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

Substance:
I – cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide
II - cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester
III - cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidine acid, methyl ester

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

- Controlled ☐
- Not Controlled X

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

- The substances lack the core structure of the fentanyls and therefore cannot be included under item 16 of Schedule I to the CDSA.

Prepared by: __________________________________________________________________________ Date: ___________
Zack Li

Verified by: __________________________________________________________________________ Date: ___________
Mark Kozlowski

Approved by: __________________________________________________________________________ Date: ___________
DIRECTOR, OFFICE OF CONTROLLED SUBSTANCES

This status was requested by: "third party information removed as per agreement with applicant"
Drug Status Report

Drug:
I – cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide
II - cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester
III - cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid, methyl ester

Drug Name Status:
I – cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide
II - cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester
III - cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidine carboxylic acid, methyl ester are the common names.

Chemical Name:
I – cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide
II - cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester
III - cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid, methyl ester

Chemical structure:

![Chemical structure images]

Molecular Formula:  I - C_{25}H_{25}N_{3}O; II - C_{25}H_{26}N_{2}O_{2}; I - C_{22}H_{28}N_{2}O_{2}

Pharmacological class / Application: Pharmaceutical-related substances

CAS-RN: I – 147292-26-0; II – 147292-29-3; III – 61380-35-6

International status:
US: cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide, cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester and cis-(+)-3-Methyl-
4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid, methyl ester 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 is 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: cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide, cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester and cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid are intermediates relating to the synthesis of lofentanil oxalate. A review of the current family of fentanyls revealed that substances included under item 16 of Schedule I to the CDSA all contain the following root structure:

![Root Structure](image)

R=ethyl group substituted variously at the 1 and 2 position  
R₁=hydrogen, methoxymethyl or carboxylate alkyl ester  
R₂=phenyl or substituted phenyl  
R₃=alkyl  
R₄=hydrogen or alkyl

Note, however, that the pharmacological activities of the substances were not considered in the earlier reviews.

According to above root structure, cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide, cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester and cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid would *not* be considered to contain all the essential structural elements, as they do not contain the N-carbonyl. Given that the substances lack the core structure of the fentanyls, the substances should not be included under the heading “Fentanyls, their salts, derivatives, and analogues and salts of derivatives and analogues, including” of item 16 of Schedule I to the CDSA.

**Recommendation:** cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxamide, cis-3-Methyl-4-(phenylamino)-1(phenylmethyl)-4-piperidinecarboxylic acid, methyl ester and cis-(+)-3-Methyl-4-(phenylamino)-1(2-phenylmethyl)-4-piperidinecarboxylic acid are not included in the Schedules to the CDSA and are not controlled substances.

**Date:** May 24th, 2012.