

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 42nd ECDD: Evaluation of benzodiazepines (etizolam and flualprazolam)

Data was obtained from 74 Member States (8 AFR, 5 EMR, 33 EUR, 11 PAH, 5 SEAR and 12 WPR) for the WHO Questionnaires for the Review of Psychoactive Substances. Of these, 31 respondents had information on the substances.

Region	Number of countries responded	Number of countries with information on each substance	
		Etizolam	Flualprazolam
AFR	1	1	0
EMR	1	0	1
EUR	19	18	14
PAH	2	2	0
SEAR	3	3	0
WPR	5	5	1
TOTAL	31	29	16

LEGITIMATE USE

Four countries reported approved human medical products containing either of the two substances under consideration (India, Italy, Japan, Republic of Korea) with three of the countries citing anxiety as an approved therapeutic indication. All four countries stated that only medical doctors/psychiatrists are allowed to prescribe it.

No countries named a marketed formulation of flualprazolam. Marketed names for etizolam include: Depas, Etirest, Etilaam or Etazam (0.25, 0.5mg and 1 mg tablets), Depas fine granules 1% and Pasaden (no dosage given).

Italy and Japan reported that etizolam is currently being used in medical or scientific research (although they provided answers indicating a medical use rather than research):

“Etizolam is authorized for the treatment of anxiety”

“medical use”

Both countries confirmed that there are clinical guidelines in their country for the prescription of etizolam.

Four countries (Australia, Belgium, France, Spain) reported that the benzodiazepines are used for industrial or other non-medical/ non-scientific purposes - however only one of these referred to legitimate purposes:

“Forensic laboratories, university research, law enforcement standards and reference materials”

The other three countries cited recreational usage (with two citing “imported” and one also citing “manufactured in their own country”).

No countries reported any approved veterinary products containing the benzodiazepines.

No countries reported the use of benzodiazepines for any cultural, religious or ceremonial purposes.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Nineteen countries reported that benzodiazepines are being misused for their psychoactive properties (as a recreational drug).

By far the most common route of administration reported was oral administration (Table 1), with “sublingual” also mentioned in one country.

Route of administration	Number of countries
Oral	14
Inhalation	1
Injection	1
Sniffing	1
Smoking	0
Other (please specify)	1
Do not know	6
Total	19

Table 1: Common routes of administration

Regarding flualprazolam, eight of the countries cited “oral” as the most common route of administration, with two also saying “sublingual”. For etizolam, fourteen countries specified “oral” as the most common route of administration, two also stated “sublingual” and two mentioned several routes, including the following detailed answer:

“Etizolam is generally consumed orally, by swallowing tablets or powder placed into gel capsules. It can also be taken sublingually (under the tongue). There are reports of snorting and rectal administration although this appears to be rare.”

The most common formulation of the benzodiazepine substances reported was tablets/capsules, followed by powder (refer to Table 2). Five countries also reported blotters/blotting paper as a formulation, one country reported crystals as another formulation and there was one other reference to “pellets, trips and caps”.

Formulation	Number of countries reporting formulations
Tablets/Capsules	16
Powder	9
Liquid or solution for oral administration/use	3
Solution for injection	1
Other (please specify)	10
Total	19

Table 2: Common formulations reported by countries

Smuggling (from other countries) was the main source of the benzodiazepines for non-medical/non-scientific use, cited by eleven of the twelve countries who could give an answer (refer to Table 3), with “post” also cited in one country.

Source	Number of countries reporting sources
Smuggling (from other countries)	11
Illegal manufacturing	3
Legal trade	1
Diversion (from legal supply chain)	0
Legal manufacturing	0
Other (please specify)	2
Do not know	7
Total	19

Table 3: Sources of benzodiazepines for non-medical or non-scientific use

Two countries (the United Kingdom of Great Britain and Northern Ireland and Finland) indicated that there are specific subpopulations known to misuse any of the benzodiazepines:

“Problem drug users, mainly heroin/crack users, especially in Scotland”

“As an expert it can be said without any supporting data to attach: The misuse is more common among people who already use (other) illicit drugs as additional or substitute for the psychoactive effects. Additionally for self-medicating purposes among the same people in order to alleviate the side effects of drug abuse (insomnia, anxiety etc.).”

Answers regarding the extent and magnitude of public health problems or social harm caused by the use of the benzodiazepines varied widely, as illustrated by the following comments from different countries:

“small magnitude of the problem”

“not really large problems, the substances show up once or twice a year in customs”

“3 samples brought to pill testing services in 4 years, 1 seizure by police in 4 years”

“the prevalence is low but harms have been seen”

“Etizolam may have contributed to death in some of these cases”.

The level of negative health-impact originating from these substances’ non-medical consumption was reported as:

Serious	Substantial	Negligible	Don’t Know
3	3	4	8

Three countries reported a serious level of negative health impact (Finland, Sweden, United Kingdom) and a further three reported a substantial level of negative impact (Estonia, Germany, Indonesia).

Those countries that reported a serious or substantial level of negative health-impact indicated that this level was chosen due to different reasons, as illustrated by the following responses from the different countries:

“Both substances have been identified in deceased and have caused intoxications”

“Etizolam seem persistent to our market although the prevalence is low. Flualprazolam is being discussed to be fast and long acting which makes it more difficult. The BDZ dependence is problematic and hard to treat, therefore we take the NPS BDZ seriously.”

“Etizolam is used to render another person unconscious for the purpose of sexual assault”

“Police in Scotland reports that the demand for such tablets has resulted in several producers setting up illicit production sites using professional tableting equipment that enable rapid, large-scale production of such tablets. Deaths involving etizolam in Scotland have increased from 58 in 2015 (56% of NPS-related deaths or 9% of all drug-related deaths) to 270 in 2016 (74% of NPS-related deaths or 33% of all drug-related deaths). In 2017, etizolam was implicated in, or potentially contributed to, 299 deaths in Scotland (more than half of the 552 deaths involving benzodiazepines for that year).”

Four countries (France, Ireland, Sweden, United Kingdom) reported emergency room/department visits related to the non-medical use of the benzodiazepines. Adverse effects such as somnolence, hallucinations, mydriasis, unconsciousness and withdrawal symptoms (etizolam) and somnolence, dizziness, difficulties speaking, unconsciousness and amnesia (flualprazolam) were listed, but may not be entirely due to the benzodiazepines – as other substances may have been involved.

Only two countries (Ireland and Spain) reported deaths (6 in total) where the benzodiazepines were the only substance involved and four countries reported deaths (15 in total) where other substances were also involved. In addition, just two countries reported deaths (576 in total: 25 from Sweden and 551 from the United Kingdom) where it was unknown if other substances were involved. Both etizolam and flualprazolam were named as the being involved with the reported deaths.

Only Japan reported that they are aware of people presenting to drug dependence treatment centres due to the use of etizolam.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Twenty countries reported that at least one of the benzodiazepines was under national control. The legislation that the control is based upon included the Controlled Substances Act (14 countries), Medicines Act (5 countries), Criminal Law Act (3 countries) and other legislation (4 countries).

The scope of the controls includes importing (18 out of 19 countries), distribution, manufacturing and possession (17 out of 20 countries), exporting and production (16 out of 20 countries), and use (14 out of 20 countries). Furthermore, none of the twenty countries said that the provisions were temporary and none reported that there have been any challenges to implementing national controls.

Reported illicit activities involving benzodiazepines were (Table 4):

Illicit Activities	Number of countries reporting
Internet sales (other or location of sellers and website unknown)	8
Internet sales (from abroad to buyers in your country)	7
Trafficking	7
Sales to people who use benzodiazepines	6
Internet sales (seller or website located in your country)	3
Diversion	2
Production of consumer products (dosage forms, packaging)	1
Manufacture of the substance by chemical synthesis	0
Manufacture of the substance by extraction from other products	0
Other (please specify)	1
Do not know	7
Total	20

Table 4: Reported illicit activities involving etizolam or flualprazolam

Of the twenty countries, eight countries (Belgium, Estonia, Finland, Germany, New Zealand, Singapore, Sweden and Thailand) gave answers to the number of seizures - and the vast majority of the seizures were cited by two countries (Finland and Sweden). In total, the combined number of seizures of flualprazolam was 1 (2016), 9 (2017), 525 (2018), and the combined number of seizures of etizolam was 742 (2016), 218 (2017), 690 (2018).

If either of the benzodiazepines were placed under international control, twenty-four (out of thirty) countries confirmed that they would have the capacity to enforce the control at the national level (with Uganda saying they wouldn't have capacity) - and twenty-five countries responded that they would have the forensic laboratory capacity to analyse the substance.