1. **Comments based on the review report**

a. **Evidence on dependence and abuse potential**

Tapentadol was developed to combine agonist activity at the μ-opioid receptor with norepinephrine reuptake inhibition for improved analgesic efficacy especially in chronic or neuropathic pain disorders. Based on the preclinical and clinical pharmacology of tapentadol as well as anecdotal data, the potential for abuse with tapentadol is consistent with currently marketed drugs such as hydromorphone, oxycodone, morphine, and tramadol. In experiments by the sponsor and reported in the New Drug Application, tapentadol substituted fully for morphine-trained rats.

The majority of the reports about tapentadol are informational including available doses, formulations, and effects, some techniques for injecting tapentadol IR, the difficulties of breaking down the tapentadol ER tablet, and the warnings not to snort or smoke crushed tapentadol due to severe burning. Due to tamper-resistant coatings, tapentadol cannot be easily injected and therefore the adverse physical health consequences may be limited.

The US Food and Drug Administration’s Center for Drug Evaluation and Research suggests that the data obtained during clinical development indicates the abuse, misuse, and diversion of tapentadol IR are likely to be extremely high and the effective management of these risks postmarking are recommended (NDA 22-304 CSS review 10-17-2008).

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

Safety assessment of tapentadol continues to rely primarily on the clinical data as it is collected in post-surveillance marketing surveys. The toxicity profile from safety tests is similar to other opioid analgesics. In clinical abuse liability studies, tapentadol was compared to hydromorphone in opioid-experienced, nondependent subjects in a single-dose, double blind, double-dummy, placebo-controlled, randomized, crossover study. Currently, a broad clinical development program including approximately 14,000 patients/subjects and post-authorization experience with an estimated exposure of 120 million Patient Treatment Days has been used to evaluate the adverse effect profile of tapentadol.

The data indicates that tapentadol IR is creating less public health burden (e.g., arrests, admissions to public detoxification programs, calls to poison centers) than oxycodone
and hydrocodone. At the current time, within 5 years of tapentadol’s launch, the
analyses of tapentadol IR data shows lower abuse than oxycodone and slightly higher
abuse than tramadol (which is not scheduled). Despite the increasing availability of
tapentadol IR, rates of abuse have remained relatively stable. Overall, tapentadol
demonstrates a lower range of events based on the URDD that classical strong opioids.

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

The magnitude of public health problems related to misuse, abuse and dependence is
minimal. Data reported by the Researched Abuse, Diversion and Addiction-Related
Surveillance (RADARS®) System from July 2009 through December 2010 indicates that
the number of unique recipients of dispensed drug (URDD) per quarter increased by
more than 70,000. The diversion rate for tapentadol IR was comparable to that of
tramadol, and notably lower than that of oxycodone and hydrocodone. From data
collected in the Opioid Treatment Program, the rate of patients entering opioid
treatment programs with tapentadol IR abuse per 100,000 population was stable over
time, comparable to the rate for tramadol and low relative to the rates for oxycodone
and hydrocodone. The highest opioid treatment program rate per 1,000 URDD for
tapentadol IR was observed shortly after tapentadol IR first became available, in the
fourth quarter of 2009.

No information or evidence available for illicit manufacture or trafficking. However, the
lack of tapentadol precursors and the complex chemical synthesis process would make
the illicit synthesis of tapentadol problematic and unlikely to occur.

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

Treatment of moderate to severe pain, both acute, chronic and neuropathic pain.

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

None

f. **Measures taken by countries to curb misuse**

Twenty-five respondents to the WHO questionnaire stated that tapentadol was currently
authorized or in the process of being authorized/registered as a medical product in their
country.

Twenty seven countries reported that tapentadol was controlled under legislation that
was intended to regulate its availability; 24 under “controlled substance act”, 2 under
“medicines law” and 1 under “other” laws, including USA, Australia, Canada, New
Zealand and UK.
g. Impact if this substance if scheduled

Twenty-three respondents reported that if Tapentadol was placed under international control, they would have the laboratory capacity to identify the substance. One respondent indicated that the availability for medical use would be affected if internationally controlled. However, this can only be guessed as tapentadol is a novel analgesic and there is very limited data.

2. Additional information to the critical review report

Tapentadol is an analgesic similar to tramadol (not scheduled) in its dual mechanism of action: it activates the μ-opioid receptor and inhibits the reuptake of norepinephrine. It also has differences with tramadol: it has weak effects on the reuptake of serotonin, is more potent, and has no known active metabolites (Schroeder et al; Raffa et al)

Tapentadol is similar to other analgesics which activate the μ-opioid receptor and are included in the Convention. The potency is estimated at 1:3.3 in relation to morphine (Mercadante Porzio, Gebbia, 2014).

Following the WHO Guidelines of the Review of Psychoactive Substances, the principle of similarity for scheduling applies with regard to the 1961 Convention, when the substance (1) is liable to similar abuse and productive of similar ill-effects as the substances in Schedule I or Schedule II; or (2) is convertible into a substance already in Schedule I or Schedule II. Tapentadol activates the mu opioid receptor, but the tamper resistant formulations make it unlikely to be abused.

References


Raffa, RB; Buschmann, H; Christoph, T; Eichenbaum, G; Englberger, W; Flores, CM; Hertrampf, T; Kögel, B; Schiene, K; Straßburger, W; Terlinden, R; Tzeschentke, TM (July 2012). Mechanistic and functional differentiation of tapentadol and tramadol. Expert Opinion on Pharmacotherapy 13 (10): 1437–49. doi:10.1517/14656566.2012.696097. PMID 22698264.

3. **Other comments or opinions**

Tapentadol has been demonstrated effective in specific pain conditions such as neuropathic pain.

Due to the complex synthesis, it is unlikely that tapentadol to be illicitly manufactured. If its availability is limited to forms which cannot be easily crushed, snorted or injected, the adverse physical health consequences may be limited.

Tapentadol is a novel drug and there is very limited information on diversion and abuse. The abuse potential seems to be limited.

Several countries have already taken preventive control measures based on the pharmacological similarities of tapentadol with other opioid analgesics.

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

Recommendation is to keep the drug under surveillance. Countries may review their situation and if necessary establish national control measures based on reports of abuse/diversion/illicit trafficking and need for therapeutic use rather than placing tapentadol under international control.