Expert Committee on Drug Dependence  
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Expert Peer Review for Carfentanil

1. Comments based on the review report

   a. Evidence on dependence and abuse potential

   Dependence potential: The pre-review indicates that data from controlled, laboratory studies on the dependence or tolerance potential of carfentanil in non-human species and humans are unavailable. The peer reviewer did find a relevant report that indicates that carfentanil potently demonstrates cross-dependency to morphine by alleviating withdrawal signs in the morphine-dependent rhesus monkey. (1)

   Abuse potential: The pre-review indicates that controlled, laboratory studies have not evaluated the abuse potential of carfentanil in any species. In vitro and in vivo studies, however, presents carfentanil as a typical μ opioid agonist, similar in pharmacology to the controlled substance, fentanyl. It binds competitively to μ opioid receptors with subnanomolar affinity (as well as to κ and δ opioid receptors). It produces effects characteristic of a regulated μ-opioid-like substance including respiratory depression, constipation, analgesia, cough reflex suppression and pupillary constriction (constipation is mentioned in the Summary, but could not be found documented in the text). Its effects are usually reversible by opioid antagonists such as naloxone and naltrexone although renarcotization can occur. The pre-review indicates that carfentanil can be easily converted into sufentanil and alfentanil that are Schedule I drugs under the 1961 Convention on Narcotic Drugs.

   b. Risks to individual and society because of misuse

The pre-review cites an EMCDDA-Europol Joint Report (2017) on carfentanil indicating “similar to other fentanils, the most serious acute health risk from using carfentanil is likely to be rapid and severe respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death. Factors that may exacerbate this risk include: the difficulty in diluting the substance, which can lead to a toxic dose being inadvertently used..." Carfentanil has been detected in over hundreds of deaths in the United States and in Europe. Carfentanil has been ruled the cause of death in some of
these incidences, but it is difficult to quantify to how many deaths it has been the primary cause considering that in most deaths multiple drugs have been identified. In a letter from the United States provided in the Annex, the Secretary of State commented, "The United States expects to confirm over 400 deaths caused by carfentanil in 2016." Carfentanil is not always routinely tested during overdose examinations making accurate estimates of its lethality further challenging. In some instances, the hazards and overdose effects in the pre-review are described for fentanyl and not specifically to carfentanil.

c. **Magnitude of the problem in countries (misuse, illicit production, smuggling etc.)**
The pre-review cites the EMCDDA (2017) report on carfentanil indicating in which it has been detected in powder form in a total of 618 cases: Estonia (110 cases), Germany (2), Finland (2), Latvia (383), Lithuania (108), Sweden (3) and the United Kingdom (10), amounting to nearly 2.7 kg of seized material. It has also been identified in seizures in the United States and Canada (where it has been sold as counterfeit oxycodone (CDN 80) or Xanax tablets). China is often identified as the source. Carfentanil appears often mixed with heroin, but has also been detected with cathinones, ketamine, other fentanyls and a variety of other drugs as well.

d. **Need of the substance for medical (including veterinary) practice**
Carfentanil has been used in veterinary medicine since 1986 (Stanley et al., 2008) and primarily used as an anesthetic agent for large animals because of its extreme (10,000x > morphine) potency. Labeled carfentanil (\([11C]\)-carfentanil) is used as a PET radiotracer. It has no marketing authorizations for as a medication for humans, and is not listed on the WHO List of Essential Medicines.

e. **Need of the substance for other purposes (e.g. industrial)**
Small quantities of carfentanil are imported for use as an analytical reference standard.

f. **Measures taken by countries to curb misuse**
The pre-review cites the EMCDDA-Europol Joint report (2017) as identifying 11 member states controlling carfentanil under drug control legislation, 3 under specific new psychoactive substances control legislation, and one under medicines legislation. The EMCDDA-Europol Joint report (2017) reported 13 member states as not subjecting carfentanil to control measures at the national level.

g. **Impact if this substance is scheduled**
Carfentanil's veterinary use appears limited, and overall scheduling carfentanil would appear to have minimal deleterious impact.
2. Are there absent data that would be determinative for scheduling?

The pre-review indicates an absence of controlled, laboratory data regarding dependence, abuse and tolerance potential, which would be helpful in making a scheduling recommendation.

3. Other comments or opinions

At the time of the writing of this peer review report (18 September 2017), only the submission of the United States was made available for the annex. Included with that submission, was a plea in a letter by the Secretary of State to include carfentanil in the UN Single Convention on Narcotic Drugs, and a very thorough report on carfentanil in a format similar to the format used for an ECDD Critical Review Report. That report included additional references to primary scientific articles on the large animal effects of carfentanil, its synthesis, and included contemporary data regarding the nature and magnitude of the public health problems related to the use of carfentanil mainly focused in the United States.

4. Expert reviewer’s view on scheduling with rationale

Carfentanil is convertible into fentanyl, a substance regulated under Schedule I of the UN Single Convention on Narcotic Drugs, and thus satisfies a sufficient condition for inclusion in that convention. It relieves withdrawal signs in the morphine-dependent monkey and thus demonstrates cross-dependency to morphine. The number and geographic extent of carfentanil seizures and associated deaths indicate it can also satisfy the sufficient condition of having similar abuse and productive of similar ill-effects as fentanyl. Carfentanil does have approved veterinary applications. Thus, it is recommended that carfentanil proceed to direct critical review.

References: