PREGABALIN
Pre-Review Report
Agenda Item 5.1

Expert Committee on Drug Dependence
Thirty-ninth Meeting
Geneva, 6-10 November 2017
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Pregabalin is a medication used world-wide in the treatment of partial onset seizures, post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, spinal cord injury neuropathic pain, and generalized anxiety disorder. The actions of pregabalin are mediated through binding with high affinity to alpha-2-delta proteins, which attenuates calcium influx into presynaptic neurons and thereby blocks the release of neurotransmitters, including the excitatory neurotransmitter l-glutamate.

Most information on the abuse potential of pregabalin comes from therapeutic clinical trial data, pharmacoepidemiological surveillance, and case reports/anecdotal reports, with only one published formal human abuse liability study. Euphoria has been noted as an adverse event in therapeutic clinical trial patients and pharmacokinetic study healthy participants. Evidence from preclinical and therapeutic clinical trials suggests the development of tolerance to the euphoric effects. Withdrawal symptoms manifest in some patients following abrupt discontinuation of pregabalin treatment (e.g., insomnia, headache, nausea, anxiety, sweating and diarrhea). For this reason it is recommended that patients undergo a short taper period (1 week) when discontinuing treatment. The one published abuse liability study assessed single doses of pregabalin 75 mg and 150 mg. This low pregabalin exposure in people without psychiatric and substance use disorder histories was not associated with increased ratings for liking. In a study submitted with the manufacturer’s New Drug Application in the United States in 2004, a single dose of pregabalin 450 mg was rated similarly to a single dose of diazepam 30 mg on measures of liking in alcohol and sedative/hypnotic recreational users. This finding contributed to the assignment of pregabalin to Schedule V of the Controlled Substance Act in the United States.

Epidemiological evidence for pregabalin abuse and dependence has been growing. It is available from adverse drug reaction reporting databases (representing 3-7% of pregabalin reports) and drug utilization reviews (with high doses prescribed at rates ranging from 1-10% of patients). In surveys of substance using populations, 3-68% of respondents endorsed non-prescribed or misuse of pregabalin. Pregabalin has been detected in urine samples of patients in opioid dependence treatment (9-12%) and in postmortem toxicological samples, with increasingly higher rates within drug dependent populations in combination with other substances. The risk of overdose death from pregabalin alone appears to be low, however, there is concern about the combination of pregabalin with opioids. Very high maximum daily doses (up to 7500 mg/day) have been described in published case reports and online anecdotal reports of pregabalin abuse.

From the available evidence, pregabalin clearly has the potential for abuse and dependence. Most published evidence is relatively recent and the extent to which pregabalin abuse may increase is not known. There is interest in pregabalin for its use in the treatment of substance use disorders (e.g., alcohol, benzodiazepine, opioids), however its use for these indications must be balanced
with its potential to be abused in this population. Its abuse potential appears lower than for opioids. Its relative abuse liability compared to other substances, particularly other psychotropic medications that people may be exposed to therapeutically (for example, benzodiazepines), has not been well studied.
1. Substance identification

A. International Nonproprietary Name (INN)

Pregabalin

B. Chemical Abstract Service (CAS) Registry Number

148553-50-8

C. Other Chemical Names

(S)-3-(aminomethyl)-5-methylhexanoic acid; (S+)-3-isobutyl-GABA

D. Trade Names

**Lyrica:** Argentina; Australia; Austria; Belgium; Bosnia & Herzegovina; Brazil; Canada; Chile; China; Croatia (Hrvatska); Czech Republic; Denmark; Ecuador; Egypt; Finland; France; Georgia; Germany; Greece; Hong Kong; Hungary; Iceland; India; Indonesia; Ireland; Israel; Italy South Korea; Japan; Latvia; Lebanon; Lithuania; Luxembourg; Malaysia; Myanmar; Netherlands; New Zealand; Norway; Norway; Oman; Peru; Philippines; Poland; Portugal; Romania; Russian Federation; Serbia; Singapore; Slovakia; Slovenia; South Africa; Spain; Sweden; Switzerland; Thailand; Tunisia; Turkey; United Kingdom; United States; Vietnam.

**Others:**

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*(Drugs.com 2017)*
E. Street Names
Gabbies; Budweisers, Bud, Bud light, Fizers
(Millar 2013, DRUGS.ie 2017, Extern 2017)

F. Physical Appearance
White to off-white crystalline solid

G. WHO Review History
Pregabalin has not been previously reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

A. Chemical Name
IUPAC Name: (3S)-3-(aminomethyl)-5-methylhexanoic acid
CA Index Name: Hexanoic acid, 3-(aminomethyl)-5-methyl-, (3S)-

B. Chemical Structure
Free base:

\[
\text{\begin{align*}
\text{CO}_2\text{H} \\
\text{NH}_2
\end{align*}}
\]
(Pfizer, 2016)

Molecular Formula: C₈H₁₇NO₂
Molecular Weight: 159.23

C. Stereoisomers
Pregabalin is the (S)-(+)–isomer of 3-isobutyl-GABA

D. Methods and Ease of Illicit Manufacturing
No information was found on methods of illicit manufacturing. Published literature describes enantioselective synthesis methods. (Burk 2003, Yu 2012)

Melting point: 176 - 178 °C
Boiling point: 144 – 147 °C
Solubility: Freely soluble in water (both basic and acidic aqueous solutions)
(ChemSpider 2017, Pfizer 2016)
E. Identification and Analysis

Several methods have been developed for identification of pregabalin. This includes liquid chromatography–tandem mass spectrometry (LC–MS–MS) methods in human urine (Heltsley 2011) and human serum (Oertel 2009); high-performance liquid chromatography (HPLC) methods in human serum (Vermeij 2004) and for capsule contents (Kasawar 2010); a high-performance liquid chromatography – mass spectrometry (HPLC-MS) method in post-mortem samples (Priez-Barallon 2014); a spectrophotometric method for capsule contents (Bali 2011); and immunoassay methods for human urine (e.g., ARK 2017).

3. Ease of Convertibility Into Controlled Substances

No information was found on the conversion of pregabalin into other controlled substances.

4. General Pharmacology

A. Routes of administration and dosage

Pregabalin pharmaceutical products are available to be taken orally.
Capsule strengths: 25, 50, 75, 100, 150, 200, 225, 300 mg
Oral Solution: 20 mg/ml

Dosage (administered orally in 2 – 3 divided doses)

Partial Onset Seizures: Initially 150 mg daily; Maintenance 150-600 mg daily.

Post-herpetic Neuralgia: Initially 150 mg daily; Maintenance 150-300 mg daily; Maximum dosage 600 mg daily.

Diabetic Neuropathy: Initially 150 mg daily; Maintenance 150-300 mg daily.

Fibromyalgia: Initially 150 mg daily; Maintenance 150-450 mg daily.

Spinal Cord Injury Neuropathic Pain: Initially 150 mg daily; Maintenance 150-300 mg daily; Maximum dosage 600 mg daily.

Generalized Anxiety Disorder: Initially 150 mg daily; Maintenance 150-600 mg daily.

Dosage needs to be lowered with renal impairment (Clcr <60 mL/minute). (AHFS 2017, Pfizer 2016 Canada, Pfizer 2016 USA, Pfizer 2017 UK)

B. Pharmacokinetics

Pregabalin has a relatively simple pharmacokinetic parameter profile compared to many psychototropic drugs.
Absorption: Pregabalin is rapidly and extensively absorbed. Plasma concentrations peak within 1.5 hours after administration, with oral bioavailability greater than 90% that is independent of dose and frequency of administration. Peak concentrations and area under the plasma concentration-time curve increase proportionally with dosage. Food slows the rate of absorption but not the extent of absorption.

Distribution: Pregabalin is a substrate for system L transporter across the blood-brain barrier. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is not bound to plasma proteins.

Metabolism: Pregabalin undergoes negligible metabolism. The N-methylated metabolite accounts for less than 1% of the dose.

Elimination: Pregabalin is eliminated primarily (98%) by renal excretion as unchanged drug, with elimination proportional to creatinine clearance. Less than 0.1% is eliminated in faeces. The mean half-life of pregabalin is approximately 6 hours (range 4 to 7 hours) and is not dose dependent. Steady-state is reached within 2 days of regular dosing. (Warner 2005, Bockbrader 2010, Schulze-Bonhage 2013)

C. Pharmacodynamics

Pregabalin binds with high affinity to the alpha-2-delta protein – a subunit of voltage-gated calcium channels located at presynaptic endings of neurons in the brain and spinal cord. This attenuates Ca2+ flux into neurons, which blocks the release of neurotransmitters, including the excitatory neurotransmitter L-glutamate. Endogenous ligands include the amino acids L-leucine, L-isoleucine, and L-valine. Despite similarities to gamma-aminobutyric acid (GABA), it does not act at GABA receptors or synapses. Pregabalin has approved indications for the treatment of partial seizures, post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, spinal cord injury neuropathic pain and generalize anxiety disorder. It appears that the therapeutic actions for all of these conditions are mediated through pregabalin’s actions on the alpha-2-delta protein. It has been suggested that these disorders may share neuronal hyperactivity in a variety of brain circuits that pregabalin helps to normalize. Further study on the actions of pregabalin in different brain regions is needed. The exact mechanism for producing euphoric effects or physical dependence is not known at this time. (Schulze-Bonhage 2013, Stahl 2013, Silverman 2008, Taylor 2007)

Pregabalin has been used off-label in the treatment of drug and alcohol withdrawal. (Freyhagen 2016) Although limited, most evidence is for the treatment of alcohol and benzodiazepine withdrawal. For example, there have been 3 small randomized-controlled studies for alcohol withdrawal (Freyhagen 2016); and there are case reports (Biermann 2007, Oulis 2008a), open-label studies (Oulis 2008b, Bobes 2012, Cho 2014), a prescription database study (Bramness 2010), and one small randomized controlled trial for the treatment of benzodiazepine withdrawal. (Hadley 2012)
5. Toxicology

Preclinical Acute Toxicology
There were no deaths following administration of single oral doses of pregabalin 5000 mg/kg or single IV doses of 300 mg/kg to mice and rats, nor changes in biochemical parameters, however, there were observations of hypoactivity, diarrhea and urine staining. Pregabalin was not genotoxic in vitro, nor in rats in doses up to 2000 mg/kg. (Pfizer 2016)

Preclinical Chronic Toxicology
There was a dose-dependent increase in hemangiosarcomas in 2 strains of mice with 200 to 5000 mg/kg in their diet for 2 years. The exposure was considered to be similar to human exposure at 600 mg/day. Tumorigenic potential is included in the Warnings and Precaution section of the product monograph. Skin lesions were seen at exposures equivalent to 2 to 8 times that of human exposure at 600 mg/day, ranging from erythema to necrosis. Ocular lesions were detected in rats at exposures more than twice those in humans at 600 mg/day. The following have been observed in animal toxicology studies with exposures from 2 to 69 weeks: ataxia and hypoactivity in rats and monkeys at repeated oral doses ≥ 500 mg/kg; tail dermatopathy and urine staining in rats ≥ 250 mg/kg and monkeys up to 500 mg/kg; urinary bladder changes and mortality with pyelonephritis/cystitis in rats at ≥ 250 mg/kg; reversible platelet count decreases of 14-36% in rats at ≥50 mg/kg in males and ≥100 mg/kg in females; no changes in hematology up to 500 mg/kg in monkeys; bone marrow total nucleated cell decreases 18-44% in rats at 150-1250 mg/kg, with no changes up to 50 mg/kg in rats nor in monkeys; no effects on body weight gain at 50 mg/kg or 150 mg/kg and no effects on monkeys up to 500 mg/kg; nasal discharge and diarrhea in monkeys at ≥100mg/kg; and deaths in 3 days in monkeys at doses of 1000 or 2000 mg/kg. (Pfizer 2016).

Preclinical Reproduction
Epididymal hypospermia and spermatogenic epithelial degeneration were observed after 4 weeks at 1250 mg/kg in rats, but not in doses up to 500 mg/kg. There were no changes in sperm count, motility or morphology in monkeys at 500 mg/kg for up to 69 weeks. There were no effects on female rat fertility when given high doses. However, male rats had reversible decreased sperm motility and fertility at ≥ 27 times human exposure. This was not seen in monkeys. Maternal toxicity in embryo-fetal development was seen in rats at ≥ 500 mg/kg and rabbits at ≥ 250 mg/kg. Fetal toxicity was observed at 2500 mg/kg in rats and at 1250 mg/kg in rabbits. Pregabalin was not teratogenetic in mice, rats or rabbits at 31 to 77 times the mean human exposure at 600 mg/day. Developmental toxicity in rat offspring was observed at ≥ 5 times the mean human exposure. (Morse 2016, Morse 2016a, Pfizer 2016)

6. Adverse Reactions in Humans
The adverse events associated with pregabalin treatment were assessed in a systematic review of 39 randomized controlled trials published between 1990 to 2010. Adverse effects significantly associated with pregabalin were dizziness, vertigo, incoordination, balance disorder, ataxia, diplopia, blurred vision, amblyopia, tremor, somnolence, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, fatigue, edema, peripheral edema, dry mouth, constipation. The adverse events associated with the highest
relative risks (RR, 95% CI) were balance disorder (8.22, 1.75 to 38.57), euphoria (6.18, 2.76 to 13.87), incoordination (4.88, 2.18 to 10.95), ataxia (4.77, 2.77 to 8.20), and edema (4.63, 2.15 to 9.95). In 28 of the studies, the relationship between dose and effects could be evaluated and it was determined that adverse events first presenting at 150 mg/day were dizziness, ataxia, somnolence, edema, and dry mouth; at 300 mg/day were vertigo, incoordination, blurred vision, amblyopia, confusional state, disturbance in attention, thinking abnormal, euphoria, asthenia, peripheral edema, and constipation; at 450 mg/day were balance disorder and fatigue; and at 600 mg/day were diplopia and tremor. (Zaccara 2011)

The most commonly observed adverse events according to pre-marketing clinical trials were mild to moderate dizziness, somnolence, peripheral edema and dry mouth. These were seen at a rate of at least 5% and were twice the rate seen with placebo. The most common adverse events leading to discontinuation were dizziness, somnolence, ataxia, asthenia, confusion, headache and nausea. Adverse events were similar between women and men. Warnings highlighted in the product monograph include peripheral edema, weight gain and creatinine kinase elevations. (Pfizer 2016)

Adverse symptoms reported through poisoning events were summarized in a retrospective review of records from 2002-2011 involving newer anticonvulsants from the Virginia Poison Centre. Twenty-three cases involving pregabalin were described in which 70% were female, with an age range of 16 to 85 years, and pregabalin doses ranging from 100 – 9,000 mg (median 2,375 mg). The clinical signs or symptoms were reported broadly to be within neuromuscular, CNS, gastrointestinal, cardiac, blood pressure and metabolic categories. The outcome severities were assessed as having no effect in 35% of cases, a minor effect in 22%, a moderate effect in 44%, with no severe effects noted (i.e., death). (Wills 2014) In addition, there are 2 published case reports of pregabalin overdose indicating minimal clinical symptoms (Miljevic 2012 – 4.2 g ingestion, Spiller 2008 – unknown amount). In another case report, ingestion of pregabalin 8.4 g resulted in loss of consciousness which was treated with supportive care. (Wood 2010)

**Drug Interactions**

The pharmacokinetic profile of pregabalin limits the potential for pharmacokinetic mediated drug-drug interactions (i.e., it is not metabolized and does not exhibit plasma protein binding). In addition, pregabalin does not inhibit or induce drug metabolizing enzymes. (Ben-Menachem 2004) The lack of interactions has been supported in published reviews where the only interactions noted were reports that carbamazepine, phenytoin, phenobarbital, gabapentin, and oxcarbazepine could reduce pregabalin levels 11 to 22% (Patsalos 2013), and that pregabalin has additive effects with oxycodone on cognitive and motor functions, and increases the effects of ethanol and lorazepam. (Ben-Menachem 2004, Patsalos 2013a)
7. Dependence Potential

A. Animal Studies

Reviews by the US Centre for Drug Evaluation and Research for Pfizer’s New Drug Application submission indicated that preclinical studies conducted in monkeys using a self-injection paradigm suggest that tolerance may develop to the euphoric effects pregabalin since self-administration decreased after one week. (Bonson 2004)

B. Human Studies

Tolerance

Reviews by the US Centre for Drug Evaluation and Research for Pfizer’s New Drug Application submission indicated that evidence from Phase2/3 clinical studies support the development of tolerance to the euphoric effects since the euphoria receded while patients were still taking pregabalin. (Bonson 2004)

Withdrawal

The US Centre for Drug Evaluation and Research reviewed evidence from the Pfizer’s New Drug Application submission in 2004 and summarized the following points which were suggestive of withdrawal symptoms and indicative of physical dependence (Bonson 2004b):

- Discontinuation-emergent symptoms from short- and long-term psychiatric studies that were more frequent in pregabalin treated patients compared to placebo treated patients were insomnia, headache, nausea, infections, diarrhea, and chills.
- Scores on the Physician’s Withdrawal Checklist in psychiatric studies were significantly different between pregabalin and placebo groups.
- Analysis of two pharmacokinetic studies showed discontinuation-emergent symptoms from pregabalin of headache, nausea and diarrhea, whereas from placebo the reports were of accidental injury, infection, skin disorder and ventricular extrasystoles.

The current product monograph from Pfizer Canada Inc. indicates that following abrupt discontinuation of pregabalin in clinical studies some patients reported symptoms of insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. In the adverse effects information section, information is included from a study of patients with pain associated with spinal cord injury. A withdrawal syndrome was reported in 4.3% of patients in the pregabalin group (n=70) at doses from 150 to 600 mg/day, with no reports in the placebo group (n=67). (Pfizer 2016) The apparent published paper of this study describes a serious adverse event in a patient one day following pregabalin discontinuation. The patient exhibited severe symptoms of spasticity with impaired coordination (more severe that previous episodes). (Siddall 2006) The monograph explicitly recommends to gradually taper pregabalin over one week when stopping treatment. (Pfizer 2016)

Published Pfizer-funded clinical trials using a discontinuation design rather than a placebo-control group have been conducted which incorporated a 1-week taper
when pregabalin was stopped (i.e., for those randomized from pregabalin to placebo and at the end of the study for those taking pregabalin throughout). In general, the adverse event rates for nausea, headache, and diarrhea did not appear to be elevated for the placebo groups. However, treatment-emergent adverse events were reported globally for the treatment groups and not specifically during or after the taper periods, making interpretation of withdrawal effects difficult. (Gilron 2011, Raskin 2014, Arnold 2014)

Discontinuation symptoms associated with a 1-week taper were specifically studied in a Pfizer-funded multi-centre, double-blind, clinical trial. (Kasper 2014) A total of 615 patients with generalized anxiety disorder were randomized to pregabalin higher dose (450-600 mg/day), pregabalin lower dose (150-300 mg/day), or lorazepam (3-4 mg/day). After 12 weeks of flexible dosing, 25% of patients in each group were randomized to undergo a 1 week blinded taper and to continue placebo for another 11 weeks, while the remainder continued on a fixed dose of active medication for another 12 weeks. At the end of 24 weeks, all subjects underwent a 1-week taper. Anyone experiencing severe withdrawal symptoms could have the taper period extended to 4 weeks. The primary outcome measure was the Physician Withdrawal Checklist (PWC) which has 20 items related to anxiolytic drug withdrawal signs and symptoms, with scores ranging from 0-60. The secondary measure was the spontaneously reported Discontinuation-Emergent Signs and Symptoms (DESS). Rates of rescue tapers were also reported. Measures were taken at the start of taper week and 1 and 2 weeks later. The changes in the Physician Checklist Scores from before and after the taper appear to be low, however, approximately 1/3 (range 22%-36%) of patients exhibited discontinuation-emergent signs and symptoms during the taper, and some patients in all groups required rescue taper procedures. The authors characterized these discontinuation symptoms as not clinically significant. (Kasper 2014)

Summary of discontinuation symptom outcomes (Kasper 2014)

<table>
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<th>Groups</th>
<th>PWC Mean Change* (95% CI)</th>
<th>% with DESS+</th>
<th>Rescue Taper** # patients</th>
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<tr>
<td>Pregabalin Higher Dose – taper at 12 weeks</td>
<td>2.1 (0.4-3.7) N=54</td>
<td>36.2% N=58</td>
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<td>Pregabalin Higher Dose – taper at 24 weeks</td>
<td>2.8 (1.6, 3.9) N=106</td>
<td>31.2% N=109</td>
<td>6</td>
</tr>
<tr>
<td>Pregabalin Lower Dose – taper at 12 weeks</td>
<td>2.0 (0.5, 3.6) N=49</td>
<td>32.7% N=52</td>
<td>6</td>
</tr>
<tr>
<td>Pregabalin Lower Dose – taper at 24 weeks</td>
<td>1.7 (0.7, 2.8) N=84</td>
<td>22.3% N=94</td>
<td>5</td>
</tr>
<tr>
<td>Lorazepam – taper at 12 weeks</td>
<td>1.6 (-0.3, 3.6) N=44</td>
<td>32.7% N=52</td>
<td>2</td>
</tr>
<tr>
<td>Lorazepam – taper at 24 weeks</td>
<td>2.2 (1.0, 3.5) N=93</td>
<td>28% N=100</td>
<td>8</td>
</tr>
</tbody>
</table>

*difference between start of 1-week taper and 2 weeks later
†symptoms included anxiety, dizziness, headache, insomnia and nausea
**includes patients who discontinued treatment early or entered the taper period
A withdrawal syndrome was noted in 32.7% (18/55) of pregabalin abuse/dependence-related reports to the German Federal Institute for Drugs and Medical Devices from 2008-2012. (Gahr 2013a)

In a review of 102 pregabalin clinical studies, none of the adverse effects described withdrawal symptoms, although the authors comment that this may have been influenced by the short treatment durations. (Schjerning 2016)

8. Abuse Potential

A. Animal Studies

Preclinical conditioned place preference studies in mice and self-administration or drug discrimination studies in monkeys have yielded conflicting results, which have been attributed to varying study conditions, including different routes of administration. (Schjerning 2016) The US Centre for Drug Evaluation and Research (Bosnon 2004, Throckmorten 2004) reviewed of evidence from Pfizer’s New Drug Application submission of preclinical behavioural studies and deemed them not valid for assessing abuse potential for a variety of reasons. However, the review pointed out a study in monkeys (n=4) that showed pregabalin produced reinforcing effects by demonstrating self-administration of greater than 10 injections per day at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug.

B. Human Studies

There is one published study that used an abuse liability study design to evaluate the effects of pregabalin alone and in combination with oxycodone. (Zacny 2012) This was a double-blind, randomized study in 16 healthy volunteers. The participants were each administered single doses of pregabalin 75 mg, pregabalin 150 mg, oxycodone 10 mg, and pregabalin 75 mg combined with oxycodone 10 mg in a cross-over design. Neither dose of pregabalin alone increased ratings of “like drug” or “take drug again”. This study demonstrated low abuse liability associated with low doses of pregabalin in people without psychiatric and substance use disorders histories.

The US Centre for Drug Evaluation and Research (Bosnon 2004, Throckmorten 2004) reviewed evidence from Pfizer’s New Drug Application submission and summarized a study that showed a single dose of pregabalin 450 mg administered to alcohol or sedative/hypnotic recreational users (n=15) was rated similarly to a single dose of diazepam 30 mg on measures of “good drug effect”, “high”, and “liking”. A 200 mg dose of pregabalin was identified as a sedative.

In a review of 102 pregabalin clinical trials, it was reported that 14 studies indicated euphoria as an adverse effect with a prevalence primarily between 1-10% (with one study reporting 26%). (Schjerning 2016) These studies spanned cohorts with fibromyalgia, painful neuropathies, postherpetic neuralgia, generalized anxiety disorder and healthy volunteers. Many studies did not indicate explicitly whether people with substance abuse were excluded or not. It was determined that euphoria
appeared to be a dose-dependent effect and transient effect. In addition, endorsements of ‘feeling good’, ‘feeling dazed’, ‘being drunk’ or ‘overdosed’ were reported in one clinical trial each. (Schjerning 2016).

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Pregabalin is indicated for partial onset seizures, post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, spinal cord injury neuropathic pain, and generalized anxiety disorder. From July 2004 to March 2012, there has been an estimated 15,951,859 million patient-years of exposure to LYRICA®. (Pfizer 2016) In England, there was a 53% increase in pregabalin prescribing between 2011 and 2013. (PHE/NHS 2014) In Denmark, pregabalin prescribing increased 10-fold over a 10 year period. (Schjerning 2016) Worldwide sales of pregabalin have had an annual growth rate of approximately 12%. (Schjerning 2016)

10. Listing on the WHO Model List of Essential Medicines

Pregabalin is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

12. **Industrial Use**

None.

13. **Non-Medical Use, Abuse and Dependence**

Although still limited, there is a variety of evidence suggesting pregabalin is subjected to non-medical use, abuse and dependence; perhaps at increasing rates.

**Adverse Drug Reaction Database Reports of Abuse**

- 6.6% (7639/115,616) of reports for pregabalin were related to abuse/dependence/misuse from 2006-2015 in the European Medicine Agency Spontaneous Adverse Drug Reaction Reporting System. (Chiappini 2016)
- 3.5% (55/1552) of reports for pregabalin were related to abuse (n=11) or dependence (n=44) reported from 2008-2012 to the German Federal Institute for Drugs and Medical Devices. (Gahr 2013a)
- 1.5% (8/521) of abuse/dependence reports were related to pregabalin from 2010-2015 in the French Pharmacovigilance Database. (Bossard 2016)
- 8% (16/198) of drug dependence reports were related to pregabalin (up to 2009) in the Swedish national register of adverse drug reactions (SWEDIS). (Schwan 2010)

**Drug Utilization Reviews Indicating High Dose Prescribing**

- Of outpatients prescribed pregabalin by UK general practitioners, 1% (136/13,480) were prescribed greater than 600 mg/day from 2004-2009. (Asomaning 2016)
- In Denmark, 9.6% (4090/42,520) of pregabalin users were prescribed greater than 600 mg/day between 2004-2013. (Schjerning 2016a)
- In Sweden, 8.5% (4130-48,550) of pregabalin users were prescribed greater than 600 mg/day. (Boden 2014)
- In Norway in 2009, of 17,111 people using pregabalin, there was high dose use noted of more than 10 defined daily doses (DDD) (n=25) or between 5-10 DDD (n=118). (Landmark 2011, Schjerning 2016)

**Indications of Non-Medical Use/Misuse/Abuse in Surveys/Questionnaires**

- 0.5% (8/1500) of respondents to an online survey endorsed misuse of pregabalin. These respondents had a lifetime prevalence of use of recreational drugs that was comparable to national UK data. (Kapil 2014)
- 7% of opioid dependent patients admitted for inpatient detoxification endorsed pregabalin misuse. (Wilens 2015)
- 3% (4/129) of substance use disorder population in Scotland used non-prescribed pregabalin. (Baird 2014)
- 68% of polysubstance use disorder patients in the National Rehabilitation Centre (NRC) in the United Arab Emirates endorsed using pregabalin non-medically (mean of 8.3 capsules ± 0.5 per day), particularly in the younger cohort. (Alblooshi 2016)
- The Swedish Poisons Information Centre was noted to have cases of intravenous injection of crushed pregabalin tablets (number not reported). (Jonsson 2014)
Postmortem Toxicology Associated with Abuse

- 2.3% (316/13,766) of all toxicologically investigated medico-legal cases from 2010-2011 in Finland had pregabalin involved. 48% (152/316) of pregabalin cases were attributed to abuse. (Hakkinen 2014)
- 4.4% (43/982) of all postmortem toxicology cases in Germany had pregabalin detected from 2010-2012. In the first year studied the rate was 2% (10/489), whereas by the second year it had substantially increased to 6.7% (33/493). Within drug dependent individuals the rate went from 5.5% (4/72) to 29.8% (26/87) over the 2 year period. (Lottner-Nau 2013)
- 4.2% (68/1623) of deceased young adults had pregabalin detected over a 3 year period in Finland. (Launiainen 2011)

Detection in Urine Drug Screening in Opioid Dependent Populations

- 9.2% (39/425) of urine samples from opioid dependence treatment patients tested positive for pregabalin over a 3 month period in 2014 in Ireland, with only 10 patients prescribed the medication. (McNamara 2015)
- 12.1% (15/124) of urine samples from opioid dependence treatment patients tested positive for pregabalin, compared to 2.7% (3/111) in a cohort of patients with other substance use disorders. (Grosshans 2013)

Case Reports of Abuse

- A systematic review (Schjerning 2016) identified 10 case reports starting in 2010 describing pregabalin abuse-related events according to ACTTION definitions. (Smith 2013) These cases involved supra-therapeutic dosing (n=10 with highest 2400 mg single dose, range 800-7500mg), diversion (n=3), tampering (n=1), and withdrawal symptoms (n=2). The people involved had a mean age of 34 years (range 19-47), 6 men and 4 women, 2 had no history of substance abuse, one case had nicotine use only, and most (n=8) had psychiatric diagnoses, primarily mood and anxiety disorders or personality disorders. (Schjerning 2016)
- Of 30 heroin users interviewed in a treatment service setting in the UK, 19 were pregabalin users (n=1 daily user, n=3 weekly, n=5 rarely, n=10 once), doses reported from 300 to 1500mg, prescribed or purchased on the street. (Lyndon 2017)

Anecdotal Online Reports

- Qualitative Google searches in 8 European languages of 108 websites were conducted on a regular basis between 2008 and 2010 documenting posts related pregabalin recreational use. From these anecdotal reports, the authors noted that primarily high doses of pregabalin (up to 5 g) were used for the euphoric effects, effects similar to alcohol, benzodiazepines and GHB, to cope with opioid withdrawal, and for entactogenic feelings or dissociative effects. Pregabalin was mostly used orally, but also by injection or rectally. Tolerance developed rapidly leading to increasing dosages and recommendations to combined use with other sedatives. Tolerance was also lost quickly once use ceased. (Schifano 2011)

Self-reported Street Prices

- Based on self-reported information (via website submission) on street prices of diverted prescription drugs, prices for pregabalin per pill have ranged from $3-5 in the
United States, $6 in Canada, £0.05-150 in United Kingdom, €2-3 in Germany and $<1-$150 in Australia. (StreetRx.com)

- Heroin users interviewed in a treatment service setting in the UK who had purchased pregabalin on the street reported paying approximately £2 per 300 mg tablet. (Lyndon 2017)

Advice for Clinicians

There have been practice guidance documents produced for clinicians reflecting the concern and growing awareness of pregabalin’s abuse potential. For example:

- In Ireland a guidance document has been produced for clinicians entitled “Pregabalin – Guidance for people working with pregabalin users. How to reduce the risks.” The document explains what pregabalin is, features of recreational use and harm reductions strategies. (Extern 2017)

- In the UK, the NHS produced a document on “Prescribing advice for Pregabalin” which recommends that clinicians be aware of the risk of abuse and addiction to pregabalin, even in patients with no known history of abuse; and consider the street value of the drug. (NHS 2017)

- Also in the UK, a document was developed to provide advice for prescribers on the risk of the misuse of gabapentin and pregabalin. PHE and NHS England (2014)

Literature Reviews

- Evoy 2017 – USA. Systematic Review key points: growth of epidemiological studies; abuse appears to be more prevalent in opioid abusers; supratherapeutic doses typically needed to achieve euphoria.

- Schjerning 2016 – Denmark. Systematic Review key points: literature suggest an important abuse potential; prescribers need to be cautious when prescribing, particularly to patients with a substance use history, and look for signs of abuse.

- Schifanaro 2014 – UK. Review key Points: Pregabalin experimenters are those with a recreational drug histories, administering excessive dosages; physician need to assess for history of substance use.

- CADTH 2012 – Canada. Systematic Review key points: Further psychopharmacological studies are needed to assess pregabalin abuse liability across a range of doses in sedative abusers, and in combination with other CNS-active drugs.


Overdose

There is a case series describing 10 patients admitted to an Emergency Department in Belfast over a one year period with pregabalin abuse. All were between 20-35 years old, with dosages ranging from 500-1400 mg. Nine were admitted for over 24 hours, 6 patients had seizures, and 2 patients were admitted to the Intensive Care Unit. (Millar 2013)

Pregabalin levels were determined in 70 postmortem cases from a 2 year period in the United Kingdom. They attributed one death to pregabalin toxicity with a concentration of 76 mg/L. Although the majority of the people had been prescribed pregabalin, other drugs
were present in all samples. In several cases, death was attributed to multiple drug toxicity involving opioids and other drugs of abuse. (Eastwood 2016)

In a review of 93 postmortem cases, 9 of them were determined to have pregabalin contribute to death. The authors comment that the prevalence of methadone and other opioids in these cases raises the profile of pregabalin as a drug with the potential for abuse, and recommends that laboratories include pregabalin in their protocols. (Elliot 2017)

In the United Kingdom and Wales there has been an increase of 24% each year in the number of gabapentoid (pregabalin and gabapentin) prescriptions from 2004 to 2015, which has been highly correlated with an increase in deaths where a gabapentoid was mentioned on the death certificate (correlation coefficient 0.96). (Lyndon 2017) In 79% of these deaths opioids were also mentioned.

Driving
In one study, pregabalin did not interfere with simulated driving ability after 2 doses of 75 mg compared to placebo in healthy volunteers. (Tujii 2014)

In 2012, 206 drivers in Finland who were apprehended for driving under the influence had pregabalin detected in serum samples at concentrations ranging from 0.68 – 111.6 mg/L. Over half of the samples were deemed to be above a therapeutic range, suggesting use for recreational purposes. Interpretation is difficult however since in most cases the driver had also taken other drugs. (Kriikku 2014)

Pregabalin and Opioids
In light of the frequency of references to pregabalin use in combination with opioids, particularly cases of overdose death, there are a potential public health implications. Therefore, understanding the nature of the combined effects is important.

In a study evaluating the respiratory effects of pregabalin and morphine together in mice, the combination produced additive depression of respiration (rather than synergistic). In addition, when pregablin was administered to morphine tolerant mice, pregabalin appeared to reverse the tolerance to respiratory depression. The authors comment that these findings support the suggestion that the combination increases the risk of overdose death. (Lyndon 2017)

In a series of preclinical studies, mice were more sensitive to sedation by pregabalin in the context of chronic morphine exposure, without evidence of rewarding effects from pregabalin. The study also showed that pregabalin may attenuate both morphine self-administration and morphine withdrawal signs. (Vashchinkina 2017)

In the abuse liability study by Zacny et.al., (2012) the hypothesis was that pregabalin would potentiate oxycodone’s abuse liability. The combination of pregabalin 75 mg and oxycodone 10 mg increased the endorsement of “take drug again” whereas neither drug alone did. However, since the drug combination also produced negative effects (headaches) the authors concluded that the study did not support the hypothesis at these doses.
Pregabalin’s effects on opioid withdrawal symptoms was studied in a small randomized, controlled trial in 34 opioid dependent participants undergoing opioid withdrawal. Patients receiving pregabalin 600mg/day over 6 days had better treatment retention compared to those receiving clonidine 600 μg/day (79% vs 47%, respectively), had lower opioid craving scores (p=0.03) and lower depression scores (p=0.2), with similar opioid withdrawal severity. (Vashchinkina 2017)

15. **Licent Production, Consumption and International Trade**
   Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. **Illicit Manufacture and Traffic and Related Information**
   Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. **Current International Controls and Their Impact**
   Pregabalin is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. **Current and Past National Controls**
   In July 2005, the United States Drug Enforcement Administration (DEA) placed pregabalin and all products containing pregabalin into Schedule V of the Controlled Substances Act (CSA). (Drug Enforcement Administration 2005)

   In the United Kingdom, the Advisory Council on the Misuse of Drugs recommended that pregabalin be controlled under the Misuse of Drugs Act 1971 as Class C substances, and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3, so as not to preclude legitimate use on prescription. (Iverson 2016).

19. **Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**
   None.
References


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Please refer to separate Annex 1 document published on ECDD website