Pre-Review Report:

MEDETOMIDINE

Expert Committee on Drug Dependence

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

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Executive Summary

Medetomidine is a potent, synthetic alpha-2 adrenergic receptor agonist developed in 1987 primarily for veterinary medicine as a sedative and analgesic. While it is not approved for human medical use, it has recently emerged as a potent adulterant in the illicit drug supply, particularly mixed with fentanyl and other synthetic opioids. Medetomidine is reported in some experimental studies to be 100 to 200 times more potent than xylazine, another common veterinary sedative found in illicit drugs.

Medetomidine is a racemic mixture comprising two stereoisomers: dexmedetomidine and levomedetomidine. Dexmedetomidine is the pharmacologically active enantiomer responsible for the alpha-2 adrenergic agonist effects, while levomedetomidine is substantially less active. Although isolated dexmedetomidine is an approved medication used for human sedation in intensive care units, the medetomidine currently occurring among the illicit drug supply is the racemic form. Toxicological testing of biological specimens from overdose patients frequently detects both enantiomers, which indicates that the substance used to adulterate illicit fentanyl is not diverted from human hospital supplies. Instead, its racemic nature suggests that it originates either from diverted veterinary pharmaceutical stocks or bulk synthesis in clandestine laboratories.

The primary risk to public health stems from its capacity to cause profound and prolonged sedation, severe bradycardia, and significant hypotension. Because medetomidine is not an opioid, its central nervous system (CNS) and potential contribution to respiratory depressant effects cannot be reversed by naloxone, complicating overdose responses. Furthermore, medetomidine is associated with a severe and rapidly onsetting withdrawal syndrome characterized by extreme hypertension, tachycardia, uncontrollable vomiting, and tremors, which among documented cases frequently requires intensive care and is poorly managed by standard opioid withdrawal protocols. Due to its rapid proliferation as a replacement for xylazine in certain illicit markets and its substantial contribution to multi-drug toxicity, medetomidine use represents an escalating public health concern.

1. Substance identification

A. International Nonproprietary Name (INN)

Medetomidine

B. Chemical Abstract Service (CAS) Registry Number

86347-14-0 (Free base)
86347-15-1 (Hydrochloride salt)

C. Other Chemical Names

4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole
(±)-4-(a,2,3-trimethylbenzyl)imidazole
Dexmedetomidine
Levomedetomidine

D. Trade Names

Domitor, Selektope

E. Street Names

Mede, rhino tranq

F. Physical Appearance

Medetomidine itself appears as a white or off-white crystalline substance, particularly in its hydrochloride salt formulation; however, when mixed with other drugs, medetomidine drug products can appear is many forms (e.g., powder, pills, falsified pharmaceuticals) *(1, 2)*.

G. WHO Review History

Medetomidine has not been previously scheduled or formally reviewed by the WHO Expert Committee on Drug Dependence (ECDD) for international control under the 1971 Convention.

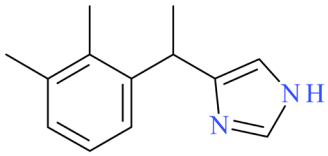
2. Chemistry

A. Chemical Name

IUPAC Name: (RS)-4-[1-(2,3-Dimethylphenyl)ethyl]-3H-imidazole
CA Index Name: 4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole

B. Chemical Structure

Free base:



Molecular Formula: $C_{13}H_{16}N_2$
Molecular Weight: 200.28 g/mol

C. Stereoisomers

Medetomidine is a racemic mixture comprising two stereoisomers: dexmedetomidine and levomedetomidine. Dexmedetomidine is the pharmacologically active enantiomer responsible for the alpha-2 adrenergic agonist effects, while levomedetomidine is substantially less active *(3, 4)*.

D. *Methods and Ease of Illicit Manufacturing*

Details regarding the illicit synthesis of medetomidine are sparse, as the substance is frequently diverted from veterinary pharmaceutical supplies or synthesized in illicit overseas laboratories supplying the grey market. Synthesis generally requires specialized chemical precursors and laboratory conditions.

E. Chemical Properties

Melting point - Standard published data for illicit formulations is limited; it exists as a stable crystalline solid at room temperature.

Boiling point - No publicly widely available data in standard monographs.

Solubility - Soluble in water (as a hydrochloride salt) and common organic laboratory solvents (e.g., methanol, acetonitrile, DMSO, ethanol) used for analytical reference preparation *(1)*.

F. Identification and Analysis

Medetomidine is available as a reference material from commercial suppliers to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations *(1)*.

Analytical methodologies for the identification of medetomidine in seized sample matrices include gas chromatography-mass spectrometry (GC-MS) and liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS) *(5)*. Medetomidine has a parent mass [M+] of m/z 200 and a protonated mass [M+H]+ of 201.1386 Da.

3. Ease of Convertibility Into Controlled Substances

There is no evidence suggesting medetomidine is used as a precursor or can be easily converted into currently controlled narcotic or psychotropic substances.

4. General Pharmacology

A. Routes of administration and dosage

In illicit uses among people who use drugs, medetomidine is consumed via injection, insufflation (snorting), or inhalation (smoking), typically as an unquantified adulterant mixed into fentanyl .

B. Pharmacokinetics

Human pharmacokinetic information on medetomidine (as a racemic mixture) is limited, but extensive information for dexmedetomidine (the pharmacologically active enantiomer of medetomidine) is available *(6)*. Medetomidine is highly lipophilic alpha-2 adrenergic agonists characterized by rapid systemic distribution and high plasma protein binding (typically >90%). Medetomidine undergoes extensive hepatic metabolism driven by N-glucuronidation and cytochrome P450-mediated aliphatic hydroxylation (notably via CYP2A6) to 3-hydroxy medetomidine, both resulting in inactive metabolites. Clinical studies suggest metabolism leaves virtually no unchanged parent drug in circulation; however, forensic testing shows parent medetomidine is readily detectable in intoxication cases *(7)*. The resulting inactive metabolites are cleared predominantly through renal excretion. Due to this efficient biotransformation and extensive tissue uptake, dexmedetomidine exhibits a short terminal elimination half-life of approximately 2 to 4 hours in humans *(8, 9)*. In patients presenting with medetomidine withdrawal symptoms, medetomidine metabolites were shown to be the best biomarker to target during testing *(10)*.

C. Pharmacodynamics

Medetomidine (racemic) is a highly selective and potent alpha-2 adrenergic receptor agonist *(11, 12)*. It binds at a ratio of 1620:1 (alpha-2 to alpha-1). Medetomidine is significantly more potent and selective than xylazine, with reports showing up to 200x higher potency and 10x higher selectivity at alpha-2. Medetomidine's activation of central alpha-2 receptors suppresses sympathetic nervous system outflow, leading to deep sedation, analgesia, and cardiovascular depression in animals and humans *(6, 13-15)*.

5. Toxicology

Medetomidine exhibits profound cardiovascular and central nervous system toxicity in humans. Cases presenting to emergency departments consistently demonstrate severe sinus bradycardia, hypotension, and prolonged, deep sedation *(16-21)*. When combined with opioids, the synergistic effects create life-threatening multi-drug toxicity, increasing the probability of a fatal overdose. LD_{50} data for medetomidine is difficult to source; however, manufacturer product sheets list an oral LD_{50} in rats of 31 mg/kg *(22)*.

6. Adverse Reactions in Humans

Acute adverse reactions include extreme unresponsiveness, confusion, shortness of breath, blurred vision, dizziness, low blood pressure, and dangerously slow heart rates *(10, 16, 17, 19-21)*. Naloxone does not reverse the effects of medetomidine. An alpha-2 adrenergic receptor antagonist (e.g., atipamezole, yohimbine) could theoretically reverse the effects of medetomidine, but these are not recommended for use in people who use recreational drugs due to the potential for precipitated withdrawal.

7. Dependence Potential

A. Animal Studies

While primarily utilized for short-term veterinary procedures, sustained alpha-2 agonism in animal models demonstrates a potential for physical dependence and rebound sympathetic hyperactivity upon cessation *(23)*.

B. Human Studies

Medetomidine induces a rapid and severe physical dependence in humans, which is observable through emergency department visits and clinical presentations *(24, 25)*. Withdrawal symptoms manifest quickly and are characterized by autonomic instability. Emergency departments in the United States report patients experiencing severe hypertension (e.g., >180/100 mmHg), extreme tachycardia (>100 bpm), intractable nausea and vomiting, profound diaphoresis (sweating), tremors, and altered mental states *(26)*.

8. Abuse Potential

A. Animal Studies

No specific animal self-administration studies to highlight abuse potential for medetomidine in isolation have been conducted.

B. Human Studies

Medetomidine is not primarily sought out for its standalone effects but is consumed involuntarily by users purchasing illicit opioids. However, its heavy sedative effect is sometimes desired by users aiming to prolong the transient effects of fentanyl *(27)*.

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

Medetomidine received FDA approval in 1996 for use in dogs. It is extensively utilized in veterinary medicine as a sedative and analgesic for dogs and cats and is used off-label in horses. It is frequently combined with ketamine or butorphanol for short veterinary procedures and can be reversed with atipamezole. Medetomidine (as a racemic mixture) is not approved for human medical use.

10. Listing on the WHO Model List of Essential Medicines

Medetomidine is not listed on the 24th WHO Essential Medicines List (EML) or the 10th WHO Essential Medicines List for Children (EMLc) updated in September 2025.

11. Marketing Authorizations (as a Medicinal Product)

Medetomidine holds marketing authorizations exclusively for veterinary use (e.g., Domitor) in numerous countries, including the United States, Canada, and European nations.

12. Industrial Use

The free base form of medetomidine is marketed under the trade name Selektope® *(28, 29)*. It is utilized as a commercial antifouling substance in marine paints to prevent barnacle settlement on ship hulls by interacting with the octopamine receptors of barnacle larvae.

13. Non-Medical Use, Abuse and Dependence

Medetomidine has rapidly emerged as a prevalent adulterant in the illicit drug supply *(30)*. Surveillance data from Philadelphia indicated that the presence of medetomidine in "dope" samples increased from 29% to 90% between May 2024 and March 2026, largely displacing xylazine *(31-33)*. In the United States, medetomidine is now present in all regions, but still most prevalent in the northeastern region. Users may frequently ingest medetomidine unknowingly when purchasing opioids on the illicit market.

According to the UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS) *(34)*, medetomidine was detected in 8,163 drug samples in 2025 and 6 to date in 2026 [at the time of reporting]. Medetomidine was first reported to the UNODC EWA in 2021 in a drug sample, and for the first time in a toxicology case in 2023. Three continents (four countries) have reported toxicology cases containing medetomidine, including postmortem and drug facilitated crimes circumstances.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

The public health impact of medetomidine can be severe. The presence of medetomidine in the illicit drug supply has driven a sharp rise in emergency department visits for complex, severe withdrawal syndromes that require intensive care unit (ICU) admission *(10, 25)*. Medetomidine withdrawal is a fast-acting, high-acuity medical emergency that evades standard withdrawal treatments, frequently forcing patients into the Intensive Care Unit (ICU) to survive severe cardiac and neurological distress, but also ICU admission is needed for administration of dexmedetomidine to overcome the withdrawal syndrome.

Medetomidine withdrawal is uniquely aggressive and dangerous *(10, 25)*. Unlike typical sedatives, the onset is rapid—within just 4 to 6 hours of the last use. The physical and neurological symptoms are severe, triggering delirium, violent tremors, and vomiting. It also causes life-threatening cardiovascular and metabolic crises, including spiking blood pressure (hypertension), rapid heart rate (tachycardia), abnormal heart rhythms (QTc

prolongation), and lactic acidosis. Because the cardiovascular and metabolic abnormalities escalate so quickly and dangerously, patients typically require admission to an ICU. Continuous, high-level monitoring is necessary to manage potential cardiac events or severe neurological distress like delirium. The most concerning aspect of medetomidine withdrawal is its resistance to standard clinical protocols. Traditional withdrawal medications—specifically benzodiazepines and opioids—offer little to no relief. This leaves medical providers with a complex treatment scenario where standard rescue medications fail to stabilize the patient, necessitating ICU-level supportive care.

15. Licit Production, Consumption and International Trade

Medetomidine licit production is confined to the manufacturing of approved veterinary pharmaceuticals and marine antifouling paints. Medetomidine is used as reference material for scientific research. It is not known to have any agricultural, industrial or cosmetic uses. Some Internet retailers have advertised it for sale as a "research chemical" or similar type of substance.

16. Illicit Manufacture and Traffic and Related Information

Medetomidine can be diverted from veterinary sources or manufactured in illicit chemical facilities. It is trafficked globally to be utilized as an active cutting agent by transnational drug trafficking organizations distributing fentanyl and similar opioids.

According to the U.S. Drug Enforcement Administration's National Drug Early Warning System, there were 12,439 drug exhibits seized from 2021 to 2025 testing positive for medetomidine, with 2025 containing 9,294 drug exhibits *(35)*.

17. Current International Controls and Their Impact

Medetomidine is not currently scheduled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

In the United States and Canada, medetomidine is legally classified as a prescription-only veterinary medication, though it generally lacks stringent controlled substance scheduling at the federal level.

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

The active enantiomer of medetomidine, dexmedetomidine, is an FDA-approved human medication used for sedation in intensive care units. Any potential scheduling of racemic medetomidine must carefully consider the regulatory impact on its active single-enantiomer counterpart used in human medicine, as well as its widespread necessity in veterinary practice and marine engineering.

Detections of medetomidine may be under-reported if this substance is not routinely screened for in all laboratories receiving samples for analysis.

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