and not

withdrawn as a result of regulatory agency or ethic committee decisions (11 patients less than the ITT population). For non-completers the last observation was carried forward. Primary comparisons concerned the effect of each pregabalin group versus placebo. The endpoint mean pain score was analysed using analysis of covariance (ANCOVA) using the baseline mean score as the covariate, in order to adjust for differences in baseline pain score among the treatment groups.

The number of patients per treatment group was determined assuming 2-sided testing to give >90% power to detect a difference in endpoint mean pain scores ≥1.3 between at least 1 pregabalin group and placebo. The difference in endpoint mean pain score of 1.3 was based on published studies in DPN and PHN.

RESULTS

Participant flow and Baseline data
Drop out rates across the treatment groups for all combined studies ranged from 9% to 23%.

In the diabetic neuropathy studies 6.1%, 5.2%, 4.5%, 2.6% and 3% of the subjects withdrew due to lack of efficacy for placebo, pregabalin 75mg, 150 mg, 300 mg and 600 mg respectively. Withdrawal rates due to adverse events were 3.7%, 2.6%, 3.9%, 9.7% and 10.9% respectively.

In the postherpetic neuralgia studies (except study 196 which results were available later) 5.9%, 0.0%, 0.0%, 0.9% and 0.0% of the subjects withdrew due to lack of efficacy for placebo, pregabalin 75mg, 150 mg, 300 mg and 600 mg respectively. Withdrawal rates due to adverse events were 7.1%, 2.4%, 8.5, 21.7% and 28.8% respectively.

The following table provide the numbers of patients randomised, numbers of completers and reasons for withdrawal (LOE= lack of efficacy, AE=adverse event), for each study.

Diabetic neuropathy				
DPN 014	**Placebo**	**Pregabalin 150**		**Pregabalin 600**
$n_{Irandomised}$	85	79		82
$n_{completed\ (\%\ Withdrawn)}$	72 (15%)	75 (5.1%)		72 (12.2%)
$N_{Wthdraw\ \ LO\ /\ AE/\ other}$	1/4/8	0/2/2		1/7/2
DPN 029	**Placebo**	**Pregabalin 75**	**Pregabalin 300**	**Pregabalin 600**
$n_{Irandomised}$	97	77	82	82
$n_{completed\ (\%\ Withdrawn)}$	89 (8.2%)	67 (13%)	76 (6.2%)	70 (15%)
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	2/3/3	4/2/4	0/3/2	0/10/2
DPN 040	**Placebo**	**Pregabalin 600**	**Amitriptyline 75**	
$n_{Irandomised}$	81	87	88	
$n_{completed\ (\%\ Withdrawn)}$	62 (24%)	62 (28%)	64 (26%)	
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	9/4/6	7/11/6	3/16/4	
DPN 131	**Placebo**	**Pregabalin 300**		
$n_{Irandomised}$	70	76		
$n_{completed\ (\%\ Withdrawn)}$	62 (11%)	65 (15%)		
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	3/2/3	1/8/2		
DPN 149	**Placebo**	**Pregabalin 150**	**Pregabalin 300**	**Pregabalin300/600**
$n_{Irandomised}$	97	99	99	101
$n_{completed\ (\%\ Withdrawn)}$	79 (18%)	82 (17%)	79 (20%)	78 (23%)
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	11/3/3	8/5/4	5/11/4	3/13/7
DPN 173	**Placebo**	**Pregabalin 150**	**Pregabalin 300**	**Pregabalin 300/600**
$n_{Irandomised}$	31	34	45	40
$n_{completed\ (\%\ Withdrawn)}$	1 (97%)	2 (94%)	2 (96%)	2 (95%)
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	1/1/27	1/2/29	2/2/37	1/9/27
Postherpetic neuropathy				
PHN-030	**Placebo**	**Pregabalin 75**	**Pregabalin 150**	
$n_{Irandomised}$	88	84	84	
$n_{completed\ (\%\ Withdrawn)}$	79 (10%)	79 (6%)	76 (8%)	
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	2/6/1	0/2/3	0/5/2	
PHN-045	**Placebo**	**Pregabalin 150**	**Pregabalin 300**	
$n_{Irandomised}$	81	81	76	
$n_{completed\ (\%\ Withdrawn)}$	61 (25%)	71 (12%)	60 (21%)	
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	7/8/5	0/9/1	1/12/3	
PHN-127	**Placebo**		**Pregabalin 300/600**	
$n_{Irandomised}$	84		89	
$n_{completed\ (\%\ Withdrawn)}$	74 (12%)		58 (35%)	
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	6/4/0		0/28/3	
PHN-132	**Placebo**	**Pregabalin 150**	**Pregabalin 300**	**Pregabalin 300/600**
$n_{Irandomised}$	53	51	62	51
$n_{completed\ (\%\ Withdrawn)}$	0 (100%)	0 (100%)	2 (97%)	0 (100%)
$N_{Wthdraw\ \ LOE\ /\ AE/\ other}$	4/3/45	2/8/40	0/6/54	0/12/39
PHN-196	**Placebo**	**PGB150**	**PGB300**	**PGB300/600**
$n_{Irandomised\ /\ n_{ITT}}$	94/93	87/87	98/98	91/90
$n_{completed\ (\%\ Withdrawn)}$	59 (37%)	61 (30%)	62 (37%)	60 (30%)
$N_{Wthdraw\ \ LOE\ /\ AE/\ /\ other}$	22/5/7	16/7/3	13/15/8	6/19/5
Diabetic Neuropathy and Postherpetic Neuralgia				
Study – 155	**Placebo**	**Flexible dose**		**Fixed dose**
$n_{Irandomised\ /\ n_{ITT}}$	65/64	141/140		132/132
$n_{completed\ (\%\ Withdrawn)}$	35 (46%%)	92 (35%)		82 (38%)
$n_{Wthdraw\ \ LOE\ /\ AE/\ /\ other}$	19/5/6	12/24/13		11/33/6

Treatment groups were similar with respect to demographic characteristics including age and sex. Within the diabetic neuropathy studies the treatment groups had a similar duration of diabetes, haemoglobin A1c levels and baseline pain score. Within the postherpetic neuralgia population, the duration of the disease in the treatment groups were comparable. The high age of the postherpetic neuralgia population is in accordance with what is expected.

The age distribution, duration of diabetes, type of diabetes and duration of postherpetic neuralgia are presented in the following table for each study.

Diabetic neuropathy				
DPN 014	**Plac**	**PGB150**		**PGB600**
Age (mean, sd)	57.1 (10.3)	56.3 (9.4)		57.8 (9.5)
Years of DM (median, range)	9 (1-34)	4 (0-40)		6.5 (1-43)
DM type I	16.5%	8.9%		2.4%
DM type II	83.5%	91.1%		97.6%
DPN 029	**Plac**	**PGB75**	**PGB300**	**PGB600**
Age (mean, sd)	57.8 (11.6)	61.3 (10.5)	59.0 (92)	62.0 (9.7)
Years of DM (median, range)	8 (0-52)	7 (1-34)	7 (0-48)	6.5 (0-32)
DM type I	14.4%	7.8%	6.2%	7.3%
DM type II	85.6%	92.2%	93.8%	92.7%
DPN 040	**Plac**	**PGB600**	**Amitryp75**	
Age (mean, sd)	60.6 (11.5)	62.0 (9.4)	57.8 (12.0)	
Years of DM (median, range)	11 (0-45)	10.5 (1-36)	9 (0-34)	
DM type I	12.3%	12.8%	17.2%	
DM type II	87.7%	87.2%	82.8%	
DPN 131	**Plac**	**PGB300**		
Age (mean, sd)	60.3 (10.3)	59.2 (12.3)		
Years of DM (median, range)	5.5 (0-44)	6 (1-62)		
DM type I	10%	15.8%		
DM type II	90%	84.2%		
DPN 149	**Plac**	**PGB150**	**PGB300**	**PGB300/600**
Age (mean, sd)	58.8 (11.8)	58.5 (12.6)	57.6 (10.5)	59.5 (11.4)
Years of DM (median, range)	11 (1-40)	12 (0-42)	12.5 (1-34)	11 (1-38)
DM type I	14%	14%	16%	14%
DM type II	86%	86%	84%	86%
DPN 173	**Plac**	**PGB150**	**PGB300**	**PGB300/600**
Age (mean, sd)	62 (12.0)	62.8 (10.6)	58.6 (11.5)	64.0 (11.7)
Years of DM (median, range)	8.5 (1-34)	10 (1-40)	10 (1-49)	10 (1-44)
DM type I	10%	18%	18%	5%
DM type II	90%	82%	82%	95%
Postherpetic neuropathy				
PHN-030	**Plac**	**PGB75**	**PGB150**	
Age (mean, sd)	71.3 (9.3)	72.9 (8.0)	70.4 (10.3)	
Months of PHN (median, range)	20 (2-189)	22 (2-159)	22-(2 –223)	
PHN-045	**Plac**	**PGB150**	**PGB300**	
Age (mean, sd)	73.2 (10.3)	71.3 10.1	71.9 10.3	
Months of PHN (median, range)	32 (0-267)	29 (5-243)	30.5 (1-215)	
PHN-127	**Plac**		**PGB300/600**	
Age (mean, sd)	70.5 (11.3)		72.4 (10.5)	
Months of PHN (median, range)	18.5 (3-151)		21 (3-187)	
PHN-132	**Plac**	**PGB150**	**PGB300**	**PGB300/600**
Age (mean, sd)	71.5 (9.1)	71.5 (11.2)	71.9 (13.6)	70.6 (11.8)
Months of PHN (median, range)	13 (3-104)	27 (3-204)	22.5 (3-161)	18 (3-218)
PHN -196	**Plac**	**PGB150**	**PGB300**	**PGB300/600**
Age (mean, sd)	70.9 (10.4)	70.5 (9.3)	70.7 (11.9)	70.7 (10.6)
Months of PHN (median, range)	31 (2-263)	22 (2-224)	29 (3-262)	22.5 (2-180)

Diabetic Neuropathy and Postherpetic Neuralgia			
STUDY 1008-155	**PLACEBO**	**FLEXIBLE DOSE**	**Fixed dose**
Age (mean, sd)	61.7 (12.6)	62.7 (10.6)	61.8 (11.0)
Months of PHN (median , range)	26.4 (3.6-106)	13.8 (3.7-245)	26.8 (3.2-126)
Years of DM (median, range)	11.5 (1.7-35.8)	10.4 (0.2-37.7)	11.4 (0.8-45.7)

Outcomes and estimation

The following table provide the results of the primary outcome: Endpoint mean pain scores - Analysis of covariance- ITT population.

Study/Treatment Group			Least Squares		Treatment Comparisons		
	N	Mean Baseline[a]	Mean endpoint[b]	SE	Difference	95% CI	Adjusted p-value[c]
DPN Pain Model					(Pregabalin — Placebo)		
Study 014 [TID, 6 weeks]							
Placebo	82	6.9	5.55	0.23			
PGB 150 mg/day	79	6.5	5.11	0.24	-0.44	(-1.08, 0.20)	0.1763
PGB 600 mg/day	82	6.7	4.29	0.23	-1.26	(-1.89, -0.64)	0.0002
Study 029 [TID 5 weeks]							
Placebo	97	6.6	5.06	0.21			
PGB 75 mg/day	77	6.7	4.91	0.24	-0.15	(-0.76, 0.46)	0.6267
PGB 300 mg/day	81	6.2	3.80	0.23	-1.26	(-1.86, -0.65)	0.0001
PGB 600 mg/day	81	6.2	3.60	0.23	-1.45	(-2.06, -0.85)	0.0001
Study 040 [TID 8 weeks]							
Placebo	80	6.3	4.60	0.26			
PGB 600 mg/day	86	6.9	3.96	0.26	-0.64	(-1.37, 0.08)	0.0822
AMT 75 mg/day	87	6.4	3.67	0.25	-0.93	(-1.65, -0.22)	0.0110
Study 131 [TID 8 weeks]							
Placebo	69	6.1	5.46	0.28			
PGB 300 mg/day	75	6.5	3.99	0.26	-1.47	(-2.19, -0.75)	0.0001
Study 149 [BID 12 weeks][d]							
Placebo	93	6.4	4.66	0.26			
PGB 150 mg/day	96	6.2	4.33	0.26	-0.33	(-0.94, 0.28)	0.5580
PGB 300 mg/day	96	6.4	4.48	0.26	-0.18	(-0.79, 0.43)	0.5580
PGB 300/600 mg/day[c]	98	6.6	3.69	0.25	-0.97	(-1.58, -0.36)	0.0054
Study 173 [BID xx weeks][e]							
Placebo	29	6.3	5.33	0.39			
PGB 150 mg/day	34	6.3	4.77	0.36	-0.55	(-1.54, 0.43)	0.4795
PGB 300 mg/day	43	6.8	4.99	0.34	-0.34	(-1.29, 0.61)	0.4795
PGB 300/600 mg/day[f]	38	6.7	4.09	0.35	-1.24	(-2.21, -0.27)	0.0375
PHN Pain Model							
Study 030 [TID 5 weeks]							
Placebo	87	6.6	5.59	0.21			
PGB 75 mg/day	83	6.7	5.46	0.21	-0.14	(-0.71, 0.43)	0.7999
PGB 150 mg/day	82	6.4	5.52	0.22	-0.07	(-0.64, 0.50)	0.7999
Study 045 [TID 8 weeks]							
Placebo	81	6.6	6.33	0.22			
PGB 150 mg/day	81	6.9	5.14	0.22	-1.20	(-1.81, -0.58)	0.0002
PGB 300 mg/day	76	7.0	4.76	0.23	-1.57	(-2.20, -0.95)	0.0002
Study 127 [TID 8 weeks]							
Placebo	84	6.4	5.29	0.24			
PGB 300/600 mg/day[f]	88	6.3	3.60	0.24	-1.69	(-2.33, -1.05)	0.0001
Study 132 [BID xx weeks][e]							
Placebo	52	6.0	6.23	0.26			
PGB 150 mg/day	51	6.9	5.05	0.26	-1.18	(-1.90, -0.46)	0.0015
PGB 300 mg/day	62	6.6	4.90	0.24	-1.33	(-2.01, -0.65)	0.0004
PGB 300/600 mg/day[f]	50	6.6	4.26	0.26	-2.02	(-2.74, -1.31)	0.0003
Study 196 [BID 13 weeks]							
Placebo	93	6.9	6.14	0.23			
PGB 150 mg/day	87	6.4	5.26	0.24	-0.88	(-1.53, -0.23)	0.008
PGB 300 mg/day	98	6.7	5.07	0.23	-1.07	(-1.70, -0.45)	0.002
PGB 300/600 mg/day[f]	88	6.7	4.35	0.24	-1.79	(-2.43, -1.15)	0.0003
Mixed study							
Study 155 [BID 12 weeks]							
Placebo	62	6.5	4.98	0.32			
PGB 150-600 /day flexible	139	6.8	3.81	0.23	-1.17	(-1.90, -0.45)	0.002
PGB 600 mg/day fixed	128	6.8	3.60	0.24	-1.38	(-2.11, -0.65)	< 0.001
Study 155: PHN group			Endpoint score				
Placebo	16	6.55	5.08			Not formally analysed	
PGB 150-600 /day flexible	36	7.04	3.88				

Study/Treatment Group			Least Squares		Treatment Comparisons		
	N	Mean Baseline[a]	Mean endpoint[b]	SE	Difference	95% CI	Adjusted p-value[c]
PGB 600 mg/day fixed	34	7.03	3.64				
Study 155: DPN group			Endpoint score				
Placebo	46	6.55	4.86				
PGB 150-600 /day flexible	103	6.67	3.73		Not formally analysed		
PGB 600 mg/day fixed	94	6.67	3.55				

DPN= diabetic neuropathy, PHN= postherpetic neuralgia, SE = Standard Error; CI = Confidence Interval; PGB = Pregabalin; AMT = Amitriptyline.

[a] The baseline score was the mean of last 7 available scores before taking study medication.

[b] The mean endpoint score was the mean of the last 7 available scores on study medication, or mean of available scores.

[c] The endpoint score were adjusted for treatment and centre (cluster) and baseline score.
The p-value is adjusted by the Hochberg procedure for multiple comparisons between treatment arms if applicable.

[d] In study DPN149 the data set analysed concerned the modified ITT population defined as all randomised patients with an at least one study medication and not withdrawn as a result of regulatory or ethic committee decisions.

[e] xx weeks indicates that the study was stopped prematurely. In study 173 the median exposure time was 2-3 weeks and 75% of the subjects received pregabalin for less than 5 weeks., in study 132 the median exposure time was less than 3 weeks, 75% of the subjects received pregabalin for less than 7 weeks.

[f] Patients randomised to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr.

Pregabalin appears to be efficacious in reducing pain in a polyneuropathy pain model (DPN) as well as in mononeuropathy pain model (PHN). A statistically significant difference in mean endpoint score between pregabalin and placebo is observed for the 300 mg and 600 mg doses. The mean differences in pain score between placebo and pregabalin ranged from -0.18 to -1.57 for the 300 mg daily dose and -0.64 to -2.02 points for the 600 mg daily dose. Results are less consistent with pregabalin 150 mg daily and 75 mg daily is not effective.

The overall picture of the primary efficacy variable is confirmed in the responder analysis (50% reduction in pain score as compared to baseline values), and the results are presented in the following table.

Responders analysis

Study/Treatment Group	n	Proportion responders[a]	Treatment Comparisons: Difference	95% CI[b]	Adjusted p-value[c]
DPN Pain Model			(Pregabalin — Placebo)		
Study 014 [TID, 6 weeks]					
Placebo	82	15%			
PGB 150 mg/day	79	19%	4.4%	1.6% ; 7.3%	0.42
PGB 600 mg/day	82	39%	24%	11%, 37%	0.002
Study 029 [TID 5 weeks]					
Placebo	97	18%			
PGB 75 mg/day	77	22%	4.6%	-7.0% ; 17%	0.41
PGB 300 mg/day	81	46%	28%	15% ; 41%	0.001
PGB 600 mg/day	81	48%	31%	17% ; 43%	0.001
Study 040 [TID 8 weeks]					
Placebo	81	30%			
PGB 600 mg/day	86	40%	9.9%	-4.5%; 24%	0.24
AMT 75 mg/day	87	46%	16%	1.7%; 30%	0.03
Study 131 [TID 8 weeks]					
Placebo	69	15%			
PGB 300 mg/day	75	40%	26%	7.1%;39%	0.001
Study 149 [BID 12 weeks]					
Placebo	93	30%			
PGB 150 mg/day	96	34%	4.3%	-9.6% ; 17%	0.74
PGB 300 mg/day	96	33%	3.4%	-10% ; 16%	0.74
PGB 300/600 mg/day[c]	98	46%	16%	2.0% ; 29%	0.04
Study 173 [BID xx weeks][d]					
Placebo	29	17%			
PGB 150 mg/day	34	32%	15%	-6.7%; 35%	0.72
PGB 300 mg/day	43	16%	-1.0%	-20% ;16%	0.78
PGB 300/600 mg/day	38	34%	17%	-4.7% ;36%	0.24
PHN Pain Model					
Study 030 [TID 5 weeks]					
Placebo	87	17%			
PGB 75 mg/day	83	21%	4.7%	-7.3% ; 16%	0.47
PGB 150 mg/day	82	22%	3.2%	-8.6% ; 15%	0.47
Study 045 [TID 8 weeks]					
Placebo	81	10%			
PGB 150 mg/day	81	26%	16%	4.2% ; 28%	0.006
PGB 300 mg/day	76	28%	18%	5.6% ; 30%	0.006
Study 127 [TID 8 weeks]					
Placebo	84	20%			
PGB 300/600 mg/day	88	50%	30%	16% ; 42%	< 0.001
Study 132 [BID xx weeks]					
Placebo	52	2%			
PGB 150 mg/day	51	14%	12%	5.2% ; 24%	0.046
PGB 300 mg/day	62	24%	22%	10% ; 34%	0.002
PGB 300/600 mg/day	50	32%	30%	19% ; 44%	0.002
Study 196 [BID 13 weeks]					
Placebo	93	8%			
PGB 150 mg/day	87	26%	19%	8.1% ; 29.7%	0.001
PGB 300 mg/day	98	27%	19%	8.4% ; 29.3%	0.001
PGB 300/600 mg/day	88	38%	30%	18.1% ; 41%	0.001
Mixed study					
Study 155 [BID 12 weeks]					
Placebo	62	24%			
PGB 150-600 mg/day	139	48%	24%	9.5% ; 36%	<0.001
PGB 600 mg/day	128	52%	28.2%	13.4% ; 41%	<0.001

[a] Subjects with 50% reduction as compared to baseline.
[b] CI95% by assessor.
[c] p by company; CMH procedure adjusted for centre, p-value adjusted for multiple comparison between treatment arms if applicable.
[d] xx weeks indicates that the study was stopped prematurely. In study 173 the median exposure time was 2-3 weeks and 75% of the subjects received pregabalin for less than 5 weeks., in study 132 the median exposure time was less than 3 weeks, 75% of the subjects received pregabalin for less than 7 weeks.

Secondary efficacy variables

Overall, the results with respect to the secondary efficacy variables (including SF McGill Pain questionnaire when analysed, sleep interference, global impression of change) were consistent with

that of the primary one, nevertheless, their results are only considered of exploratory value. For example, regarding the global impression of change, 12.5% to 39.2% of the patients rated much/very much improved in the placebo-arms, from 21.3% to 33.8% in the PGB 75 mg arm, from 22.2% to 45.8% in the PGN 150 mg arm, from 27.2% to 55.7% in the PGB 300 mg arm and from 36.5% to 69.2% in the PGB 300/600 mg arms.

Based upon the longitudinal analyses of the weakly mean pain scores the onset of treatment effect was observed by week 1. The magnitude of effect was maintained relative to placebo through to the end of studies.

Results with respect to quality of life/mood evaluations showed no consistent pattern except on the bodily pain dimension, which is not unexpected.

Ancillary analyses

- *Impact of dizziness and somnolence*

Dizziness and somnolence may have an impact on the pain perception. Somnolence is an adverse event of pregabalin with an high incidence rate ranging from 20%-30% in the neuropathy studies. In order to estimate the magnitude of this effect the applicant initially performed, for some studies, separate analysis of the primary endpoint for patients without dizziness and somnolence. As these data might suggest a reduction of the effect in the absence of somnolence was observed, further analyses were requested to assess the impact of somnolence as well as to assess the clinical relevance of the overall effect. See "Discussion on clinical efficacy".

- *Impact of rescue medication on the results*

It was questioned whether and to what extent the use of concurrent medication could influence the results, taking into consideration the two types of co-medication allowed; i.e. chronic co-medication kept stable during the PHN studies and paracetamol allowed as needed during all studies.

Considering that paracetamol is not considered sufficiently effective in the treatment of neuropathic pain and that its use as rescue medication was limited and homogeneous (from 1% to 7% in the placebo arms and from 1% to 7.9% in the PGB arms), it is a priori not expected to have had an impact on the observed effect size.

An analysis estimating the treatment effect after adjustment for stable concurrent medications in the PHN studies did not show any relevant difference.

Supportive studies

Patients in pivotal neuropathic pain studies had the option to continue treatment in open label extension studies. The main objective of these studies was to assess the safety profile of long-term exposure but long-term efficacy was also examined. Dose adjustments of pregabalin were allowed within the range of 75 to 600 mg/day as well as alternative pain medications. Overall in the open-label extension studies, the most commonly selected pregabalin dose range was 300 to 449 mg/day. Due to their design and the number of drop-outs, these studies do not provide definitive evidence to establish the maintenance of the efficacy.

An ad hoc analysis of the open-label VAS scores from 4 extension studies was conducted on a cohort of patients who had at least 1 year exposure to pregabalin in the open-label phase. The cohort comprised 217 patients; 69 in the placebo, 59 in the 150 mg/day pregabalin, 23 in the 300 mg/day pregabalin and 66 in the 600 mg/day pregabalin-treatment group. The patient's pain scores were stable over time but such retrospective cohort analysis are not that informative as patients who benefit continue in the study.

- Analysis performed across trials

A meta-analysis incorporating all 9 completed fixed-dose neuropathic pain trials (studies DPN-014, -029, -040, -131, -149 and PHN-030, -045, -127 and -196) was performed. The amitriptyline arm (study DPN-040) and the non-effective dose arms of 75 mg/day (studies DPN-029, PHN-030) were excluded. For Studies -127, -149, and -196, patients with a CLcr>30 and ≤60 mL/min randomised to the 300/600 mg/day group received 300 mg/day and those with CLcr >60 mL/min received 600 mg/day.

The analysis was adjusted for age, neuropathic pain model (PHN or DPN), baseline pain, study, dosing regimen (BID or TID) and treatment group (dose). The treatment effect is larger in PHN

compared to DPN. The difference, ranged between 0.28 and 0.47 depending on the dose group is considered substantial. Differences in effect size in BID and TID regimes is only substantial for the 300 mg dose, and the clinical relevance of the difference is questionable.

Epilepsy

Three multicenter, randomised, double blind, placebo controlled parallel group add-on studies (009, 011, and 034) were submitted to support the claim of adjunctive treatment in partial seizures with/without generalised seizures. Doses ranged from 50 to 600 mg daily given three (TID) or twice (BID) daily. Study duration was 11/12 weeks. In two studies (009, 011) patients were titrated up to their fixed dose, in one study (034), no titration scheme was used. Three open label, uncontrolled, extension studies (010, 012, 035) were conducted. The main features of the pivotal studies are presented in the following table.

Study	Design	Treatment arms	Assessments
009 USA, Canada June 1998-September 1999	RD, DB, Plac, PA Baseline: 8 weeks Titration: 1 week DB: 11 weeks Withdrawal: 1 week Follow up: 4-6 weeks	PBO PGB 600 mg/day BID PGB 600 mg/day TID	*Primary*: RRatio *Secondary*: Responder rate, PCH, seizure free interval, RRatio per seizure type, seizure freedom
011 Europe, South Africa, Australia April 1998-November 1999	RD, DB, Plac, PA Baseline: 8 weeks Titration: 1 week DB: 11 weeks Withdrawal: 1 week Follow up: 4-6 weeks	PBO PGB 150 mg/day TID PGB 600 mg/day TID	*Primary*: RRatio Secondary: Responder rate, PCH, SGTC, seizure free interval, RRatio per seizure type, seizure freedom
034 USA, Canada November 1998-September 1999	RD, DB, Plac, PA Baseline: 8 weeks Titration: - DB: 12 weeks Withdrawal: 6 days Follow up: 4-6 weeks	PBO PGB 50 mg/day BID PGB 150 mg/day BID PGB 300 mg/day BID PGB 600 mg/day BID	*Primary*: RRatio *Secondary*: Responder rate, PCH, seizure free interval, RRatio per seizure type, seizure freedom, QOLIE-31, Mastery Scale, Headache Pain Scale, Treatment Satisfaction and Compliance Scale, QOL Change Scale

RD: randomized, DB: double blind, Plac: placebo, PA: parallel arms
RRatio: Response ratio
PCH: percent change from baseline
QOLIE-31: Quality of life in epilepsy

Study Participants

Patients with medically refractory partial seizures (simple partial, complex partial, and secondarily generalised), male and female, from the age of 12 (034) to 18 (009, 011) years on, and of any race, were eligible to participate. Patients were diagnosed as suffering from epilepsy with partial seizures following standard procedures, and were considered refractory to treatment if they had received at least 1-3 standard anti-epileptic drugs (AED's) at doses within an acceptable therapeutic range, without sufficient effect. The following table summarises the inclusion and exclusion criteria.

Inclusion criteria
• Diagnosis of epilepsy with partial seizures, as defined in the International League Against Epilepsy Classification of Seizures. Recent EEG (within preceding 2 years) must be consistent with the diagnosis of focal epilepsy
• Pre-screening Seizure Frequency of minimally 3 partial seizures during the month prior to screening
• Baseline Seizure Frequency of minimally 6 partial seizures during the baseline phase, with no 4 week seizure-free period
• Currently receiving at least 1 and not more than 3 AED's that are within a clinically acceptable therapeutic range
• History of being refractory to more than one marketed AED at maximum-tolerated dosages
• Aged (12*) 18 years or older, weighing (>40kg*) between 50 to 135 kg
• Males, and nonpregnant, nonlactating females who were premenarchal, postmenopausal, surgically sterilized, or using a reliable method of contraception (barrier or hormonal) and had a negative pregnancy test prior to study entry
• Normal ECG including a 2-minute rhythm strip, Funduscopy and visual acuity assessment at screening without abnormal findings, Chest X-ray at screening without abnormal findings
• CT scan/MRI within 2 years prior to screening without abnormal findings

Exclusion criteria
• Absence seizures
• Lennox-Gastaut Syndrome
• Progressive neurologic or systemic disorders
• Treatable causes of seizures
• WBC < 2500/mm^3; neutrophil count <1500/mm^3; platelet count <100x10^3/mm^3
• History or clinical evidence of cardiovascular, haematologic, hepatic, or renal disease
• Status epilepticus within the previous year
• Significant psychiatric disorder or recurrent episodes of severe depression. Patients with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant were allowed to enter the study
• Administration of any investigational drug within 30 days prior to screening
• Administration of any concomitant medication that could alter the effectiveness of the patient's medication response or seizure frequency
• Alcohol or drug abuse within the previous year
• Treatment with gabapentin, unless discontinued at least 1 week prior to entry into baseline
• Pregnancy or nursing

***** Protocol difference in study 034

Treatments

Apart from pregabalin and placebo (see table with main feature of the studies), patients remained on their current AED therapy, except for those drugs that were excluded in the exclusion criteria or otherwise (i.e. vigabatrin, gabapentin, macrolide antibiotics, antihistamines, phenothiazines and antiarrhythmics). The concomitant AED's were to be kept stable during the trial, but could be decreased in case of danger of toxicity. Patients who suffered from mild depression could stay on their antidepressive medication during the trial.

Outcomes/endpoints

The primary outcome parameter was the Response Ratio (RRatio) after 11 (12) weeks of fixed dose treatment. The RRatio is calculated by dividing the difference between the 28-day seizure rate during treatment (T) and baseline (B) by the sum of baseline (B) and treatment (T) rate and multiplying it by 100. A RRatio of –33 is equivalent to a 50% reduction in seizure rate.

Several secondary endpoints were assessed, in particular:

1. Responder Rate, i.e. the percent of patients who had at least a 50% reduction in 28-day seizure frequency compared to baseline seizure frequency.
2. Percent change (PCH) of seizure frequency from baseline.
3. Analysis per seizure type.
4. Seizure-free analysis (number of seizure-free days)
5. Health outcome assessment (study 034 only)

The observed seizure rate during baseline and treatment was standardised for a 28-day period, based on the patient's daily diary data using the following procedure:

$$\text{28-day rate} = \frac{\text{Number of partial seizures in period}}{\text{[number of days in period-number of missing diary days in period]}} \times 28$$

Sample size

The sample size estimate of each study was based on the RRatio and the Responder Rate of previous experiences with add-on studies of gabapentin. Assuming a RRatio of –15 for pregabalin, –3 for placebo, and a 10% dropout rate at week 12, a total of 80 patients per treatment group were to be randomised to provide >80% power (α=0.05, 2-sided) for the ITT population. Similarly, with an assumed 30% Response Rate for pregabalin and 10% for placebo, 80 patients were to be randomised, expecting a 10% dropout rate.

Statistical methods

The primary efficacy outcome parameter (RRatio) was analysed using analysis of variance (ANOVA) based on ranks with treatment and centre as main effects. For the multiple testing (two dose regimens

against placebo and each other) that was performed, the Hochberg's procedure was followed, ranking the p-values for multiple comparisons from highest to lowest values.

The secondary outcome parameter (Responder Rate) was summarised by treatment group and analysed using the Cochran-Mantel-Haenzel chi-square test, adjusting for centre.

All other outcome parameters were presented as descriptives.

Results

Participant flow and baseline characteristics

The following table describes dose related participant flow over studies. The occurrence of adverse events was clearly dose related.

Study	Treatment	Eligible/ Randomised (ITT)	Withdrawal for adverse event N (%)	Withdrawal for lack of efficacy N (%)	Completed study N (%)
009		378/313 (312)	55 (17.6)	8 (2.6)	237 (75.7)
	Placebo		7 (7.1)	5 (5.1)	81 (82.7)
	600 mg/day PGB/TID		21 (18.9)	2 (1.8)	85 (76.6)
	600 mg/day PGB/BID		27 (26.0)	1 (1.0)	71 (68.3)
011		344/288 (287)	33 (11.5)	6 (2.1)	241 (83.7)
	Placebo		6 (6.2)	5 (5.2)	84 (86.6)
	150 mg/day PGB/TID		10 (10.1)	0 (0)	88 (88.9)
	600 mg/day PGB/TID		17 (18.5)	1 (1.1)	69 (75)
034		586/455 (453)	46 (10.1)	13 (2.9)	378 (83.1)
	Placebo		5 (5.0)	5 (5.0)	87 (87)
	50 mg/day PGB/BID		6 (6.8)	1 (1.1)	78 (88.6)
	150 mg/day PGB/BID		1 (1.1)	1 (1.1)	81 (92)
	300 mg/day PGB/BID		13 (14.4)	2 (2.2)	71 (78.9)
	600 mg/day PGB/BID		21 (23.6)	4 (4.5)	61 (68.5)

The baseline characteristics of the study population show an equal distribution of males and females over the different studies, the majority being Caucasian, and representative of the Western population. Further main characteristics are similar as well and representative of the target adult population with partial epilepsy. However, only 17 elderly (>65 years) were included, and 10 adolescents between the age of 12-16 years. The median baseline 28-day seizure frequency was sufficiently high (range 9.3-12.0) to be able to demonstrate a treatment effect. The majority of patients used 2 concurrent AED's; the most frequently used drugs being carbamazepine and lamotrigine, or their combination.

Outcomes and estimation

It is recommended in the CPMP guideline to define the proportion (pre-defined) responders as primary measure, since it reflects both seizure reduction and its clinical significance. The response ratio is not considered the best outcome parameter, since the distribution of the RRatio is often found to be non-normal which may biase the estimate and it is difficult to establish the clinical relevance of the effect based on this parameter. Efficacy will primarily be evaluated on the basis of the responder data (responders being defined as those subjects with >50% reduction in seizures).

Results regarding RRatio and Responder analyses are provided in the following tables. No efficacy was demonstrated for the 50 mg/day PGB. Efficacy has been demonstrated in the dose range of 150-600 mg/day of pregabalin for the primary outcome measure RRatio and is in general supported by the outcome measures Responder Rate. Overall, approximately 35% of patients can be regarded as responders to the 600 mg/day pregabalin, taking the placebo response into account. This number is reduced to 25% for the 300 mg/day dose, and further reduced to <20% for the 150 mg/day dose. The clinical relevance for the latter dose may be considered questionable. Although the data may suggest that the TID dosing schedule is favourable this is unlikely to be clinically relevant.

Summary of efficacy on the primary outcome measure (RRatio analyses)

Study	Treatment arms	N	RRatio	Treatment differences		p-value
				Mean (SE)	95% CI	
009	PGB 600 mg/day BID	103	-28.4	-29.0 (5.0)	[-38.9, -19.0]	P< 0.0001
	PGB 600 mg/day TID	111	-36.1	-36.7 (5.0)	[-46.4, -27.0]	P< 0.0001
	PBO	98	0.6			
011	PGB 600 mg/day TID	92	-31.4	-32.3 (4.2)	[-40.6, -24.0]	P< 0.0001
	PGB 150 mg/day TID	99	-11.5	-12.4 (4.1)	[-20.5, -4.3]	P= 0.0007
	PBO	96	0.9			
034	PGB 600 mg/day BID	89	-37.4	-33.5 (4.8)	[-42.9, -24.1]	P< 0.0001
	PGB 300 mg/day BID	90	-27.8	-24.0 (4.8)	[-33.3, -14.6]	P< 0.0001
	PGB 150 mg/day BID	86	-20.5	-16.6 (4.8)	[-26.1, -7.2]	P< 0.0001
	PGB 50 mg/day BID	88	-6.2	-2.3 (4.8)	[-11.7,7.1]	P= 0.4232
	PBO	100	-3.8			

PCH: Percent Change from Baseline; PGB: Pregabalin; PBO: Placebo; BID: Twice Daily; TID: Three times Daily

Summary of efficacy on the secondary outcome measure (% responders analyses)

Study	Treatment arms	Responder Rate n/N (%)	Treatment differences		
			Percent (SE)	95% CI	p-value
009	PGB 600 mg/day BID	44/103 (43)	33.5 (5.7)	[22.4, 44.7]	P< 0.001
	PGB 600 mg/day TID	54/111 (49)	39.5 (5.6)	[28.5, 50.4]	P< 0.001
	PBO	9/98 (9)			
011	PGB 600 mg/day TID	40/92 (44)	37.2 (5.7)	[26.0, 48.5]	P< 0.001
	PGB 150 mg/day TID	14/99 (14)	7.9 (4.3)	[-0.5, 16.3]	P= 0.087
	PBO	6/96 (6)			
034	PGB 600 mg/day BID	45/89 (51)	36.6 (6.3)	[24.1, 49.0]	p< 0.001
	PGB 300 mg/day BID	36/90 (40)	26.0 (6.2)	[13.8, 38.2]	p< 0.001
	PGB 150 mg/day BID	27/86 (31)	17.4 (6.1)	[5.5, 29.3]	p< 0.006
	PGB 50 mg/day BID	13/88 (15)	0.8 (5.1)	[-9.3, 10.8]	p= 0.840
	PBO	14/100 (14)			

Secondary outcome measures (PCH, seizure-free analysis, health outcome)
Efficacy on the secondary outcome percent change from baseline (PCH) was consistent with RRatio and Responder Rate. The analysis of seizure freedom is rather limited, and would be more relevant if evaluated after a longer period of time (1 year). No data were available with respect to the health questionnaires assessed in study 034.

Clinical studies in special populations

No studies were performed in children and adolescents, or in elderly.

Supportive studies
Six supportive studies (007, 008, 010, 012, 035, and 145) have been submitted, three of them (010, 012, and 035) being the open label extension studies of the pivotal efficacy studies.

The objectives of study 007 were to evaluate the efficacy and safety of pregabalin at 600 mg/day as compared with gabapentin at 300 mg/day in hospitalized patients with complex partial (CP) seizures, with or without secondary generalization, who had their concomitant antiepileptic drugs (AEDs) discontinued as part of an inpatient hospitalization for clinical seizure monitoring. This trial explores the paradigm of pre-surgical patients which involves patient very difficult to treat. The gabapentin arm in this trial is a pseudo-placebo arm because 300 mg/d of gabapentin is a sub-therapeutic dose. This trial does not add relevant information on the potential efficacy of pregabalin. Patients from this study continued in open label treatment (008).

Study 145 is a double-blind controlled titration study that was prematurely ended due to the clinical hold imposed by the FDA. Only 3 patients enrolled in this study.

The open label extension studies of the pivotal efficacy studies aimed to evaluate long-term safety, tolerance and efficacy of pregabalin administered as adjunctive therapy at dosages from 75 to 600 mg/day on a twice a day (BID) or 3 times a day (TID) dosing schedule in patients with refractory partial seizures. Subjects were the ones who had chosen to enter open label treatment after participating in the controlled studies. In addition, newly recruited patients were allowed to enter. For these newly recruited patients, the inclusion criteria were broadened with respect to the minimum amount of seizures required in the preceding 8 weeks (4, instead of 6). No primary or secondary outcome parameters were pre-defined. Outcomes were described for Responder Rate, PCH, and seizure-freedom. Assessments were taken at week 4, 8, 16, 24, and every 12 weeks henceforth. A responder rate of 37% and a median percent reduction from baseline of 38% were seen for the evaluable population during the initial 12-week period of open-label. For a cohort of patients followed for 2 years, the responder rate and median percent change at subsequent intervals were maintained over time. Nevertheless, the gradual dropout of patients over time because of lack of efficacy or tolerance to the study drug was not evaluated against the background of the positive responder's cohort of the two years follow-up. Moreover, information on dosing and dose adjustments during long-term treatment was lacking and is essential for a reliable judgement. Similarly, limited information was given on the occurrence of withdrawal or rebound phenomena after withdrawal of the study drug both in the short- and long-term trials.

- Discussion on clinical efficacy

Peripheral Neuropathy

To support the neuropathic pain claim, twelve randomised placebo controlled studies were submitted. Six studies concerned the diabetic neuropathy model and five studies the postherpetic neuralgia model. One study concerned both models. Doses ranged from 75 to 600 mg daily given twice or three times daily. Study duration ranged from 5 to 13 weeks.

Pregabalin appears to be efficacious in reducing pain in those polyneuropathy and mononeuropathy pain models. A statistically significant difference in mean endpoint score between pregabalin and placebo was observed for the 300 mg and 600 mg doses, with mean differences in pain score ranged from -0.18 to -1.57 and -0.64 to -2.02 points for 300 mg and 600 mg respectively. Results are less consistent with pregabalin 150 mg daily and 75 mg daily is not effective. The overall picture of the primary efficacy variable was confirmed in responder analysis.

Nevertheless, the following issues were discussed regarding clinical efficacy:

- clinical relevance of the effect, taking into account the neuropathic pain model, the dose and regimen (BID and TID), the influence of somnolence;
- the posology to be recommended;
- the maintenance of the effect.

In addressing the clinical relevance, no distinction was initially made between indication (DPN versus PHN), and dose regime used (BID or TID). For an indication in peripheral neuropathic pain, efficacy should be demonstrated in two peripheral neuropathic pain models, clinical relevance should be established for each pain model separately. A meta-analysis indicated the treatment effect is larger in PHN compared to DPN. The pain scores differ between the BID and TID regimes, but the clinical relevance of this difference is questionable.

Dizziness and somnolence may have an impact on the pain perception. Somnolence is an adverse event of pregabalin with an incidence rate ranging from 20%-30% in the neuropathy studies. In order to estimate the magnitude of this effect the applicant initially performed, for some studies, separate analysis of the primary endpoint for patients without dizziness and somnolence. As these data might suggest a reduction of the effect in the absence of somnolence, further analyses were requested to assess the impact of somnolence as well as to assess the clinical relevance of the overall effect. The applicant evaluated the pain scores and treatment differences for patients with and without somnolence separately. The difference in pain score for patients with/without somnolence were minimal but this was not the case for the responders analysis. The analysis originally presented was not split by indication (while the age per indication differs considerably and patients of elder age might be more sensitive to somnolence) or dose regime, but was provided later.

The clinical relevance of the observed effect was therefore originally not considered sufficiently addressed for PHN and DPN separately and therefore, separate analysis of responder rates taking into account the dose regime (TID versus BID) and the absence/presence of somnolence were requested.

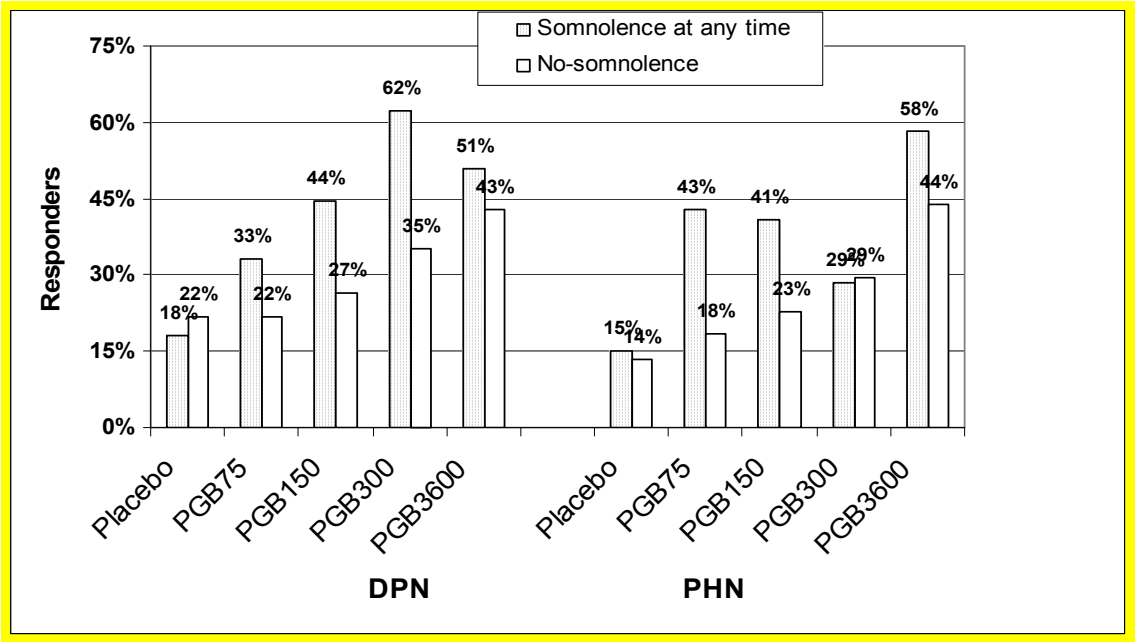
The applicant argued that the observed effect on neuropathic pain is clinically relevant by relating the observed response on the pain scale and PGIC (Patient's global impression of change), for both diabetic neuropathy and postherpetic neuropathy. The proportion of patients achieving a clinical relevant response (defined as very much or much improved on the PGIC) is given in the next table based on 9 studies):

PGIC category*

	DPN				PHN			
	Pregabalin n=828		Placebo n=413		Pregabalin n=657		Placebo n=341	
Very much improved	15.1%	**47.8%**	6.3%	**29.5%**	9.6%	**32.3%**	4.7%	**17.0%**
Much improved	32.7%		23.2%		22.7%		12.3%	
Minimally improved	25.9%		24.9%		25.6%		19.1%	
No change	19.4%	49.8%	33.7%	65.4%	30.0%	62.6%	45.2%	74.5%
Minimally worse	4.5%		6.8%		7.0%		10.3%	
Much worse	2.2%	2.4%	4.6%	5.1%	3.5%	5.2%	6.5%	8.5%
Very much worse	0.2%		0.5%		1.7%		2.1%	

*Adapted from table 2 provided by the MAH, by assessor

In addition, a clinically meaningful effect on responder rates is evident in patients who do not experience somnolence as well in patients who report somnolence across the neuropathic pain studies, however, point estimate of responder rates are lower in the absence of somnolence. This effect is consistent over the dose range. 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. In conclusion, the observed effect on the pain score is considered clinically relevant for both diabetic neuropathy as well as post-herpetic neuropathy even if the observed effect is larger in presence of somnolence.



Efficacy of 150mg/day in neuropathic pain was not consistent, nevertheless as it could be of benefit in some patients and represents a well-tolerated starting dose, it was accepted as starting dose.

Comparable bioavailability of the BID/TID regime has been shown; the treatment regimens were bioequivalent with respect to the AUC and Cmax, however, Cmin was somewhat lower in the BID regime. In general, the overall safety profile is in favour of the BID regime but the efficacy profile is in favour of the TID regime. Nevertheless, the confidence interval for the difference between regimens was [-0.2; 0.6], based on a meta-analysis with the nine completed neuropathic pain studies, and responder rates for BID and TID were similar across the dose range, as shown in the table below. The applicant also provided data showing that BID and TID safety profiles do not differ shortly after initiation (one week) of treatment, even in elderly patients. Therefore, it was agreed that both BID and TID regimens would be acceptable which would allow the physician to adapt the treatment to the individual patient's need.

Proportion of 50% Responders by Treatment Group (BID vs. TID) – Nine Completed Neuropathic Pain studies

Treatment Group	TID Dosing		BID Dosing	
	Nb Assessed	Nb of Responders (%)	Nb Assessed	Nb of Responders (%)
Placebo	580	103 (17.8%)	186	35 (18.8%)
Pregabalin 150mg/day	242	54 (22.3%)	183	56 (30.6%)
Pregabalin 300mg/day	262	101 (38.5%)	233	69 (29.6%)
Pregabalin 600mg/day	306	137 (44.8%)	147	67 (45.6%)

Initial studies were considered too short to establish maintenance of effect. Studies submitted later (studies 196 and 155) were of at least 12 weeks duration which substantiated the maintenance of the effect. In Study 196 in patients with PHN, the observed effect size was of the same order of magnitude as earlier studies and the effect did not diminish over the 12 week fixed dose phase. Study 149 in diabetic patients was also of 12 weeks duration. The results of the new study 155 were less convincing due to a more complicated study design. Therefore the maintenance of effect over a time period of up to 12 weeks is considered established. Long-term efficacy (i.e. > 12 weeks) is difficult to assess because only open label studies are available. In a cohort of 517 patients treated for at least 420 days, mean pregabalin dose was maintained over time and pooled VAS scores were stable. Although the value of the cohort study is limited for addressing the long term efficacy, these data argue for the maintenance of an effect and do not suggest that tolerance could be a major issue.

Epilepsy

To support the claim of adjunctive treatment in partial seizures with/without generalised seizures, three randomised placebo controlled add-on studies were submitted. The dose ranged from 50 to 600 mg daily in similar dosing schedules as for the neuropathic pain. Study duration was 11/12 weeks.

Efficacy has been demonstrated in the dose range of 150-600 mg/day in a dose dependent way; approximately 35% of responders to the 600 mg/day pregabalin, 25% for the 300 mg/day dose, and <20% for the 150 mg/day dose, after adjusting for placebo. Although the effect of the 150 mg/day dose was inconsistent , 150 mg/day is an acceptable starting dose. Additional outcome measures, such as percent change from baseline (PCH) and the number of patients experiencing a substantial amount of seizure-free days were supportive to some extent, but less favourable.

Although efficacy in short-term trials has been demonstrated, long-term maintenance of efficacy is not established. Long-term efficacy data, based on the open-label studies, is of limited value because the population studied was a mixed one (responders, (partial) responders and patients converting from placebo to pregabalin). 33% of patients dropped out of the open-label extension studies due to lack of efficacy. Of the patients who discontinued due to lack of efficacy, 39% of them displayed an increase in seizure frequency compared to baseline. Whether or not tolerance to the study drug was developed, was investigated through data from a two years cohort. In this cohort, of good responders, minimal dose adjustments were needed to maintain efficacy, which would support the fact that tolerance to the product is not a major concern.

With respect to the TID and BID dosing, one head to head epilepsy study (009) was performed and showed a slightly better response with TID as compared to BID. Nevertheless, study 009 was not prospectively powered to detect a difference between the BID and TID regimens, and the observed difference in responder rate (5.9%) was not statistically significant (p=0.430). The Applicant also performed a pooled analysis of the epilepsy studies showing that the 95% confidence interval on the treatment difference in responder rate between 600mg/day BID and TID was –9.8 to 9.9, and 5.3 to 29.2 for 150mg/day (300 mg/day was only studied in BID regimen). Regarding the safety profile, TID dosing seemed more favourable in the epilepsy population, especially with regard to dizziness and

somnolence, but this was in contrast to what was found for the incidence of these adverse events in the overall safety profile of pregabalin and the safety profiles of BID and TID were similar in study 009. In addition, the applicant provided data showing that BID and TID safety profiles do not differ shortly after initiation (one week) of treatment. Therefore, it was agreed that both BID and TID regimens would be acceptable, which would allow the physician to adapt the treatment to individual patient's need.

Clinical safety

Safety of pregabalin was assessed on all subjects who participated in any study, controlled and uncontrolled, with pregabalin until the time of cut-off that was determined for the integrated safety database. This does not include data from studies 155 and 196 which were submitted later.

- Patient exposure

An overview of the number of subjects receiving study medication and included the safety database is given in the following table.

	Placebo	Pregabalin	Comparator	Total[a]
Clinical Pharmacology (Phase 1) Studies	134	440	140	472
Phase 2/3 Studies Not in Integrated Safety Database				
Acute Dental Pain	120	267	114	501
Studies Conducted in Japan	14	51	--	65
Clinical Phase 2/3 Integrated Safety Database	**2544**	**8228**	**729**	**9849**
Chronic Pain	1189	3490	94	3931
Neuropathic Pain	764	2099	87	2409
Diabetic Neuropathy	459	1327	87	1525
Postherpetic Neuralgia	305	772		884
Other Nonneuropathic Pain	416	1364		1484
Other Neuropathic Pain	9	27	7	38
Epilepsy (Adjuvant Therapy in Partial Seizures)	294	1613	51	1660
Psychiatry	1061	3125	584	4258
Generalized Anxiety Disorder	656	1954	412	2687
Other Psychiatry	405	1171	172	1571

[a] Patients who received ≥1 treatment may be included in ≥1 column but are counted once in the "total" column.

As of the day of database lock, 5232 patients were randomised to pregabalin in the controlled studies, 59.2% being exposed for $\geq$ 6 weeks, and 15.2% being exposed for $\geq$ 12 weeks. In the combined controlled and uncontrolled studies, 8228 patients were randomised to pregabalin, 55.8% being exposed $\geq$ 12 weeks, and 26.3% being expose for $\geq$ 1 year. Forty seven patients (0.6%) reached the maximum exposure time, i.e. ≥3 years. In the open extension studies with flexible dosing regimes, approximately one-third of the patients were exposed to a dose range of 300-450 mg/day pregabalin, comprising the average recommended dose. Another one-third of patients were exposed to the maximum dose of 600 mg/day pregabalin. Approximately 8% of patients in the controlled and uncontrolled studies were exposed to 600mg/day for ≥ 1 year.

- Adverse events

Overall 65% of placebo-treated patients and 79.6% of pregabalin treated patients experienced adverse events during the controlled trials.

A summary of adverse events in >2% of all pregabalin-treated patients by decreasing frequency (all controlled studies, combined regimens) is provided in the table below.

	[Number of Patients (%)]							
Preferred Term	Placebo N = 2290	150 PGB N = 1077	200 PGB N = 207	300 PGB N = 1100	400 PGB N = 360	450 PGB N = 501	600 PGB N = 1738	All PGB[a] N = 5232
Dizziness	199 (8.7)	163* (15.1)	63* (30.4)	330* (30.0)	119* (33.1)	203* (40.5)	619* (35.6)	1520* (29.1)
Somnolence	179 (7.8)	144* (13.4)	61* (29.5)	235* (21.4)	89* (24.7)	144* (28.7)	491* (28.3)	1183* (22.6)
Headache	307 (13.4)	117 (10.9)	45* (21.7)	94 (8.5)	70* (19.4)	64 (12.8)	206 (11.9)	611 (11.7)
Dry mouth	79 (3.4)	58* (5.4)	33* (15.9)	76* (6.9)	42* (11.7)	70* (14.0)	188* (10.8)	477* (9.1)
Infection	179 (7.8)	86 (8.0)	30 (14.5)	83 (7.5)	44 (12.2)	52 (10.4)	104 (6.0)	422 (8.1)
Asthenia	118 (5.2)	65 (6.0)	18* (8.7)	64 (5.8)	34* (9.4)	31 (6.2)	161* (9.3)	384* (7.3)
Amblyopia[b]	48 (2.1)	47* (4.4)	10* (4.8)	64* (5.8)	21* (5.8)	36* (7.2)	156* (9.0)	340* (6.5)
Nausea	161 (7.0)	56 (5.2)	19 (9.2)	54 (4.9)	38* (10.6)	44 (8.8)	115 (6.6)	330 (6.3)
Peripheral oedema	31 (1.4)	41* (3.8)	4 (1.9)	91* (8.3)	7 (1.9)	25* (5.0)	122* (7.0)	294* (5.6)
Thinking abnormal	37 (1.6)	25 (2.3)	14* (6.8)	32* (2.9)	38* (10.6)	35* (7.0)	144* (8.3)	292* (5.6)
Weight gain	19 (0.8)	38* (3.5)	5 (2.4)	52* (4.7)	19* (5.3)	33* (6.6)	142* (8.2)	291* (5.6)
Constipation	49 (2.1)	38* (3.5)	7 (3.4)	43* (3.9)	27* (7.5)	30* (6.0)	93* (5.4)	243* (4.6)
Ataxia	24 (1.0)	20 (1.9)	7* (3.4)	33* (3.0)	9* (2.5)	20* (4.0)	141* (8.1)	239* (4.6)
Accidental injury	67 (2.9)	32 (3.0)	4 (1.9)	42 (3.8)	8 (2.2)	19 (3.8)	96* (5.5)	221* (4.2)
In coordination	17 (0.7)	10 (0.9)	11* (5.3)	29* (2.6)	27* (7.5)	40* (8.0)	93* (5.4)	215* (4.1)
Euphoria	11 (0.5)	9 (0.8)	12* (5.8)	52* (4.7)	22* (6.1)	49* (9.8)	57* (3.3)	203* (3.9)
Pain	89 (3.9)	47 (4.4)	12 (5.8)	40 (3.6)	9 (2.5)	14 (2.8)	67 (3.9)	199 (3.8)
Diarrhoea	123 (5.4)	25 (2.3)	9 (4.3)	31 (2.8)	18 (5.0)	21 (4.2)	63 (3.6)	177 (3.4)
Nervousness	52 (2.3)	22 (2.0)	18* (8.7)	21 (1.9)	20* (5.6)	23* (4.6)	54 (3.1)	158 (3.0)
Flu syndrome	77 (3.4)	27 (2.5)	10 (4.8)	33 (3.0)	16 (4.4)	23 (4.6)	40 (2.3)	153 (2.9)
Amnesia	24 (1.0)	16 (1.5)	4 (1.9)	25* (2.3)	9* (2.5)	15* (3.0)	78* (4.5)	151* (2.9)
Insomnia	86 (3.8)	22 (2.0)	17* (8.2)	23 (2.1)	22* (6.1)	17 (3.4)	47 (2.7)	149 (2.8)
Confusion	12 (0.5)	17 (1.6)	3 (1.4)	27* (2.5)	9* (2.5)	21* (4.2)	64* (3.7)	142* (2.7)
Increased appetite	20 (0.9)	17 (1.6)	6* (2.9)	21 (1.9)	10* (2.8)	18* (3.6)	54* (3.1)	127* (2.4)
Tremor	30 (1.3)	13 (1.2)	3 (1.4)	17 (1.5)	7 (1.9)	4 (0.8)	77* (4.4)	126* (2.4)
Flatulence	27 (1.2)	20 (1.9)	8* (3.9)	18 (1.6)	6 (1.7)	19* (3.8)	45* (2.6)	122* (2.3)
Diplopia	11 (0.5)	17 (1.6)	1 (0.5)	23* (2.1)	2 (0.6)	7 (1.4)	56* (3.2)	108* (2.1)
Any AE	**1488 (65.0)**	**736 (68.3)**	**171 (82.6)**	**879 (79.9)**	**282 (78.3)**	**442 (88.2)**	**1493 (85.9)**	**4163 (79.6)**

* Statistically significantly different from placebo based on odds ratio or Fisher's Exact test ($p<0.05$)

[a] Includes other doses of pregabalin (e.g., 50 or 75 mg/day). Dose is total daily dose in mg/day given BID or TID.

[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

The most common adverse reactions were dizziness (29.1%) and somnolence (22.6%) in the pregabalin-treated patients. Other adverse events that were more frequently reported in pregabalin-treated patients than placebo-treated patients were dry mouth (9.1%), asthenia, amblyopia, peripheral oedema, thinking abnormal, and weight gain. The incidences of dry mouth, asthenia, amblyopia, peripheral oedema, and thinking abnormal were generally higher at doses greater than 150 mg/day but with no consistent pattern of dose response.

Apart from dizziness and somnolence, the majority of the other adverse reactions are also CNS related, and appear dose related, and of mild to moderate severity. The overall incidence of CNS adverse events was higher in the patients with epilepsy than in patients with neuropathic pain. In this regard, the use of concurrent CNS active drugs in the patients with epilepsy should be noted. The median time to onset of the CNS adverse events was short 1-2 days. Dizziness and somnolence did not resolve by the last day on study medication in 31% and 45% respectively, of subjects, experiencing these adverse events.

Accidental injury was mainly reported for the highest dose pregabalin.

Amblyopia, mainly referred to as 'blurred vision', was the main visual disturbance found.

Peripheral oedema (PE) was found mainly in the elderly from the neuropathic pain studies being seen in approximately 11% of patients after 1 – 3 months of treatment and persisted in 54% of these specific patients.

Weight gain was in general a dose-dependent finding across studies, which was first observed as an adverse event with a median time to onset of 2 weeks. Based on the incidences in both the controlled and uncontrolled studies, weight gain is persistent over time.

See Discussion on clinical safety regarding somnolence/dizziness, peripheral oedema, weight gain and visual field abnormalities.

A summary of BID and TID regimen adverse event profiles (all controlled studies including the later submitted study 196 but not study 155 which included a flexible dose arm) is provided in the table below. The overall safety profile of BID and TID dosing is in favour of the BID, particularly for the most common adverse events dizziness and somnolence.

Table 8. Summary of BID and TID Regimen Adverse Event Profiles (Controlled Studies All Indications)

Adverse Events (%)	Placebo	Pregabalin total daily dose					
		150mg/day		300mg/day		600mg/day	
		BID	TID	BID	TID	BID	TID
N	**2384**	**357**	**807**	**460**	**764**	**551**	**1251**
Overall incidence	**64.7**	**63.0**	**70.8**	**72.2**	**83.5**	**82.8**	**87.3**
Severe AE	8.1	7.3	9.3	11.3	11.6	11.8	13.0
Discontinued	6.8	6.4	7.7	13.3	13.5	19.4	20.1
Most common adverse events:							
Dizziness	8.7	15.7	15.2	26.1	33.0	34.7	36.5
Somnolence	7.7	11.5	13.8	12.0	25.8	22.9	30.5
Headache	13.0	7.0	12.1	3.7	10.3	8.3	13.1
Dry mouth	3.4	3.4	6.3	4.8	8.0	9.1	11.8
Asthenia	5.2	4.2	6.8	5.0	5.9	8.0	9.7
Amblyopia	2.1	2.2	5.1	3.7	6.7	7.4	9.6
Thinking abnormal	1.6	2.5	2.2	2.6	3.0	6.7	8.8
Weight gain	0.8	3.6	3.5	6.5	4.3	10.3	7.3
Nausea	7.0	2.2	6.1	2.2	5.9	5.4	7.0
Peripheral edema	1.8	9.2	2.9	11.1	7.6	8.2	6.9
Infection	7.7	8.4	8.6	5.7	8.9	6.0	5.9

Source: Appendix 5.6, Tables 5.6.4–5.6.7
Key: AE=adverse event; BID=twice daily; discontinued=discontinued for adverse events; TID=three times daily

- Serious adverse event/deaths/other significant events

Serious adverse events
An overview of the occurrence of serious adverse events in the different patient groups is presented in the table below.

Overview of serious adverse events by indication

	[n (%) of Patients With Serious Adverse Events]					
	DPN	PHN	NeP	Epilepsy	GAD	All Studies[a]
Completed Controlled						
Placebo	**N = 459**	**N = 305**	**N = 764**	**N = 294**	**N = 484**	**N = 2290**
All	11(2.4)	8(2.6)	19(2.5)	13(4.4)	6(1.2)	47(2.1)
Treatment Related	3(0.7)	1(0.3)	4(0.5)	2(0.7)	2(0.4)	8(0.3)
All PGB	**N = 979**	**N = 577**	**N = 1556**	**N = 758**	**N = 1149**	**N = 5232**
All	38(3.9)	18(3.1)	56(3.6)	29(3.8)	7(0.6)	119(2.3)
Treatment Related	3(0.3)	3(0.5)	6(0.4)	4(0.5)	2(0.2)	15(0.3)
Combined DB/OL	**N = 1327**	**N = 772**	**N = 2099**	**N = 1613**	**N = 1954**	**N = 8228**
All	203(15.3)	116(15.0)	319(15.2)	185(11.5)	29(1.5)	619(7.5)
Treatment Related	14(1.1)	16(2.1)	30(1.4)	17(1.1)	3(0.2)	58(0.7)

N = Total number of patients in the patient population.
[a] Includes serious adverse events in nonneuropathic pain studies and other psychiatry studies.

The overall incidence of serious adverse events in the controlled studies was 2.3% in the pregabalin treated patients, versus 2.1% in the placebo treated patients. The most common treatment-related serious adverse events in the initial combined controlled and uncontrolled population were accidental injury (8 patients), visual field defect (6 patients), confusion (4 patients), ventricular extrasystoles (4 patients), congestive heart failure (3 patients), ataxia (3 patients), dizziness (3 patients), amblyopia (2

patients), diplopia (2 patients), myopathy (2 patients), somnolence (2 patients), and syncope (2 patients). The incidence increased when combining the controlled and uncontrolled studies, indicating an increase of incidence over time.

Death

As of the data cut-off for the integrated clinical safety database, 49 patients in the Phase 2/3 clinical program had died. This total includes:

- 1 patient who received placebo in the Phase 2/3 controlled studies;
- 6 patients who received at least one dose of pregabalin in the Phase 2/3 controlled studies; and
- 42 patients who died during or following pregabalin treatment in the open-label extension studies.

The highest proportion of deaths was in the elderly PHN population (17 deaths, 2.2%; 34.8 deaths per 1000 patient years) and the lowest was in the GAD population (1 death, 0.05%; 2.0 deaths per 1000 patient years). The difference in death rates across indications may be explained at least in part by the relative ages and co-morbid conditions of the different populations.

None of the deaths in pregabalin-treated patients was considered related to treatment. The most frequent causes of death among patients treated with pregabalin were cardiovascular events and carcinomas. There were three sudden death, 2 in patients with diabetic neuropathy and 1 in a patient with epilepsy.

Special safety issue

Abuse potential: The abuse potential of pregabalin was studied in a separate study (098) versus diazepam and placebo. Pregabalin did not have the profile of a prototypic drug of abuse when compared with diazepam.

Withdrawal and rebound phenomena: No proper studies were performed to assess withdrawal and rebound phenomena in particular in patients with epilepsy. As a consequence, the summary of product characteristics states that in accordance with current clinical practice, if pregabalin has to be discontinued either in neuropathic pain or epilepsy, it is recommended this should be done gradually over a minimum of 1 week.

Ophthalmic assessment: Clinically, visual field defects during treatment with pregabalin have been prospectively investigated by closely monitoring patients at regular intervals during the short- and long-term studies. At the time of the original submission, 6 cases (being unexplained) of visual field defects were found with pregabalin and clarifications were requested. To address this issue, the applicant provided pharmacological data from the literature to demonstrate that pregabalin and vigabatrin are different in their mechanism of action. In addition the safety database was extended and the applicant reviewed their current data extensively: ten cases (0.3%) were unexplained at that time. Data were collected for up to 2.5 years of treatment with pregabalin. Review of the new data supported the applicant's conclusion from the first submission of the dossier that the prevalence of visual field defects is low, and appears to be related to underlying pathology of the patients rather than to treatment with pregabalin. However, the 10 unexpected cases still require caution. From vigabatrin it is known that visual field defects are cumulative upon exposure. See discussion on clinical safety.

Cardiotoxicity: ECG assessments were made in all studies with PGB at several times (3-4) during treatment. In general no significant abnormalities were reported. No QTc prolongation was reported. A slight increase of premature ventricular contractions was found in the elderly patients with diabetes.

Reproductive function: In preclinical investigations, sperm abnormalities were reported, especially with respect to morphology, at exposure levels 10 times those used in humans. One clinical study (072) was performed to assess reproductive function in healthy male subjects. 46 subjects (16 on placebo and 32 on PGB 600 mg/day) were treated for 14 weeks (2 weeks titration included). Subjects were between the age of 18 and 55 years. Reproductive function was assessed on sperm count, motility (reduction of more than 5-10% of baseline), and morphology. Five subjects (3 PGB/2PBO) were reported with > 15% reduction from baseline in motility. It was concluded that short-term treatment with pregabalin does not induce major reproductive abnormalities. No long-term studies have been performed, nor studies related to age.

- Laboratory findings

Classical laboratory parameters were measured during controlled trials. Findings of potential clinical importance to be discussed were related to creatine kinase, white blood cells and platelet. In addition, glycaemia is discussed in relation to body weight gain.

Creatine Kinase: Although the mean change from baseline in creatine kinase among pregabalin treated patients was significantly different from placebo for each treatment group, there was no dose response relationship. In the combined controlled and uncontrolled studies, the mean increase in creatine kinase (13.425 U/L) was similar in magnitude to that observed in the controlled studies. A potentially clinically important increase in creatine kinase occurred in 1.7% of patients. Serious adverse events of creatine phosphokinase were reported in 3 pregabalin-treated patients with epilepsy. Myopathy/rhabdomyolysis was reported in 2 patients. Overall, pregabalin appears to elevate creatine kinase levels in some patients. Review of individual patient cases does not suggest a clinically important risk of renal dysfunction associated with the elevations in creatine kinase.

White blood cell: Differences in WBC mean change from baseline was statistically significant in pregabalin group than in placebo group (controlled studies) with a decrease of $0.22\times10^3/\mu L$ versus a decrease of $0.11\times10^3/\mu L$. There is no pattern of consistent decrease but the incidence of infection deemed to increase with the time of exposure to pregabalin. Hence, it was questioned whether the immune system may become compromised over time. Since the increase of infections during long-term pregabalin exposure is difficult to judge for the lack of a placebo arm, the incidence of new infections was calculated as of the time of open-label treatment. It appeared that the incidence of new infections was not larger during long-term treatment than the incidence during short-term treatment. Neither elderly, nor diabetic patients were more at risk. Therefore, the decrease in WBC does not appear clinically significant.

Platelets: Short-term pregabalin treatment decreases platelet numbers, but platelet function (as measured by platelet aggregation and Platelet Function Analyzer (PFA) closure time) remains intact. No bleeding abnormalities were associated with the platelet decrease. Long-term pregabalin treatment showed an initial decrease in platelet count over time until 12-15 months, whereas beyond that time, a gradual increase was seen. Hence, long-term pregabalin exposure leads to a slight elevation in platelets. In the light of the pre-clinical finding of haemangiosarcoma in mice where platelet activation is seen, patients with increased platelet counts were reviewed separately. From these data it was concluded that no persistent platelet elevations were present. See discussion on clinical safety.

Body weight and glycaemia in patients with DPN: Among patients who had baseline and termination weight measurements in the controlled studies, the mean change in weight was 1.6 kg for pregabalin-treated patients and 0.3 kg for placebo-treated patients. Therefore, it was questioned whether weight gain during treatment with pregabalin would compromise the diabetic patient. New data were provided with respect to weight gain and changes in HbA_{1C}, changes in the use of diabetic medication over time, and the incidence of metabolic and/or cardiac events. Short-term treatment with pregabalin did not show any changes in HbA_{1C}, changes in the use of diabetic medication different from placebo or changes in the incidence rate of metabolic or cardiac events. Similarly, long-term pregabalin treatment was not associated with loss of glycaemic control in a two-year cohort of diabetic patients who gained weight. However, long-term data with respect to the possible adjustment to diabetic medication were not provided. Although the incidence of metabolic and/or cardiac events in the combined controlled and uncontrolled studies was higher in DPN patients who gained weight, these patients also had longer mean pregabalin exposure (approximately 500 days). See discussion on clinical safety.

- Safety in special populations

The safety profile in elderly is not much different from the general profile of pregabalin, except for the occurrence of peripheral oedema (around 11%). Peripheral oedema was, irrespective of age, not associated with hypertension. In the elderly, the incidence of accidental injury was associated with dizziness.

- Discontinuation due to adverse events

The main reason for discontinuation of pregabalin was the occurrence of dizziness and/or somnolence especially in the higher dose range.

- Discussion on clinical safety

The overall safety profile of pregabalin is what can be expected from the mode of action of the compound. Dizziness and/or somnolence are the main adverse events (about 30% and 23% respectively). These events did not resolve by the end of double blind treatment in 31% and 45% respectively, of subjects, experiencing these adverse events.. Additionally, the following adverse events were discussed: peripheral oedema, weight gain, decrease in platelets, visual field defects and, based on pre-clinical toxicological finding, haemangiosarcoma (in mice).

Dizziness/somnolence

The impact of dizziness and/or somnolence in elderly and in particular in regard of the high incidence of accidental injury was questioned. After review of the data both during short- and long-term treatment, it appeared that the incidence of dizziness is not increased in the elderly. However, they appear more susceptible to the persistence of dizziness. They are also more at risk for the occurrence of accidental injury associated with dizziness. As a consequence, a warning has been recommended to state in the summary of product characteristics that pregabalin has been associated with dizziness and somnolence which could increase the occurrence of accidental injury in the elderly population. The wording in the SPC being - 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.

Peripheral oedema and weight gain

Peripheral oedema and weight gain are notable findings. They are unexplained. Both raised concerns: peripheral oedema, which is predominantly found in the elderly for its possible relation with cardiac events, weight gain for patients with diabetes.

After re-review of the data, both during short- and long-term treatment, peripheral oedema is regarded a separate finding of pregabalin, and not primary or secondary to alterations in cardiovascular function. No consistent temporal relationship of hypertension and peripheral oedema was observed and a clinically meaningful or sustained increases in measured blood pressure in patients with peripheral oedema were not observed.

Weight gain in the diabetic population was not different from the weight gain in the overall population treated with pregabalin. During short-term treatment, weight gain is not associated with an increase in HbA_{1C}, which is the severity marker for diabetes. In a two-year cohort, long-term pregabalin treatment was not associated with loss of glycaemic control in diabetic patients who gained weight. Nevertheless, changes in anti-diabetic medication were difficult to assess in this cohort. As a consequence, the applicant's proposal to state in the summary of product characteristics that some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications, has been accepted.

Platelets and pre-clinical toxicology: haemangiosarcoma in mice

During long-term exposure to pregabalin (data up to 2-3 years), a change in platelet numbers is observed. After an initial decrease, a gradual increase in platelet counts is observed beyond the exposure time of one year. In view of the pre-clinical toxicological finding of haemangiosarcoma in mice, patients with increased platelet levels were reviewed separately. No persistency in the elevation of platelet count was reported.

The development of haemangiosarcoma in the animal studies (mice) is thought to be mediated by platelet activation. The triggers behind the platelet activation have not been fully elucidated. It appears that the mechanism hypothesized is not present in the rat. The threshold of platelet activation leading to haemangiosarcoma transformation is a function of dose. To address the issue of the human risk of tumour formation in relation to the pre-clinical findings of haemangiosarcoma, the applicant provided data on the threshold of platelet activation needed for tumour formation in mice and long-term human data of platelet morphology. Platelet activation in mice was seen at 5 times the human exposure after 1 month of dosing: with no consistent effects on platelet activation were observed at the maximum human exposure. Having platelet data in man for up to 4 years of pregabalin exposure, the applicant concluded that, if present, any abnormality would have been found in man. The data are however limited. Although the animal data do not raise such a concern as to preclude an approval and there is no evidence to suggest an associated risk to humans, it cannot be fully concluded that the mechanism of haemangiosarcoma formation does not pose any risk in man.

Long-term exposure data in man are limited to a small number of subjects. Therefore it was agreed that the applicant will provide additional long-term clinical data concerning assessment of platelet morphology, a surrogate marker of platelet activation, in humans receiving pregabalin.

Visual field abnormalities
Visual field defect was a late finding during the use of vigabatrin and prompted the need for careful evaluations to screen possible effects on visual fields and visual acuity. In the clinical safety database (visual field testing in over 3500 patients of whom nearly 700 patients with exposures of at least 2 years), there were 10 unexplained cases of visual field defect (0.3%). The exposure time varied between 42 and 939 days (median: 186 days) of treatment with pregabalin. In the majority of cases, a unilateral nasal visual field defect was observed. The MAH retested 4 out of the 10 unexplained cases; 2 subjects had changes consistent with an artefact (false positive), one subject was normal and in the other case a pre-existing corneal defect explained the defect. The very low incidence of unexplained visual field defects, the lack of a specific pattern of defect, their variability after retesting and the size of the 'visual fields database' make it unlikely that pregabalin is a causal factor for visual field defects. As precautionary measure, visual system adverse events will be carefully assessed in periodic safety reports under a separate heading.

Safety in adolescents
Neither efficacy nor safety was demonstrated in adolescents. The number of patients (n=10) was too small and consequently the Applicant's claim in adolescents has been withdrawn. A neurotoxicological study in juvenile rats (see non-clinical section) stressed the need for special attention to the effects of pregabalin on growth and (cognitive) development in children and adolescents. Additional non-clinical studies have been requested to investigate reversibility of reproductive and neurobehavioral/cognitive effects. Upon request, the applicant proposed the following paediatric development plan: Pharmacokinetic evaluation in lead-in phases to the efficacy and safety studies, Efficacy and safety studies in children and adolescents (4-18 year-olds, randomised, double-blind, placebo-controlled add-on study of 12 week duration with a cognitive test battery as secondary endpoint), Efficacy and safety study in infants, toddlers and young children (>1 month to <4 year-olds, 3-4 weeks study with seizure count based on EEG and/or video-EEG monitoring) and Open-label long-term extension of efficacy and safety studies. Efficacy and safety studies will be run in a sequential approach, with the efficacy and safety established in the older paediatric age group prior to proceeding with the clinical study in the younger age group. Monitoring of growth, sexual development, cognitive and behavioural assessments were planed but it was questioned whether the number of patients and the duration of studies were sufficient. In conclusion, the proposed clinical development plan in children was acceptable. However, the study protocols and time frame in which these studies are implemented should be part of the post marketing commitment. The applicant agreed to undertake a long-term observational study in paediatric patients and committed to submit a protocol for such study to CPMP.

Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Non-clinical pharmacology and toxicology

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). Although its precise mechanism of action is still unclear, pregabalin, decreases central neuronal excitability by binding to an auxiliary subunit (α_2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system.

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. Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred 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. Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Pregabalin was not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.

Pregabalin induces haemangiosarcoma in mice. This apparently has an epigenetic origin. The mechanism resulting in haemangiosarcoma formation has been investigated up to an acceptable extent. The development of haemangiosarcoma in the animal studies (mice) is thought to be mediated by platelet activation. The triggers behind the platelet activation have not been fully elucidated. It appears that the mechanism hypothesized is not present in the rat. The threshold of platelet activation leading to haemangiosarcoma transformation is a function of dose. 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.

Long-term exposure data in man are limited to a small number of subjects. Therefore it was agreed that the applicant would provide additional long-term clinical data concerning assessment of platelet morphology, a surrogate marker of platelet activation, in humans receiving pregabalin. as a post-approval commitment.

Animal juvenile toxicity studies indicated an effect on CNS, growth and female reproductive function at clinically relevant exposures. Reversibility of effects has not been studied. Upon CPMP's request in view of further paediatric development, the applicant agreed to conduct an additional study in juvenile rats to assess reversibility of alterations in acoustic startle response and impaired performance in learning and memory as a post-approval commitment.

Efficacy

The pharmacokinetics of pregabalin are uncomplicated. Since pregabalin is not metabolised and exclusively excreted in urine, patients with renal impairment require dose adjustments.

To support the neuropathic pain claim, twelve randomised placebo controlled studies were submitted. Six studies investigating the diabetic neuropathy model and five studies investigated the postherpetic neuralgia model. One study investigated both models. Doses ranged from 75 to 600 mg daily given twice or three times daily. Study duration ranged from 5 to 13 weeks.

To support the claim of adjunctive treatment in partial seizures with/without generalised seizures, three randomised placebo controlled add-on studies were submitted. The dose ranged from 50 to 600 mg daily in similar dosing schedules as for the neuropathic pain. Study duration was 12 weeks.

Efficacy of pregabalin in neuropathic pain has been demonstrated in two models of peripheral neuropathic pain (diabetic polyneuropathy and postherpetic neuropathy), which supports an indication in the 'treatment of peripheral neuropathic pain'. Clinical relevance of the observed effect has been substantiated in terms of responder and by relating the change in pain score to the patient global impression of change, in both pain models. Responder rates were higher in patients with somnolence as compared to patients without somnolence.. However, a clinically meaningful effect on responder rates is evident in patients who do not experience somnolence as well in patients who report somnolence across the neuropathic pain studies It was recommended to provide this information in the SPC in section 5.1. No definite conclusions on long-term efficacy in neuropathy can be drawn based upon the open label (extension) studies. However, the cohort study presented supports the maintenance of the effect and development of tolerance is less likely as the mean daily dose remained stable over time. Efficacy of TID seemed better than BID but the clinical relevance of this difference is questionable and the overall safety profile of pregabalin is in favour of the BID regimen. Therefore it was agreed to accept both BID and TID to give the physician the choice of the best regimen for individual patients.

Pregabalin is acceptable as add-on treatment in epilepsy in adults. The original claim in adolescents has been dropped. Long-term data are not sufficient to establish maintenance of effect but this does not raise a concern for the potential risk of tolerance. One head to head epilepsy study (-009) was

performed and showed a slightly better response with TID as compared to BID dosing, but the observed difference in responder rate (5.9%) was not considered clinically relevant. Therefore, as for neuropathic pain, it was agreed to accept both the BID and TID regimens to allow the physician the choice of the best regimen for individual patients.

The applicant outlined a clinical developmental plan for the use of pregabalin in children/adolescents taking into account the observations of the animal juvenile toxicity studies. Further animal studies have been requested before starting paediatric clinical development. The paediatric development was deemed acceptable, however, timeframe and clinical protocols should be submitted as a post marketing commitment.

Safety

The overall safety profile of pregabalin is what can be expected from the mode of action of the compound. Dizziness and somnolence are the main adverse events (about 30% and 23% respectively). These events appear persistent in 31% and 45% respectively, of subjects, experiencing them. Additionally, peripheral oedema and weight gain are notable findings.

Pregabalin induces hemangiosarcoma in mice. This apparently has an epigenetic mechanism. The mechanism resulting in the hemangiosarcoma formation has been investigated up to an acceptable extent. The development of hemangiosarcoma in the animal studies (mice) is thought to be mediated by platelet activation. The trigger behind the platelet activation have not been fully elucidated. It appears that the mechanism hypothesized is not present in rat. The threshold of platelet activation leading to haemangiosarcoma transformation is a function of dose. Even if the risk does not seem major, it cannot be fully concluded whether the mechanism of hemangiosarcoma formation does not pose any risk in man. Long-term exposure data in man are limited to a small number of subjects. Whether platelet activation occurs in subjects with a long time use of pregabalin should be evaluated as part of a post marketing commitment.

Long-term pregabalin treatment was not associated with loss of glycaemic control in diabetic patients gaining weight, although it cannot be excluded that a lack of glycaemic control has been compensated for by adaptations to the anti-diabetic medication in the open label extension studies. The SPC wording proposed by the applicant: *"In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications."* resolves the issue.

The potential of pregabalin for developing visual field defects has been sufficiently studied. The very low incidence of unexplained visual field defects, the lack of a specific pattern of these defects, the variability of these defects after retesting and the size of the 'visual field database' makes it unlikely that pregabalin is a causal factor for developing visual field defects. In addition, the applicant committed to assess all visual adverse events under a separate heading in periodic safety reports.

Benefit/risk assessment

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA).

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Efficacy and safety of pregabalin in peripheral neuropathic pain in adults has been demonstrated both in diabetic polyneuropathy and postherpetic neuropathy. Effects in patients without somnolence are considered clinically meaningful even if the effect appears greater in patients with somnolence. Efficacy and safety of pregabalin as an adjunct to other anti-epileptic agents in adults with partial epilepsy has been demonstrated. Long-term data on efficacy are limited but this does not raise a concern for the potential risk of tolerance. Dizziness and somnolence are the main adverse events. The adverse event profile for BID and TID regimens shortly after initiation of treatment did not differ between the dosing schedules. Both schedules are equally tolerated, also in the elderly. Efficacy results of TID seemed better than BID but the clinical relevance of this difference is questionable.

Therefore, both the BID and TID regimens have been approved which will allow physicians the choice of the best regimen for individual patients.

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 is not fully characterised; however, pregabalin-induced platelet changes associated with endothelial cell proliferation and tumour formation in mice are not present in rats or in humans, based on the available data. Based on this mechanistic approach there is no evidence to suggest an associated risk to man . Long-term data in humans are limited and a risk management programme to follow a potential risk of tumour in man may not provide relevant information. Therefore it was agreed that the applicant will provide additional long-term clinical data concerning the assessment of platelet morphology, a surrogate marker of platelet activation, in humans receiving pregabalin as a post approval commitment.

Animal juvenile toxicity studies indicated an effect on CNS function (hyperactivity and bruxism) and growth and female reproductive function at clinically relevant exposures. Reversibility of some of these effects will have to be assessed prior to paediatric development.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Lyrica in the treatment of peripheral neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation was favourable and therefore recommended the granting of the marketing authorisation.