PREGABALIN RISK MANAGEMENT PLAN

RMP Version number: 13.2

Data lock point for this RMP: 30 June 2021 (Post-marketing database); 31 January 2020 (Clinical data)

Date of final sign off: 20 August 2021

Rationale for submitting an updated RMP:

In accordance with the pregabalin PRAC Type II Variation Assessment Report (Procedure No. EMEA/H/C/WS1919), the RMP will be updated to include a more complete presentation of results from the following PASS study Pregabalin Pregnancy Outcomes Study (A0081359). Furthermore, with the completion of the Pregabalin Pregnancy Outcomes Study (A0081359), the MAH in agreement with PRAC will remove "Pregnancy and Lactation" as Missing information from the RMP. There will be no updates to the important risks. Additionally, no new safety concerns or any change in characterization of existing risks was identified based on review of the completed studies. The DLP for the PM case data will be updated to 30 June 2021. DLP for clinical data will remain 31 January 2020.

Based on the conclusion of study A0081359, the language regarding the use of pregabalin during pregnancy will be updated in the RMP in alignment to the updated SmPC.

The CSR for the Pregabalin Ophthalmological Safety Study (A0081096) has been included in Annex II.

In line with the preliminary PSUR assessment report, the Targeted Questionnaire for abuse and dependence will be changed to a Data Capture Aid. The RMP including annex 4 will be updated accordingly. The Pfizer targeted questionnaire internal process for pregabalin will be retired.

Summary of significant changes in this RMP:

- Module SII: Based on the conclusion of study A0081359, the language regarding the use of pregabalin during pregnancy will be updated in the RMP in alignment to the updated SmPC.
- Module SIV: Based on the conclusion of study A0081359, the language regarding the use of pregabalin during pregnancy will be updated in the RMP in alignment to the updated SmPC.
- Module SV: Post-marketing data for Post-authorisation Off-Label Use updated per DLP
- Module SVI: In line with the preliminary PSUR assessment report, the Targeted Questionnaire for abuse and dependence will be updated to a Data Capture Aid.

- Module SVII: Provide a more complete presentation of study results for PASS A0081359 (A Non-Interventional Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes) as requested by the Rapporteur in the 2nd RSI. Based on the completion of the PASS A0081359, the MAH in agreement with PRAC will remove "Pregnancy and Lactation" as Missing information from the RMP. Post-marketing data will be updated per DLP.
- Module SVIII: Based on the completion of the PASS A0081359, the MAH in agreement with PRAC will remove "Pregnancy and Lactation" as Missing information.
- Part III: Removal of "Pregnancy and Lactation" as Missing information and the Targeted Questionnaire for abuse and dependence will be updated to a Data Capture Aid.
- Part V: Removal of "Pregnancy and Lactation" as Missing information and the Targeted Questionnaire for abuse and dependence will be updated to a Data Capture Aid.
- Annex 2, Annex 3, Annex 4, Annex 8: Revisions for RMP 13.2.

Date of final sign off: 20 August 2021

Other RMP versions under evaluation: pregabalin RMP version 13.0, dated 09 June 2020 and version 13.1, dated 02 April 2021.

Details of the currently approved RMP:

Version number: 12.3

Approved with procedure: EMEA/H/C/WS1364

Date of approval (opinion date): 29 November 2018

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's applicant's QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

α2-δ	Alpha-2-delta
ACR	American College of Rheumatology
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
BSE	Bovine Spongiform Encephalopathy/Encephalitis
CFS	Chronic Fatigue Syndrome
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CPMP	Committee for Proprietary Medicinal Products
CR	Controlled-Release
CSR	Clinical Study Report
CT	Clinical Trial
CVMP	Committee for Veterinary Medicinal Products
DCA	Data Capture Aid
DSM	Diagnostic and Statistical Manual
DUS	Drug Utilisation Study
EEA	European Economic Area
EMA	European Medicines Agency
ER	Extended-Release
EU	European Union
FAR	Final Assessment Report
FDA	(US) Food and Drug Administration
GAD	Generalised Anxiety Disorder
GPRD	General Practice Research Database
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQOL	Health-Related Quality-of-Life
IBS	Irritable Bowel Syndrome
ILAE	International League Against Epilepsy
IR	Immediate-Release
IV	Intravenous
MAH	Marketing Authorisation Holder
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
NCS	National Co-morbidity Survey
NeP	Neuropathic Pain
NHIS	National Health Interview Survey
NHNN	National Hospital for Neurology and Neurosurgery
OR	Odds Ratio
PDPN	Painful Diabetic Peripheral Neuropathy
PK	Pharmacokinetic

PL	Package Leaflet
PND	Painful Neuropathic Disorder
POPNO	Patients with Chronic Pain of Predominately Neuropathic Origin
PSUR	Periodic Safety Update Report
PT	Preferred Term
PubMed	National Library of Medicine online database
Pv	Pharmacovigilance
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RR	Relative Risk
SE	Standard Error
SMR	Standard Mortality Ratio
SmPC, SPC	Summary of Product Characteristics
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SPDR	Swedish Prescribed Drug Register
SSRI	Selective Serotonin Reuptake Inhibitors
SU	Standard Unit
TCA	Tricyclic Antidepressant
TSE	Transmissible Spongiform Encephalopathy/Encephalitis
UK	United Kingdom
US	United States

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Pregabalin
Pharmacotherapeutic group(s) (ATC Code)	N03AX16
Marketing Authorisation Holder Applicant	Pfizer Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Lyrica, Pregabalin Pfizer
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Pregabalin is an α2-δ ligand.
	Summary of mode of action Although its precise mechanism of action is still unclear, pregabalin is thought to exert its pharmacologic activity by decreasing neuronal excitability by binding to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels.
	Important information about its composition Pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P.
Hyperlink to the Product Information:	Module 1.3.1.
Indication(s) in the EEA	Current: NeP Treatment of central and peripheral NeP in adults. Epilepsy As adjunctive therapy in adults with partial seizures with or without secondary generalisation. GAD

	Treatment of GAD in adults. Approved indications in the US are NeP associated with DPN, NeP associated with spinal cord injury, Post herpetic neuralgia, Adjunctive therapy for the treatment of partial onset seizures in patients 1 month of age and older and Fibromyalgia.
	Proposed: N/A
Dosage in the EEA	Current : The dose range is 150 to 600 mg per day given in either 2 or 3 divided doses. Lyrica may be taken with or without food. NeP: Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval. Epilepsy: Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage of 600 mg per day can be achieved after an additional week. GAD: The dose range is 150 to 600 mg per day. The need for treatment should be reassessed regularly. Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week, the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day can be achieved after an additional week.
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current: Hard capsule: 25, 50, 75, 100, 150, 200, 225, and 300 mg Oral solution: 20 mg/mL (The oral solution was first launched on 14 May 2012 and is marketed

	in several countries worldwide, including selected European Member States.)
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

α2-δ = Alpha-2-delta; DPN = Diabetic Peripheral Neuropathy; GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain; US = United States.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication: Currently approved:

- Neuropathic pain (NeP):

  Treatment of central and peripheral NeP in adults.

- Epilepsy:

  As adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- Generalised Anxiety Disorder (GAD):

  Treatment of GAD in adults.

- Approved indications in the United States (US) are NeP associated with diabetic peripheral neuropathy, NeP associated with spinal cord injury, post-herpetic neuralgia, adjunctive therapy for the treatment of partial onset seizures in patients 1 month of age and older, and fibromyalgia.

Search Strategy

The National Library of Medicine online database (PubMed) was searched for primary literature and review articles focused on incidence, prevalence, and mortality of epilepsy, NeP, GAD, and fibromyalgia. Searches were confined to English language articles involving humans over the age of 18 years. Search terms used for this section are included in the footnote on the bottom of this page.[1] The search included any estimates representative of countries within the European Union (EU).

Indication: Neuropathic Pain (NeP)

NeP results, most notably, from dysfunction at the level of the peripheral nerves. Common causes include diabetes, acquired immune deficiency syndrome, and malignancies. Due to this aetiology, the majority of work in this area samples from populations with one of the aforementioned disorders. As such, the following review often highlights the epidemiology of NeP relative to specific disease. From an epidemiological perspective, it is also important to note the complexity in diagnosing and quantifying pain and the lack of a "gold standard" with regard to measurement hinders estimation.

[1] Throughout the literature review, pregabalin indications were represented by the following Boolean search terms: [epilepsy OR seizures OR convulsions], ["neuropathic pain" OR "nerve pain" OR "diabetic neuropathy" OR "peripheral neuropathy" OR "postherpetic neuralgia"], ["generalised anxiety disorder" OR GAD OR anxiety], and [fibromyalgia OR "rheumatic disease"].

Incidence:

US

No published estimates were found regarding the incidence of NeP in the US.

Europe

Despite the availability of drugs with known efficacy, many believe that NeP is often under-diagnosed and inadequately treated. Based on this premise, Hall et al. (2006) reported the epidemiology and drug treatment of NeP as managed by United Kingdom (UK) primary care physicians.[1] Data from computerised UK General Practice Research Database (GPRD) from January 1992 to April 2002 yielded the following estimates per 100,000 person-years of observation: 40 (95% Confidence Interval [CI]: 39-41) for post herpetic neuralgia, 27 (95% CI: 26-27) for trigeminal neuralgia, 1 (95% CI: 1-2) for phantom limb pain and 15 (95% CI: 15-16) for painful diabetic neuropathy. Rates decreased over time for phantom limb pain and post herpetic neuralgia, but increased for painful diabetic neuropathy and trigeminal neuralgia ($p<0.001$).

To estimate the incidence of central post-stroke pain, Andersen et al. (1995) conducted a prospective survey evaluating pain among 267 consecutive patients at 1 week, and at 1, 6, and 12 months after stroke.[2] Central post-stroke pain was found in 16 (8%) patients but was not related to age or sex. Pain onset was noted most frequently within 1 month of stroke (68%).

Prevalence:

US

Data from a large US health insurance claims database were used to estimate Painful Neuropathic Disorders (PNDs) among adults in 2000.[3] Among 55,686 patients with PNDs, the most frequent mentions (i.e., largest proportions of affected patients) were of back and neck pain with neurological involvement (62.3%), causalgia (12.1%) and diabetic neuropathy (10.8%). When compared with age-and gender-matched controls, persons with PNDs were more likely to have chronic comorbid disorders including osteoarthritis, chronic obstructive pulmonary disease, coronary heart disease, and depression.

Europe

Torrance and colleagues (2006) conducted a study to understand the epidemiology of chronic pain among 2957 patients recruited from three UK family medical practices. [4] The overall prevalence of any chronic pain was 48%, whereas the prevalence of pain of predominately neuropathic origin was 8%. It is important to note that due to the survey methods employed, clinical confirmation of cases was not possible. Therefore, it is difficult to discern whether reported estimates are valid. Additionally, data from medical practices are not wholly representative of the UK population at large.

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Patients with NeP identified within UK family medical practices were more likely to be female, slightly older (mean age of 53 versus 49 years), no longer married, living in council-rented accommodations, unable to work, report no educational qualifications, and be smokers relative to respondents without NeP (Patients With Chronic Pain Of Predominately Neuropathic Origin [POPNO] versus patients without POPNO, $p<0.05$).[4] Examination of non-response within this survey did find that responders were more likely to be younger and female. Additional factors associated with NeP include: increased height, white race, hypertension, and diabetes.[2]

NeP pain has been defined as ''pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".[5] Hence, NeP can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, Human Immunodeficiency Virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries (e.g., brachial-plexus avulsion).[5]

The main existing treatment options:

Medications used as first-line treatments for NeP included certain antidepressants (i.e., Tricyclic Antidepressants [TCAs] and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel Alpha (2)-delta ($\alpha 2$-δ) ligands (i.e., gabapentin and pregabalin), and topical lidocaine.[5] Opioid analgesics and tramadol were recommended as second-line treatments that can be considered for first-line use in selected clinical circumstances.[5] Other medications that generally would be used as third-line treatments include certain other antidepressant and antiepileptic medications, topical capsaicin, mexiletine, and N-Methyl-d-Aspartate receptor antagonists.[5]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality estimates regarding NeP are specific to the underlying disorder. In the case of diabetes, Acquired Immunodeficiency Syndrome (AIDS) and malignancies, mortality estimates are known to be considerably higher than the general population.

Important co-morbidities:

Search Strategy

PubMed was searched for primary literature and review articles focused on the important comorbidities of NeP. Searches were confined to English language articles involving humans over the age of 18 years. Search terms used for this section are included in the

footnote on the bottom of this page.[2] A special effort was made to locate estimates representative of the EU.

Diabetes

Incidence

The incidence of NeP among persons with diabetes was not found in the literature reviewed.

Prevalence

Davies et al. (2006) examined the prevalence of Painful Diabetic Peripheral Neuropathy (PDPN) via a postal survey of patients with type-2 diabetes.[6] Among the participants (n = 326, 93% response), 83% (269) agreed to a neurological history and examination. The Odds Ratio (OR) for PDPN or mixed pain (i.e., neuropathy compared with no neuropathy) was 7.9 (95% CI: 3.5-17.2).

Partanen and colleagues (1995) evaluated the natural history of peripheral neuropathy in patients with type-2 diabetes.[7] At baseline, the degree of NeP was similar among diabetic patients and control patients. At the 10-year examination, however, persons with diabetes experienced significantly more pain than did controls ($p < 0.001$).

Kiziltan and colleagues (2007) studied peripheral neuropathy among 318 consecutive patients with diabetic foot ulcers. Overall, 26.4% of patients experienced NeP.[8]

The authors noted that both negative sensory symptoms (i.e., numbness) and NeP were significantly more prevalent among women versus men (63.7% vs 40.8%, $p < 0.01$ and 38.5% vs 18.3%, $p < 0.01$, respectively) but that atrophy was more prevalent among men than women (22.8% vs 46%, $p < 0.01$).

Mortality

No mention of mortality was found regarding NeP and diabetes. Published reports do note that both pain and severity of neuropathy are associated with quality-of-life deficits among diabetics.[6]

Co-prescribed Medicinal Products

Sulfonylureas (i.e., glucotrol), biguanides (i.e., glucophage), thiazolidinediones (i.e., rosiglitazone maleate), insulin, and aspirin.

[2] Throughout the literature review, comorbid disorders were represented by the following Boolean search terms: [migraine OR headache], [depression OR "major depression" OR "depressive symptoms" OR dysthymia], [cancer OR tumor OR malignancy], [insomnia OR "sleep disturbance"]. Data regarding stroke, diabetes, social phobia, chronic fatigue syndrome, and irritable bowel syndrome were searched using the simple terms.

AIDS

Incidence

The incidence of NeP among persons with AIDS was not found in the literature reviewed.

Prevalence

Pain is a common problem for persons with HIV disease, yet little research has been done to assess its aetiology, distribution, and management. Within the literature reviewed, only 3 studies provided information specific to NeP. For example, Simpson and colleagues (2002) found that the average score for pain among clinical trial participants, based on the Gracely scale, was equivalent to moderate NeP.[9] Later work found that pain measures did not change appreciably over time, but there was a weak inverse correlation between epidermal nerve fiber densities and the total neuropathy score and NeP.[10] Breitbart and colleagues (1996) also found that 62% of ambulatory AIDS patients participating in a series of cross-sectional studies reported persistent or frequent pain; in a subsample of 151 patients with neurological assessments, 46% had 1 or more NePs.[11]

Mortality

No mention of mortality as it relates to AIDS and NeP was found.

Co-prescribed Medicinal Products

A number of medications may be prescribed to persons with AIDS, depending on the complications experienced. For the treatment of the underlying HIV infection, nucleoside/nucleotide reverse transcriptase inhibitors (i.e., zidovudine +lamivudine, Azidothymidine + lamivudine [3TC]), non-nucleoside reverse transcriptase inhibitors (i.e., delavirdine), and protease inhibitors (i.e., amprenavir) are commonly used.

Cancer

Incidence

The incidence of NeP among persons with cancer was not found in the literature reviewed.

Prevalence

Literature in this area has demonstrated that a sizable percentage of cancer patients experience NeP. This pain was commonly attributable to the cancer itself.[12,13] Among, 593 cancer patients treated by a pain service, Grond and colleagues (1999), found that 5% (32) of patients presented with NeP while 31% (181) presented with "mixed" pain (combination of nociceptive and NeP). Work by Caraceni et al. (1999)[13] found that 7.7% (84) of their sample (n = 1095 derived from an international, multicentre survey of pain specialists and their patients) experienced NeP only, 3.6% (39) experienced visceral and NePs, and 5.2% (57) experienced somatic, visceral, and NePs. It is important to note that all

of the above-mentioned statistics were derived from pain-based clinics. Therefore, it is possible that estimates among all cancer patients may be lower.

One (1) study conducted outside of the pain clinic setting examined postmastectomy pain among a convenience sample of 95 women who had undergone breast cancer surgery. Stevens and colleagues (1995) found that 20% (n = 19) of these women experienced postmastectomy pain.[14] Pain was described as chronic, stable pain of long duration that began days to weeks after surgery.

Mortality

In the literature reviewed, no mention of mortality was found in the context of cancer and NeP.

Co-prescribed Medicinal Products

Chemotherapies (i.e., tamoxifen, cisplatin, fluorouracil), non-opioid or opioid analgesics, and antidepressants (Selective Serotonin Reuptake Inhibitors [SSRIs] or benzodiazepines).

Indication: Epilepsy

Epilepsy is among the most common of serious neurological disorders. The worldwide incidence of epilepsy is estimated to be approximately 50 cases per 100,000 persons per year (Range, 40 to 70 per 100,000/yr).[15,16] Estimates are higher in developing countries and are quoted in a range of 100 to 190 per 100,000 per year.[17] Reported prevalence estimates average at 18.5 per 1000, but the range is considerable (i.e., 1.5/1000 to 57/1000).[17] In what follows, the epidemiology of epilepsy specific to the US and EU is described.

Incidence:

US

Work by Hauser et al. (1993) showed that the age-adjusted incidence of epilepsy in Rochester, Minnesota was 44 per 100,000 person-years from 1935 through 1984.[18] While the overall trend in disorder did not change significantly, there were significant differences with regard to age-distribution. Specifically, the incidence in those less than 10 years of age decreased 40%, whereas the incidence among the elderly nearly doubled.

Europe

Several studies have also estimated the incidence of convulsive disorders. For instance, within the UK, MacDonald et al. (2000) used a General Practice Linkage Scheme with the National Hospital for Neurology and Neurosurgery (NHNN) to prospectively ascertain incident cases of neurological disorders. With regard to epilepsy, the authors reported an incidence of 46 per 100,000/year (95% CI: 36-60).[19] Based in the Netherlands, (Kotsopoulous et al., 2005) have estimated the overall incidence of unprovoked seizures and epilepsy at 55 and 30 per 100,000, respectively.[20]

Forsgren et al. (1996) found similar estimates with regard to incidence. In a population based study of epileptic seizures in Swedish adults, the authors reported an incidence of 56 in 100,000 person-years for first unprovoked seizures.[21] Interesting to note, however, is that the data did not yield a difference in incidence between the sexes. Age-specific estimates did increase with age, but were more pronounced among men.

The highest estimates with regard to incidence were reported by a Dutch survey by Shackleton et al. (1997). [22] Using drug-dispensing data for epilepsy medications, the authors reported an overall incidence of epilepsy at 72 per 100,000. Elevation in this report may be due, in part, to issues of specificity with regard to diagnosis. The use of case-finding algorithms based on medication usage may have over-estimated the number of new epilepsy patients.

Prevalence:

US

Data from the National Health Interview Survey (NHIS) was used to estimate the burden of epilepsy in the US from 1986 to 1990; during this time, approximately 1.1 million persons reported having epilepsy annually.[23] The overall prevalence was 4.7 cases per 1000 persons. More recent data from adults participating in the 2003 California Health Interview Survey found that 1.2% of adults reported being ever told they had epilepsy or seizure disorder, 0.7% were classified with active epilepsy.[24]

Europe

With regard to active epilepsy, data from the NHNN found a lifetime prevalence of 4 per 1000 persons (95% CI: 4-5).[19] Similarly, a report commissioned by the International League Against Epilepsy (ILAE), found that the lifetime prevalence of epilepsy was about 5% and that no marked differences existed among different European regions or countries.[25]

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Data from the NHIS over the period from 1986 to 1990 suggests that the prevalence of epilepsy is lowest for persons aged 65 years or older and highest for those aged 15 to 64 years. Age-adjusted estimates were similar for women and men and by geographic region. However, other data suggest that estimates vary by gender and ethnicity. For example, the meta-analysis reported by Kotsopoulous and associates (2002) suggests that men are slightly more likely to develop epilepsy than women.[15] Furthermore, data from clinically-based studies suggest that the rate of epilepsy is 1.3 to 2.2 times greater for non-white males than for white males and 1.4 to 1.7 times greater for non-white females than for white females.[26] A community-based cross-sectional study in Bradford, England also demonstrated that persons of South Asian descent had a lower OR of epilepsy when compared to the rest of the population (OR: 0.46; 95% CI: 0.38-0.57).[27]

Risk factors for epilepsy include oxygen deprivation (e.g., during childbirth), brain infections (e.g., meningitis, encephalitis, cysticercosis, or brain abscess), traumatic brain injury or head

injury, stroke (resulting from a block or rupture of a blood vessel in the brain), other neurologic diseases (e.g., Alzheimer disease), brain tumours, certain genetic disorders. In almost two-thirds of the cases of epilepsy, a specific underlying cause is not identified. In such situations, the cause may be labeled cryptogenic if the cause is unknown, or idiopathic if the epilepsy is not associated with other neurologic disease but is consistent with certain syndromes that may be inherited.[28]

The main existing treatment options:

Antiepileptic drugs are the mainstay of treatment for most people and there are now several drugs available.[28] Drugs may be given as monotherapy or in combination. Other treatment options that may be considered when seizures are not well controlled include surgery and vagal nerve stimulation.[28]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Despite generally good prognosis, epilepsy is potentially life-threatening and confers an excess risk of mortality (Standard Mortality Ratio [SMR] of 2 to 3 versus "standard population" for all-cause mortality).[16,29,30] This risk was most notable among patients with acute symptomatic epilepsy, remote symptomatic epilepsy, and epilepsy due to congenital neurological deficits.[29] Based on the ILAE European report, however, only one-third of deaths among patients with epilepsy are actually attributed to the seizure disorder.[25] Sudden unexplained death has been noted in young persons with active epilepsy, particularly when patients are asleep. Within Europe, the risk of such complication ranges from 1.3 to 9.31 per 1000 patients.[25]

Important co-morbidities:

Search Strategy

PubMed was searched for primary literature and review articles focused on the important comorbidities of epilepsy. Searches were confined to English language articles involving humans over the age of 18 years. Search terms used for this section are included in the footnote on the bottom of this page.[3] A special effort was made to locate estimates representative of the EU.

[3] Throughout the literature review, comorbid disorders were represented by the following Boolean search terms: [migraine OR headache], [depression OR "major depression" OR "depressive symptoms" OR dysthymia], [cancer OR tumor OR malignancy], [insomnia OR "sleep disturbance"]. Data regarding stroke, diabetes, social phobia, chronic fatigue syndrome, and irritable bowel syndrome were searched using the simple terms.

Migraine Headaches

Incidence

Data suggest that the incidence of epilepsy-migraine co-morbidity ranges from 21% to 24%.[31,32] One study conducted by Ottman and Lipton (1994) found that the cumulative incidence of migraine to age 40 was 24% in probands with epilepsy, 23% in relatives with epilepsy, and 12% in relatives without epilepsy.[32] The rate ratios for migraine in probands and relatives with epilepsy were significantly elevated compared with relatives without epilepsy (Relative Risk [RR]: 2.4; 95% CI: 2.0-2.9 and RR: 2.4; 95% CI: 1.6-3.8, respectively). The highest rate ratio was for probands with epilepsy attributable to head trauma (RR: 4.1; 95% CI: 2.9-5.7).

Prevalence

The prevalence of epilepsy-migraine co-morbidity ranged from 14% to 27% within patient populations,[33,34] data from the general population estimated co-morbidity at approximately 18%.[35] Population-based data also found a higher frequency of migraine among patients with epilepsy relative to the general population (OR: 2.0; 95% CI: 1.7-2.3 and OR: 2.6; 95% CI: 2.2-3.0, respectively).[35]

Mortality

Within the co-morbidity literature, there was no mention of mortality. There was, however, evidence suggesting that comorbid migraine had a negative effect on the prognosis of epilepsy. A study by Velioğlu et al. (2005) demonstrated that patients with epilepsy and migraine had a lower probability of being seizure-free.[36] The authors also found that epilepsy-migraine patients had a higher incidence of intractable seizures, a longer duration of disease, a better chance of remission with polytherapy, and a lower early treatment response relative to epilepsy-only controls. The comorbid patients also had more seizure control and medication problems for at least the 2-years of follow-up.

Co-prescribed Medicinal Products

Abortive prescription medications (i.e., isometheptene, triptans), TCAs (i.e., amitriptyline), topiramate, calcium channel blockers, and beta-blockers.

Depression

Incidence

The incidence of epilepsy-depression co-morbidity was not available in the published literature.

Prevalence

The majority of data demonstrated considerable co-morbidity between epilepsy and depression. In the studies reviewed, prevalence estimates among patient populations ranged

from 21% to 55%.[37,38,39,40,41] Population estimates also found increased depression among adults with epilepsy versus their non-epileptic counterparts (i.e., 2 to 3 times as likely to have depression).[42] Cross-sectional data derived from Dutch general practitioners did not, however, find a similar correlation (OR comorbidity: 1.3; 95% CI: 0.9-2.1).[43] The authors noted that this finding might be due, in part, to varying methodologies between studies (i.e., diagnostic criteria, rigor of study design, etc.).

Mortality

Estimates specific to mortality were not found in the context of epilepsy-depression co-morbidity. Data collectively suggest, however, that psychiatric co-morbidity significantly reduces Health-Related Quality-Of-Life (HRQOL) above and beyond that expected by epilepsy alone.[38,40,44,45] Work by Johnson and associates (2004) found that depression exerted an independent and adverse effect on HRQOL.[44] Depression was also deemed a more powerful predictor of HRQOL than frequent, severe, and chronic seizures.

Co-prescribed Medicinal Products

SSRIs, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and TCAs.

(Note: Co-morbid depression is a documented predictor of pharmacoresistant epilepsy.[46]).

Stroke

Incidence

The incidence of post-stroke epilepsy ranged from 2.5% to 11.5% among patient samples.[47,48,49,50,51,52] The range in estimates is due to the length of follow-up, which included anywhere from a few days to 3 years. Research by Burn and colleagues (1997) estimated that the RRs of seizures among stroke survivors, in comparison to the general population, was 35.2 in the first year post-stroke and 19.0 in the second year.[50]

Prevalence

The prevalence of stroke was 4-to 5-times greater among patients with epilepsy relative to the general population (i.e., Prevalence Ratio [PR]: 3.9; 95% CI: 2.7-5.3 and PR: 4.7; 95% CI: 3.4-6.2).[35]

Mortality

Univariate analyses have demonstrated that there is no difference in mortality between epileptic patients with and without seizure up to one-year post-stroke.[49]

Co-Prescribed Medicinal Products

Thrombolytics (i.e., alteplase), Angiotensin-Converting-Enzyme (ACE) inhibitors (i.e., ramipril), statins, antiplatelet agents, and warfarin.

Indication: GAD

Treatment of GAD in adults.

While generalised anxiety had been described as early as 1894,[53] the diagnostic term GAD was first used in the third edition of the Diagnostic and Statistical Manual (DSM-III).[54] In the manuals that followed (i.e., DSM-IIIR and DSM-IV), the diagnosis of GAD became more refined to include: "excessive (but not unrealistic) anxiety and worry about more than 1 life circumstance" in which a person finds it "difficult to control the worry". [55,56] Duration of illness was also changed from 1 month in DSM-III to 6 or more months in DSM-IIIR and DSM-IV. In what follows, the epidemiology of GAD in both in the US and in Europe is described.

Incidence:

US

No published estimates referencing the incidence of GAD within the US were found. The only data regarding GAD incidence were collected in Canada.

Canada

Using data from the 16-year follow-up of an adult sample of the Stirling County Study, Murphy et al. (1988) found the incidence of anxiety disorders (reflected as estimate per 1000 per year) to be 2.3 (1.4-3.8) and 6.3 (3.8-10.4) for men and women, respectively.[57]

Europe

Conducting a 2-phase Norwegian population survey (n = 1879 with complete Phase 1 data), Sandanger et al. (1999) estimated the incidence rate of first episode of any psychiatric disorder at 8.0 per 1000 person-years.[58] The combined estimate for panic and GAD was 1.10 per 1000 person-years (1.5 women, 0.8 men). Overall, panic/GAD occurred significantly less than other psychiatric disorders (i.e., depression, phobias, etc.).

Prevalence:

US

Despite differences in methodologies, there is relatively good agreement across studies that the 1-year prevalence of DSM-III/DSM-IIIR ranges for GAD vary from 1.1% to 3.6% in adults,[59] whereas lifetime estimates range from 4.1% to 6.6%.

Heralded as one of the landmark works in this area, Kessler and colleagues' National Co-morbidity Survey (NCS) estimated that lifetime prevalence of GAD in US adults was 5.1% (Standard Error [SE]: 0.3);[60] upon replication of this work, estimates increased slightly to 5.7% (SE: 0.3).[61] When severity of disorder was assessed, approximately one-third of the cases of persons with GAD (32.3%) were classified as serious.[62]

Europe

As part of the World Health Organisation study on Psychological Problems in General Health Care, Weiller et al. (1998) reported the prevalence of anxiety syndromes in 5 European primary care settings.[63] Approximately 5% of primary care attendees listed anxiety-related problems as the main reason for contact. When interviewed, GAD was by far the more frequent disorder with a current prevalence of 8.5%. In 43.7% of the cases, persons also had current depression. When examined by subtypes of anxiety syndromes (n = 1973), 4.8% had GAD without depression and 3.7% had GAD and depression.

The 1-year prevalence of GAD in Germany has been estimated at 1.5% (95% CI: 1.2-1.9) using strictly defined, 12-month threshold DSM-IV criteria.[59] Using a nationally representative sample of 4,181 adults in Germany (via the German National Health Interview and Examination Survey, Mental Health Supplement), Carter et al. (2001) also estimated that approximately 3.6% (95% CI: 3.1-4.2) of respondents demonstrated subthreshold levels of GAD in the past 12 months.

In a cross-sectional study to describe the 12-month and lifetime prevalence estimates of mental disorders in Europe, the European Study of the Epidemiology of Mental Disorders (ESEMeD/MHEDEA) team found that of 21,425 respondents, the overall 12-month prevalence of GAD was 1.0% (95%CI: 0.8-1.2).[64] The lifetime prevalence was, as expected, higher at approximately 2.8% (95% CI: 2.5-3.1).

Work out of Norway has also yielded elevated estimates of GAD in the general population.[65] Among 2066 residents of Oslo, the 12-month and lifetime prevalence of GAD was 1.9% (SE: 0.3) and 4.5% (SE: 0.5), respectively.

Wittchen and Jacobi critically reviewed 27 studies based in Europe to estimate the prevalence of mental disorders.[66] Using meta-analytic techniques, the 12-month prevalence of GAD ranged from 0.2% to 4.3% (median: 1.7; interquartile range: 0.8-2.2).

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Regardless of geography, women are approximately twice as likely to report GAD when compared with men.[59,60,64,67] There also appears to be an increasing linear trend with regard to prevalence up until the age of 60 years, when estimates decline.[61] With regard to race/ethnicity, non-Hispanic blacks and Hispanics appear to have a lower risk than non-Hispanic whites of GAD.[61] The rates of anxiety disorders as a whole decline monotonically with increasing income and education, so that all comparisons between the lowest and highest income groups are significant.[60]

Factors that may increase the risk of developing GAD include the following: being female, childhood trauma, illness, stress, some personality types and personality disorders, family history, and substance abuse.[68]

The main existing treatment options:

The 2 main treatments for GAD are medications and psychotherapy. Several different types of medications are used to treat GAD and they include pregabalin, antidepressants, buspirone and benzodiazepines.[68]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality estimates with respect to GAD were limited to discussion of suicidality. These data are discussed in Table 25. However, persons with GAD report a high degree of professional help-seeking, substantial medication use for GAD symptoms, and interference in their daily activities.[67]

Important co-morbidities:

Search Strategy

PubMed was searched for primary literature and review articles focused on the important comorbidities of GAD. Searches were confined to English language articles involving humans over the age of 18 years. Search terms used for this section are included in the footnote on the bottom of this page.[4] A special effort was made to locate estimates representative of the EU.

Depression

Incidence

The incidence of GAD-depression co-morbidity was not found in the published literature.

Prevalence

The prevalence of co-morbidity varied by depression diagnosis and sample studied (i.e., elderly, inpatients, etc.). Among the studies evaluating GAD-major depression co-morbidity, the prevalence of co-morbid depression ranged from 1.6% to 30.6%.[69,70,71]. One (1) of the highest estimates (30.6%) represents data from Lenze et al. (2000).[71] The authors evaluated co-morbid anxiety disorders among depressed elderly patients and found substantial co-occurrence. Over one-quarter of their sample (27.5%) had symptoms consistent with a diagnosis of GAD. Among those with significant depressive symptoms and those with major depression, 13.6% and 30.6% had diagnoses of GAD. Data from the NCS also delineated co-morbidity with depression by 30-day and lifetime-GAD.[67] Overall, Wittchen and

[4] Throughout the literature review, comorbid disorders were represented by the following Boolean search terms: [migraine OR headache], [depression OR "major depression" OR "depressive symptoms" OR dysthymia], [cancer OR tumor OR malignancy], [insomnia OR "sleep disturbance"]. Data regarding stroke, diabetes, social phobia, chronic fatigue syndrome, and irritable bowel syndrome were searched using the simple terms.

colleagues (1994) found that the odds of major depression and dysthymia were significantly elevated among persons with GAD (Major depression: OR 30-day: 13.9; 95% CI: 7.9-24.3 and $OR_{lifetime}$: 9.7; 95% CI: 6.7-14.1; Dysthymia: OR 30-day: 24.8; 95% CI: 12.4-49.5; and $OR_{lifetime}$: 13.5; 95% CI: 10.0-14.1).

With regard to depression subtypes, Pini et al. (1997) found that GAD was more likely to co-occur with dysthymia versus bipolar or unipolar depression (OR: 5.36; 95% CI: 1.6-18.4 versus OR: 0.56; 95% CI: 0.2-1.8 and OR: 0.42; 95% CI: 0.1-1.2). In their sample of psychiatric outpatients, the prevalence of GAD was as follows: 65.2% with dysthymia, 31.6% with bipolar depression, and 37.1% with unipolar depression.[72] Rihmer and colleagues (2001), however, found that co-morbidity was highest among persons with bipolar II disorder.[73] When compared to other depressive diagnoses, co-morbidity estimates for bipolar II were not significantly higher than those for major depression, bipolar I, or a combination of major depression and bipolar II.

Mortality

Holwerda and colleagues (2007) initiated a study to assess whether GAD and GAD-depression co-morbidity were associated with mortality among 4051 older persons in Amsterdam.[70] In elderly persons, depression increased the rate of mortality among men only (Hazard Ratio [HR]: 1.44; 95% CI: 1.09-1.89). Neither GAD nor GAD-depression co-morbidity were associated with excess mortality. Others have also noted that co-morbidity between GAD and depression is associated with disability, high utilisation of health care resources, and suicidality.[69,74]

Co-prescribed Medicinal Products

SSRIs, SNRIs, TCAs, and benzodiazepines.

Social Phobia

Incidence

The incidence of GAD-social phobia co-morbidity was not found in the published literature.

Prevalence

Among patients with a primary diagnosis of GAD, Brawman-Mintzer et al. (1993) found that 23% (n = 25) also had a diagnosis of social phobia.[75] Goisman and colleagues (1995) reported a slightly higher estimate. Data from their multicenter study of patients with DSM-IIIR index anxiety diagnoses, the authors found that among patients with a lifetime mention of GAD, 33% had an additional diagnosis of social phobia.[76] Data from the NCS supports these findings, as the odds of depression were significantly elevated among persons with 30-day or lifetime reports of GAD (i.e., OR 30-day: 6.9; 95% CI:4.3-10.9 and $OR_{lifetime}$: 3.8; 95% CI: 2.8-5.0).[67]

Mortality

No mention of mortality as it relates to GAD-social phobia co-morbidity was found. Data did, however, portray anxiety disorders as chronic conditions, with low rates of recovery and high probabilities of recurrence. In fact, Bruce et al. (2005) found that social phobia had the smallest probability of recovery over 12 years of follow-up.[77] Co-morbid GAD decreased the probability of recovering from social phobia, while increasing the likelihood of its recurrence. In contrast, none of the co-morbid conditions predicted the recurrence of GAD.

Co-prescribed Medicinal Products

SSRIs, monoamine oxidase inhibitors (i.e., phenelzine, tranylcypromine), and benzodiazepines (i.e., clonazepam).

Insomnia

Incidence

The incidence of GAD-insomnia co-morbidity was not found in the published literature.

Prevalence

A community survey in Quebec found that patients with GAD frequently presented with symptoms of fatigue and insomnia-type sleep disturbances.[78] When insomnia was listed as a reason for health care consultation, the OR for the association with a positive GAD screening result was increased 5.4-fold (95% CI: 1.97-14.5). Additional work in France found the prevalence of current GAD in relation to insomnia complaints at 3.2% (95% CI: 2.3-3.7).[79] Univariate analyses have also found an association between GAD and insomnia among general hospital inpatients (OR: 3.1; 95% CI: 1.1-8.7).[80] This apparent association was, however, diminished when multivariate analyses were conducted.

Mortality

Mortality was not found within the GAD-insomnia literature. Instead, the body of work spoke to issues related to insomnia, including deficits in daily functioning. Within the clinical trial literature, there was evidence that pharmaceuticals could improve symptoms of insomnia among persons with GAD.[81,82,83] Data also suggest that cognitive behavioural therapy could lessen the severity of insomnia among persons with GAD.[84]

Co-prescribed Medicinal Products

Benzodiazepines (i.e., triazolam) and non-benzodiazepine hypnotics (i.e., zolpidem and trazadone).

Indication: Fibromyalgia

Documentation of a condition deemed as exaggerated tenderness to palpitation has been noted in the medical literature since the mid-19th century.[85] Coined "fibrositis" by British

physicians, this term was included in a North American textbook of rheumatology in 1943.[86,87] It was not until the mid-1970s when Smythe and colleagues at the University of Toronto associated systemic symptoms (i.e., sleep electroencephalogram abnormalities and quantification of tender points) with the disorder that substantive advancements were made in the understanding of this condition.[88] Based on a lack of objective inflammation in patients, the term fibromyalgia was proposed to best describe the syndrome.[89] Definition of the syndrome was refined in 1990 for statistical and epidemiological purposes.[90] Now known as the American College of Rheumatology (ACR) criteria, diagnosis of fibromyalgia requires the concurrent presence of widespread pain (axial plus upper and lower segment plus left- and right- sided pain) and tenderness on palpation in at least 11 of 18 tender point sites.[91] In what follows, the epidemiology of fibromyalgia is described, both in the US and in Europe.

Incidence:

US

A retrospective cohort study of a large, stable health insurance claims database (62,000 nationwide enrollees per year) by Weir et al.[92] identified 2595 incident cases of fibromyalgia between 1997 and 2002 and determined that the age-adjusted rates in the US were 6.88 cases per 1000 person-years for males and 11.28 cases per 1000 person-years for females. Females were 1.64 times (95% CI 1.59–1.69) more likely than males to have fibromyalgia.

Europe

Two (2) studies have estimated the rates of fibromyalgia in Europe. The first, by Forseth et al., assessed the incidence of fibromyalgia among women residing in a small town in South Norway.[93] Using the ACR criteria for diagnosis of fibromyalgia, the annual incidence of fibromyalgia in women aged 20 to 49 years was 583 per 100,000.

Gallagher et al. conducted a study among patients registered with a general practitioner contributing to the GPRD in the UK[94] with the main objective of identifying patterns in incidence of fatigue symptoms and diagnoses presenting in UK primary care. The study found that although the overall incidence of all fatigue syndromes decreased from 87 per 100,000 patients in 1990 to 49 in 2001, the incidence of fibromyalgia increased from less than 1 per 100,000 to 35 per 100,000. The sex-specific incidence in 2001 was determined to be 14 cases per 100,000 among women and 3 cases per 100,000 among men. It is important to note, however, that these estimates may be exaggerated as it was unlikely that the general practitioners used established criteria in diagnosing fibromyalgia.

Prevalence:

Recent data suggest that chronic widespread pain, the cardinal symptom of fibromyalgia, is common in the general population (prevalence of 7.3% to 12.9%) and is comparable in reports from the UK, Canada, Israel, US, and Sweden.[95,96,97,98,99,100] The following text highlights published prevalence estimates of fibromyalgia using general population samples (range, 0.66% to 10.5%). On average, these estimates are considerably lower than those

gleaned from rheumatology practices where upwards of 10% to 20% of patients are reported to be affected.[101]

US

A 1995 community study by Wolfe et al. used the 1990 ACR classification criteria to determine the prevalence and characteristics of fibromyalgia in the general US population. The age- and sex-adjusted prevalence of fibromyalgia was 2% (95% CI: 1.4-2.7) overall (3.4% and 0.5% for women and men, respectively). It was noted that the prevalence of fibromyalgia increased steadily through to 80 years of age, at which point it declined.[99]

Europe

Studies conducted within Scandinavian countries have estimated the prevalence of fibromyalgia between 0.66% and 10.5% using ACR-90 criteria.[102,103,104] The range in estimates may be due, in part, to patient demographics (i.e., age and sex), study methodologies, and differences in pain histories (i.e., length and intensity). For example, Forseth and Gran[102] found a higher prevalence of fibromyalgia than did other studies. This difference has been attributed to the fact that 57% of the respondents reported chronic pain. Wolfe et al.[99] reported the prevalence of chronic pain in women to be approximately 29%, similar to other investigations.[89,95,103] The authors evaluated the prevalence of fibromyalgia among women aged 20 to 49 years in a small town municipality in Norway. After clinical examination of a random sample (n = 242) of positive responders (i.e., those who gave at least 1 affirmative response regarding pain and/or stiffness of at least 3 months' duration), it was estimated that 10.5% (95% CI: 6.4-14.6) of women had fibromyalgia. The following year, Prescott and colleagues[103] reported the prevalence of fibromyalgia in the adult Danish population at 0.66% (95% CI: 0.28-1.29); all those diagnosed were women. In this study, 65 subjects were clinically examined, 8 fulfilled ACR-90 criteria for diagnosis.

Additional data found evaluating fibromyalgia prevalence in Europe was limited to a cross-sectional, population-based study in Italy.[105] Using a random sample of the adult population of Marches, Salaffi and colleagues noted that 2.22% (95% CI: 1.36-3.19) had fibromyalgia.

All diagnoses were determined by trained rheumatologists blinded to survey results.

Other Regions

Additional data were found regarding fibromyalgia prevalence representing diverse populations from countries around the globe, including Bangladesh, Brazil, Canada, Japan, Mexico, and Turkey.[97,101,106,107,108,109,110] Collectively, the research shows a range in prevalence from 1.4% to 7.3%. The highest estimates were reported by White and Thompson, who assessed disease prevalence in a small Amish community in Ontario, Canada.[108] Due to the unique characteristics of this population, generalisability of this sample to other groups is not possible.

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The demographic profile of fibromyalgia is consistent globally. Fibromyalgia affects more women than men and increases in prevalence with age. Fibromyalgia is also more prevalent among disadvantaged groups, including persons from lower socioeconomic classes, those with little to no education, and persons widowed or lacking a nuclear family.[97,99,101,104,109]

Causes and/or risk factors for fibromyalgia are unknown, but some factors have been loosely associated with disease onset: stressful or traumatic events (e.g., car accidents), post-traumatic stress disorder, repetitive injuries, illness (e.g., viral infections), certain diseases (i.e., Systemic Lupus Erythematosus, Rheumatoid Arthritis [RA], Chronic Fatigue Syndrome [CFS]), genetic predisposition, obesity.[111]

The main existing treatment options:

A multidisciplinary treatment is recommended, including screening and treatment for depression. The main treatment options include pharmacotherapy, aerobic exercise and muscle strengthening exercise, education and relaxation therapy, and cognitive behavioural therapy.[111]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Data regarding mortality and chronic pain are conflicting, perhaps due to uncontrolled confounding data by underlying new pathology.[112] With regard to fibromyalgia specifically, 3 studies were assessed: two found no elevation in mortality estimates, whereas 1 documented an increased risk of death in persons with fibromyalgia relative to the general population.

A cross-sectional study of approximately 8000 adults in Finland identified 54 subjects with fibromyalgia. Ten (10) years later, there was little difference in mortality rates between these subjects (22.6/1000 person-years) and those without fibromyalgia (16.6/1000 person-years) and no excess deaths after adjusting for sex and age differences.[113] On the other hand, Dreyer et al. followed 1361 patients with fibromyalgia from 1984 to 1999 to assess mortality rates relative to the Danish general population. Overall, no increased risk of death was noted among patients (SMR: 1.3; 95% CI: 0.9-1.7).[114] When stratified by sex, however, the authors noted an increased risk of death from suicide, liver cirrhosis/biliary tract disease, and cerebrovascular disease among women only comparing fibromyalgia patients to the general population.

Wolfe et al.[115] in a cohort study of 1747 fibromyalgia patients followed-up over 25 years found an excess risk for dying (SMR: 1.45; 95% CI, .19 – 1.86), using population mortality rates as a comparison. The causes of death in excess were accidental deaths (SMR: 4.5; 95% CI: 2.0-10.1), infection (SMR: 4.5; 95% CI: 1.7–11.9), and pneumonia (SMR: 3.3; 95% CI: 1.2-8.8). Mortality was also higher in those who initially had higher levels of disability.

Important co-morbidities:

Search Strategy

PubMed was searched for primary literature and review articles focused on the important comorbidities of fibromyalgia. Searches were confined to English language articles involving humans over the age of 18 years. Search terms used for this section are included in the footnote on the bottom of this page.[5] A special effort was made to locate estimates representative of the EU.

Chronic Fatigue

Incidence

Only 1 study was found to address the incidence of fibromyalgia and its associated co-morbidities. Examining data from a large insurance claims database with approximately 62,000 members, Weir et al. found an elevated risk of CFS among both males and females with fibromyalgia (RR_{male}: 7.1; 95% CI: 4.5-11.1 and RR_{female}: 5.6; 95% CI: 4.4-7.3).[92] However, it is important to note that this database was established to provide insurance to employees of a specific religious organization. As such, the data may not be generalisable to other populations.

Prevalence

One (1) of the first studies investigating the co-occurrence of fibromyalgia and CFS found that among 27 patients with CFS, 70% (n = 19) had persistent and diffuse musculoskeletal pain consistent with fibromyalgia.[116] Later work utilising diagnostic criteria within patient samples reported lower estimates of disorder co-morbidity ranging from 17% to 42%.[117,118,119,120]

Two (2) studies published in 2000 were found to investigate fibromyalgia-CFS co-morbidity among population-based samples. Within a random sample of Chicago, Illinois residents, Jason and colleagues reported that of the 32 persons with CFS, 15.6% met American Chemical Society criteria for fibromyalgia.[121] In contrast, data from a general population survey of Canadian adults found that approximately 60% of fibromyalgia cases had co-morbid CFS. When stratified by sex, a larger percentage of males with fibromyalgia fulfilled CFS criteria compared with females (80% versus 58%, respectively).[122]

[5] Throughout the literature review, comorbid disorders were represented by the following Boolean search terms: [migraine OR headache], [depression OR "major depression" OR "depressive symptoms" OR dysthymia], [cancer OR tumor OR malignancy], [insomnia OR "sleep disturbance"]. Data regarding stroke, diabetes, social phobia, chronic fatigue syndrome, and irritable bowel syndrome were searched using the simple terms.

Mortality

No mention of mortality as it relates to fibromyalgia-depression co-morbidity was found. However, data do suggest that symptoms of both disorders significantly affect the quality of one's life, particularly in financial and occupational realms.[123,124]

Co-prescribed Medicinal Products

Nonsteroidal anti-inflammatory drugs, SSRIs, SNRIs and TCAs.

Depression

Incidence

Weir et al. found an elevated risk of depression (including single and recurrent episodes of Major Depressive Disorder [MDD]) among both males and females with fibromyalgia (RR_{male}: 2.9; 95% CI: 2.2-3.9 and RR_{female}: 2.9; 95% CI: 2.4-3.4).[92] Again, it is important to note that this database was established to provide insurance to employees of a specific religious organization and may not be generalisable to other populations.

Prevalence

The association between chronic medical conditions and depression is well-documented in the literature [125,126]; however, co-morbidity with fibromyalgia may be particularly robust.[127,128]. In 1995, Wolfe et al. demonstrated a 3-fold increase in the odds of depression among persons with fibromyalgia relative to those without the disease.[99] Since that time, several other population-based studies have supported this elevation.[129,130,131] For example, Patten et al. found that fibromyalgia was one of the surveyed conditions most strongly associated with major depression (OR: 3.4; 95% CI: 2.9-4.0)[129] and Raphael et al. found that the odds of current MDD was nearly 3-fold higher in community women with fibromyalgia than in those without fibromyalgia (OR: 2.57; 95% CI: 1.6-4.1).[130]

Studies using patient samples suggest that major depression affects 18% to 49% of patients with fibromyalgia.[120,121,132,133,134] Based on an analysis of case-control data, however, it has been suggested that co-morbidity between fibromyalgia and depression may represent a bias of treatment-seeking.[135] Thus, population estimates may be a more accurate representation of disorder co-occurrence.

Mortality

No mention of mortality as it relates to fibromyalgia-depression co-morbidity was found. Data do suggest, however, that symptoms of both disorders significantly affect the quality of one's life.[136,137]

Co-prescribed Medicinal Products

SSRIs, SNRIs and TCAs.

Irritable Bowel Syndrome (IBS)

Incidence

Weir et al. found an elevated risk of IBS among both males and females with fibromyalgia (RR_{male}:4.0; 95% CI: 3.0-5.3 and RR_{female}: 4.5; 95% CI: 3.9-5.1).[92] Again, it is important to note that this database was established to provide insurance to employees of a specific religious organization and may not be generalisable to other populations.

Prevalence

Data have shown that people with IBS are likely to have co-morbid conditions including fibromyalgia, migraine, and depression. Referred to in the literature as "functional somatic syndromes" or "affective spectrum disorders,"[138,139] speculation exists whether these disorders share a common biological mechanism. In an early study to explore this hypothesis, Hudson et al. noted that 39% of patients with fibromyalgia also had symptoms consistent with IBS.[120]

Since that time, several groups have studied the prevalence of IBS among patients with fibromyalgia and vice versa. Overall, published data suggest significant co-morbidity. In 1991, Veale and colleagues observed that IBS was present in 70% of fibromyalgia patients versus 12% of controls.[140] Comparing patients with fibromyalgia to healthy controls, all recruited from hospital-based clinics, Aaron and colleagues noted that the lifetime prevalence of IBS was 77% among persons with fibromyalgia versus 18% of controls ($p \leq 0.01$).[118] In 1999, data from a cross-sectional study showed 32% of patients with IBS having symptoms of fibromyalgia compared with 4% of patients without IBS ($p < 0.001$).[141] Conversely, Lubrano et al. observed 130 patients with IBS and found that 20% also had fibromyalgia; the presence of fibromyalgia was not, however, correlated with the severity of IBS.[142] Finally, the most recent data utilising patient populations found that IBS prevalence was significantly higher among patients with fibromyalgia compared with control patients (i.e., 63% versus 15% using Rome I criteria for IBS diagnosis, $p < 0.001$).[143] No difference in prevalence was noted when respondents were subclassified according to their bowel symptom predominance (i.e., diarrhoea, constipation, or alternating symptoms).

Two (2) recent studies have also examined this co-morbidity at the general population level. Using data from a public health survey of a Norwegian adult population, Vandivik and colleagues noted that the odds of fibromyalgia was nearly 4 times higher among persons with IBS versus those without IBS (OR: 3.6; 95% CI: 2.7-4.8).[144] Estimates were similarly elevated among a cohort assembled in the US. Among members of a large US health plan, Cole et al. noted an 80% higher odds of fibromyalgia among persons with IBS when compared to healthy controls (OR: 1.8, 95% CI: 1.7-1.9).[145]

Mortality

No mention of mortality as it relates to fibromyalgia-IBS co-morbidity was found. Data do suggest, however, that symptoms of both disorders significantly affect the quality of one's life.[146]

Co-Prescribed Medicinal Products

SSRIs, SNRIs, and TCAs.

Module SII. Non-Clinical Part of the Safety Specification

Non-clinical safety information findings observed during the development programme for pregabalin have been adequately evaluated and addressed in the extensive clinical development programme and postmarketing experience. A summary of the non-clinical work with emphasis on areas relative to the known and potential safety risks is presented below.

A comprehensive programme was conducted to evaluate the toxicological profile of pregabalin. The acute toxicity of pregabalin is low. Animals given oral doses of pregabalin in acute and repeat dose studies were hypoactive, hyperactive, and/or ataxic, signs commonly observed with Central Nervous System (CNS) active drugs. No significant target organ toxicity was observed in rats treated for up to 52 weeks or in monkeys treated for up to 69 weeks at exposures at least 8 times the mean human exposure at the maximum recommended dose. Effects of pregabalin in juvenile animals were similar to those in adults. Pregabalin was not genotoxic in vitro or in vivo.

Outline of safety concerns not adequately addressed by clinical data or which are of unknown significance.

Haemangiosarcoma in mice.

Pregabalin is not genotoxic based on an extensive battery of in vitro and in vivo tests.

Two (2)-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 B6C3F1 and CD1 strains of mice, no statistically significant increased incidence of tumours was found at exposures similar to the mean human exposure, but a statistically significant increased incidence of haemangiosarcoma was observed in mice at higher exposures (approximately 5 times higher than exposures expected at the maximum recommended human dose of 600 mg/day). The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans, and hypoxia and endothelial cell proliferation are not present in rats. Vitamin E supplementation of diet inhibited the induction of hepatic endothelial cell proliferation in mice following 2 weeks of pregabalin administration. The inhibition of pregabalin-induced increases in endothelial cell proliferation by Vitamin E provides confirmatory evidence for the proposed mode of action for the pregabalin-induced haemangiosarcomas in mice.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity: • Hypoactivity in rats and mice (5000 mg/kg single dose)	No relevance because of high dose.
• Repeat-dose toxicity o Hypoactivity in rat and monkey (500 mg/kg/day) o Death in monkey (500 mg/kg/day BID) o Urinary bladder changes in rat (250 mg/kg/day) o Decreased total nucleated cells in rat bone marrow (250 mg/kg/day) o Spermatogenic epithelial degeneration in rat (1250 mg/kg/day) o An increased incidence of retinal atrophy was observed in aged rats. Histopathology of the lesion was consistent with age-related retinal atrophy. • Tail dermatopathy in monkey (25 mg/kg/day)	No relevance because of high dose. Increased retinal atrophy is an exacerbation of a background fining in rats, and is of unknown relevance to humans. No relevance as it is animal specific finding (tail dermatopathy in monkeys).
• Genotoxicity	N/A
• Carcinogenicity Haemangiosarcoma Two (2)-year study in rats and mice; no tumours in rats at exposures of up to 24-times the exposures expected at the maximum recommended human dose (600 mg/day). Increased incidence of haemangiosarcoma in mice at 5-the exposures expected at the maximum recommended human dose (600 mg/day). Inhibition induced by Vitamin E supplementation.	Angiosarcomas are rare in humans. One (1) case of Angiosarcoma has been reported, but the information provided is minimal and it is unclear as to whether the patient actually had taken pregabalin. No evidence suggests that mouse exposure is relevant to human exposure.
• Developmental and reproductive toxicity o Decreased sperm motility in rat (250 mg/kg/day), decreased fertility and epididymal sperm count, abnormal sperm morphology, increased time to mating in rat (1250 mg/kg/day) o Decreased foetal body weight in rat (2500 mg/kg/day) o Decreased foetal body weight and decreased ossification in rabbit (250 mg/kg/day) o Increased skeletal variations in rat (1250 mg/kg/day) o Decreased foetal and neonatal survival in rat (250 mg/kg/day) o Developmental toxicity in rat (100 mg/kg/day)	No clinical studies have investigated the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. 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 childbearing potential.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
• Safety Pharmacology:	N/A

CNS = Central Nervous System, N/A = Not Applicable.

Angiosarcomas are rare malignant tumours originating in the endothelial cells of either blood vessels (i.e., haemangiosarcoma) or lymph vessels (i.e., lymphangiosarcoma). The incidence of haemangiosarcoma is approximately 1 case per 500,000 person-years (50,000 times less common than in mice). Known risk factors for haemangiosarcoma include exposure to vinyl chloride, thorium oxide, arsenic, inhaled plutonium, and radiation therapy.

A single case of Angiosarcoma was reported in a female patient of unknown age and race. It was unclear whether or not this patient had actually received a dose of pregabalin. This case contained no further information. This spontaneous report was from the Pfizer safety database was not medically confirmed.

The Sponsor confirms that there is no evidence to suggest that the tumour findings in mice would imply an associated risk to humans.

Module SIII. Clinical Trial Exposure

The active substance, pregabalin, is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. Pregabalin binds with high affinity to an auxiliary subunit (α2-protein) of voltage-gated calcium channels in the CNS. Pregabalin is indicated in the EU for the treatment of peripheral and central NeP in adults, epilepsy as adjunctive therapy in adults with partial seizures with or without secondary generalisation, and GAD. In addition, pregabalin is approved for fibromyalgia and NeP associated with spinal cord injury in the US. The dose range is 150 mg to 600 mg per day given in either 2 or 3 divided doses.

Pregabalin immediate-release (IR) is available as a capsule/hard capsule/gelatin coated capsule containing 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg of pregabalin, and as a 20 mg/mL oral solution. In the US, pregabalin controlled-released formulation is available as 82.5 mg, 165 mg, and 330 mg extended-release tablets. In Japan, oral disintegrating tablet formulation is available as 25 mg, 75 mg, and 150 mg tablets.

Clinical trial exposure data presented in Table 2 through Table 13 are updated with a data lock point of 31 January 2020. Although not a currently approved indication for pregabalin, restless leg syndrome is being presented separately in the clinical trial exposure tables within this section, as studies have been conducted in patients with restless leg syndrome. The data were formerly included in other categories (eg, other pain and other psychiatry).[6]

Table 2. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
All Indications Combined		
Cumulative up to 1 month	27,446	696,152
Cumulative up to 3 months	22,399	1,665,677
Cumulative up to 6 months	13,461	2,509,743
Cumulative up to 12 months	8,455	3,592,323
Cumulative up to 24 months	5,299	4,661,588
Cumulative up to 36 months	2,172	5,147,767
Cumulative up to 48 months	1,029	5,401,182
Cumulative up to 60 months	551	5,557,046
Cumulative up to 72 months	391	5,667,315
Cumulative up to 84 months	256	5,723,434
Cumulative up to 96 months	94	5,735,908
Cumulative up to 108 months	11	5,736,615
Total Cumulative Person Time	**81,564**	**52,094,750**
Indication 1-Epilepsy		
Cumulative up to 1 month	4,918	131,825

[6] Same principle applied as in EMEA/743133/2009: HMA/EMA Recommendations on the handling of requests for access to Periodic Safety Update Reports (PSURs); available on EMA website http://www.ema.europa.eu

Table 2. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
Cumulative up to 3 months	4,566	376,314
Cumulative up to 6 months	4,125	673,951
Cumulative up to 12 months	3,010	1,111,026
Cumulative up to 24 months	2,269	1,649,619
Cumulative up to 36 months	1,148	1,902,172
Cumulative up to 48 months	507	2,040,068
Cumulative up to 60 months	355	2,147,432
Cumulative up to 72 months	292	2,239,222
Cumulative up to 84 months	237	2,293,986
Cumulative up to 96 months	94	2,306,460
Cumulative up to 108 months	11	2,307,167
Total Person time for Epilepsy Indication	21,532	19,179,242
Indication 2-NeP		
Cumulative up to 1 month	10,995	282,480
Cumulative up to 3 months	9,000	643,919
Cumulative up to 6 months	4,611	888,369
Cumulative up to 12 months	2,414	1,218,545
Cumulative up to 24 months	1,630	1,600,429
Cumulative up to 36 months	907	1,810,656
Cumulative up to 48 months	477	1,915,487
Cumulative up to 60 months	176	1,958,802
Cumulative up to 72 months	92	1,976,942
Cumulative up to 84 months	19	1,978,297
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person time for NeP Indication	30,321	14,273,926
Indication 3-GAD		
Cumulative up to 1 month	3035	77,082
Cumulative up to 3 months	2509	167,317
Cumulative up to 6 months	1111	241,859
Cumulative up to 12 months	754	313,284
Cumulative up to 24 months	296	335,075
Cumulative up to 36 months	13	339,443
Cumulative up to 48 months	13	342,544
Cumulative up to 60 months	3	342,605
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person time for GAD Indication	7734	2,159,209
Indication 4-Fibromyalgia		
Cumulative up to 1 month	4,050	101,431
Cumulative up to 3 months	3,240	248,605
Cumulative up to 6 months	2,190	377,445
Cumulative up to 12 months	1,249	489,871
Cumulative up to 24 months	512	538,458
Cumulative up to 36 months	20	544,872

Table 2. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
Cumulative up to 48 months	18	550,787
Cumulative up to 60 months	17	555,911
Cumulative up to 72 months	7	556,250
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person time for Fibromyalgia Indication	11,303	3,963,630
Indication 5-Other Pain		
Cumulative up to 1 month	2319	50,185
Cumulative up to 3 months	1367	103,880
Cumulative up to 6 months	698	150,389
Cumulative up to 12 months	493	219,565
Cumulative up to 24 months	346	282,877
Cumulative up to 36 months	82	295,083
Cumulative up to 48 months	13	296,541
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person time for Other Pain Indication	5318	1,398,520
Indication 6-Other Psychiatry		
Cumulative up to 1 month	1713	42,133
Cumulative up to 3 months	1342	101,780
Cumulative up to 6 months	558	140,626
Cumulative up to 12 months	390	182,031
Cumulative up to 24 months	152	193,771
Cumulative up to 36 months	2	194,182
Cumulative up to 48 months	1	194,396
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person time for Other Psychiatry Indication	4158	1,048,919
Indication 7-Restless Leg Syndrome		
Cumulative up to 1 month	416	11,016
Cumulative up to 3 months	375	23,862
Cumulative up to 6 months	168	37,104
Cumulative up to 12 months	145	58,001
Cumulative up to 24 months	94	61,359
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA

Table 2. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
Cumulative up to 108 months	0	NA
Total Person time for Restless Leg Syndrome Indication	1198	191,342

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain, NA = Not Applicable.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026, 1008-000-164, 1008-000-166, 1008-000-202, 1008-008, 1008-010, 1008-012, 1008-015, 1008-033, 1008-035, 1008-060, 1008-061, 1008-074, 1008-082, 1008-084, 1008-088, 1008-093, 1008-100, 1008-114, 1008-134, 1008-165, 1008-174, 1008-183, 1008-192, 1008-197, 1008-198, A0081005, A0081006, A0081007, A0081015, A0081031, A0081036, A0081040, A0081046, A0081057, A0081059, A0081065, A0081068, A0081075, A0081078, A0081084, A0081088, A0081090, A0081094, A0081095, A0081097, A0081101, A0081106, A0081121, A0081128, A0081139, A0081140, A0081160, A0081164, A0081173, A0081197, A0081251, A0081252, A0081286, A9001464
Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041, A0081075, A0081105 and A0081106 are excluded.
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure
from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 3. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
All Indications Combined		
Cumulative up to 1 month	15,912	397,726
Cumulative up to 3 months	12,724	908,327
Cumulative up to 6 months	5,791	1,045,173
Cumulative up to 12 months	650	1,114,526
Cumulative up to 24 months	333	1,181,277
Cumulative up to 36 months	145	1,204,230
Cumulative up to 48 months	4	1,204,640
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for All Indications Combined	35,559	7,055,899
Indication 1–Epilepsy		
Cumulative up to 1 month	2,250	57,809
Cumulative up to 3 months	1,955	160,230
Cumulative up to 6 months	1,470	207,812
Cumulative up to 12 months	313	254,694
Cumulative up to 24 months	239	318,087
Cumulative up to 36 months	145	341,040
Cumulative up to 48 months	4	341,450
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Epilepsy Indication	6,376	1,681,122
Indication 2-NeP		
Cumulative up to 1 month	5735	147,566
Cumulative up to 3 months	4821	340,842
Cumulative up to 6 months	2198	373,849
Cumulative up to 12 months	0	NA
Cumulative up to 24 months	0	NA
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for NeP Indication	12,754	862,257
Indication 3-GAD		
Cumulative up to 1 month	2099	53,169
Cumulative up to 3 months	1716	96,221
Cumulative up to 6 months	332	114,927
Cumulative up to 12 months	192	116,501

Table 3. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
Cumulative up to 24 months	0	NA
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for GAD Indication	4339	380,818
Indication 4-Fibromyalgia		
Cumulative up to 1 month	2,568	65,008
Cumulative up to 3 months	2,108	163,630
Cumulative up to 6 months	1,459	186,974
Cumulative up to 12 months	0	NA
Cumulative up to 24 months	0	NA
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Fibromyalgia Indication	6,135	415,612
Indication 5-Other Pain		
Cumulative up to 1 month	1943	41,294
Cumulative up to 3 months	1076	74,174
Cumulative up to 6 months	147	75,060
Cumulative up to 12 months	0	NA
Cumulative up to 24 months	0	NA
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Other Pain Indication	3166	190,528
Indication 6-Other Psychiatry		
Cumulative up to 1 month	901	21,864
Cumulative up to 3 months	673	49,368
Cumulative up to 6 months	17	49,447
Cumulative up to 12 months	0	NA
Cumulative up to 24 months	0	NA
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA

Table 3. Clinical Trial Pregabalin Capsule Formulation Duration of Exposure (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Other Psychiatry Indication	1591	120,679
Indication 7-Restless Leg Syndrome		
Cumulative up to 1 month	416	11,016
Cumulative up to 3 months	375	23,862
Cumulative up to 6 months	168	37,104
Cumulative up to 12 months	145	58,001
Cumulative up to 24 months	94	61,359
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Restless Leg Syndrome Indication	1198	191,342

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain, NA = Not Applicable.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026

Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Data from studies 1008-081 and 1008-153 are reported under study 1008-081.
Liquid doses from A0081041 and A0081105 are excluded.

Table 4. Clinical Trial Oral Solution Exposure by Duration and Indication for Controlled Studies and Non Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Persons Time (Days)
All Indications		
Cumulative up to 1 month	374	10,157
Cumulative up to 3 months	349	29,061
Cumulative up to 6 months	327	54,869
Cumulative up to 12 months	298	101,277
Cumulative up to 24 months	258	117,002
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Cumulative Person Time	1,606	312,366
Indication 1-Epilepsy		
Cumulative up to 1 month	374	10,157
Cumulative up to 3 months	349	29,061
Cumulative up to 6 months	327	54,869
Cumulative up to 12 months	298	101,277
Cumulative up to 24 months	258	117,002
Cumulative up to 36 months	0	NA
Cumulative up to 48 months	0	NA
Cumulative up to 60 months	0	NA
Cumulative up to 72 months	0	NA
Cumulative up to 84 months	0	NA
Cumulative up to 96 months	0	NA
Cumulative up to 108 months	0	NA
Total Person Time for Epilepsy Indication	1,606	312,366

NA = Not Applicable.
Controlled Protocols: A0081041, A0081042, A0081105
Non Controlled Protocols: A0081075 and A0081106
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 5. Clinical Trial Pregabalin Capsule Formulation By Age Group and Gender (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Age Group (Years)	Persons		Person Time (Days)	
	M	F	M	F
All Indications Combined				
Age < 18 Years	91	123	7,800	11,346
18 <= Age <= 64 Years	5,075	7,356	427,377	560,674
65 <= Age <= 74 Years	1,092	1,174	68,226	74,998
75 <= Age <= 84 Years	426	495	23,672	26,854
Age >= 85 Years	34	46	1,729	1,964
Total	6,718	9,194	528,804	675,836
Indication 1-Epilepsy				
Age < 18 Years	85	75	7,320	6,502
18 <= Age <= 64 Years	978	1,075	170,870	152,704
65 <= Age <= 74 Years	17	12	2,102	932
75 <= Age <= 84 Years	3	5	179	841
Total	1,083	1,167	180,471	160,979
Indication 2-NeP				
18 <= Age <= 64 Years	1778	1525	126,096	105,535
65 <= Age <= 74 Years	857	727	52,898	44,331
75 <= Age <= 84 Years	381	391	20,479	21,008
Age >= 85 Years	32	44	1,606	1,896
Total	3048	2687	201,079	172,770
Indication 3-GAD				
18 <= Age <= 64 Years	735	1154	41,779	64,874
65 <= Age <= 74 Years	37	113	1,422	5,594
75 <= Age <= 84 Years	10	47	467	2,229
Age >= 85 Years	1	2	68	68
Total	783	1316	43,736	72,765
Indication 4-Fibromyalgia				
Age < 18 Years	6	48	480	4,844
18 <= Age <= 64 Years	180	2156	13,677	156,296
65 <= Age <= 74 Years	11	148	799	9456
75 <= Age <= 84 Years	2	17	224	1198
Total	199	2369	15,180	171,794
Indication 5-Other Pain				
18 <= Age <= 64 Years	803	816	31,460	30,684
65 <= Age <= 74 Years	141	133	5,229	5,755
75 <= Age <= 84 Years	24	25	1,125	752
Age >= 85 Years	1	NA	55	NA
Total	969	974	37,869	37,191

Table 5. Clinical Trial Pregabalin Capsule Formulation By Age Group and Gender (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Age Group (Years)	Persons		Person Time (Days)	
	M	F	M	F
Indication 6-Other Psychiatry				
18 <= Age <= 64 Years	489	403	27,837	21,205
65 <= Age <= 74 Years	4	4	197	192
75 <= Age <= 84 Years	1	NA	16	NA
Total	494	407	28,050	21,397
Indication 7-Restless Leg Syndrome				
18 <= Age <= 64 Years	112	227	15,658	29,376
65 <= Age <= 74 Years	25	37	5579	8738
75 <= Age <= 84 Years	5	10	1182	826
Total	142	274	22,419	38,940

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain, NA = Not Applicable, M = Male, F = Female.

Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026

Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.

Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.

Liquid doses from A0081041, and A0081105 are excluded.

Table 6. Clinical Trial Pregabalin Capsule Formulation By Age Group and Gender (by Indication)-All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Age Group (Years)	Persons		Person Time (Days)	
	M	F	M	F
All Indications Combined				
Age <18	150	170	52,692	48,342
18≤ Age ≤64	8,949	12,646	2,167,272	2,436,868
65≤ Age ≤74	1,738	1,981	363,013	338,692
75 <= Age <= 84 Years	688	828	158,110	148,448
Age ≥ 85	54	86	7,065	9,989
Missing from CRF	57	84	1,991	3,706
Total	11,636	15,795	2,750,143	2,986,045
Indication 1–Epilepsy				
Age <18	144	122	52,212	43,498
18≤ Age ≤64	2,203	2,297	1,095,037	1,058,561
65≤ Age ≤74	70	44	26,795	19,996
75 <= Age <= 84 Years	17	19	7,718	3,179
Age ≥ 85	NA	1	NA	78
Missing from CRF	1	NA	93	NA
Total	2,435	2,483	1,181,855	1,125,312
Indication 2–NeP				
18 <= Age <= 64 Years	3469	3316	667,910	496,476
65 <= Age <= 74 Years	1370	1291	292,735	233,582
75 <= Age <= 84 Years	602	660	138,798	127,216
Age ≥ 85	51	81	6,459	9,090
Missing from CRF	56	84	1,898	3,706
Total	5548	5432	1,107,800	870,070
Indication 3–GAD				
18 <= Age <= 64 Years	1063	1611	122,275	169,397
65 <= Age <= 74 Years	67	193	7,322	27,851
75 <= Age <= 84 Years	18	77	2,976	11,533
Age >= 85 Years	2	4	430	821
Total	1150	1885	133,003	209,602
Indication 4-Fibromyalgia				
Age <18	6	48	480	4,844
18 <= Age <= 64 Years	272	3424	42,432	476,589
65 <= Age <= 74 Years	23	248	2,485	26,013
75 <= Age <= 84 Years	2	27	224	3,183
Total	303	3,747	45,621	510,629
Indication 5–Other Pain				
18 <= Age <= 64 Years	947	962	127,582	110,309
65 <= Age <= 74 Years	175	160	27,653	21,697
75 <= Age <= 84 Years	42	32	6,953	2,171
Age >= 85 Years	1	NA	176	NA
Total	1165	1154	162,364	134,177
Indication 6–Other Psychiatry				
18 <= Age <= 64 Years	883	809	96,378	96,160

Table 6. Clinical Trial Pregabalin Capsule Formulation By Age Group and Gender (by Indication)-All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Age Group (Years)	Persons		Person Time (Days)	
	M	F	M	F
65 <= Age <= 74 Years	8	8	444	815
75 <= Age <= 84 Years	2	3	259	340
Total	893	820	97,081	97,315
Indication 7-Restless Leg Syndrome				
18 <= Age <= 64 Years	112	227	15,658	29,376
65 <= Age <= 74 Years	25	37	5,579	8,738
75 <= Age <= 84 Years	5	10	1,182	826
Total	142	274	22,419	38,940

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain, NA = Not Applicable, M = Male, F = Female.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026, 1008-000-164, 1008-000-166, 1008-000-202, 1008-008, 1008-010, 1008-012, 1008-015, 1008-033, 1008-035, 1008-060, 1008-061, 1008-074, 1008-082, 1008-084, 1008-088, 1008-093, 1008-100, 1008-114, 1008-134, 1008-165, 1008-174, 1008-183, 1008-192, 1008-197, 1008-198, A0081005, A0081006, A0081007, A0081015, A0081031, A0081036, A0081040, A0081046, A0081057, A0081059, A0081065, A0081068, A0081075, A0081078, A0081084, A0081088, A0081090, A0081094, A0081095, A0081097, A0081101, A0081106, A0081121, A0081128, A0081139, A0081140, A0081160, A0081164, A0081173, A0081197, A0081251, A0081252, A0081286, A9001464

Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041, A0081075, A0081105 and A0081106 are excluded.
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure
from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 7. Clinical Trial Oral Solution Exposure by Age Group, Gender, and Indication for Controlled Studies and Non Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Age Group (Months/Years)	Persons		Persons Time (Days)	
	M	F	M	F
All Indications Combined				
1 month to 23 months	41	37	12,432	12,578
2 to 6 years	96	70	32,887	21,873
7 to 11 years	53	48	16,060	13,557
12 to 16 years	16	11	3,902	3,645
17 to 21 years	2	NA	68	NA
Total	208	166	65,349	51,653
Indication 1 – Epilepsy				
1 month to 23 months	41	37	12,432	12,578
2 to 6 years	96	70	32,887	21,873
7 to 11 years	53	48	16,060	13,557
12 to 16 years	16	11	3,902	3,645
17 to 21 years	2	NA	68	NA
Total	208	166	65,349	51,653

NA = Not Applicable, M = Male, F = Female.
Controlled Protocols: A0081041, A0081042, A0081105
Non Controlled Protocols: A0081075 and A0081106
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 8. Clinical Trial Pregabalin Capsule Formulation By Dose (by Indication)– Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
All Indications Combined		
All Pregabalin Dosing Groups	15,912	1,204,640
0 mg/day < Dose <= 75 mg/day	6,911	33,673
75 mg/day < Dose <= 150 mg/day	12,643	191,231
150 mg/day < Dose <= 300 mg/day	12,634	475,959
300 mg/day < Dose <= 450 mg/day	6,299	236,900
450 mg/day < Dose <= 600 mg/day	4,731	263,454
600 mg/day < Dose	367	2,733
Indication 1-Epilepsy		
All Pregabalin Dosing Groups	2,250	341,450
0 mg/day < Dose <= 75 mg/day	799	8,034
75 mg/day < Dose <= 150 mg/day	1,476	37,965
150 mg/day < Dose <= 300 mg/day	1,548	125,579
300 mg/day < Dose <= 450 mg/day	979	84,586
450 mg/day < Dose <= 600 mg/day	1,047	85,158
600 mg/day < Dose	18	128
Indication 2-NeP		
All Pregabalin Dosing Groups	5735	373,849
0 mg/day < Dose <= 75 mg/day	3480	13,737
75 mg/day < Dose <= 150 mg/day	5085	80,811
150 mg/day < Dose <= 300 mg/day	4639	155,323
300 mg/day < Dose <= 450 mg/day	1686	27,687
450 mg/day < Dose <= 600 mg/day	1919	95,704
600 mg/day < Dose	26	102
Indication 3-GAD		
All Pregabalin Dosing Groups	2099	116,501
0 mg/day < Dose <= 75 mg/day	440	1798
75 mg/day < Dose <= 150 mg/day	1455	28,678
150 mg/day < Dose <= 300 mg/day	1667	29,873
300 mg/day < Dose <= 450 mg/day	1180	31,672
450 mg/day < Dose <= 600 mg/day	613	22,007
600 mg/day < Dose	309	2473
Indication 4-Fibromyalgia		
All Pregabalin Dosing Groups	2,568	186,974
0 mg/day < Dose <= 75 mg/day	706	2,845
75 mg/day < Dose <= 150 mg/day	2,386	16,865
150 mg/day < Dose <= 300 mg/day	2,366	65,158
300 mg/day < Dose <= 450 mg/day	1,557	70,137
450 mg/day < Dose <= 600 mg/day	507	31,953
600 mg/day < Dose	11	16
Indication 5-Other Pain		
All Pregabalin Dosing Groups	1943	75,060
0 mg/day < Dose <= 75 mg/day	1049	3076
75 mg/day < Dose <= 150 mg/day	1330	18,214
150 mg/day < Dose <= 300 mg/day	1260	26,926

Table 8. Clinical Trial Pregabalin Capsule Formulation By Dose (by Indication)– Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
300 mg/day < Dose <= 450 mg/day	426	5818
450 mg/day < Dose <= 600 mg/day	465	20,808
600 mg/day < Dose	2	13
Indication 6-Other Psychiatry		
All Pregabalin Dosing Groups	901	49,447
0 mg/day < Dose <= 75 mg/day	68	272
75 mg/day < Dose <= 150 mg/day	549	4856
150 mg/day < Dose <= 300 mg/day	820	20,095
300 mg/day < Dose <= 450 mg/day	451	16,399
450 mg/day < Dose <= 600 mg/day	180	7824
600 mg/day < Dose	1	1
Indication 7-Restless Leg Syndrome		
All Pregabalin Dosing Groups	416	61,359
0 mg/day < Dose <= 75 mg/day	369	3911
75 mg/day < Dose <= 150 mg/day	362	3842
150 mg/day < Dose <= 300 mg/day	334	53,005
300 mg/day < Dose <= 450 mg/day	20	601

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026.
Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041, A0081105 are excluded.

Table 9. Clinical Trial Pregabalin Capsule Formulation By Dose (by Indication)– All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
All Indications Combined		
All Pregabalin Dosing Groups	27,446	5,736,615
0 mg/day < Dose <= 75 mg/day	10,950	101,437
75 mg/day < Dose <= 150 mg/day	21,735	737,836
150 mg/day < Dose <= 300 mg/day	22,156	1,684,210
300 mg/day < Dose <= 450 mg/day	13,173	1,234,490
450 mg/day < Dose <= 600 mg/day	9,337	1,970,187
600 mg/day < Dose	512	7,765
Indication 1-Epilepsy		
All Pregabalin Dosing Groups	4,918	2,307,167
0 mg/day < Dose <= 75 mg/day	1,890	21,318
75 mg/day < Dose <= 150 mg/day	4,213	253,242
150 mg/day < Dose <= 300 mg/day	4,199	474,087
300 mg/day < Dose <= 450 mg/day	3,087	520,203
450 mg/day < Dose <= 600 mg/day	2,459	1,034,158
600 mg/day < Dose	99	4,159
Indication 2-NeP		
All Pregabalin Dosing Groups	10,995	1,978,297
0 mg/day < Dose <= 75 mg/day	5972	61,443
75 mg/day < Dose <= 150 mg/day	9221	354,411
150 mg/day < Dose <= 300 mg/day	7884	692,847
300 mg/day < Dose <= 450 mg/day	3268	269,065
450 mg/day < Dose <= 600 mg/day	3465	599,381
600 mg/day < Dose	49	665
Indication 3-GAD		
All Pregabalin Dosing Groups	3035	342,605
0 mg/day < Dose <= 75 mg/day	557	2570
75 mg/day < Dose <= 150 mg/day	1736	42,184
150 mg/day < Dose <= 300 mg/day	2572	113,885
300 mg/day < Dose <= 450 mg/day	1963	119,291
450 mg/day < Dose <= 600 mg/day	837	62,009
600 mg/day < Dose	316	2666
Indication 4-Fibromyalgia		
All Pregabalin Dosing Groups	4,050	556,250
0 mg/day < Dose <= 75 mg/day	921	4,475
75 mg/day < Dose <= 150 mg/day	3,701	38,895
150 mg/day < Dose <= 300 mg/day	3,880	181,941
300 mg/day < Dose <= 450 mg/day	2,879	178,560
450 mg/day < Dose <= 600 mg/day	1,525	152,251
600 mg/day < Dose	33	128
Indication 5-Other Pain		
All Pregabalin Dosing Groups	2319	296,541
0 mg/day < Dose <= 75 mg/day	1172	7,429
75 mg/day < Dose <= 150 mg/day	1604	38,634
150 mg/day < Dose <= 300 mg/day	1661	95,150
300 mg/day < Dose <= 450 mg/day	790	59,854

Table 9. Clinical Trial Pregabalin Capsule Formulation By Dose (by Indication)– All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
450 mg/day < Dose <= 600 mg/day	719	95,124
600 mg/day < Dose	13	145
Indication 6-Other Psychiatry		
All Pregabalin Dosing Groups	1713	194,396
0 mg/day < Dose <= 75 mg/day	69	291
75 mg/day < Dose <= 150 mg/day	898	6628
150 mg/day < Dose <= 300 mg/day	1626	73,295
300 mg/day < Dose <= 450 mg/day	1166	86,916
450 mg/day < Dose <= 600 mg/day	332	27,264
600 mg/day < Dose	2	2
Indication 7-Restless Leg Syndrome		
All Pregabalin Dosing Groups	416	61,359
0 mg/day < Dose <= 75 mg/day	369	3911
75 mg/day < Dose <= 150 mg/day	362	3842
150 mg/day < Dose <= 300 mg/day	334	53,005
300 mg/day < Dose <= 450 mg/day	20	601

GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026, 1008-000-164, 1008-000-166, 1008-000-202, 1008-008, 1008-010, 1008-012, 1008-015, 1008-033, 1008-035, 1008-060, 1008-061, 1008-074, 1008-082, 1008-084, 1008-088, 1008-093, 1008-100, 1008-114, 1008-134, 1008-165, 1008-174, 1008-183, 1008-192, 1008-197, 1008-198, A0081005, A0081006, A0081007, A0081015, A0081031, A0081036, A0081040, A0081046, A0081057, A0081059, A0081065, A0081068, A0081075, A0081078, A0081084, A0081088, A0081090, A0081094, A0081095, A0081097, A0081101, A0081106, A0081121, A0081128, A0081139, A0081140, A0081160, A0081164, A0081173, A0081197, A0081251, A0081252, A0081286, A9001464
Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
Thirteen subjects from study A0081094 took pregabalin but are missing total daily dose information.
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041, A0081075, A0081105 and A0081106 are excluded.

Table 10. Clinical Trial Oral Solution Exposure by Dose and Indication for Controlled Studies and Non Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Duration of Exposure	Persons	Person Time (Days)
All Indications		
All Pregabalin Dosing Groups	374	117002
0 mg/day < Dose <= 75 mg/day	320	21350
75 mg/day < Dose <= 150 mg/day	339	38345
150 mg/day < Dose <= 300 mg/day	247	46145
300 mg/day < Dose <= 450 mg/day	75	10001
450 mg/day < Dose <= 600 mg/day	8	1110
600 mg/day < Dose	3	51
Indication 1 – Epilepsy		
All Pregabalin Dosing Groups	374	117002
0 mg/day < Dose <= 75 mg/day	320	21350
75 mg/day < Dose <= 150 mg/day	339	38345
150 mg/day < Dose <= 300 mg/day	247	46145
300 mg/day < Dose <= 450 mg/day	75	10001
450 mg/day < Dose <= 600 mg/day	8	1110
600 mg/day < Dose	3	51

Controlled Protocols: A0081041, A0081042, A0081105
Non Controlled Protocols: A0081075 and A0081106
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 11. Clinical Trial Pregabalin Capsule Formulation By Ethnic Origin (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Ethnic Origin	Persons	Person Time (Days)
All Indications Combined		
White	11,398	779,832
Black	860	57,104
Asian or Pacific Islander	2,755	279,986
Hispanic	461	43,485
American Indian or Alaskan Native	88	6,725
Other	283	31,414
Missing from CRF	67	6,094
Total	15,912	1,204,640
Indication 1–Epilepsy		
White	1,667	191,916
Black	67	6,294
Asian or Pacific Islander	370	104,563
Hispanic	99	24,805
American Indian or Alaskan Native	3	247
Other	44	13,625
Total	2,250	341,450
Indication 2–NeP		
White	3453	207,134
Black	408	33,759
Asian or Pacific Islander	1634	118,138
Hispanic	71	3679
American Indian or Alaskan Native	3	102
Other	116	9664
Missing from CRF	50	1373
Total	5735	373,849
Indication 3–GAD		
White	1766	99,545
Black	92	2674
Asian or Pacific Islander	63	4503
Hispanic	113	5249
American Indian or Alaskan Native	4	138
Other	61	4392
Total	2099	116,501
Indication 4–Fibromyalgia		
White	1,856	126,024
Black	64	4,137
Asian or Pacific Islander	507	46,999
Hispanic	56	3,037
American Indian or Alaskan Native	74	6,063
Other	11	714
Total	2,568	186,974
Indication 5–Other Pain		
White	1545	61389
Black	145	5454
Asian or Pacific Islander	158	4659
Hispanic	65	2237

Table 11. Clinical Trial Pregabalin Capsule Formulation By Ethnic Origin (by Indication)–Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Ethnic Origin	Persons	Person Time (Days)
Other	30	1321
Total	1943	75,060
Indication 6–Other Psychiatry		
White	748	42,352
Black	67	2880
Asian or Pacific Islander	20	891
Hispanic	48	2,422
American Indian or Alaskan Native	4	175
Other	14	727
Total	901	49,447
Indication 7–Other Restless Leg Syndrome		
White	363	51,472
Black	17	1906
Asian or Pacific Islander	3	233
Hispanic	9	2056
Other	7	971
Missing from CRF	17	4721
Total	416	61,359

CRF = Case Report Form; GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026.
Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
The following studies included patients for whom race/ethnicity was not specified/collected;
study number (n effected): 1008-03J (30), 1008-04J (34).
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041 and A0081105 are excluded.

Table 12. Clinical Trial Pregabalin Capsule Formulation By Ethnic Origin (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Ethnic Origin	Persons	Person Time (Days)
All Indications Combined		
White	18,105	4,502,641
Black	1,242	199,307
Asian or Pacific Islander	3,383	528,686
Hispanic	731	167,152
American Indian or Alaskan Native	100	15,183
Other	634	95,518
Missing from CRF	3,251	228,128
Total	27,446	5,736,615
Indication 1–Epilepsy		
White	3,384	1,754,545
Black	114	62,892
Asian or Pacific Islander	539	214,659
Hispanic	166	105,876
American Indian or Alaskan Native	3	4,813
Other	207	55,929
Missing from CRF	505	108,453
Total	4,918	2,307,167
Indication 2–NeP		
White	5324	1,486,628
Black	565	86,402
Asian or Pacific Islander	2024	245,090
Hispanic	86	16,842
American Indian or Alaskan Native	4	1110
Other	263	27,271
Missing from CRF	2729	114,954
Total	10,995	1,978,297
Indication 3–GAD		
White	2587	308,131
Black	136	9089
Asian or Pacific Islander	71	5923
Hispanic	163	13,561
American Indian or Alaskan Native	6	587
Other	72	5314
Total	3035	342,605
Indication 4–Fibromyalgia		
White	3,168	464,779
Black	129	15,611
Asian or Pacific Islander	529	51,940
Hispanic	125	15,013
American Indian or Alaskan Native	78	7,082
Other	21	1,825
Total	4,050	556,250
Indication 5–Other Pain		
White	1871	266,088
Black	160	14,931

Table 12. Clinical Trial Pregabalin Capsule Formulation By Ethnic Origin (by Indication)–All Clinical Trial Populations (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Ethnic Origin	Persons	Person Time (Days)
Asian or Pacific Islander	179	7701
Hispanic	66	4939
American Indian or Alaskan Native	1	685
Other	42	2197
Total	2319	296,541
Indication 6–Other Psychiatry		
White	1408	170,998
Black	121	8476
Asian or Pacific Islander	38	3140
Hispanic	116	8865
American Indian or Alaskan Native	8	906
Other	22	2011
Total	1713	194,396
Indication 7–Other Restless Leg Syndrome		
White	363	51,472
Black	17	1906
Asian or Pacific Islander	3	233
Hispanic	9	2056
Other	7	971
Missing from CRF	17	4721
Total	416	61,359

CRF = Case Report Form; GAD = Generalised Anxiety Disorder; NeP = Neuropathic Pain.
Protocols: 03J, 04J, 1008-000-125, 1008-000-155, 1008-000-157, 1008-000-167, 1008-007, 1008-009, 1008-011, 1008-014, 1008-017, 1008-021, 1008-022, 1008-025, 1008-026, 1008-029, 1008-030, 1008-031, 1008-032, 1008-034, 1008-040, 1008-045, 1008-072, 1008-080, 1008-083, 1008-085, 1008-087, 1008-091, 1008-092, 1008-094, 1008-104, 1008-105, 1008-108, 1008-112, 1008-127, 1008-131, 1008-132, 1008-145, 1008-149, 1008-160, 1008-173, 1008-181, 1008-196, 1008_152, 1008_81, 1008_90, A0081004, A0081012, A0081030, A0081037, A0081041, A0081047, A0081056, A0081060, A0081063, A0081064, A0081066, A0081071, A0081077, A0081079, A0081081, A0081087, A0081092, A0081100, A0081103, A0081104, A0081105, A0081107, A0081120, A0081124, A0081133, A0081141, A0081143, A0081147, A0081153, A0081157, A0081163, A0081171, A0081180, A0081183, A0081185, A0081186, A0081208, A0081211, A0081229, A0081241, A0081242, A0081244, A0081265, A0081276, A0081279, A0081296, A6061021, A6061026, A9011006, B0261001, B3291026, 1008-000-164, 1008-000-166, 1008-000-202, 1008-008, 1008-010, 1008-012, 1008-015, 1008-033, 1008-035, 1008-060, 1008-061, 1008-074, 1008-082, 1008-084, 1008-088, 1008-093, 1008-100, 1008-114, 1008-134, 1008-165, 1008-174, 1008-183, 1008-192, 1008-197, 1008-198, A0081005, A0081006, A0081007, A0081015, A0081031, A0081036, A0081040, A0081046, A0081057, A0081059, A0081065, A0081068, A0081075, A0081078, A0081084, A0081088, A0081090, A0081094, A0081095, A0081097, A0081101, A0081106, A0081121, A0081128, A0081139, A0081140, A0081160, A0081164, A0081173, A0081197, A0081251, A0081252, A0081286, A9001464.
Data from studies 1008-081 and 1008-153 are reported under protocol 1008-081.
The following studies included patients for whom race/ethnicity was not specified/collected;
study number (n effected): 1008-03J (30), 1008-04J (34), A0081005/A0081015 (172),
A0081006/A0081040 (104), A0081065 (323), A0081094 (1929), and A0081139 (691).
Ten subjects from study A0081296 did not take pregabalin during the study and are not included in this table.
Liquid doses from A0081041, A0081075, A0081105 and A0081106 are excluded.
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure
from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Table 13. Clinical Trial Oral Solution Exposure by Ethnic Origin and Indication for Controlled Studies and Non Controlled Studies (All Subjects Who Have at Least 1 Dose of Study Medication Recorded)

Ethnic Origin	Persons	Person Time (Days)
All Indications Combined		
White	259	80,988
Black	9	2,161
Asian or Pacific Islander	96	32,359
Hispanic	1	71
Other	9	1,423
Total	374	117,002
Indication 1-Epilepsy		
White	259	80,988
Black	9	2,161
Asian or Pacific Islander	96	32,359
Hispanic	1	71
Other	9	1,423
Total	374	117,002

Controlled Protocols: A0081041, A0081042, A0081105
Non Controlled Protocols: A0081075 and A0081106
Subjects on active in parent studies who entered study 1106 are reported in parent study counts in the listings and have cumulative duration of exposure from the parent study and study 1106 reported on the tables.
All other subjects who entered study 1106 have duration of exposure from study 1106 only reported on the tables and counted in study 1106 for the listings.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Important Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Hypersensitivity to the active ingredient or to any of the excipients

Reason for exclusion: Patients with a hypersensitivity to the active ingredient in pregabalin or to any of the excipients should not take pregabalin.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity and allergic reactions was an identified risk for pregabalin, however, in agreement with PRAC was removed in RMP version 12.0. as this risk is well characterised and post-marketing data did not provide new information that would allow for further reduction or mitigation of this risk. Also, there are no special monitoring recommendations that could potentially further reduce the frequency or severity of these events occurring in patients taking pregabalin, as well as no additional pharmacovigilance or risk minimisation activities associated with this risk are necessary.

Patients with renal impairment

Is it considered to be included as missing information? No

Reason for exclusion: CLcr ≤30 mL/min (Subjects with lower CLcr were studied in Clinical Pharmacology studies and appropriate dosing reductions as labelled in SmPC were derived).

Rationale: Dosage reduction in patients with compromised renal function must be individualised according to CLcr ≥60mL/min starting dose 150 mg per day, maximum dose 600 mg per day, divided BID or TID. CLcr ≥30 to <60 mL/min starting dose 75 mg per day, maximum dose 300 mg per day, divided BID or TID. CLcr ≥15 to <30 mL/min starting dose 25-50 mg per day, maximum dose 150 mg per day, QD or divided BID. CLcr <15 mL/min starting dose 25 mg per day, maximum dose 75mg per day, QD.

Paediatric Patients

Is it considered to be included as missing information? No

Reason for exclusion: Aged younger than 18 years were generally excluded from protocols for all indications except in some selected epilepsy protocols. The pregabalin safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study in patients 1 month to 16 years of age, n=65; and two 1 year open label follow on safety study studies in patients 1 month to 16 years of age, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased,

and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia.

Rationale: A paediatric development program in children with epilepsy has been completed.

Patients with generalised anxiety disorder with HAM-A less than 20 or where comorbid depressive symptoms predominated

Is it considered to be included as missing information? No

Reason for exclusion: In GAD studies, patients with HAM-A score of less than 20 or where comorbid depressive symptoms predominated were excluded.

Rationale: There is no impact on patient safety.

Suicide risk

Is it considered to be included as missing information? No

Reason for exclusion: Suicide/suicide ideation has been reported in patients treated with anti-epileptic agents. A meta analysis of randomised placebo-controlled studies of anti-epileptic drugs (not limited to pregabalin) has shown a small increased risk of suicidal ideation and behaviour. Therefore, it is inadvisable for patients with known risk of suicide to begin pregabalin treatment.

Rationale: No risk factors and risk groups were identified. There is no public health impact of this potential risk. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Pregnant and lactating patients

Is it considered to be included as missing information? No

Reason for exclusion: Clinical studies have not been undertaken in pregnant patients and the implications for the well being of the foetus are therefore unknown.

Epidemiology studies: The objectives of study A0081359 were to describe the use of pregabalin in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin. This study evaluated use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden (Refer to for summary of results).

Rationale: Clinical studies have not been undertaken in pregnant patients and the implications for the well being of the foetus are therefore unknown. Pregabalin is excreted in breast milk. As stated in the SmPC, Lyrica 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 childbearing potential.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Populations excluded from the clinical programme include children and women who were pregnant or lactating or women of child bearing potential who may become pregnant. Eleven (11) paediatric patients (aged older than 12 but younger than 16 years) were enrolled in the pre-authorisation epilepsy trials. A paediatric program to characterise the safety and efficacy of pregabalin in children with epilepsy is currently ongoing.

As described in the original marketing authorisation application, the safety database included elderly and very elderly patients, with 622 patients aged 65 to 74 years and 376 patients aged 75 years or older; most of these patients were enrolled in NeP studies (432 patients aged 65 to 74 years and 341 patients aged ≥75 years). Overall, the safety profile in pregabalin-treated patients aged 65 years or older did not differ from the profile of patients younger than 65 years old. In addition, the GAD Type II variation (submitted July 2005) included a study of elderly (aged 65 years or older) GAD patients (177 pregabalin; 96 placebo) and compared the Adverse Event (AE) profile from this study to that of the other adult GAD studies. The types of AEs most commonly reported were similar for both the elderly and the adult studies, but the frequency of many of the events (e.g., dizziness, somnolence, headache, infection, dry mouth, and amblyopia) was lower in the elderly study than in the adult study. The incidence of peripheral oedema in the elderly GAD study (4% pregabalin, 3% placebo) was slightly higher than in the adult GAD studies (2% pregabalin, 0.4% placebo).

Clinically important differences in pregabalin Pharmacokinetics (PKs) due to race and gender have not been observed and are not anticipated.

There were no specific exclusion criteria for hepatic impairment or cardiac impairment. General exclusion criteria used as standard protocol language stated no serious hepatic or cardiac problems that might compromise patient safety or interpretation of study result. In most pregabalin studies, patients with a Creatinine Clearance (CLcr) of <60 mL/min or 30 mL/min were excluded.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 14. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Studies in animals have shown reproductive toxicity. 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 childbearing potential. The objectives of study A0081359 were to describe the use of pregabalin in pregnancy and to estimate the risk of major

Table 14. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin. This study evaluated use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden. The total number of users of pregabalin in a pregnancy ending in a live birth or stillbirth in the study period was 325/666,146 (0.048%) in Denmark, 965/643,088 (0.16%) in Finland, 307/657,451 (0.046%) in Norway, and 1275/1,152,002 (0.11%) in Sweden.
Breastfeeding women	A lactation study (A0081181) was completed in August 2013, with CSR finalised on 03 March 2014. Study A0081181 was an open-label, multiple-dose (150 mg given twice daily [BID]), PK, and safety study in 10 healthy lactating females who were at least 12 weeks postpartum and actively breastfeeding at the time of study enrolment. The results of A0081181 indicate that pregabalin does distribute into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which was 7% of the body weight normalised maternal dose. Overall, the PKs of pregabalin in lactating females were consistent with that reported previously in healthy adult volunteers. Pregabalin was well tolerated in healthy lactating women in this study and the safety profile was consistent with the known profile for pregabalin. The 2 most commonly reported AEs were dizziness (n = 6) and headache (n = 2). Pregabalin is excreted into the milk of lactating women. As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin.
Children	Children below the age of 12 years were not enrolled in clinical trials except in some epilepsy protocols. Pregabalin is not approved for use in children. A paediatric investigation in patients with epilepsy has recently been completed.

Table 14. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Since pregabalin is minimally metabolised by the liver, no dosage adjustment is required for patients with hepatic impairment.
• Patients with other relevant co-morbidity such as cardiovascular disease	Patients with cardiovascular disease were not excluded from the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	All disease severities were studied in clinical trials.
• Immuno-compromised patients	Immuno-compromised patients were not specifically excluded from clinical trials.
• Patients with renal impairment	Dosage reduction in patients with compromised renal function must be individualised according to CLcr: • CLcr >60 mL/min: starting dose 150 mg, maximum dose 600 mg BID or 3 times daily (TID). • CLcr >30 to <60 mL/min: starting dose 75 mg, maximum dose 300 mg BID or TID. • CLcr >15 to < 30mL/min: starting dose 25 to 50 mg, maximum dose 150 mg daily (QD) or BID. • CLcr <15 mL/min: starting dose 25 mg, maximum dose 75 mg QD.
Other • Elderly	Use in elderly patients (over 65 years of age): Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in CLcr associated with increasing age. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

AE = Adverse Event; BID = Twice Daily Administration; CLcr = Creatinine Clearance; CSR = Clinical Study Report; PK = Pharmacokinetic; QD = Every Day; TID = Three Times Daily Administration.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Off-Label Use

Pregabalin is approved for treatment of central and peripheral neuropathic pain (NeP) in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalisation, for treatment of GAD in adults and for treatment of Fibromyalgia (not approved in EU).

In the postmarketing experience, since first approval and through 30 June 2021, 212,043 adverse event cases have been received by the MAH; 24,433 of these cases contain pregabalin use in unapproved indications corresponding to a 11.5% proportional reporting rate, 1350 of these cases contain pregabalin use in paediatric patients, corresponding to a 0.6% proportional reporting rate. Among these 24,433 cases, 2263 cases originated from European Union countries.

The most common unapproved indications (> 250) are Arthralgia (777), Restless legs syndrome (665), Rheumatoid arthritis (526), Osteoarthritis (523), Arthritis (503), Multiple sclerosis (490), Type 2 diabetes mellitus (478), Migraine (409), Headache (397), Spinal osteoarthritis (362), Hypoaesthesia (343) Depression (342).

Fibromyalgia is not an approved indication in the EU. A search of the cumulative postmarketing experience (212,043 adverse event cases) revealed 550 patients treated for Fibromyalgia in the EU.

Routine Pharmacovigilance activities did not identify data that would suggest off-label use is a safety concern for pregabalin.

SV.2. Post-Authorisation Exposure

SV.2.1. Method Used to Calculate Exposure

The worldwide exposure estimate is based on audited pharmacy and/or wholesaler sales of pregabalin received from IMS Quintiles. The worldwide market experience information is based on Standard Units (SUs) sold from the third quarter of 2004 through the fourth quarter of 2019, with data extrapolated to 31 January 2020. One (1) SU is equal to 1 capsule.

Dividing the total SUs by an estimated daily regimen of 2 units daily, and by 365 days per year, yields an estimate of total patient-years of exposure to pregabalin. This estimate provides only an approximation of patient exposure. Many factors such as varying dosing levels and frequency, multiple dosing strengths, compliance issues and relationship between sales data and actual prescriptions confound a precise calculation of exposure.

Please note that the above breakdowns and calculation of patient-years provides only a gross approximation of patient exposure and should not be used to determine AE incidence or rates. The following factors hamper an accurate calculation of the total number of patients exposed to pregabalin:

- Dosing frequency varies for this product based on patient response, formulation prescribed, and treatment indication. The patient exposure estimate has been calculated using the most commonly prescribed dosing frequency, 2 times daily.
- The duration of treatment with pregabalin may vary extensively from patient to patient.
- Lack of adherence, as not all patients comply with their prescribed dosage regimen.
- As the patient exposure calculation is based on sales data, it does not necessarily correlate with the amount of pregabalin administered.
- As multiple dosage forms are available for pregabalin, the number of units used to achieve a daily dose may vary from patient to patient.
- The recommended daily dose differs in different patient populations.

SV.2.2. Exposure

The worldwide exposure to pregabalin since the product was first approved is estimated to be 53,774,130 patient- years. The estimated cumulative patient exposure is based on worldwide sales of 39,282,002,038 units and an estimated daily regimen of 2 units of Pregabalin from the third quarter of 2004 through fourth quarter of 2019, with data extrapolated to 31 January 2020.

Cumulative estimated exposure by indication, gender, age group, dose, formulation and region based on and extrapolated from data provided by IMS Quintiles are summarized in Table 15 and Table 16. The cumulative contribution contains all SU (standard units) and KG (kilogram) history from product launch in third quarter 2004 through fourth quarter 2020, with data extrapolated to 31 January 2020. The prescription data are inclusive of 6 years of history from first quarter 2014 through fourth quarter 2020. Age/Gender/Dosing data are inclusive of 3 years of history from first quarter 2017 through fourth quarter 2019.

Table 15. Cumulative Estimated Exposure for Pregabalin by Sex, Age, and Region (in Patient Years)

Indication Group	Sex			Age (years)				Region			
	F	M	UNK	0-16	17-65	> 65	UNK	EU	Japan	NA	ROW
Neuropathies/ Neuralgias	19,594,002	17,626,055	291,670	24,786	13,656,874	23,708,369	121,699	6,236,278	28,832,180	1,411,054	1,032,215
Fibromyalgia	1,194,718	193,325	13,477	4,022	1,165,498	229,460	2,540	325,324	288,305	621,573	166,318
Other	7,848,920	6,171,868	82,431	20,745	6,570,708	7,459,584	52,182	5,558,840	7,468,900	592,476	483,004
Generalized Anxiety Disorder	282,709	183,264	-	231	358,485	107,257	-	323,808	-	1,140	141,024
Seizure	64,638	68,481	-	423	95,091	37,606	-	113,661	7,770	10,811	878
Unknown	65,847	92,725	-	710	75,310	82,552	-	111,157	30,306	8,422	8,687

EU = European Union, NA = North America, ROW = Rest of the World, UNK = Unknown, M = Male, F = Female.

Table 16. Cumulative Estimated Exposure for Pregabalin by Dose and Formulation (in Patient Years)

Indication Group	Dosage Form		Dose(mg/day)										
	Oral	UNK	25 mg	50 mg	75 mg	100 mg	100 mg/ 5 mL	150 mg	200 mg	225 mg	300 mg	330MG	NA INTSTR[a]
Neuropathies/ Neuralgias	37,482,513	29,215	14,599,634	498,829	19,810,820	458,150	1,794	1,705,822	145,295	32,519	199,254	4,427	55,185
Fibromyalgia	1,390,247	11,273	125,355	118,077	560,124	180,156	242	218,238	83,867	39,004	38,836	-	37,621
Other	14,095,131	8,088	4,997,842	569,378	6,532,545	461,241	8,414	1,020,218	170,708	31,619	292,301	-	18,954
Generalized Anxiety Disorder	465,972	-	125,524	28,020	164,562	26,984	759	90,066	3,313	2,156	24,588	-	-
Seizure	132,212	908	36,582	5,898	52,374	6,392	192	24,887	1,451	647	4,696	-	-
Unknown	158,571	-	64,853	4,589	60,116	2,737	-	12,723	3,750	5,574	4,230	-	-

a. Packs with an unknown composition according to IMS.
UNK = Unknown, mg = milligram, mL = milliter.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

In response to the CHMP conclusion for PSUR 10 (December 2009), the MAH interacted with experts in the field of addiction about the potential for abuse with pregabalin. The conclusions were submitted to the CHMP in September 2010. The interactions essentially confirmed the current knowledge that abuse, when it occurs, tends to be in the population who have a history of abuse, and thus no labeling revision was warranted. The Final Assessment Report (FAR) for PSUR 14 requested a cumulative review on abuse, misuse and dependence in order to update Summary of Product Characteristics (SmPC) wording on this safety issue. Following review of responses submitted in December 2013, the PRAC recommended updates to Section 4.4 of the SPC (FAR, 05 February 2014), endorsed by CHMP on 20 February 2014. The MAH has accepted the PRAC-recommended labeling changes to add wording regarding dependence, and a labeling variation was submitted in April 2014 (favourable opinion July 2014).

As requested by PRAC in the final assessment report adopted with recommendation on 11 September 2014, the MAH has changed abuse, misuse and dependence from a potential risk to an identified risk (see SVII.2). Based on the pregabalin PRAC PSUR Assessment Report (EMEA/H/C/PSUSA/00002511/201701), the MAH has renamed the important identified risk Abuse, Misuse, and Drug dependence to "Abuse and Drug dependence" and removed the important risk "misuse" from both the RMP and PSUR. The Preferred Term (PT) "Misuse" refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information but still for therapeutic purposes. An example for misuse could be that a patient deliberately took the medication once daily instead of spreading the daily dose over the day. The MAH agrees with the PRAC statement (Pregabalin PSUR Single Assessment procedure (EMEA/H/C/PSUSA/00002511/201701) that the majority of cases of the risk "abuse, misuse and dependence" concerned misuse and lumping these reports together is not informative in further characterising the cases of abuse. Moreover, in line with the PSUR Single Assessment procedure (EMEA/H/C/PSUSA/00002511/201701), the MAH has revised the Targeted Questionnaire (updated to Data Capture Aid) to focus on abuse and has removed questions relating to misuse. In the RMP, since there is no specific safety issue related to misuse that requires regulatory action, the deletion of misuse from the list of safety concerns (as proposed by the MAH in the ongoing type II variation to update the RMP (EMEA/H/C/WS1364) was agreed by the PRAC in the Rapporteur's preliminary assessment report for procedure no. PSUSA/00002511/201801, dated 4 July 2018). Consistently, the MAH proposes not to re-include "misuse" in the important identified risk of "abuse and dependence" and to accordingly update the search criteria (i.e. removing Misuse PTs: Intentional product use issue, and Intentional product misuse) also in the RMP. Please see SVII.2.1.1.

Regarding potential for misuse for illegal purposes, there is a theoretical increased risk of abuse of a liquid formulation (oral solution) through Intravenous (IV) administration in individuals who have a history of substance abuse or dependence. Currently, there are no cases reporting intravenous abuse with this oral solution.

Euphoria and drug interactions (e.g., with lorazepam, ethanol, and CNS depressants) are identified risks in Module SVII.

Module SVII. Identified and Potential Risks:

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Due to the completion of the Pregnancy Outcomes Study (A0081359), the MAH in agreement with PRAC, has removed Pregnancy and lactation as Missing information.

SVII.2.1. Important Risks Removed from the List of Safety Concerns

SVII.2.1.1. Important Identified Risks Removed from the List of Safety Concerns

Not applicable.

SVII.2.1.2. Important Potential Risks Removed from the List of Safety Concerns

Not applicable.

SVII.2.1.3. Missing Information Removed from the List of Safety Concerns

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
Pregnancy and lactation	No clinical studies have investigated the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. 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 childbearing potential. The objectives of study A0081359 were to describe the use of pregabalin in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin. This study evaluated use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden. The total number of users of pregabalin in a pregnancy ending in a live birth or stillbirth in the study period was 325/666,146 (0.048%) in Denmark, 965/643,088 (0.16%) in Finland, 307/657,451 (0.046%) in Norway, and 1275/1,152,002 (0.11%) in Sweden. The distribution of those with a potential indication for pregabalin use, inferred by recorded disease diagnosis, differed between countries, with GAD being the most commonly recorded diagnosis of potential indication in Finland, Norway, and Sweden, and neuropathic pain as the main recorded diagnosis of potential indication in Denmark. The maternal age distribution was similar in the four countries. Prevalence of

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
	smoking was 28-40% of the pregabalin-exposed births and 6-15% in AED-unexposed births. Most of the comorbidities and medication use was markedly more prevalent in the pregabalin-exposed than in the unexposed births. Births exposed to the active comparators had covariate profiles more similar to those of the pregabalin-exposed than to the unexposed births. *Major malformations* Meta-analysis of prevalence of major congenital malformations occuring in first-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group, ranging between 5.91% vs. unexposed, and 6.01% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of major congenital malformations occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine first-trimester exposed pregnancies were 4.05%, 4.85%, not reportable (not reportable due to the possibility of estimating a low number of individuals (<5) in other cells), and not reportable, respectively. Regarding any congenital malformations, the adjusted prevalence ratios (aPRs) in the standard meta-analysis for first-trimester were: pregabalin-exposed vs.: unexposed, 1.13 (95% CI 0.96-1.33); lamotrigine, 1.36 (1.07-1.72); duloxetine, 1.37 (1.06-1.77); lamotrigine or duloxetine, 1.24 (1.00–1.54). Restricting to pregabalin, lamotrigine, and duloxetine monotherapy only marginally changed the results. For first-trimester pregabalin monotherapy vs. unexposed, 1.14 (0.96-1.35); lamotrigine monotherapy, 1.29 (1.01-1.65); duloxetine monotherapy 1.39 (1.07-1.82); lamotrigine or duloxetine monotherapy 1.24 (1.00-1.54). *Sensitivity analyses* In the main analyses defining pregabalin monotherapy as not excluding SSRIs and benzodiazepines, the relative risk estimates in all countries with a meta-analysis crude and adjusted prevalence ratio (aPR) of all major malformations compared with unexposed of 1.29 95% CI (1.09-1.51) and 1.13 95% CI (0.96–1.33) respectively. For the sensitivity analysis of monotherapy excluding SSRIs and benzodiazepine in addition to AEDs, the crude PR of the meta-analysis was 1.41 (1.16-1.72); the aPR was not estimated due to low (<5) cell counts. An additional sensitivity analysis including the 2nd trimester induced abortions in the analyses of pregnancies (available in Denmark, Finland, and Norway) produced similar or slightly higher estimates as in the results not including the 2nd trimester induced abortions. However, the inclusion of the 2nd trimester induced abortions added only 1-3% extra pregabalin-exposed pregnancies (data not reportable due to restrictions on providing results with low (<5) cell counts). *Specific major malformations* For the specific malformations, a few noticeable associations were observed, though it must be noted that no correction for multiple comparisons was conducted. In the meta-analyses of the nervous system, for pregabalin vs. unexposed aPR (95% CI) 2.03 (0.88–4.64), pregabalin vs. lamotrigine 4.41 (1.37–14.22), pregabalin vs. duloxetine 2.80 (0.57–13.70), and pregabalin vs. lamotrigine or duloxetine 3.83 (1.20–12.22). Similarly, for eye malformations: pregabalin vs. unexposed aPR (95% CI) 2.09 (1.12–3.90), pregabalin vs. lamotrigine 1.88 (0.63–5.65), pregabalin vs. duloxetine 0.82 (0.34–2.00) and pregabalin vs. lamotrigine or duloxetine 2.26 (0.92–5.53). For orofacial clefts: pregabalin vs. unexposed aPR (95% CI) 2.89 (1.19–7.03), pregabalin vs. lamotrigine 4.19 (1.22–14.36),

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
	pregabalin vs. duloxetine 3.35 (0.54–20.61), and pregabalin vs. lamotrigine or duloxetine 5.08 (1.59–16.24). In addition, for urinary malformations: pregabalin vs unexposed 1.41 (0.85–2.35), pregabalin vs. lamotrigine 3.03 (1.34–6.84), pregabalin vs. duloxetine 2.14 (0.89–5.13) and pregabalin vs. lamotrigine or duloxetine 1.66 (0.80–3.47). Finally, for genital malformations: pregabalin vs. unexposed 1.46 (0.89–2.39), pregabalin vs. lamotrigine 2.13 (1.05–4.32), pregabalin vs. duloxetine 2.64 (1.13–6.17), and pregabalin vs. lamotrigine or duloxetine 2.26 (1.17–4.38). For the other congenital malformations, no marked increase in the PRs among the pregabalin-exposed were observed compared to the comparators. The estimates were imprecise due to low number of exposed outcomes, and zero exposed outcomes were frequent in one or more countries. *Birth outcomes* Meta-analysis of prevalence of stillbirths occuring in any-trimester pregabalin-exposed pregnancies were not reportable (not reportable due to the possibility of estimating a low number of individuals (<5) in other cells). Meta-analysis of prevalence of stillbirths occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 0.33%, not reportable, not reportable, and not reportable, respectively. Meta-analysis of prevalence of low birthweight occuring in any-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group: 6.58% vs. unexposed, 6.62% vs. lamotrigine, 6.40% vs. duloxetine, and 6.49% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of low birthweight occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 4.43%, 5.77%, 6.85% and 6.05 respectively. Meta-analysis of prevalence of preterm birth occuring in any-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group: 6.57% vs. unexposed, 8.16% vs. lamotrigine, 7.81% vs. duloxetine, and 6.49% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of pre-term birth occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 5.33%, 8.06%, 8.88% and 8.23% respectively. Meta-analysis of prevalence of small for gestational age occuring in any-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group: 4.69% vs. unexposed, 4.69% vs. lamotrigine, 4.60% vs. duloxetine, and 4.62% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of pre-term birth occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 3.75%, 4.13%, not reportable and 4.41% respectively. Meta-analysis of prevalence of low Apgar score at 5 minutes occuring in any-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group: 2.95% vs. unexposed, 2.83% vs. lamotrigine, 2.79% vs. duloxetine, and 2.70% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of pre-term birth occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 1.33%, 2.21%, not reportable and 2.25% respectively.

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
	Meta-analysis of prevalence of microcephaly occuring in any-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group: 3.02% vs. unexposed, 2.96% vs. lamotrigine, 2.96% vs. duloxetine, and 2.91% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of pre-term birth occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 2.69%, 2.97%, 2.72% and 2.90% respectively. Results for the meta-analysis of stillbirth showed an aPR and (95% CI) 1.72 (1.02-2.91) for pregabalin-exposed compared to unexposed, and 1.87 (0.81-4.32) for comparison with lamotrigine, 1.46 (0.57-3.72) comparted to duloxetine, and 2.71 (1.25-5.90) compared with the combined lamotrigine and duloxetine group. In the post-hoc meta-analysis including countries with zero events, stillbirth was no longer associated with pregabalin exposure. Results for the meta-analysis for low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed of 1.05 (0.91–1.21), 1.13 (0.99–1.29), 1.21 (1.01–1.44), 1.18 (0.95–1.48), and 1.09 (0.88–1.36) respectively, but with estimates closer to null effect for comparison to the active comparators. Although the prevalence of SGA was slightly elevated in the pregabalin-exposed compared to offspring unexposed to AEDs, it was not elevated in comparison with the active comparators. Pregabalin monotherapy compared to unexposed showed similar aPRs (95% CI) for low birth weight 1.06 (0.90–1.24), preterm birth 1.14 (0.99–1.32), SGA 1.19 (0.98–1.45), 1.05 (0.82–1.36) for low Apgar score at 5 minutes, and microcephaly 1.00 (0.78–1.27). *Postnatal neurodevelopmental outcomes* Meta-analysis incidence rate per 10,000 person-years ADHD occuring in any-trimester pregabalin-exposed pregnancies varied depending on the comparison group: 48.19 vs. unexposed, not reportable vs. lamotrigine, 48.64 vs. duloxetine, and not reportable vs. duloxetine or lamotrigine. Meta-analysis incidence rate per 10,000 person-years ADHD occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 19.62, 30.12, not reportable and 34.66 respectively. Meta-analysis incidence rate per 10,000 person-years ASD occuring in any-trimester pregabalin-exposed pregnancies varied depending on the comparison group: not reportable vs. unexposed, non-estimable due to 0 cases in one or more cells vs. lamotrigine, 16.86 vs. duloxetine, and 17.53 vs. duloxetine or lamotrigine. Meta-analysis incidence rate per 10,000 person-years ASD occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 9.26, 14.77, not reportable and 16.30 respectively. Meta-analysis incidence rate per 10,000 person-years ID occuring in any-trimester pregabalin-exposed pregnancies was not reportable. Meta-analysis incidence rate per 10,000 person-years ID occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine any-trimester exposed pregnancies were 24.71, not reportable, 42.76 and 34.40 respectively. In the meta-analyses of the neurodevelopmental outcomes (ADHD, ASD, and ID), results for ADHD were an adjusted hazard ratio and (95% CI) for pregabalin-

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
	exposed vs.: unexposed, 1.32 (1.04–1.67); lamotrigine, 1.09 (0.79–1.52); duloxetine, 1.11 (0.76–1.61); duloxetine or lamotrigine, 1.20 (0.89–1.63). Crude estimates suggested markedly stronger associations indicating that confounder adjustment at least partly explained this association. For ASD and ID, the point estimates were close to unity. The results of this study do not provide strong evidence of human teratogenicity, or effects on birth outcomes and postnatal neurodevelopmental outcomes after pregabalin exposure. However, in line with previous studies, a small increased risk of adverse birth outcomes in the pregabalin-exposed group compared with unexposed or active comparator groups cannot be completely ruled out, and the associated estimates remain imprecise despite inclusion of data from four countries. Of note, prevalence of smoking during pregnancy, a known risk factor associated with adverse birth outcomes, and included in the PS-adjusted models, was 28-40% of the pregabalin-exposed births and 6-15% in AED-unexposed births. Regarding the criteria for proof of teratogenicity mentioned by Shepard , the present available information on pregabalin exposure lacks sufficient number of exposed cases and even though detailed propensity score adjusted estimates have been provided, residual confounding cannot be excluded since this was an observational study. Also, no relative risks for any of the outcomes were observed with a maximum upper CI in the Mantel-Haenszel meta-analyses greater than 1.76 (excluding specific malformations and stillbirths with imprecise estimates due to low number of cases). *Conclusion* In conclusion, the study is consistent with the earlier evidence from published population-based studies of an absence of substantially increased risks of congenital malformations, adverse birth outcomes, or postnatal neurodevelopment in pregabalin-exposed fetuses in identifiable pregnancies. Based on this study, the information on major congenital malformations, birth outcomes (other than congenital malformations) and postnatal neurodevelopmental outcomes in pregabalin exposed offspring has been extended. Several estimates in this study were imprecise due to the low number of events and the results should be interpreted with caution. Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment. Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). A warning has been added to section 4.4. of the SmPC regarding Women of childbearing potential/Contraception: Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6). <u>Lactation:</u>

Table 17. Important Missing Information to be Removed from the List of Safety Concerns

Missing information	Change in the level of scientific evidence for the association
	Pregabalin is excreted in the milk of lactating women. As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Pharmacokinetics in Breastfeeding Mothers: The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

SVII.3. Details of Important Identified, Important Potential Risks, and Missing Information

The summary of the postmarketing experience in this section covers the period since the first marketing authorisation (06 July 2004) through 30 June 2021.

Details for important identified and potential risks are presented below, including updated information for the event outcome and event seriousness. The Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) listed for each risk were aligned with the current version of MedDRA (version 24.0) used at the cut-off date (30 June 2021). Notable changes to search strategies are discussed further below.

For the important identified risk Drug interactions (lorazepam, alcohol, and CNS depressants), CNS depressants are defined as "non-benzodiazepine sedatives/hypnotics such as barbiturates, anxiolytics and tranquilizers such as benzodiazepines, muscle relaxants, general anaesthetics, antipsychotics, other opioids, alcohol".

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

Table 18. Important Identified Risk: Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury

Potential mechanisms	Potential mechanisms for dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury have not been established.
Evidence source and strength of evidence	Clinical studies, postmarketing safety database.
Characterisation of the risk[a]	Data from clinical studies: OR [95% CI] Pregabalin 600 mg/day/Placebo: 7.261 [6.097-8.648] Pregabalin any dose/Placebo: 4.393 [3.859-5.002] Severity and nature of risk: Clinical studies: Mild-1329; Moderate–784; Severe– 62. Outcomes from clinical studies (pregabalin-treated patients): Recovered. 81%, Not recovered, 19%. In the postmarketing experience, since first approval and through 30 June 2021, a total of 212,043 AE reports have been received by the MAH; 45,373 of these cases contain non-clinical trial reports of dizziness, somnolence, loss of consciousness, syncope, or potential for accidental injury AEs, corresponding to a 21.4% proportional reporting rate.
Risk factors and risk groups	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall), especially in the elderly population.
Preventability	Patients are advised not to drive, operate complex machinery, or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.
Impact on the risk-benefit balance of the product	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population and may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery, or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.
Public health impact	None identified.

a. The clinical studies-based odds ratios, outcomes, and severities all utilise the 2008 SmPC dataset.

AE = Adverse Event; CI = Confidence Interval; MAH = Marketing Authorisation Holder; OR = Odds Ratio.

Table 19. Important Identified Risk: Discontinuation Events

Potential mechanisms	A potential mechanism for discontinuation events has not been established.
Evidence source and strength of evidence	Clinical studies, postmarketing safety database.
Characterisation of the risk[a]	Data from clinical studies: OR [95% CI] Pregabalin 600 mg/day/Placebo: 0.338 [0.014-8.229] Pregabalin Any dose/Placebo: 0.456 [0.029-7.294] OR is considered statistically not significant as CI includes 1. Outcomes from clinical studies (pregabalin-treated patients): Recovered 100%. Severity and nature of risk: Clinical studies: Severe–1. In the postmarketing experience, since first approval and through 30 June 2021, 212,043 cases have been received by the MAH; 5886 (2.8%) non-clinical trial cases reported at least 1 discontinuation event related AE. Within the 5886 cases, 5999 AEs were reported, irrespective of relatedness.
Risk factors and risk groups	Patients using pregabalin.
Preventability	The SmPC recommends a gradual discontinuation of pregabalin over a 1-week period.
Impact on the risk-benefit balance of the product	After discontinuation of either short-term or long-term pregabalin treatment, withdrawal symptoms have been observed in some patients. If pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.
Public health impact	None identified.

AE = Adverse Event; CI = Confidence Interval; MAH = Marketing Authorisation Holder; OR = Odds Ratio.

a. The clinical studies-based odds ratios, outcomes, and severities all utilise the 2008 SmPC dataset.

Table 20. Important Identified Risk: Drug interactions (lorazepam, ethanol, and CNS depressants)

Potential mechanisms	Non-specific CNS depressant effect.
Evidence source and strength of evidence	Postmarketing safety database.
Characterisation of the risk	In the postmarketing experience, since first approval and through 30 June 2021, a total of 212,043 cases have been received by the MAH; 759 cases reported drug interactions with ethanol or CNS depressants (corresponding to 0.4%of the total non-clinical dataset) contain 1 or more drug interaction-related AEs.
Risk factors and risk groups	Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, PK interactions. Accordingly, in in-vivo studies, no clinically relevant PK interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone, or ethanol. Population PK analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine, and topiramate had no clinically significant effect on pregabalin clearance. Drug interactions with CNS depressants are identified safety concerns with pregabalin that emerged in clinical development and in the postmarketing experience. These AEs are monitored and reviewed in the PSUR under the heading "Drug interactions *(lorazepam, ethanol, and CNS depressants)*".
Preventability	Preventability by minimising coadministration of other CNS depressants.
Impact on the risk-benefit balance of the product	Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam. Patients drinking alcohol or taking concomitant oxycodone or lorazepam may experience drug interactions.
Public health impact	Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam. Patients drinking alcohol or taking concomitant oxycodone or lorazepam may experience drug interactions.

AE = Adverse Event; AER = Adverse Event Reaction; CNS = Central Nervous System; MAH = Marketing Authorisation Holder; PD = Pharmacodynamic; PK = Pharmacokinetic; PSUR = Periodic Safety Update Report.
CNS depressants are defined as (non-benzodiazepine sedatives/hypnotics such as barbiturates, anxiolytics and tranquilizers such as benzodiazepines, muscle relaxants, general anaesthetics, antipsychotics, other opioids, alcohol).

Table 21. Important Identified Risk: Euphoria

Potential mechanisms	The mechanism of euphoria has not been established.
Evidence source and strength of evidence	Clinical studies, postmarketing safety database.
Characterisation of the risk[a]	Data from clinical studies: [95% CI] Pregabalin 600 mg/day/Placebo: 3.118 [1.604-6.064] Pregabalin Any dose/Placebo: 3.255 [1.973-5.369] Outcomes from clinical studies (pregabalin-treated patients): Recovered 91%, Not recovered 9%. Severity and nature of risk: Clinical studies: Mild–110; Moderate–50; Severe–4 In the postmarketing experience, since first approval and through 30 June 2021, 212,043 cases have been received by the MAH; 2189 (1.0%) non-clinical trial cases reported at least 1 euphoria related AE. Within the 2189 cases, 2247 AEs were reported, irrespective of relatedness.
Risk factors and risk groups	Known drug abusers
Preventability	None identified.
Impact on the risk-benefit balance of the product	None identified
Public health impact	The MAH is not aware of reported illegal use of pregabalin in the EU that would represent a public health hazard.

a. The clinical studies-based odds ratios, outcomes, and severities all utilise the 2008 SmPC dataset.

AE = Adverse Event; CI = Confidence Interval; EU = European Union; MAH = Marketing Authorisation Holder; OR = Odds Ratio.

Table 22. Important Identified Risk: Congestive Heart Failure

Potential mechanisms	The causative mechanism of CHF in patients receiving pregabalin is unknown.
Evidence source and strength of evidence	Non-clinical and clinical data and postmarketing database.
Characterisation of the risk[a]	Data from clinical studies: OR [95% CI] Pregabalin 600 mg/day/Placebo: 1.370 [0.306-6.130] Pregabalin Any dose/Placebo: 1.682 [0.469-6.036] OR is considered statistically not significant as CI includes 1. Outcomes from clinical studies (pregabalin-treated patients): Recovered 55%, Not recovered 45%. Severity and nature of risk: Clinical studies: Mild–1; Moderate–6; Severe–4. In the postmarketing experience, since first approval and through 30 June 2021, 212,043 cases have been received by the MAH; 1133 (0.5%) non-clinical trial cases reported at least 1 congestive heart failure related AE. Within the 1133 cases, 1193 AEs were reported, irrespective of relatedness.
Risk factors and risk groups	Patients with diabetes.
Preventability	There is no evidence that pregabalin exerts a negative chronotropic or inotropic effect on the myocardium.
Impact on the risk-benefit balance of the product	There have been postmarketing reports of CHF in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin usually resolves the reaction.
Public health impact	Patients developing CHF could experience increased numbers of hospitalisations.

AE = Adverse Event; CHF = Congestive Heart Failure; CI = Confidence Interval; MAH = Marketing Authorisation Holder; OR = Odds Ratio.

a. The clinical studies-based odds ratios, outcomes, and severities all utilise the 2008 SmPC dataset.

Table 23. Important Identified Risk: Vision-Related Events

Potential mechanisms	The aetiology of vision related events such as Vision blurred is unknown.
Evidence source and strength of evidence	Clinical studies, postmarketing safety database.
Characterisation of the risk[a]	Data from clinical studies: OR [95% CI] Pregabalin 600 mg/day/Placebo: 3.760 [2.860-4.944] Pregabalin Any dose/Placebo: 2.826 [2.265-3.525] Outcomes from clinical studies (pregabalin-treated patients): Recovered 66%, Not recovered 34%. Severity and nature of risk: Clinical studies: Mild–408; Moderate–178; Severe–27. In the postmarketing experience, since first approval and through 30 June 2021, a total of 212,043 AE reports have been received by the MAH. Of the total, 14,986 (7.1%) non-clinical postmarketing cases reported at least 1 vision-related event (corresponding to 19,756 AEs).
Risk factors and risk groups	None identified.
Preventability	None identified.
Impact on the risk-benefit balance of the product	Transient visual blurring and other changes in visual acuity have been reported in patients treated with pregabalin. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.
Public health impact	Review of clinical trial and postmarketing data on reported pregabalin cases does not suggest a public health impact.

a. The clinical studies-based odds ratios, outcomes, and severities all utilise the 2008 SmPC dataset.

AE = Adverse Event; CI = Confidence Interval; MAH = Marketing Authorisation Holder; OR = Odds Ratio.

Table 24. Important Identified Risk: Abuse and Drug Dependence

Potential mechanisms	None identified
Evidence source and strength of evidence	Postmarketing safety database
Characterisation of the risk	No cases were identified from the 2015 cumulative Meta-analysis of Clinical trials (all Phase 2 to 4 randomised, double-blind, placebo controlled trials of greater than 7 day's duration: pregabalin 13,850 patients, placebo 7566 patients. In the postmarketing experience, since first approval and through 30 June 2021, a total of 212,043 AE reports have been received by the MAH. Of the total, 3070 (1.4%) non-clinical postmarketing cases reported at least 1 abuse or drug dependence related event (corresponding to 3379 AEs).
Risk factors and risk groups	Patients with a history of substance abuse.
Preventability	Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).
Impact on the risk-benefit balance of the product	Individual patients, particularly those with a history of substance abuse, could potentially abuse pregabalin. Before taking pregabalin, patients should tell their doctor if they have a history of alcoholism or drug dependence.
Public health impact	The MAH is not aware of reported illegal use of pregabalin in the EU that would represent a public health hazard.

AE = Adverse Event; EU = European Union; MAH = Marketing Authorisation Holder.

Important Potential Risks:

Table 25. Important Potential Risk: Suicidality

Potential mechanisms	None identified
Evidence source and strength of evidence	Clinical data and postmarketing safety database.
Characterisation of the risk	Pregabalin Any dose/Placebo: OR [95% CI] ranges from 0.85 [0.258-2.796] to 1.891 [0.381-9.381] depending on statistical method used (Assessment of Suicidality submitted to EMA on 30 April 2008) Risk Difference Pregabalin – Placebo: The US FDA calculated 0.52/1000 patients; the MAH calculated 0.03/1000 patients based on the updated data. Outcomes from clinical studies (pregabalin-treated patients)[a]: Recovered 96%, Not recovered 4%. Severity and nature of risk[a]: Clinical studies: Mild–35; Moderate–39; Severe–33. In the postmarketing experience, since first approval and through 30 June 2021, 212,043 cases with at least 1 AE have been received by the MAH; 2963 non-clinical trial cases (containing 3296 AEs) reported a suicidality-related AE, corresponding to a 1.4% proportional reporting rate.
Risk factors and risk groups	None identified
Preventability	Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered (from SmPC).
Impact on the risk-benefit balance of the product	Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Public health impact	There is no public health impact of this potential risk.

a. The clinical studies- outcomes and severities all utilise the 2008 SmPC dataset.

AE = Adverse Event; FDA = Food and Drug Administration; MAH = Marketing Authorisation Holder; OR = Odds Ratio; SmPC = Summary of Product Characteristics.

Table 26. Important Potential Risk: Off-Label Use in Paediatric Patients

Potential mechanisms	Suitability of the formulation for paediatric administration, especially with the availability of the oral solution.
Evidence source and strength of evidence	Postmarketing safety database
Characterisation of the risk	In the postmarketing experience, since first approval and through 30 June 2021, 212,043 AE cases have been received by the MAH; 1350 of these cases reported pregabalin use in paediatric patients related AEs, corresponding to a 0.6% proportional reporting rate. Paediatric patients were defined in this search as patients younger than age of 18 years.
Risk factors and risk groups	No specific group within the paediatric population.
Preventability	None identified.
Impact on the risk-benefit balance of the product	Paediatric patients could potentially be treated with pregabalin as an off label indication.
Public health impact	MAH review of data from a clinical programme in the paediatric population and from the postmarketing safety database has not identified any particular paediatric-specific risk or concern with pregabalin. However, the MAH recognizes the concern that the availability of the oral solution formulation may lead to increased off-label use in paediatric patients.

AE = Adverse Event; MAH = Marketing Authorisation Holder

SVII.3.2. Presentation of the Missing Information

None.

Module SVIII. Summary of the Safety Concerns

Table 27. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury Euphoria Discontinuation Events Drug interactions (lorazepam, ethanol, and CNS depressants) Congestive Heart failure (CHF) Vision-related events Abuse and Drug Dependence
Important potential risks	Suicidality Off-label use in paediatric patients
Missing information	None.

CHF = Congestive Heart Failure.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Pharmacovigilance (Pv) activities for identified and potential risks and missing information are summarised in the tables below.

III.1. Routine Pharmacovigilance Activities

Table 28. Safety Concern-Identified Safety Concerns

Areas Requiring Confirmation or Further Investigation	Proposed Routine Pv Activities	Objectives
1. Dizziness, Somnolence, Loss of Consciousness, Syncope and Potential for Accidental Injury	Routine Pv	To continue to monitor and gain further information about dizziness, somnolence, loss of consciousness, syncope, and the potential for accidental injury.
2. Discontinuation Events	Routine Pv	To continue to monitor and gain further information about discontinuation events.
3. Drug interactions (lorazepam, ethanol, and CNS depressants)	Routine Pv	To continue to monitor and gain further information about drug interactions.
4. Euphoria	Routine Pv	To continue to monitor and gain further information about euphoria.
5. Congestive Heart Failure (CHF)	Routine Pv	To continue to monitor and gain further information about CHF.
6. Vision-Related Events	Routine Pv	Vision-related events emerged as an identified risk in clinical development and in the postmarketing period. To increase understanding of potential underlying mechanism(s) leading to the occurrence of vision related events.
7. Abuse and Drug Dependence	Routine Pv, DCA	To monitor and further characterise information about abuse and drug dependence.

CHF = Congestive Heart Failure; Pv = Pharmacovigilance.

Table 29. Safety Concern-Potential Safety Concerns

Areas Requiring Confirmation or Further Investigation	Proposed Routine Pv Activities	Objectives
1. Suicidality	Routine Pv Prospective assessments in all new pregabalin clinical trials.	To monitor and further characterise suicidality.
2. Off-label use in Paediatric patients	Routine Pv	To monitor and further characterise any off-label use in the paediatric population.

Pv = Pharmacovigilance.

Specific adverse reaction follow-up questionnaires for Lyrica (pregabalin) Data Capture Aid- Abuse:

The Data Capture Aid (DCA) (formerly known as Lyrica Target Questionnaire) is a follow up survey of 11 questions sent to Healthcare Practitioners (HCPs) following report of an adverse event related to potential abuse of pregabalin. It was designed by the MAH, and then implemented in 2015 after agreement with the European Medicines Agency (EMA) and the Pharmacovigilance Risk Assessment Committee (PRAC). The DCA is included in Annex 4 and it is part of the Routine Pharmacovigilance activities performed by the MAH.

III.2. Additional Pharmacovigilance Activities

Table 30. Required Additional Pharmacovigilance Activities (Category 3)

PASS Study Name	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
Pregabalin Withdrawal Study in GAD for EU (A0081147)	Long Term Safety And Efficacy Study Of Pregabalin In Subjects With Generalized Anxiety Disorder	To characterize the safety and efficacy of pregabalin in subjects with GAD at low and high doses relative to placebo and lorazepam following 3 and 6 months of treatment.	Double-blind, randomized, placebo and comparator controlled study in outpatient GAD subjects to characterize the long term efficacy and safety of pregabalin including drug discontinuation symptoms following treatment at low and high doses for up to 6 months.	Male and Females Age 18 to 65 Years of Age.	Final Report: 15 October 2012
Pregabalin Lactation Study (A0081181)	A Multiple Dose Pharmacokinetic Open Label Study of Pregabalin in Healthy Lactating Women	To assess Pregabalin distribution into human breast milk; estimate resulting infant daily doses.	Study A0081181 was an open-label, multiple-dose (150 mg given twice daily [BID] for 2 days), pharmacokinetic, and safety study in 10 healthy lactating females who were at least 12 weeks postpartum, not currently pregnant, and actively breastfeeding at the time of study enrolment.	10 healthy lactating females who were at least 12 weeks postpartum and actively breastfeeding at the time of study enrolment.	Final Report: 03 March 2014
Study 09GR148	Investigative study to determine the effect of	The study was intended to investigate retinal	Pigmented and non-pigmented rats were administered	Young adult female rats	Final Report: 20 September 2011

Table 30. Required Additional Pharmacovigilance Activities (Category 3)

PASS Study Name	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
	prolonged administration of CI-1008 on the incidence of retinal degeneration and disc shedding in albino (Wistar) rats and of retinal degeneration in pigmented (Long Evans) rats raised in dim or bright cyclic light.	degeneration observed in a previous 2-year rat carcino-genicity study	control article or pregabalin and subjected to either a dim or bright light cycle.		
Pregabalin DUS Study A0081266	Pregabalin Drug Utilisation Study (A0081266)	Describe the characteristics of patients prescribed pregabalin, with particular focus on any substance abuse history and dosing patterns for the drug (i.e., dosing by diagnosis (as a proxy for indication).	Retrospective Database study UK: The Health Improvement Network (THIN). Pregabalin prescriptions between September 2004 and July 2009. Sweden: Swedish Prescribed Drug Register (SPDR). Pregabalin prescriptions Between 01 July 2005 and 31 May 2011.	UK: 18,951 patients in the THIN database prescribed pregabalin between September 2004 and July 2009. Sweden: 129,216 patients prescribed pregabalin between 01 July 2005 and 31 May 2011.	Final Report: 26 March 2012
Pregabalin Long-Term Safety Study (A0081106)	Study A0081106: A 12-month open-label safety and	The overall objective was to characterize the safety and	A 12 month, open-label, flexible dose, multicenter	Paediatric subjects 1 month to 16 years of age with	Final Report: 21 January 2020

Table 30. Required Additional Pharmacovigilance Activities (Category 3)

PASS Study Name	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
	tolerability extension study of pregabalin as adjunctive therapy in paediatric subjects 1 month through 16 years of age with partial onset seizures (POS) and in paediatric and adult subjects 5 to 65 years of age with generalised tonic-clonic seizures (PGTC)	tolerability of pregabalin as adjunctive therapy administered for up to 12 months in epilepsy patients.	study to evaluate the safety and tolerability of pregabalin as adjunctive therapy.	POS and paediatric and adult subjects 5 to 65 years of age with PGTC seizures.	
Pregabalin Pregnancy Outcomes Study (A0081359)	Pregabalin Pregnancy Outcomes Study (A0081359)	The study objectives are to describe the use of pregabalin exposure in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations and neurodevelop mental outcomes with the use of pregabalin.	A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes.	Study population for the main analysis will include pregnancies ending in live or still birth in Denmark, Finland, Norway, and Sweden.	Final Report: 01 June 2020
Pregabalin Ophthalmological Safety Study (A0081096)	Pregabalin Ophthalmologica l Safety Study (A0081096)	Vision-related events emerged as an identified risk in clinical development and in the postmarketing period. To increase	A Prospective Randomised 12-Week Controlled Study of Visual Field Change in Subjects with Partial Seizures	Male or female subjects, 18 to 65 years old with a diagnosis of focal onset epilepsy with partial onset seizures and taking 1 to 3 antiepileptic	Final Report: January 2021

Table 30. Required Additional Pharmacovigilance Activities (Category 3)

PASS Study Name	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		understanding of potential underlying mechanism(s) leading to the occurrence of vision related events.	Receiving Pregabalin or Placebo.	drugs (including vagus nerve stimulator device), were screened for participation in the study.	

DUS = Drug Utilization Study, Q = Quarter, BID = Twice daily.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 31. Required Additional Pharmacovigilance Activities (Category 3)

Study (Name/Title) Status (Ongoing/Planned)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities.				
Pregabalin Evaluating the Abuse Potential of Lyrica When Taken Orally Concomitantly with Oxycodone Hydrochloride in Healthy Non-drug Dependent, Recreational Opioid Users (A0081365) Study A0081365: A Phase 4, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Single-Dose, Six-Way Crossover Study Ongoing	To determine the abuse potential of orally administered pregabalin taken concomitantly with oxycodone HCl in non-dependent, recreational opioid users under a fasted condition. To evaluate additional pharmacodynamic (PD) effect and PK of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition. To evaluate safety	Abuse and Drug Dependence	Final Report	August 2022 (planned)

Table 31. Required Additional Pharmacovigilance Activities (Category 3)

Study (Name/Title) Status (Ongoing/Planned)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition.			

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

N/A

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The safety information in the proposed product information is aligned to the reference medicinal product. Risk minimisation measures are judged effective, if no negative trends or worsening outcomes are identified.

V.1. Routine Risk Minimisation Measures

Table 32. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important identified risks	
Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions SmPC Section 4.7 Effects on ability to drive and use machines SmPC Section 4.8 Undesirable effects.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury is included in SmPC section 4.4 Interaction with other medicinal products and other forms of interactions for Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury is included in SmPC section 4.5 Effects on ability to drive and use machines for Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury is included in the SmPC section 4.7 Undesirable effects for Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury is included in SmPC section 4.8 Other routine risk minimisation measures beyond the Product Information: None.
Discontinuation Events	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects.

Table 32. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for Discontinuation Events (Withdrawal) is included in SmPC section 4.4 Undesirable effects for Discontinuation Events are included in SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: None.
Drug interactions (lorazepam, ethanol, and CNS depressants)	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning on concomitant use with opioids is included SmPC section 4.4 Interaction with other medicinal products and other forms of interactions for Drug Interactions is included in SmPC section 4.5. Other routine risk minimisation measures beyond the Product Information: None.
Euphoria	Routine risk communication SmPC Section 4.8 Undesirable effects.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Undesirable effects for Euphoria are included in SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: None.
Congestive Heart Failure (CHF)	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects.

Table 32. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for CHF is included in SmPC section 4.4 Undesirable effects for CHF are included in SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: None.
Vision-Related Events	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for Vision-Related Events is included in SmPC section 4.4 Undesirable effects for Vision-Related Events is included in SmPC section 4.8 Pharmacodynamic properties for Vision-Related Events are included in SmPC section 5.1. Other routine risk minimisation measures beyond the Product Information: None.
Abuse and Drug Dependence	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for Abuse and Drug Dependence is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risks	
Suicidality	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use.

Table 32. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Special warnings and precautions for Suicidality is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: None.
Off-Label Use in Paediatric Patients	Routine risk communication SmPC Section 4.1 Therapeutic indications SmPC Section 4.2 Posology and method of administration. SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Therapeutic indications for Off-Label Use in Paediatric Patients is included in SmPC section 4.1 Posology and method of administration for Off-Label Use in Paediatric Patients is included in SmPC section 4.2. Pharmacodynamic properties for Off-Label Use in Pediatric Patients are included in SmPC section 5.1. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information: None	

CHF = Congestive Heart Failure; SmPC = Summary of Product Characteristics.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table 33. Summary Table of pharmacovigilance (Pv) activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pv Activities
Important Identified Risk		
Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury	Routine risk minimisation measures: SmPC Sections 4.4 (Special Warnings and Precautions for Use) SmPC section 4.5 (Interactions with other medicinal products and other forms of interactions) SmPC section 4.7 (Effects on ability to drive and use machines), SmPC section 4.8 (Undesirable Effects) Other routine risk minimisation measures beyond the Product Information: None.	None
Discontinuation Events	Routine risk minimisation measures: SmPC Sections 4.4 (Special Warnings and Precautions for Use) SmPC section 4.8 (Undesirable Effects). Other routine risk minimisation measures beyond the Product Information: None.	None
Drug interactions (lorazepam, ethanol, and CNS depressants)	Routine risk minimisation measures: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interactions). SmPC Section 4.4 (Special warnings and precautions for use). Other routine risk minimisation measures beyond the Product Information: None.	None
Euphoria	Routine risk minimisation measures: SmPC Section 4.8 (Undesirable Effects) Other routine risk minimisation measures beyond the Product Information: None.	None

Table 33. Summary Table of pharmacovigilance (Pv) activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pv Activities
Congestive Heart Failure (CHF)	Routine risk minimisation measures: SmPC Sections 4.4, (special warnings and precautions for use) SmPC section 4.8 (undesirable effects). Other routine risk minimisation measures beyond the Product Information: None.	None
Vision-Related Events	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions) SmPC section 4.8, (Undesirable Effects) SmPC section 5.1(Pharmacodynamic properties). Other routine risk minimisation measures beyond the Product Information: None.	None
Abuse and Drug Dependence	Routine risk minimisation measures: SmPC Section 4.4, (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.	Abuse and Drug dependence DCA.
Important Potential Risk		
Suicidality	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.	None

Table 33. Summary Table of pharmacovigilance (Pv) activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pv Activities
Off-label use in paediatric patients	Routine risk minimisation measures: SmPC Sections 4.1 (Therapeutic indications) SmPC section 4.2 (Posology and method of administration). SmPC Section 5.1 Pharmacodynamic properties. Other routine risk minimisation measures beyond the Product Information: None.	None
Missing Safety Information: None		

CHF = Congestive Heart Failure; Pv = Pharmacovigilance; SmPC = Summary of Product Characteristics.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Pregabalin

This is a summary of the RMP for pregabalin. The RMP details important risks of pregabalin, how these risks can be minimised, and how more information will be obtained about pregabalin's risks and uncertainties (missing information).

Pregabalin's SmPC and its PL give essential information to healthcare professionals and patients on how pregabalin should be used.

This summary of the RMP for pregabalin should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of pregabalin's RMP.

I. The Medicine and What It Is Used For

In the EU, pregabalin is authorised for the treatment of Neuropathic Pain, Epilepsy, and Generalised Anxiety Disorder and (see SmPC for the full indication). It contains pregabalin as the active substance and it is given by orally.

Further information about the evaluation of pregabalin's benefits can be found in pregabalin's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage ***http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000546/WC500046600.pdf.***

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of pregabalin, together with measures to minimise such risks and the proposed studies for learning more about pregabalin's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of pregabalin is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of pregabalin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of pregabalin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 34. List of Important Risks and Missing Information

Important identified risks	Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury
	Discontinuation Events
	Drug interactions (lorazepam, ethanol, and CNS depressants)
	Euphoria
	Congestive Heart Failure
	Vision-related events
	Abuse and Drug Dependence[a]
Important potential risks	Suicidality
	Off-label use in paediatric patients
Missing information	None.

a. Abuse and Drug Dependence is an identified risk in the EU only.

II.B. Summary of Important Risks

Table 35. Summary of Important Identified and Potential Risks

Important Identified Risk: Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall), especially in the elderly population.

Table 35. Summary of Important Identified and Potential Risks

Risk minimisation measures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions SmPC Section 4.7 Effects on ability to drive and use machines SmPC Section 4.8 Undesirable effects. Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Discontinuation Events	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Patients using pregabalin.
Risk minimisation measures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects. Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Drug interactions (lorazepam, ethanol, and CNS depressants)	
Evidence for linking the risk to the medicine	Post-marketing data.
Risk factors and risk groups	Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, PK interactions. Accordingly, in in-vivo studies, no clinically relevant PK interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone, or ethanol. Population PK analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine, and topiramate had no clinically significant effect on pregabalin clearance. Drug interactions with CNS depressants are identified safety concerns with pregabalin that emerged in clinical development and in the postmarketing experience. These AEs are monitored and reviewed in the PSUR under the heading "Drug interactions (lorazepam, ethanol, and CNS depressants)".

Table 35. Summary of Important Identified and Potential Risks

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 (Interaction with other medicinal products and other forms of interactions). SmPC Section 4.4 (Special warnings and precautions for use) Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Euphoria	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	Known drug abusers.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 (Undesirable Effects) Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Congestive Heart Failure	
Evidence for linking the risk to the medicine	Non-clinical and clinical data, and cumulative review, and postmarketing database.
Risk factors and risk groups	Patients with diabetes.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 (special warnings and precautions for use) SmPC section 4.8 (undesirable effects). Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Vision-related Events	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data.
Risk factors and risk groups	None identified.

Table 35. Summary of Important Identified and Potential Risks

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions) SmPC section 4.8, (Undesirable Effects) SmPC section 5.1 (Pharmacodynamic properties). Other routine risk minimisation measures beyond the Product Information: None.
Important Identified Risk: Abuse and Drug Dependence	
Evidence for linking the risk to the medicine	Postmarketing safety database.
Risk factors and risk groups	Patients with a history of substance abuse.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk: Suicidality	
Evidence for linking the risk to the medicine	Clinical data, cumulative reviews, postmarketing safety database.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 (Special warnings and Precautions). Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risk: Off Label Use in paediatric patients	
Evidence for linking the risk to the medicine	Postmarketing safety database.
Risk factors and risk groups	No specific group within the paediatric population.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.1 (Therapeutic indications) SmPC section 4.2 (Posology and method of administration). SmPC Section 5.1 Pharmacodynamic properties. Other routine risk minimisation measures beyond the Product Information: None.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of pregabalin.

II.C.2. Other Studies in Post-Authorisation Development Plan

Table 36. Required Additional Pharmacovigilance Activities (Category 3)

Study Name / Status	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
Category 3 - Required additional pharmacovigilance activities					
Pregabalin Evaluating the Abuse Potential of Lyrica When Taken Orally Concomitantly with Oxycodone Hydrochloride in Healthy Non-drug Dependent, Recreational Opioid Users (A0081365) Ongoing	Study A0081365: A Phase 4, Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Single-Dose, Six-Way Crossover Study	To determine the abuse potential of orally administered pregabalin taken concomitantly with oxycodone HCl in non-dependent, recreational opioid users under a fasted condition. To evaluate additional pharmacodynamic (PD) effect and PK of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition. To evaluate safety of pregabalin and oxycodone HCl taken alone and concomitantly in non-dependent, recreational opioid users under a fasted condition	Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Single-Dose, Six-Way Crossover Study	Male and Females Ages 18 to 65 Years of Age	Final Report: August 2022 (planned)

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

RMP Version number: 13.2

Data lock point for this RMP: 30 June 2021 (Post-marketing database); 31 January 2020 (Clinical data)

Date of final sign off: 20 August 2021

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Follow-up forms

A DCA is in place as part of routine pharmacovigilance for events of abuse.

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Follow-up Questions

Please provide additional details on a separate page if needed and reference the question number.

1. What was the indication for Lyrica (pregabalin) prescription? (Select all applicable responses)?

- ☐ Neuropathic pain
- ☐ Generalized Anxiety Disorder (GAD)
- ☐ Diabetic neuropathy
- ☐ Post-herpetic neuralgia
- ☐ Epilepsy
- ☐ Fibromyalgia
- ☐ Other
- ☐ Don't know
- ☐ Lyrica (pregabalin) was obtained without a prescription

2. For how long has this patient been treated with Lyrica (pregabalin)?

- ☐ <1 day (24 hours)
- ☐ 1 day - 1 week
- ☐ >1 week - 1 month
- ☐ >1 month - 6 months
- ☐ >6 months – 1 year
- ☐ >1 year

3. Does Lyrica (pregabalin) abuse cause any of the following problems in the patient? (*select all applicable responses*)

- ☐ Social ☐ Occupational ☐ Psychological
- ☐ Physical ☐ Other

4. What was the route of administration of the abused Lyrica (pregabalin)? (*select all applicable responses*)

- ☐ Intravenous ☐ Oral ☐ Inhalation ☐ Rectal
- ☐ Other

5. What was the prescribed Lyrica (pregabalin) dose for this patient at the time of the reported abuse?

- ☐ <150 mg/day
- ☐ 150 - 600 mg/day
- ☐ >600 - 900 mg/day
- ☐ >900 - 1800 mg/day
- ☐ >1800 mg/day

6. What was the Lyrica (pregabalin) dose the patient abused?

- ☐ <150 mg/day
- ☐ 150 - 600 mg/day
- ☐ >600 - 900 mg/day
- ☐ >900 - 1800 mg/day
- ☐ >1800 mg/day

☐ Don't know

☐ Lyrica (pregabalin) was not prescribed (as no pregabalin prescription was obtained)

7. For how long has this patient abused Lyrica (pregabalin)?

☐ <1 day (24 hours)

☐ 1 day - 1 week

☐ >1 week - 1 month

☐ >1 month - 6 months

☐ >6 months – 1 year

☐ >1 year

8. Does the patient have a history of Mental Illness (specify disorder/treatment) prior to abusing the product?

(Select all applicable responses)

☐ No ☐ Don't know ☐ Prefer not to answer

☐ Yes:

☐ **Substance-related Disorders** (e.g., Alcohol Dependence)

☐ **Schizophrenia**

☐ **Other Psychotic Disorders** (e.g., Schizoaffective Disorder)

☐ **Mood Disorders** (e.g., Depression, Bipolar Disorder)

☐ **Anxiety Disorders** (e.g., Panic Disorder)

☐ **Eating Disorders** (e.g., Bulimia)

☐ **Sleep Disorders** (e.g., Narcolepsy)

☐ **Impulse Control Disorders** (e.g., Compulsive Gambling)

☐ **Personality Disorders** (e.g., Borderline Personality Disorder)

9. Has the patient used Lyrica (pregabalin) to relieve symptoms of withdrawal from other substances? *(Select one response)*

☐ Yes ☐ No ☐ Don't know ☐ Not applicable

10. Please mark if the patient was taking any of the following types of medications/substances <u>at the time of the adverse event or within two weeks *prior*</u> to the onset of the adverse event *(select all applicable responses)*

☐ No ☐ Don't know ☐ Prefer not to answer

☐ Yes:

☐ **Pain relievers (excluding NSAIDS)** (☐ morphine, ☐ codeine, ☐ hydrocodone, ☐ Methadone, ☐ Oxycodone, ☐ other)

☐ **Sedatives/hypnotics** (☐ alprazolam, ☐ diazepam, ☐ zolpidem, ☐ other)

☐ **Stimulants** (☐ amphetamine, ☐ methamphetamine, ☐ other)

☐ **Illegal Drugs** (☐ cocaine, ☐ heroin, ☐ phencyclidine, ☐ ketamine, ☐ marijuana, ☐ other)

☐ **Alcohol**

☐ **Tobacco**

11. Has the patient abused any of the following (i.e. use in a manner that causes social, occupational, psychological or physical problems)? (*Select all applicable responses)*

☐ No ☐ Don't know ☐ Prefer not to answer

☐ Yes:

☐ Alcohol, prior to treatment with Lyrica (pregabalin)

☐ Alcohol, after treatment with Lyrica (pregabalin)

☐ Illegal Drugs, prior to treatment with Lyrica (pregabalin)

☐ Illegal Drugs, after treatment with Lyrica (pregabalin)

☐ Prescription Drugs, prior to treatment with Lyrica (pregabalin)

☐ Prescription Drugs, after treatment with Lyrica (pregabalin)

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

RMP Version number: 13.2

Data lock point for this RMP: 30 June 2021 (Post-marketing database); 31 January 2020 (Clinical data)

Date of final sign off: 20 August 2021

There are no additional Risk Minimization activities for Pregabalin.