1. Comments based on the review report

a. Evidence on dependence and abuse potential

**Dependence potential**

Animal studies: The evidence for the ability of Tramadol to produce physical dependence in animals is not consistent across species: symptoms of withdrawal were not detected in mice and were not consistently observed in rats. In rhesus monkeys only mild to moderate symptoms of withdrawal were noted.

Human Studies: In humans tramadol produces opioid-like effects after oral administration but not by the parenteral route and the evidence for physical dependence is minimal. Withdrawal symptoms are mild and bear some resemblance to those seen following discontinuation of selective serotonin reuptake inhibitors. In summary the report states that “……..tramadol has a relatively low dependence potential and that dependence is associated with the use of tramadol over an extended period of time (more than a few weeks to months)”.

**Abuse potential**

Animal studies: Data from animal studies indicate that tramadol is an atypical opioid analgesic with mild opioid-like effects. Self-administration studies in monkeys and rats show that tramadol has some abuse potential but less so than morphine.

Human studies: Several studies have confirmed the mild opioid activity of tramadol when ingested. In one study non-dependent subjects identified 200mg and 400mg (but not 50 or 100mg) of tramadol as hydromorphone or opioid-like. In another study of non-dependent opioid abusers the 400mg dose but not the 200mg dose was readily self-administered indicating that self-administration of tramadol is dose dependent. This study demonstrated that tramadol has reinforcing properties in this population. Abuse liability has also been shown in recreational users. Tramadol abuse is frequently seen in individuals with a history of substance abuse. In summary the report states that “….tramadol has a low abuse potential relative to the prototypic morphine”.

b. Risks to individual and society because of misuse

Few cases of fatal poisoning involving tramadol alone have been reported; more common are intoxications involving co-ingestion of alcohol or other drugs. The
symptoms are those seen following intoxications with other opioid analgesics. If used in combination with serotonergic agents, tramadol may induce the serotonin syndrome. The resulting hyperthermia could be potentially fatal. As well, few cases of severe respiratory depression associated with tramadol use have been reported but these were overdoses. Seizures have occurred at therapeutic doses but these reports are rare. Seizures seem to be associated with doses above the maximum daily recommended dose.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

Data on adverse events in connection to tramadol from the Uppsala Monitoring Centre do not show a trend for drug abuse or drug dependence worldwide. Data from some countries that have reported abuse and dependence (eg China, Egypt, and Iran), were missing. There are growing reports of abuse of tramadol in some African and West Asian countries; large seizures have been reported in north and west Africa. Abuse of tramadol has also been reported in Egypt, Iran, Jordan, Lebanon, Libya, Mauritius, Saudi Arabia and Togo and Gaza. Intentional overdose, suicide, suicidal attempts and deaths have been reported.

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

In most countries tramadol is used to treat moderate to severe pain or moderate to moderately severe pain (USA). Tramadol is listed as a step-2 analgesic in the WHO guidelines for cancer pain relief. However, as stated in the review “the analgesic effect of tramadol monotherapy is modest”. It is not listed in the WHO Model List of Essential medicines but it is listed in several national essential medicines lists.

e. Need of the substance for other purposes (e.g. industrial)

None.

f. Measures taken by countries to curb misuse

In many countries tramadol is only available by prescription. Tramadol is under national control in Bahrain, Mauritius, Australia, Iran, Sweden, Bolivarian Republic of Venezuela, Ukraine, Egypt, Jordan and Saudi Arabia. In China it is listed as a second category psychoactive substance. In 2013, the United Kingdom’s Advisory Council on Misuse of Drugs recommended that tramadol be controlled as a Class C substance under the Misuse of Drugs Act 1971.

g. Impact if this substance if scheduled

Eight countries have indicated that if tramadol were placed under international control, availability for medical use would be impacted.
2. **Additional information to the critical review report**

3. **Other comments or opinions**

a) In 2010 the FDA added a warning of suicide risk to the labels of tramadol HCl and tramadol/acetaminophen. The information emphasized the risk of suicide in patients at risk for addiction and those taking tranquillizers or antidepressant drugs. Tramadol-related deaths have been reported in patients with histories of emotional problems or suicide ideation, histories of substance abuse and histories of misusing other CNS depressants such as alcohol, tranquillizers etc. (FDA 2010)

b) In the USA tramadol is not currently controlled under the CSA but at least 10 states have controlled tramadol under State law (DEA, 2013).

c) In Northern Ireland the number of tramadol-related deaths has increased significantly in the past decade. Deaths occurred in combination with other drugs, with alcohol or with tramadol alone (Randall and Crane, 2014).

d) In an on-line survey conducted in 2012 (n= 7,360) in the UK, 5% (n=326) of participants reported having used tramadol in the past 12 months. One third of these obtained it by prescription but 1/3 got it from a friend. Most users reported using tramadol for pain relief but 44% (n=163) reported using it to relax, to sleep, to get high or to relieve boredom. Nineteen percent said they took higher doses than prescribed and 10% said that had difficulty stopping. Twenty eight percent reported combining tramadol with alcohol or other drugs to heighten the effect (Winstock et al, 2014).

**References**


4. **Expert reviewer’s view on scheduling with rationale**

As stated in the review “the analgesic effect of tramadol monotherapy is modest”. Although tramadol has been described as having low abuse potential and low dependence potential, in many countries increasing reports of abuse and deaths have been documented, thereby posing a risk to public health. Recommendation is to schedule tramadol under Schedule IV of 1971 convention.