

**1-(3-4-
methylenedioxybenzyl)piperazine
(MDBZP)**

Pre-Review Report

Expert Committee on Drug Dependence

Thirty-fifth Meeting

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**World Health
Organization**

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Summary

There is very little information available for 1-(3,4-methylenedioxybenzyl)piperazine (MDBZP or MDBP). It is a piperazine derivative but its effects are largely unknown. MDBZP has never been licensed as a medicine but is a metabolite of a withdrawn nootropic medicine, fipexide. This was withdrawn due to adverse toxic effects (fever and hepatotoxicity). Use of MDBZP has been noted by governmental organizations in the USA but there are no reports for other countries. The mode of abuse is believed to be similar to that of “Ecstasy” with many users seeking MDMA-like effects, particularly with concomitant BZP or TFMPP use. There are no published non-fatal or fatal hospital admissions. No specific studies have been performed to determine the abuse or dependence potential of MDBZP.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable.

B. *Chemical Abstract Service (CAS) Registry Number*

Free base: 32231-06-4

C. *Other Names*

1-(3,4-methylenedioxybenzyl)piperazine,
3,4-methylenedioxybenzylpiperazine, 1-piperonylpiperazine,
piperonylpiperazine, methylenedioxybenzylpiperazine, MDBZP,
1-(benzo[1,3]dioxol-5-ylmethyl)piperazine, MDBP.

D. *Trade Names*

KRKA (refer annex 1).

E. *Street Names*

MDBZP is not known to be associated with any particular street names.

F. *Physical properties*

White to yellow or yellow-brownish crystal solid.

G. *WHO Review History*

Several reports suggest misuse of MDBZP over the last years. At the time being, neither BZP nor any other substituted piperazine is listed in the Schedules of the United Nations 1971 Convention on Psychotropic Substances. In order to bring more conclusive scientific evidence on the overall risks of MDBZP for an eventual international scheduling, the WHO Secretariat has decided to initiate at the 35th ECDD a pre-review.

2. Chemistry

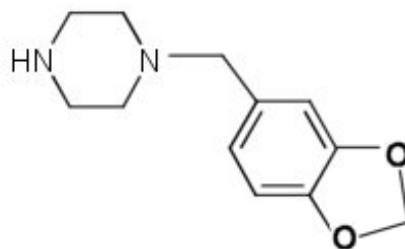
A. *Chemical Name*

IUPAC Name: 1-(benzo[1,3]dioxol-5-ylmethyl)piperazine

CA Index Name: 1-(benzo[1,3]dioxol-5-ylmethyl)piperazine

B. *Chemical Structure*

Free base:



Molecular Formula:	C ₁₂ H ₁₆ N ₂ O ₂
Molecular Weight:	220.27 g/mol (free base)
Melting point:	36-40 °C (lit.)
Boiling point:	147-149 °C (lit.)
Fusion point:	158.4 °C (lit.)

C. Stereoisomers

MDBZP has no chiral centres and therefore no stereoisomers.

D. Synthesis

MDBZP is an entirely synthetic compound but the exact manufacturing process is not known.

E. Chemical description

MDBZP is a substituted piperazine, with a methylenedioxy- moiety as per the structure of MDMA. MDBZP shares the same substitutions on the benzene ring as methylenedioxyamphetamine (MDA).

F. Chemical properties

No information.

G. Chemical identification

Methods for the identification of MDBZP have been provided by Wohlfarth et al. (2010) and Abdel-Hay et al. (2011).

3. Ease of convertibility into controlled substances

No information available.
No study data available.

4. General pharmacology

4.1. Pharmacodynamics

Neuropharmacology and effects on central nervous system

No studies have been performed using MDBZP itself but MDBZP is a primary and proposed active metabolite of fipexide which has been shown to increase noradrenaline in animals and to have dopaminergic effects (Stancheva *et al.*, 1993; Lucchi *et al.*, 1986; Rolandi *et al.*, 1984).

Effects on cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems

No study data available.

Behavioural studies in animals

No study data available.

Effects on cognition and behaviour in humans

No study data are available for MDBZP. However, a parent substance, fipexide, has shown some positive cognitive effects (e.g. memory and attention) (Bompani and Scali, 1986). There are no published, unpublished or anecdotal reports of the effects of MDBZP. In particular, no user reports are presented on common Internet sites (Erowid and The Lycaeum).

Effects in humans

No study data are available for MDBZP. However, a parent substance, fipexide, has shown some positive cognitive effects (e.g. memory and attention) (Bompani and Scali, 1986). There are no published, unpublished or anecdotal reports of the effects of MDBZP. In particular, no user reports are presented on common Internet sites (Erowid and The Lycaeum).

Interactions with other substances and medicines

Although MDBZP may affect the monoamine systems, there are no specific data and therefore it is difficult to determine any potential interactions with other substances or medicines.

4.2. Routes of Administration

There is no information available about route of administration and dosage.

4.3. Pharmacokinetics

In rats, studies have indicated that MDBZP is metabolized by demethylenation and subsequent methylation to *N*-(4-hydroxy-3-methoxybenzyl)piperazine followed by partial glucuronidation or sulfation (Staack and Maurer, 2004a; Maurer *et al.*, 2004). Additionally, researchers found degradation of the piperazine moiety to *N*-(3,4-methylenedioxybenzyl)ethylenediamine and 3,4-methylenedioxybenzylamine and *N*-dealkylation to piperazine (Staack and Maurer, 2004a).

Furthermore, MDBZP is a primary metabolite of fipexide which is also metabolised to 4-chlorophenoxyacetic acid, 1-[2-(4-chlorophenoxy)acetyl]piperazine, *N*-(4-hydroxy-3-methoxybenzyl)piperazine, piperazine, *N*-(3,4-methylenedioxybenzyl)ethylenediamine, and *N*-[2-(4-chlorophenoxy)acetyl]ethylenediamine (Staack and Maurer, 2004b; Sleno *et al.*, 2007).

5. Toxicology

There are no published pre-clinical safety data available concerning the toxicity, reproductive impact and mutagenic/carcinogenic potential of MDBZP. Furthermore, there are no user reports (published or anecdotal) regarding its use, nor are there any published or reported cases of intoxication.

6. Adverse reactions in humans

Of indirect relevance, fipexide use has been reported to result in fever and serious liver cell necrosis and fulminant liver failure (Guy *et al.*, 1990; Durand *et al.*, 1992). There are no study data to suggest or confirm that MDBZP (as an active metabolite) was the cause of these effects.

7. Dependence potential

No study data available.

8. Abuse potential

No study data available.

9. Therapeutic applications, extent of therapeutic use and epidemiology of medical use

MDBZP has not been used in therapy. As described elsewhere, fipexide was a nootropic used in the treatment of cognitive disorders (Bompani and Scali, 1986) but was later withdrawn due to its adverse effects (particularly hepatic toxicity).

10. Listing on the WHO Model List of Essential Medicines

MDBZP is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

Based on the WHO questionnaire in 2008 for review of psychoactive substances for 35th ECDD (annexe 1), of the 59 countries that responded, only Mongolia authorized MDBP as a medical or veterinary product. The brand name is "KRKA" and reported its "indication" to be "Fluphenazine deconcate", and also off-label use as "Moditen depo". The dosage is 25 mg/ml and it is in ampoule form. Brunei, Mongolia and Tuvalu indicated that they import the substance

12. Industrial use

MDBZP has no industrial use.

13. Non-medical use, abuse and dependence

MDBZP use has been mentioned in the USA (DEA, 2004). There is no information available about route of administration and dosage.

Of the 59 countries responding to the WHO questionnaire for review of psychoactive substances for the 35th ECDD, 19 countries reported that the substance is not used in a harmful way and 14 countries have no information on the abuse of the substance.

14. Nature and magnitude of public health problems related to abuse and dependence

As for BZP and TFMPP, MDBZP use appears to be associated with situations similar to that of “Ecstasy”, or with users who are seeking effects similar to “Ecstasy” (MDMA in particular) and therefore instances of misuse, abuse and dependence would be limited to such individuals rather than the general population (DEA, 2004). The mode of use could involve the combinational use (intentionally or unintentionally) of other piperazine-derivatives (e.g. BZP) or other substances. No fatal or non-fatal intoxications of MDBZP (with or without other substances) have been reported.

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Besides Mongolia there are no other countries who have tracked illicit activities involving the substance. Mongolia reported clandestine manufacturing and also smuggling (Annex 1).

17. Current international controls and their impact

Not applicable in relation to affecting impact of medical use.

18. Current and past national controls

The WHO questionnaire for review of psychoactive substances in 2008 (annex 1) found that Denmark, Japan, Mongolia and Tuvalu controlled MDBP under legislation that is intended to regulate availability of substances of abuse. In Japan MDBP is controlled as designated substances under the Pharmaceutical Affairs Law in Japan since January 2008.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No data.

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ANNEX 1:WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: 1-(3-4-methylenedioxybenzyl) piperazine (MDBZP)

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for MDBP by 59 countries.

LEGITIMATE USE

Of the responded countries only Mongolia authorized MDBP as a medical or veterinary product and the USA legitimated TFMPP for technical use only. There are no countries where other legitimate use is reported. The substance is granted market admission since 1995 in Mongolia under the brand name "KRKA" and reported its "indication" to be "Fluphenazine deconcate", and also off-label use as "Moditen depo". The dosage is 25 mg/ml and it is in ampoule form. 3 countries indicated that they import the substance. These are Brunei, Mongolia and Tuvalu.

ABUSE

Of the 59 countries responding, 19 countries reported that the substance is not used in a harmful way and 14 countries have no information on the abuse of the substance.

CONTROL

Denmark, Japan, Mongolia and Tuvalu reported that MDBP is controlled under legislation that is intended to regulate availability of substances of abuse. In Japan MDBP is controlled as designated substances under the Pharmaceutical Affairs Law in Japan since January 2008.

Besides Mongolia there are no other countries who have tracked illicit activities involving the substance. They reported clandestine manufacturing and also smuggling is reported. There are no reports on the quantity of the seizures.

IMPACT OF SCHEDULING

Scheduling is unlikely to have any impact on human and animal medical care

Brand Name

KRKA

Form

Ampoule 25mg/ml

Technical Use

Industrial use