Health Canada
Santé Canada

STATUS DECISION OF CONTROLLED AND NON-CONTROLLED SUBSTANCE(S)

Substance: I- Midazolam impurity A
II- Midazolam impurity B
III- Midazolam impurity E
IV- Midazolam impurity G
V- Midazolam impurity H

Based on the current information available to the Office of Controlled Substances, it appears that the above substance is:

Controlled	✓
Not Controlled	☐

under the schedules of the *Controlled Drugs and Substances Act* (CDSA) for the following reason(s):

- The substances are impurities of midazolam and all contain the core structure of the 1,4-benzodiazepines and are therefore captured under Item 18 of Schedule IV to the CDSA.

Prepared by: _____ Date: _____
Vincent Marleau

Verified by: _____ Date: _____
Mark Kozlowski

Approved by: _____ Date: _____
DIRECTOR, OFFICE OF CONTROLLED SUBSTANCES

This status was requested by: Nacer Silarbi, OCS

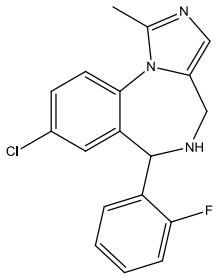
Drug Status Report

Drug:
I- Midazolam impurity A
II- Midazolam impurity B
III- Midazolam impurity E
IV- Midazolam impurity G
V- Midazolam impurity H

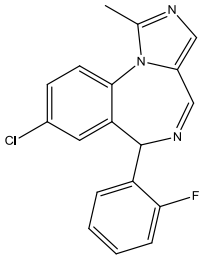
Drug Name Status:
I- Midazolam impurity A
II- Midazolam impurity B
III- Midazolam impurity E
IV- Midazolam impurity G
V- Midazolam impurity H are the common names.

Chemical Name:
I- (6RS)-8-chloro-6-(2-fluorophenyl)-1-methyl-5,6-dihydro-4H-imidazo[1,5-a][1,4]benzodiazepine
II- (6*RS*)-8-chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine
III- [(2*RS*)-7-chloro-5-(2-fluorophenyl)2,3-dihydro-1*H*-1,4-benzodiazepin-2-yl]methanamine
IV- 8-chloro-1-methyl-6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (desfluoromidazolam)
V- 6-chloro-4-(2-fluorophenyl)-2-methylquinazoline

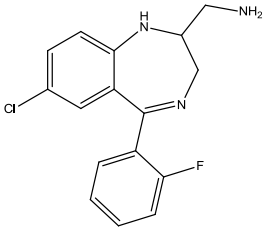
Chemical structure:



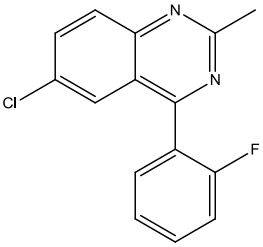
I



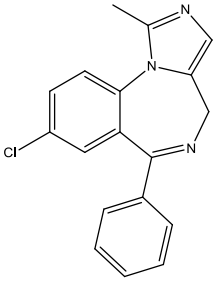
II



III



IV



V

Molecular Formula: I- $C_{18}H_{15}ClFN_3$; II- $C_{18}H_{13}ClFN_3$; III- $C_{16}H_{15}ClFN_3$; IV- $C_{15}H_{10}ClFN_2$; V- $C_{18}H_{14}ClN_3$.

CAS-RN: I- N/A; II- N/A ; III- N/A ; IV- N/A ; V- N/A.

Pharmacological class / Application: Pharmaceutical-related impurity

International status:

US: Midazolam impurity A, midazolam impurity B, midazolam impurity E, midazolam impurity and midazolam impurity H are not listed specifically in the Schedules to the US *Controlled Substances Act* and are not mentioned anywhere on the DEA website.

United Nations: The substances are not listed on the Yellow List - List of Narcotic Drugs under International Control, the Green List - List of Psychotropic Substances under International Control, nor the Red List - List of Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control.

Canadian Status: Midazolam impurity A, midazolam impurity B, midazolam impurity E, midazolam impurity and midazolam impurity H are not listed specifically in the schedules to the CDSA. The substances are synthetic impurities of midazolam, which is currently listed as sub-item 18(22.1) in Schedule IV to the CDSA under the heading "Benzodiazepines and their derivatives". The substances also contain the core structure of the 1,4-benzodiazepines and are therefore considered captured under sub-item 18(22.1) of Schedule IV to the CDSA. A number of synthetic impurities relating to midazolam were reviewed previously and also considered captured under item 18 of Schedule IV to the CDSA.

Recommendation: Midazolam impurity A, midazolam impurity B, midazolam impurity E, midazolam impurity and midazolam impurity H are included under item 18 of Schedule IV to the CDSA and are controlled substances.

Date: September 11th, 2012.