Health Canada Santé Canada

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

Substance: (-)-trans-(1S,2S)-U-504888 (U-50488)

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 drug is currently not listed specifically on the CDSA.
- The structure of the substance is not similar to any substance on the schedules to the CDSA.

Supporting document(s) attached: X

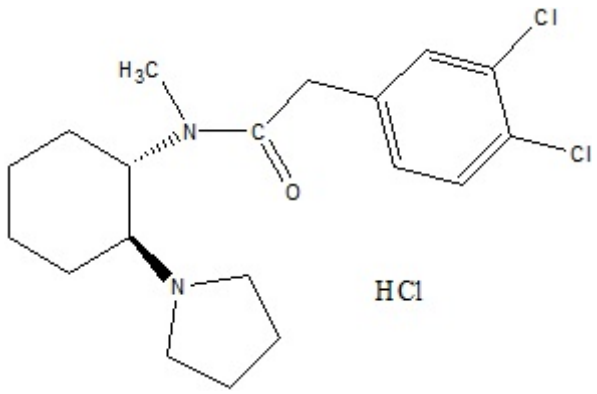
Prepared by: _____ Date: 2005-07-18
TIANA BRANCH

Verified by: See email Date: 2005-07-14
MICHAEL LEBELLE

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

Drug: U-50488
Drug Name Status: U-50488 is the common name.
Chemical Name:
trans-(1S,2S)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamide hydrochloride
Other Names: U-111

Chemical structure:



Molecular Formula: $C_{19}H_{26}Cl_2N_2O$. HCl
Pharmacological class / Application: kappa opioid receptor agonist

International status:

US: The drug is not currently listed on the US Controlled Substances Act and is not mentioned on the DEA website. However, the CSA includes in the term, "narcotic drug", "Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation," and also defines opiate as, "any drug or other substance having an addiction-forming or addiction-sustaining liability similar to morphine or being capable of conversion into a drug having such addiction-forming or addiction-sustaining liability." The status of U-50488 would have to be confirmed with the DEA.

United Nations: The drug is not listed on the Yellow List - List of Narcotic Drugs under International Control. The drug is not listed on the Green List - List of Psychotropic Substances under International Control

Canadian Status: The drug is currently not listed specifically on the CDSA. The structure of the substance is not similar to any substance on the schedules to the CDSA.

Attached to this report is a Note to File that was developed as the result of a need to make status decisions on enkephalins. The memo discusses the use of item I of Schedule I to the CDSA, "Opium Poppy (Papaver somniferum), its preparations, derivatives, alkaloids and salts, including:" and other items of schedule I to control opiates. The memo mentions the policy adopted by OCS in regard to cannabinoid receptor agonists and antagonists. The former are considered to be included in item I of Schedule II as "similar synthetic preparations."

The recommendation made in the Note to File appears to have been adopted for the enkephalins. There are at least two listed on the List of Non-controlled Substances maintained by OCS. Because of this, U-50488 should be considered to be not included in item I of Schedule I to the CDSA.

Recommendation: U-50488 is not currently included in the schedules to the CDSA and is not a controlled substance.

July 14, 2005

Government of Canada / Gouvernement du Canada

MEMORANDUM NOTE DE SERVICE

TO / A: Note to File

FROM / DE: Senior Science Advisor
Office of Controlled Substances

SECURITY -- CLASSIFICATION -- DE SÉCURITÉ
OUR FILE -- N/RÉFÉRENCE
YOUR FILE -- V/RÉFÉRENCE
DATE: March 6, 2002

SUBJECT
OBJECT: **Opiates - Controlled Drugs and Substances Act**

OCS was recently asked for the status of several enkephalins and other small peptide fragments. All of these substances are opiate receptor agonists. The endorphins, endogenous ligands of the opiate receptors and neuropeptides, are similar substances.

Item 1 of Schedule I to the CDSA reads as follows:

> Opium Poppy (Papaver somniferum), its preparations, derivatives, alkaloids and salts, including:
>
> (1) Opium
> (2) Codeine
> (3) Morphine
> (4) Thebaine
>
> and the salts, derivatives and salts of derivatives of the substances set out in subitems (1) to (4), including:
>
> .....
> .....
>
> but not including
>
> .....

Item 1 appears to include: substances prepared from and derived from opium poppy; and the alkaloids and the salts of alkaloids of the opium poppy. The three major alkaloids, codeine, morphine and thebaine are listed as examples. In addition, item 1 includes the salts,

derivatives, and salts of derivatives of opium and the three major alkaloids. The item then lists a further 27 substances as examples of substances included in item 1. The key link between the initial four substances and the additional 27 substances is the word "derivative."

As derivative is not defined in the Act, the dictionary definition applies. One dictionary gives the meaning of derivative in the context of chemistry as: "a compound derived or obtained from another and containing essential elements of the parent substance." Another gives a more general interpretation as: "that which is derived; anything obtained or deduced from another."

Over the years, I have espoused a more narrow interpretation of derivative which would include only the products from one chemical step. That is, if the listed substance could be converted to another in one chemical reaction, the product should be considered a derivative of the first. I believe the technical staff of Health Canada with a background in chemistry would accept this and would be able to support the status of a substance on this basis. However, one could also take the position that several chemical steps could be permitted in the conversion of a listed substance to a derivative. This latter position would be difficult to defend from several perspectives. It would be difficult to determine which substances are controlled under the Act. One could convert morphine, for example, through several chemical reactions to some larger or smaller molecule with little similarity to morphine and the resulting substance would be considered to be controlled. This interpretation also prevents the general public from knowing which substances are controlled by the Act. Finally, assertions in regard to the controlled status of substances under this interpretation can be easily countered by demonstrating that many compounds that are derivatives of the listed substances are not considered to be controlled.

The list of substances in item 1 to the CDSA was mostly imported directly from the Schedule to the Narcotic

Control Act. During the development of the CDSA, the review of the substances included under opium poppy was limited to ensuring that there were no obvious errors. There was no review of the rationale for the inclusion of substances. There was also no review of the appropriateness of including substances in Item 1 as opposed to other items.

This rather long preamble serves only to highlight the absence of a recent review of the rationale and policy for the inclusion of substances under item 1 of Schedule I.

The absence of documented inclusion criteria for substances under item 1 makes it difficult to assess the status of new substances under this item. It is questionable whether all of the substances listed in subitems 5-31 are derivatives of subitems 1-4. The rationale for inclusion of substances in item 1 is further confounded by the existence of item 10, morphinans, in Schedule I. Structurally, many of the substances included in item 1 could be considered to be morphinans. The absence of policy differentiation between substances listed on item 1 and item 10 results in apparent inconsistencies. Nalbuphine and buprenorphine are included in item 10 and cyprenorphine is included in item 1 (but not including provision). All three substances are structurally similar.

The absence of a solid derivative link among the substances listed in item 1, implies that perhaps substances were included based on another criteria. Pharmacological action is one possibility. It is likely that all of the substances on item 1 are narcotic agonists or antagonists. Pharmacological action appears to be the basis for considering some substances to be included under cannabis in Schedule II to the CDSA. Anandamide, a cannabinoid receptor activator, although not derived from cannabis and not obviously structurally similar to the cannabinoids is considered to be subject to the CDSA by inclusion in Schedule II (Cannabis, etc.).

I have not been able to find a recent (during 2001) status decision for a substance that states the substance is included under the opium poppy item based

on its pharmacological activity (opiate agonist or antagonist).

I recommend therefore that:

- substances be considered to be included in Item 1 of Schedule I only if the substance can be considered to be derived from subitems 1 to 4 of item 1.

- greater consideration be given to using item 10 of Schedule I for the control of substances structurally related to the opium alkaloids.

- pharmacological (opiate receptor) activity of a substance not be considered sufficient to control a substance under item 1 of Schedule I.

Where a substance must be controlled due to its opiate receptor activity but its structure does not support its inclusion in either item 1 or 10 of Schedule 1, the substance may be added as a separate item to Schedule 1.

In the case of the enkephalins, it is recommended that they not be considered to be controlled by the CDSA.

It is of course also recommended that criteria for inclusion in item 1 of Schedule I be documented.

M. LeBelle