Expert Peer Review for Pregabalin

1. Comments based on the review report

   a. Evidence on dependence and abuse potential

   Dependence potential: Pregabalin, a gabapentinoid, is an analogue of gamma amino butyric acid (GABA) and binds with high affinity to the alpha-2-delta proteins-a subunit of voltage-gated calcium channels located at presynaptic endings of neurons in the brain and spinal cord. It attenuates calcium influx into the neurons blocking the release of neurotransmitters, including the excitatory neurotransmitter l-glutamate-without acting on GABA receptors. Pregabalin does not bind to benzodiazepine or opioid receptors. The pre-review report described preclinical studies in monkeys which showed tolerance to the euphoric effects of pregabalin evidenced by a decrease in self-administration after one week. There are also phase 2/3 clinical studies in humans supporting the development of tolerance to its euphoric effects.

   There are a number of published reports indicative of withdrawal symptoms and physical dependence with pregabalin use in humans. Results from clinical studies in Pfizer’s recent product monograph to Canada also described withdrawal symptoms such as insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhoea following abrupt discontinuation of pregabalin. Its more favourable pharmacokinetic profile compared with gabapentin has been implicated in its greater liability for dependence.

   Abuse potential: The animal studies described in the pre-review report did not yield a consensus statement regarding the abuse potential of pregabalin. However, a study was described where 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 pregabalin) in monkeys.

   Reports from clinical trials in humans showed various rates of euphoria ranging from high (in patients with Generalized Anxiety Disorder without a history of drug or alcohol abuse) to low (in those treated with pregabalin for neuropathic pain). Euphoria was also
reported in healthy patients during pharmacokinetic studies. In addition, results from a clinical trial showed measures of “good drug effect”, “high”, and “liking” after a single dose of pregabalin; these ratings were similar to those following a single dose of diazepam 30 mg. It has been suggested that pregabalin has a low abuse liability when taken alone. The report described a double-blinded randomized study in which individuals were assigned to four groups and given different doses of pregabalin (75mg and 150mg), oxycodone or a combination of pregabalin and oxycodone. Individuals in the pregabalin-alone group showed significantly low ratings of “like drug” or “take drug again”; suggesting higher abuse liability when pregabalin is taken with other substances.

b. **Risks to individual and society because of misuse**

Apart from euphoria, very common adverse effects of pregabalin include dizziness and somnolence. Ataxia, asthenia, seizures and confusion can also occur. Pregabalin misuse and overdose has necessitated presentations and admissions to emergency departments. In Belfast, six of the ten patients who presented to the emergency department with pregabalin-related drug overdose had convulsions and two required intensive care admission. There were no deaths. Reports from the Virginia Poison Centre did not show deaths following pregabalin-related drug overdose. However varying degrees of severity of effects- moderate, mild and “no effects” were described. Non-fatal overdose has been documented with up to 15,000 mg of pregabalin (25 times the maximum recommended safe dose of 600 mg per day).

Although pregabalin misuse and abuse has been associated with mortalities, poly drug use or use with other substances e.g. alcohol is usually described. In 70 postmortem cases reviewed in the United Kingdom, other drugs were also present in all samples. A toxic level of pregabalin (a concentration of 76 mg/L) was identified in only one case. In fatal cases of pregabalin abuse, toxicological evidence of pregabalin as well as other substances has been typical. The report did not demonstrate any instance where pregabalin alone was implicated following post-mortem toxicology.

The pre-review report described a comparative clinical study which showed that pregabalin did not interfere with simulated driving ability after 2 doses of 75 mg (within the therapeutic range). However, pregabalin has been detected in serum samples of 206 drivers apprehended for driving under the influence in Finland. In these cases, serum concentrations ranged from 0.68 – 111.6 mg/L with over half being above the therapeutic range (suggestive of recreational use). Interpretation was difficult though since the driver had taken other drugs in most cases. There are rare reports of suicide attempts and self-induced harm associated with pregabalin but reports of harm to others are unknown.
c. **Magnitude of the problem in countries (misuse, illicit production, smuggling etc)**

It has been reported that pregabalin abuse and misuse is occurring at rapidly increasing rates in many countries. The pre-review report described a systematic review of the abuse and misuse of pregabalin and gabapentin published in March 2017. In this review, reports related to pregabalin abuse/dependence/misuse were recorded in different Adverse Drug Reaction Reporting Databases- in France, Germany, Europe, and Sweden constituting 1.5 %, 3.5 %, 6.6 % and 8% of the reports respectively. Drug utilization reviews showed high prescription doses of greater than 600 mg/day in the UK, Denmark and Sweden-1%, 8.5 and 9.6 % of the prescriptions respectively. Furthermore, pregabalin misuse was endorsed by 0.5% (8/1500) of respondents in an online survey; this was comparable to a national UK data. Pregabalin misuse was reported in 7% of opioid dependent patients admitted for detoxification, 3% of persons with substance use disorder in Scotland and 68% of polysubstance use disorder patients in the United Arab Emirates. In Germany there was a substantial increase in pregabalin-related deaths evidenced by post-mortem toxicology reports (2% in the first year studied to 6.7% in the second year from 2010-2012). Within the 2 year period, an increase from 5.55 to 29.8% was recorded within the drug dependent individuals. Pregabalin was detected following post-mortem toxicology in Finland. It was also found in urine samples of opioid dependent patients in Ireland. The systematic review also evaluated different (published) case reports of pregabalin abuse. In all these reports, other substances (nicotine, alcohol, cannabis, heroin, cocaine and benzodiazepines) were used in addition.

Data regarding illicit trade, its scope and magnitude were not available from the pre-review report. However there is evidence regarding illicit marketing of pregabalin for recreational uses through online pharmacies. There are anecdotal reports of widespread distribution in prisons in the United States and Scotland. Data was not available with regards to illicit production of pregabalin.

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d. **Need of the substance for medical (including veterinary) practice**

Pregabalin has approved indications as an adjuvant therapy of partial-onset seizures, for the treatment post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, spinal cord injury, neuropathic pain and generalized anxiety disorder. Pregabalin also has a number of off-label therapeutic uses including the treatment of benzodiazepine and alcohol withdrawal. In addition to the indications described in the pre-review report, other off-label uses of pregabalin include the treatment of pain associated with chronic prostatitis, inflammatory arthritis, postoperative pain management, somatoform disorders, post-traumatic stress disorders, schizophrenic anxiety, essential tremors and chemotherapy-induced neuropathic pain. Pregabalin is not listed in the WHO Model
list of essential medicines but most current guidelines consider the gabapentinoids including pregabalin and gabapentin as first-line treatment for neuropathic pain. There is no evidence of veterinary use.

e. Need of the substance for other purposes (e.g. industrial)
Pregabalin has no known industrial use.

f. Measures taken by countries to curb misuse
The United States Drug Enforcement Administration placed pregabalin and all products containing pregabalin into Schedule V of the Controlled Substances Act (CSA) indicating a low risk of inflicting abuse or addiction. In the United Kingdom, recommendations were made by the Advisory Council on the Misuse of Drugs that pregabalin be controlled as a Class C substance under the Misuse of Drugs Act 1971 and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as Schedule 3 to ease legitimate prescriptions. In Norway and Canada, pregabalin is scheduled as a prescription drug.

g. Impact if this substance is scheduled
The GABA analogues (pregabalin and gabapentin), GABA agonists (e.g. the benzodiazepines and barbiturates) and GABA-transaminase inhibitors (e.g. valproate) are all classified as GABAergic drugs but have important pharmacologic distinctions. Various drugs that are GABAergic are under international control and pregabalin has been found to produce a number of effects that are similar to those of some controlled substances. It is not expected that scheduling of pregabalin should represent a negative impact for legitimate and therapeutic use.

2. Are there absent data that would be determinative for scheduling?
   None

3. Other comments or opinions
   No other comments
4. Expert reviewer’s view on scheduling with rationale

Pregabalin has widespread therapeutic uses. The extensive applications have been associated with rapidly increasing rates of prescriptions. The increasing evidence of misuse and abuse in many countries is becoming a growing cause for concern.

Pregabalin has been observed to have the capacity to produce a state of dependence and has a side effect profile similar to other central nervous system depressants in Schedule IV of the 1971 Convention: “Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little too great.”

In as much as the therapeutic usefulness of pregabalin has been greatly established, the impact of misuse and abuse on public health needs to be analytically evaluated. On this basis, I recommend that the Expert Committee should proceed to a critical review of pregabalin.