ACMD

Advisory Council on the Misuse of Drugs

Recently encountered uncontrolled novel benzodiazepines and related compounds (2024 update)

Contents

1. Introduction

1.1. Benzodiazepines are sedative and anxiolytic compounds that were first synthesised in the 1950s. Many have been licensed as medicines in the UK and internationally for the treatment of anxiety, insomnia, muscle spasms, spasticity or epilepsy. Examples include diazepam, temazepam and lorazepam.

1.2. Benzodiazepines are associated with important health harms including drowsiness, psychomotor impairment, unsteadiness and incoordination, memory loss and confusion. Higher doses may cause loss of consciousness and respiratory depression, especially if used in combination with alcohol or other sedatives. Regular use is also associated with tolerance and dependence, with the development of severe withdrawal symptoms on discontinuation after regular use for more than a few weeks in some cases.

1.3. There has been increasing non-medical use of novel (sometimes called 'designer') benzodiazepines in recent years. Many of these were previously developed as potential medicines and some are licensed as medicines in other countries. There are also compounds that, although not technically benzodiazepines, share similarities in structure and/or pharmacology. Some of these related compounds are also considered in this report.

1.4. Novel benzodiazepines and related compounds have been associated with significant health harms including an increase in annual numbers of deaths where a benzodiazepine has been implicated. Drug-related deaths involving a benzodiazepine have been especially common in Scotland.

1.5. The ACMD has previously provided advice on novel benzodiazepines, most recently in 2020 [ACMD, 2020a]. That report recommended 3 further compounds that had been identified in seized materials in the UK for control under Class C of the Misuse of Drugs Act (MDA) 1971, consistent with other classified benzodiazepines. These compounds were also recommended for listing in Schedule 1 of the Misuse of Drugs Regulations (MDR) 2001 (as amended) because they have no recognised medicinal use. The remaining 10 compounds considered at that time remained uncontrolled under the MDA, but most are likely to be captured by the Psychoactive Substances Act 2016 (PSA).

1.6. Since that report was published, the ACMD has become aware of further benzodiazepines and related compounds that are not controlled under the MDA being detected in Europe and, in some cases, the UK.

1.7. Evidence was therefore sought from stakeholders about 18 different compounds detected in international markets to establish their prevalence in the UK. This report reviews the evidence of harms and misuse of these compounds and their prevalence in the UK.

2. Legal control

2.1. Because of the large number of benzodiazepines and related compounds that are or may in future be detected in the UK, the ACMD has previously considered the possibility of a generic control based on their chemical structure, similar to the approach used in Germany [Buzer.de, 2023]. This, however, has not been considered feasible because in UK law, text must be used to describe the complex generic structures being controlled. This contrasts with German legislation, which allows chemical structures to be drawn. For this reason, all benzodiazepines and related compounds that are controlled under the MDA 1971 are listed by name (Annex A).

2.2. In the UK all but 2 benzodiazepines that are licensed as medicines are placed in Class C of the MDA and listed in Schedule 4 Part 1 of the MDR. A recently added example is remimazolam (Byfavo®). The two exceptions are midazolam and temazepam, which are placed in Schedule 3 of the MDR because of their potency, increased misuse potential and risk of diversion.

2.3. Many benzodiazepines that are not licensed as medicines in the UK have also been controlled as Class C drugs and are listed in either Schedule 1, Schedule 3 or Schedule 4 Part 1 of the MDR. Control and scheduling of individual benzodiazepines in the UK under the MDA and MDR are summarised in Annex A.

2.4. The compounds considered in this report are not currently controlled under the MDA, but those that are not medicinal products are likely to be captured by the Psychoactive Substances Act 2016 (PSA) if intended for human consumption.

2.5. None of the compounds considered in this report are licensed as medicines in the UK and the Medicines and Healthcare products Regulatory Authority (MHRA) has confirmed that no clinical trials involving them have been authorised in the UK.

2.6. Five of the compounds considered (gidazepam, cinazepam, bentazepam, tofisopam and rilmazafone), however, are licensed as medicines in other countries. The MHRA, an executive agency of the Department of Health and Social Care (DHSC) that decides which compounds satisfy the definition of a medicinal product for the purposes of the Human Medicines Regulations (2012), has advised that these compounds should be regarded as medicinal products for the purpose of the 'medicinal products' exemption to the PSA. The MHRA has not been made aware of legitimate importing of any of the compounds considered in this report, but cannot exclude their manufacture in the UK by licensed manufacturers. Furthermore, legislation allows members of the public to import medicines for their own personal use without notification of the MHRA. It is therefore not possible to exclude completely the medicinal use of any of these compounds in the UK.

2.7. The chemistry, pharmacology, toxicology, medical and non-medical use and health and social harms of benzodiazepines and related compounds as a

group are well known and were described in detail in our earlier report [ACMD, 2020a]. There may, as yet be limited or no evidence of human harms for recently emerging compounds, but it is likely that those that share pharmacological properties with established benzodiazepines will have a similar pattern of potential health harms.

3. Compounds detected in Europe and the UK

3.1. Detections in Europe of benzodiazepines and related compounds that are not currently controlled via the MDA in the UK are summarised in Table 1. Synonyms and chemical structures of these compounds are provided in Annex B. For ease of reference between the report text, tables and Annex B, each of the compounds considered are also numbered (#1 to #18).

3.2. To evidence the identification and prevalence of novel benzodiazepines in the UK, the ACMD's Novel Psychoactive Substances (NPS) Committee wrote to stakeholders in July 2023 requesting available data on detections of the 18 compounds listed in Table 1.

3.3. Stakeholders provided analytical data from drug seizures (including from prisons and at UK Borders), samples from patients attending emergency departments with drug toxicity and post mortem toxicology samples. The stakeholders providing evidence and the type of evidence provided are listed in Annex C.

3.4. UK stakeholders reported the detection of 6 of the 18 aforementioned compounds and the overall annual number of samples containing these is summarised in Table 1. Two of these (methylclonazepam #3 and clobromazolam #8) were considered in our previous report but were not recommended for control because no UK detections had been reported at that time.

3.5. The chemistry, pharmacology and evidence of misuse in the UK and other countries of the 18 compounds that have been detected internationally are considered in more detail below.

Table 1. Benzodiazepines and related compounds not listed in the Misuse of Drugs Act that have been detected in Europe and/or the UK.

	Name	Medicinal license in any other country	Year of first detection		Reported UK detections						
			Europe	UK	2018	2019	2020	2021	2022	2023*	TOTAL
1,4 benzodiazepines											
#1	Gidazepam	Yes	-	2022	-	-	-	-	1	3	4
#2	Desalkylgidazepam	No	2022	2022	-	-	-	-	75	46	121
#3	Methylclonazepam	No	2018	2020	-	-	23	104	117	5	249
#4	Cinazepam	Yes	2019	-	-	-	-	-	-	-	-
#5	Cloniprazepam	No	2016	-	-	-	-	-	-	-	-
#6	Difludiazepam	No	2017	-	-	-	-	-	-	-	-
#7	Thionordazepam	No	2017	-	-	-	-	-	-	-	-
Triazolobenzodiazepines											
#8	Clobromazolam	No	2016	2022	-	-	-	-	53	27	80
#9	4'-Chloro-deschloroalprazolam	No	2023	2022	-	-	-	-	3	4	7
Thienotriazolodiazepines											
#10	Fluclotizolam	No	2017	-	-	-	-	-	-	-	-
#11	Deschloroclotizolam	No	2021	-	-	-	-	-	-	-	-
#12	Flubrotizolam	No	2021	-	-	-	-	-	-	-	-
#13	Fluetizolam	No	2022	-	-	-	-	-	-	-	-
Thienodiazepine											
#14	Bentazepam	No**	2014	-	-	-	-	-	-	-	-
2,3 Benzodiazepine											
#15	Tofisopam	Yes	2018	2023	-	-	-	-	-	1	1
Imidazopyrrolobenzodiazepine											
#16	Bretazenil	No	2021	-	-	-	-	-	-	-	-
Benzodiazepine pro-drugs											
#17	Rilmazafone	Yes	2022	-	-	-	-	-	-	-	-
#18	Alprazolam triazolobenzophenone	No	2014	-	-	-	-	-	-	-	-

*Part year data to July 2023, except OHID (to December 2023) and IONA data (to March 2023); **Previously (but not currently) licensed in Spain

(A) 1,4 Benzodiazepines

3.6. Commonly encountered examples of 1,4 benzodiazepines include the licensed medicines diazepam, lorazepam, fludiazepam, nordazepam and clonazepam (all Class C, Schedule 4 Part 1 compounds). There are also several novel unlicensed 1,4 benzodiazepine compounds that are already controlled under the MDA 1971. These include flunitrazepam, diclazepam, norfludazepam (all Class C, Schedule 1) and phenazepam (Class C, Schedule 3).

(#1) Gidazepam and (#2) desalkylgidazepam

3.7. Gidazepam is an anxiolytic benzodiazepine derivative that has been licensed for prescription-only medicinal use in Russia and Ukraine since 1997. It is available in oral or sublingual preparations for the treatment of anxiety, alcohol withdrawal and migraines and as a premedication for surgery [Morozov et al, 1998; Maskell et al, 2023]. Gidazepam is not licensed for medicinal use in the UK and its active metabolite, desalkylgidazepam, is not licensed as a medicine anywhere in the world.

3.8. Following oral administration to human subjects, gidazepam is rapidly absorbed [Litvin et al, 2004] and converted to its active metabolite desalkylgidazepam. This occurs so quickly that the parent drug is generally only detected in biological samples if highly sensitive analytical methods are used. Desalkylgidazepam is thought to be responsible for all pharmacological effects following gidazepam administration. It is very slowly eliminated with a mean half-life of 87 hours. Note that these data are from studies involving oral gidazepam administration and no studies examining human use of desalkylgidazepam via any route have been identified.

3.9. Like ‘classical’ benzodiazepines, gidazepam and desalkylgidazepam both interact with gamma amino butyric acid type A (GABA-A) receptors. Gidazepam is a partial agonist (mean Ki 2200 nM) but desalkylgidazepam has a much greater affinity (Ki 3.5 nM) and has more potent antiepileptic activity in animal studies.

3.10. User reports suggest that desalkylgidazepam is available for sale via the internet as pellets or tablets (dose 1-3 mg) and typical doses used are between 6 and 9 mg. Users report prolonged predominantly anxiolytic rather than hypnotic effects [Maskell et al, 2023].

3.11. Reported adverse effects from therapeutic use of gidazepam include drowsiness, weakness, myasthenia gravis, addiction, dysmenorrhea, allergic reactions, impaired coordination, ataxia and severe muscle weakness [Maskell et al, 2023].

3.12. Desalkylgidazepam was first detected in international drug markets in February 2022 in the United States of America (USA) and April 2022 in Canada. It has been identified in tablets sold as other benzodiazepines such as flualprazolam or flubromazepam. It was also notified to the European Monitoring Centre for Drug and Drug Addiction (EMCDDA) during 2022.

3.13. In a series of 63 cases in Canada, where desalkylgidazepam was detected in post mortem samples, other substances were detected in all cases. The most frequent of these were fentanyl (with its metabolite norfentanyl or the fentanyl precursor 4-anilino-N-phenethylpiperidine or 4-ANPP) as well as caffeine, methamphetamine, amphetamine, bromazolam, acetylfentanyl, tetrahydrocannabinol (THC) and its metabolite carboxy-THC, cocaine (and its metabolites) and etizolam. Femoral blood desalkylgidazepam concentrations ranged from 5.6 to 220.6 ng/ml (Median 25.8 ng/ml) [Mérette et al, 2023].

3.14. Desalkylgidazepam was first detected in the UK during 2022 in police, Border Force and prison drug seizures and in samples submitted to the WEDINOS study. There were no reports of gidazepam detections in these samples.

3.15. The Identification of Novel Psychoactive Substances (IONA) clinical study collected clinical information and blood and urine samples from patients attending participating emergency departments with drug toxicity from May 2015 to March 2023. Desalkylgidazepam was detected in at least one sample (blood or urine) in 14 patients between January 2022 and March 2023. In 4 of these cases gidazepam was also identified, indicating that the parent drug had been ingested. Desalkylgidazepam was detected in 13/99 (13%) patients recruited in Scotland, 1/4 (25%) recruited in Wales and none of 404 (0%) recruited in England.

3.16. Data from the EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS (EU-MADNESS) study demonstrates that desalkylgidazepam (but not gidazepam) has been detected in post mortem samples taken for the investigation of drug-related deaths in at least 9 UK cases in 2022 and early 2023, 7 in Scotland and 2 in Northern Ireland. Separately, Scottish forensic laboratories have reported the detection of desalkylgidazepam in 5 post mortem cases, but these may be some of the same cases reported by the EU-MADNESS study. It is not possible to determine from the data available the role of desalkylgidazepam in the causes of death in any of these cases. No information on drug-related deaths involving these compounds is available for England or Wales.

3.17. The lack of gidazepam detections by some laboratories may be due to a lack of an appropriate reference standard until late 2023. Prior to that, any identification of gidazepam will only have been presumptive in blood/plasma samples via the use of theoretical mass spectrometry data, as used for the IONA study.

(#3) Methylclonazepam

3.18. Methylclonazepam is a 1,4-benzodiazepine originally developed as a pharmaceutical by Hoffman-La Roche in the 1970s. It has similar anxiolytic properties to lorazepam [Ansseau et al, 1985], but has never been licensed as a medicine anywhere in the world.

3.19. It is structurally related to flunitrazepam, differing by the substitution of the fluorine with a chlorine atom. It also shares structural similarities with the established compounds clonazepam and diclazepam, as well as cloniprazepam (#5, also considered in this report).

3.20. Computational quantitative structure-activity relationship analysis (QSAR) based on chemical structure predicts high biological activity for methylclonazepam [Catalani et al, 2021]. Consistent with this, *in vivo* studies in rats demonstrated that methylclonazepam is equal in potency to nitrazepam and clonazepam, and is more potent than diazepam for muscle relaxant and anticonvulsant actions [Fukuda et al, 1977].

3.21. Methylclonazepam was first notified in Sweden in December 2017, in a border seizure of 100g of pale-yellow powder.

3.22. Methylclonazepam was considered in our previous report on novel benzodiazepines [ACMD 2020a]. At that time the specialist benzodiazepine charity Postscript360 provided evidence that clients in receipt of treatment for benzodiazepine dependency had reported anecdotally either the use or purchase of methylclonazepam. There was, however, no evidence provided of detections of methylclonazepam in drug seizures or in samples from cases of drug related death in the UK. Control via the MDA was therefore not recommended at that time.

3.23. Evidence provided for this current report demonstrates that methylclonazepam has been detected in police and prison drug seizures since 2019 and in samples submitted to the WEDINOS study since 2020, with the overall numbers of detections increasing between 2019 and 2022. It has also now been detected in post mortem samples taken for the investigation of drug-related deaths in 3 cases reported by the National programme on Substance Abuse Deaths (NPSAD) in 2020 and 2021.

(#4) Cinazepam

3.24. Cinazepam, structurally related to phenazepam, is converted in the body to its active metabolite 3-hydroxyphenazepam, a compound already controlled via the MDA. High biological activity is predicted by computational QSAR analysis based on chemical structure [Catalani et al, 2021] and both cinazepam and 3-hydroxyphenazepam appear to have high-potency binding (in the nanomolar range) to the GABA-A receptor [Makan et al, 2007]. Cinazepam is a partial agonist while its metabolite is a full agonist and the effects of the two

compounds on GABA uptake and release differ [Borisova et al, 2021]. These pharmacological differences may explain why the effects of cinazepam administration are dissimilar to those of other benzodiazepines. Cinazepam is reported to produce hypnotic and anxiolytic effects but relatively weak sedative and muscle relaxant effects. The median elimination half-life of cinazepam was reported as 16–23 hours.

3.25. Cinazepam is licensed for the treatment of insomnia in Ukraine under the trade name Levana® in doses of 0.5 to 2 mg daily [Interchem, 2020]. It has also been used in medical manufacturing in that country and has recently been included in the patent of a novel therapy for treating anxiety disorders, epilepsy, and pain.

3.26. Cinazepam was first notified in Europe in 2019, when Swedish police seized 5 white tablets containing the compound [EMCDDA, 2021]. There is currently no direct evidence of prevalence or health harms associated with cinazepam in the UK.

(#5) Cloniprazepam

3.27. Cloniprazepam is structurally similar to clonazolam (Class C, Schedule 1) and metabolised to (and could be considered a pro-drug of) clonazepam (Class C, Schedule 4 Part 1) [Mortelé et al, 2018]. Cloniprazepam is not licensed as a medicine in the UK or elsewhere.

3.28. High biological activity is predicted for this compound by computational QSAR analysis based on chemical structure [Catalani et al, 2021]. As evidence of its potency for binding to GABA-A receptors, it is a more potent inhibitor of 3H-flunitrazepam binding to cerebellar or hypocampal membranes diazepam [Sieghart, 1983]. Oral doses used range from 0.5 to 4 mg but are typically between 1 and 2 mg [Mooseman & Auwärter, 2018]. Symptoms occur 15-45 minutes after ingestion, with clinical effects lasting 6-9 hours [Orsolini et al, 2020].

3.29. The compound was first notified in recreational drug markets in January 2016 in Sweden, from a police seizure of 25 white capsules. Sales of the substance have been reported online as packs of 20, 60, 120 and 240 capsules of 2.5 mg strength. In the UK to date, cloniprazepam has not been detected in drug seizures and no deaths or other harms have been recorded.

(#6) Difludiazepam

3.30. Difludiazepam is structurally related to diazepam and fludiazepam (both Class C, Schedule 4 Part 1), differing by the addition of fluoro- substituents in the 6-position (fludiazepam) and at both the 2 and 6 positions (diazepam) of the unfused phenyl ring (Annex B). It is also structurally related to norfludiazepam (Class C, Schedule 1), It was originally described in a 1972 patent, and has been used in research to determine the shape and function of the GABA

receptor complex [Orsolini et al, 2020]. It is not licensed as a medicine in the UK or elsewhere.

3.31. No information on its pharmacology has been identified, but high biological activity is predicted by computational QSAR analysis based on chemical structure [Catalani et al, 2021].

3.32. This compound was first notified in Sweden in May 2017, following a border seizure of 1g of pale-beige power originating from China. Seizures made by law enforcement in Sweden have been labelled as ‘sample for research’.

3.33. To date, difludiazepam has not been detected in drug seizures and no deaths or other harms have been recorded in the UK.

(#7) Thionordazepam

3.34. Thionordazepam is structurally related to nordazepam and diazepam (both Class C, Schedule 4 Part 1), and can be used in the synthesis of alprazolam.

3.35. No information on the pharmacology of thionordazepam has been identified, but, as with many other compounds in this group, high biological activity is predicted by computational QSAR analysis based on chemical structure [Catalani et al, 2021].

3.36. This compound was first notified in Sweden in June 2017, following a border seizure of 2g of pale-yellow powder. To date, this compound has not been detected in drug seizures in the UK and no deaths or other harms have been recorded here.

(B) Triazolobenzodiazepines

3.37. These compounds differ from the 1,4 benzodiazepines as they incorporate a triazolo ring applied to the diazepam ring. Commonly encountered examples include the licensed medicine alprazolam, the previously licensed compound triazolam (both Class C, Schedule 4 Part 1 compounds) and several unlicensed compounds already controlled via the MDA 1971 including bromazolam, clonazolam, flualprazolam and flubromazolam (all Class C, Schedule 1).

(#8) Clobromazolam

3.38. Clobromazolam (phenazolam) is the 2-chloro derivative of bromazolam and shares structural similarities with clonazolam, flubromazolam, phenazepam, alprazolam and triazolam. It differs from triazolam by the replacement of chlorine with bromine at the 8-position on the benzodiazepine moiety. It was

first developed for human use in the 1980s but has never been licensed as a medicine anywhere in the world [Polívka et al, 1983].

3.39. Consistent with the high biological activity predicted by computational QSAR [Catalani et al, 2021], clobromazolam has similar binding affinity for GABA-A receptors as flualprazolam [Manchester et al, 2022]. Oral administration in mice resulted in central nervous system depression, ataxia and convulsive reactions at doses of 0.2–1 g/kg, with symptoms lasting more than 24 hours [Polívka et al, 1983; Orsolini et al, 2020]. No human studies evaluating clobromazolam have been identified.

3.40. Clobromazolam was first detected in recreational drug markets in Sweden in 2016 [Wagman et al 2021], notified to the EMCDDA in 2016 [EMCDDA, 2021] and was considered in the previous ACMD report [ACMD 2020a]. At that time, however, there was no evidence of use in the UK and it was therefore not recommended for control. Clobromazolam has since also been detected in the USA [CFSRE, 2022] and Australia, including as a component of counterfeit Xanax tablets [Syrjanen et al 2023].

3.41. In the UK clobromazolam has been detected in police, Border Force and prison drug seizures and in samples submitted to the WEDINOS study since 2022.

3.42. In the IONA study, clobromazolam was detected in samples from 3 patients attending emergency departments, 2 in Scotland and one in the north of England, with all presenting during 2022.

3.43. Clobromazolam has been detected in post mortem samples taken for the investigation of drug-related deaths in at least 3 cases in 2022 and early 2023, 2 in Scotland and 1 in Northern Ireland. It is not possible to determine from the data available whether clobromazolam toxicity caused or contributed to each of the deaths.

(#9) 4'-Chloro-deschloroalprazolam

3.44. This compound is an analogue of alprazolam, having the same molecular formula and weight, but with the chlorine attached to a different location on the molecule. Because of this structural similarity, it may be difficult to distinguish the two compounds analytically, to the extent that 4'-chloro-deschloroalprazolam has previously been misidentified as alprazolam in forensic samples [Reber et al 2023]. As a result, its role in drug-related deaths may not be recognised.

3.45. No published information on the pharmacology or toxicology of 4'-Chloro-deschloroalprazolam has been identified.

3.46. 4'-Chloro-deschloroalprazolam was detected in capsules seized by Australian police in December 2021 [Trigg et al, 2022]. It was also first identified in the

south and mid-west USA between July and September 2022 [NFLIS 2022]. In Europe it was notified to the EMCDDA in 2023.

3.47. A small number of samples analysed in Scotland were found to contain 4'-chloro-deschloroalprazolam but there are no reports of detections from elsewhere in the UK or in post mortem samples.

(C) Thienotriazolodiazepines

3.48. These compounds are not benzodiazepines, but share structural similarities. They incorporate thiophene and triazole rings attached to a diazepine core. Examples that are already controlled via the MDA include brotizolam (Class C, Schedule 4 Part 1) and etizolam (Class C, Schedule 1). Like benzodiazepines, they act at GABA-A receptors.

(#10) Fluclotizolam

3.49. Fluclotizolam differs from brotizolam and etizolam by the substituents at the thiophene and phenyl ring. Based on its similarity to these compounds, fluclotizolam is expected to have sedative hypnotic effects. There are conflicting anecdotal reports on doses used, though claims have been made that it has an approximately 3-fold higher potency and a shorter half-life compared to etizolam [Orsolini et al, 2020].

3.50. This compound was first notified in Sweden in October 2017, following a police seizure of 94 pale-green tablets. It was also identified in Denmark in the same month, in a border seizure of 10 blotters originating from the Netherlands. In the USA, it was identified in one human case in Pennsylvania in October 2021 [CFSRE, 2021] and increases in online mentions of the drug from late 2021 were reported by the National Drugs Early Warning System [NDEWS, 2021]. So far it has not been detected in drug seizures or reported to be associated with deaths or other harms in the UK.

(#11) Deschloroclotizolam

3.51. This compound differs from fluclotizolam (#10) only by the absence of the fluorine group on the phenyl ring. No information is available on its pharmacology.

3.52. It was first identified in recreational drug markets in Sweden in 2021, but to date there are no reports of detections of deschloroclotizolam in the UK.

(#12) Flubrotizolam

3.53. Flubrotizolam differs from fluclotizolam (#10) only in that it has a different halogen (bromine rather than fluorine) attached to the thieno ring. It is reported to have potent sedative and anxiolytic effects [NADDI, 2022], although there is little evidence published about its pharmacological effects. High biological activity is predicted by computational QSAR analysis based on chemical structure [Catalani et al, 2021].

3.54. It was notified to the EMCDDA in 2021, while in the USA online mentions peaked in mid-2021 and again during 2022 [NDEWS, 2022]. No detections in the UK have been reported.

(#13) Fluetizolam

3.55. This compound is structurally similar to etizolam, differing only in the halogen attached to the phenyl component (fluorine rather than chlorine). Based on its chemical structure it has high predicted biological activity predicted by computational QSAR analysis [Catalani et al, 2021]. There is, however, no published information on its pharmacology or toxicology.

3.56. Fluetizolam was first notified in Europe in 2022 and was also detected in a clinical case in Los Angeles, California, in October of that year. It has not so far been identified in the UK.

(D) Others

(#14) Bentazepam

3.57. Bentazepam is a thienodiazepine, i.e. a benzodiazepine derivative where the diazepine ring is fused to a thiophene instead of benzene. This class of compounds also includes etizolam, metizolam, and fluclotizolam, but bentazepam differs from these three substances due to the presence of a cyclohexane ring fused to the thiophene instead of a triazole ring fused to the benzodiazepine component.

3.58. Bentazepam was previously used as a medicine in Spain. It is known to produce anxiolytic, anticonvulsant, sedative and muscle relaxant effects and is used for the treatment of anxiety, including when associated with social phobia and post-traumatic stress disorder [Honorato et al, 1990]. Low and typical doses used respectively are 15–30 mg and 30–50 mg, with pronounced effects experienced with doses greater than 50 mg. Clinical effects develop 15–45 minutes after oral intake and may last for up to 8 hours after administration [Orsolini et al, 2020]. Unlike other benzodiazepines, hepatitis and severe liver damage have been associated with therapeutic use

[de-la-Serna et al, 1997; Andrade et al, 1994] as well as cases of colitis [Fernández-Bañares et al, 2003].

3.59. The compound was first notified in Sweden in March 2014, in a police seizure of 6 white tablets and was notified to the EMCDDA in 2019 [EMCDDA 2021]. There is no current evidence of prevalence or health harms associated with bentazepam in the UK.

(#15) Tofisopam

3.60. Tofisopam is a 2,3-benzodiazepine containing a stereogenic centre which therefore exists as a pair of enantiomers. It is licensed as a medicine in some European countries, under the name Grandaxin, and is administered orally at a dose of 300 mg daily for the treatment of neurosis and somatic disorders associated with tension, anxiety, vegetative disorders, lack of energy and motivation, apathy, fatigue, depressed mood and alcohol withdrawal syndrome [Orsolini et al, 2020].

3.61. Unlike ‘classical’ benzodiazepines, tofisopam does not act on the GABA-A receptor. It was thought to enhance the binding of other benzodiazepines to their binding sites [Petócz, 1993] but there is also evidence that it acts as an inhibitor of phosphodeasterases (PDE), especially PDE-4A1, PDE-10A1, PDE 3 and PDE 2A3. [Rundfeldt et al, 2010]. Tofisopam has predominantly anxiolytic effects with less marked sedative and muscle relaxant effects in humans. It may also have stimulant effects, but sedation may occur after high doses. Tofisopam may also enhance the effects of other depressants, such as barbiturates and ethanol [Petócz, 1993]. The lack of action at the GABA-A receptor raises the possibility that sedative effects may not be reduced by the benzodiazepine antidote flumazenil.

3.62. Tofisopam is rapidly absorbed from the intestinal tract but undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations are reached within 1–1.5 hours. The major pathway for the metabolic transformation of tofisopam is demethylation and its elimination half-life is 6–8 hours.

3.63. Tofisopam was first notified in Europe in November 2017, following a border seizure of 80 white tablets in Sweden. A single drug sample submitted for analysis in Scotland in 2022 was found to contain tofisopam, but there are no reports of detections from elsewhere in the UK or in post mortem samples. A single sample was submitted to WEDINOS in 2023, where the purchaser had intended to obtain tofisopam but analysis was unable to identify the contents.

(#16) Bretazenil

3.64. Bretazenil, an imidazopyrrolobenzodiazepine, is similar in structure to the benzodiazepine antagonist flumazenil. Unlike flumazenil, however, it acts as a benzodiazepine receptor partial agonist [Haefely et al, 1990], enhancing GABA-stimulated chloride flux, but not to the same extent as a full agonist [Facklam et al, 1992]. Bretazenil is rapidly absorbed and has an elimination half-life of 2-4.5 hours [Potocar & Nutt, 1994; Gonzales-Lopez et al 1986; Colino et al, 1991].

3.65. Animal studies suggested that bretazenil could be useful clinically as a potent anxiolytic and anticonvulsant drug with limited sedative or muscle relaxant effects [Potier et al, 1988; Honorato et al, 1990]. In humans, however, effective anxiolytic doses ranged from 0.5 to 4 mg [Haefely et al, 1990; Potocar & Nutt, 1994] but sedative effects were observed at doses as low as 0.2 mg [Saletu et al, 1989] and marked sedation occurred after oral doses of 0.5 mg [van Steveninck et al, 1996]. Other reported adverse effects from use included chronic liver disease [de-la-Serna et al, 1997; Andrade et al, 1994]. These adverse effects, especially sedation, discouraged its further clinical development and it has not been licensed as a medicine in any country.

3.66. Studies in humans did suggest that bretazenil has some abuse liability, but this was less marked than for the full benzodiazepine receptor agonists diazepam and alprazolam [Busto et al, 1994].

3.67. Bretazenil was first notified to the EMCDDA in 2021, but to date, detections of this compound have not been reported in the UK.

(#17) Rilmazafone

3.68. Rilmazafone is licensed as a medicine in Japan for the treatment of insomnia in a daily dose of 1-2 mg. It is not itself a benzodiazepine and is not directly psychoactive, but it is metabolised to active metabolites with triazolo benzodiazepine structures similar to alprazolam that have sedative and anxiolytic effects [Krondstrand et al 2023]. It can therefore be considered a benzodiazepine pro-drug.

3.69. In human subjects, blood rilmazafone concentrations could not be detected after oral administration, presumably due to rapid conversion to its active benzodiazepine metabolites. Time to peak concentrations and half-lives for these metabolites respectively were 0.5-1.5 hours and 1 hour for rilmazolam (M-1), 1–3 hours and 2-4 hours for desmethylrilmazolam (M-2), 1.5–2 hours and 2 hours for carboxyrilmazolam) and 24 hours and 11-16 hours for di-desmethylrilmazolam (M-3). All metabolites demonstrated sleep-inducing effects in studies involving monkeys, except carboxyrilmazolam. Rilmazolam and desmethylrilmazolam had particularly high sleep-inducing actions [Yamamoto et al 1984a; Yamamoto et al 1984b; Krondstrand et al, 2023].

3.70. Rilmazafone has been sold in Japan as a legal replacement for controlled sedative-hypnotics and user reports on research drug internet fora suggest that it has similar effects to lorazepam [Krondstrand et al 2023].

3.71. Rilmazafone was first notified to the EMCDDA in 2022. Forensic analysis of post mortem samples from 2 patients in Sweden conducted in that year reported the presence of rilmazafone metabolites (but not the parent drug) in both cases alongside various therapeutic medicines. In one case accidental poisoning with rilmazafone was determined to be the cause of death. In the other case the cause of death was determined to be intoxication with loperamine, but with rilmazafone and alimemazine making a possible contribution [Krondstrand et al 2023].

3.72. Rilmazafone has not been detected in the UK, but in the absence of appropriate analytical standards it can only have been presumptively detected in blood/plasma samples using theoretical mass spectrometry data.

(#18) Alprazolam triazolobenzophenone

3.73. This compound was developed by the Upjohn Company in the 1980s as a water-soluble pro-drug of alprazolam intended for administration as an injection or infusion. It rapidly converts to alprazolam at neutral pH.

3.74. Alprazolam triazolobenzophenone was first notified by Spain in March 2014, in a border seizure of 1 kg of powder that had originated from India. There is no current evidence of prevalence or health harms associated with this compound in the UK.

3.75. It is possible that alprazolam triazolobenzophenone could have been missed in analysis of post mortem samples because of its rapid metabolism to alprazolam and the detection of that compound might not be recognised as arising from use of alprazolam triazolobenzophenone. Also, in the absence of appropriate reference standards it could only be detected presumptively in blood/plasma samples using theoretical mass spectrometry data.

4. Conclusions

4.1. A further 18 novel benzodiazepines or related compounds have appeared in international and UK drug markets since our last report on novel benzodiazepines in 2020.

4.2. Of these, **desalkylgidazepam (#2)**, **methylclonazepam (#3)** and **clobromazolam (#8)** have been detected by multiple sources in drug seizures, submitted drug samples and post mortem toxicology case work in the UK. There have also been occasional UK detections of **4'-Chloro-deschloroalprazolam (#9**) and **gidazepam (#1).** These five compounds (or their active metabolites) have chemical structures similar to those of more established benzodiazepines and/or evidence of similar pharmacology. While the evidence of harms from these specific compounds is limited, it is very likely that these will be similar to those of more established benzodiazepines and therefore a similar level of control under the MDA as Class C compounds is appropriate.

4.3. There are also nine benzodiazepines or related compounds that have been detected in Europe, although not so far in the UK. These are **cloniprazepam (#5), difludiazepam (#6), thionordazepam (#7), clobromazolam (#8), fluclotizolam (#10), deschloroclotizolam (#11), flubrotizolam (#12), fluetizolam (#13) and bentazepam (#14)**. These also present a potential risk of harm in the UK because of (a) direct evidence of harms associated with misuse and/or (b) their close structural similarity to currently controlled benzodiazepines that are known to be associated with harms.

4.4. A tenth compound, **rilmazafone (#17)**, although not a benzodiazepine, is converted to benzodiazepine metabolites in the body. Low doses are required for its clinical effects, which are similar to those of currently controlled benzodiazepines. Rilmazafone has not yet been detected in the UK, but it has been detected in Europe where it is reported to have caused at least one overdose death.

4.5. There is a significant risk of the 10 compounds listed in paragraphs 4.3 and 4.4 appearing in the UK, and of delays in their detection as the laboratory assays used may not look for them, one reason being lack of availability and affordability of appropriate chemical standards. To illustrate this, methylclonazepam and clobromazolam had been detected in Europe but not in the UK at the time of evidence collection for our previous report, but there have now been many detections of both of these compounds. In view of their potential harms, it is therefore also appropriate for these 10 substances to be classified as Class C compounds under the MDA 1971 now, based on their potential harms, rather than waiting for their detection in the UK before taking further action.

4.6. For the remaining 3 compounds considered in this report, the ACMD considers that there is currently inadequate evidence of harms or potential harms. Therefore, they do not require control via the MDA of 1971 unless further evidence of harms appears in the future:

Cinazepam (#4) has complex pharmacology, being a partial agonist but with a major metabolite that is a full agonist. The result is relatively weak sedative and muscle relaxant effects. Although detected in Europe in 2019, Cinazepam has not yet been detected in the UK. As a medicinal product, it is exempted from the PSA (2016).

Tofisopam (#15) is a 2,3-benzodiazepine that does not act on the GABA receptor, and in comparison to most 1,4 benzodiazepines, is of lower potency and higher recommended medicinal dosage (300 mg/day). There has been only a single detection of tofisopam in the UK. It is also exempted from the PSA (2016) because it meets the definition of a medicinal product.

Alprazolam triazolobenzophenone (#18) is not a benzodiazepine but is converted to the Class C compound alprazolam in the body. Although first detected in Europe in 2014, it has rarely been encountered since and never in the UK.

4.7. It should be noted that the previous lack of appropriate standards for gidazepam, rilmazafone and alprazolam triazolobenzophenone may have resulted in their involvement in fatal cases of toxicity not being recognised. It is less likely that these compounds would not be identified correctly in seized drug samples as if necessary these samples will be sent on for more complex analysis in specialist laboratories using techniques like Nuclear Magnetic Resonance (NMR) and/or high-resolution mass spectrometry (HRMS).

4.8. All but two of the 15 compounds recommended for control under the MDA 1971 are not currently licensed as medicines in any country in the world. These 13 unlicensed compounds should therefore be placed in Schedule 1 of the MDR. They should also be designated as controlled drugs to which section 7(4) of the MDA 1971 applies, since they have no recognised medicinal use outside of research in the UK.

4.9. Gidazepam (#1) and rilmazafone (#17) are licensed as medicines in other countries but not in the UK. Of particular importance, gidazepam is licensed in Ukraine and there are currently substantial numbers of Ukrainian refugees in the UK. It is important that scheduling decisions affecting these compounds do not create a barrier to legitimate prescribing for those already stabilised on these medicines that is disproportionate to their risks of misuse.

4.10. The ACMD, however, has not received any evidence of the licensed importing or prescribing of gidazepam or rilmazafone on a named patient basis to patients in the UK. The ACMD therefore advises that these compounds should also be placed in Schedule 1 of the MDR, consistent with the ACMD Standard Operating Procedure [ACMD 2021], and be designated as controlled drugs to which section 7(4) of the MDA 1971 applies.

4.11. If there are people in the UK who need prescriptions of these compounds, personal licenses can be granted to allow import of Schedule 1 drugs in exceptional circumstances [Home Office, 2019], although this could be

challenging for patients and healthcare professionals to negotiate and might compromise ongoing treatment. A license is also required should visitors need to bring medicines into the UK that are listed in Schedule 1.

4.12. Should evidence emerge of significant legitimate importing or prescribing on a named patient basis of gidazepam or rilmazafone, the Government may consider one or both of the following actions:

(a) Commissioning guidance for healthcare professionals on how to safely transfer patients from these drugs to a suitable alternative that is licensed in the UK.

(b) Placing them in Schedule 4 Part 1 of the MDR (consistent with most benzodiazepines that are licensed in the UK). Under these circumstances they should not be designated as controlled drugs to which section 7(4) of the MDA 1971 applies.

5. Recommendations

Recommendation 1: The ACMD recommends that the following 15 substances are classified under Class C of the Misuse of Drugs Act 1971, consistent other classified benzodiazepines. Note that IUPAC names are provided in Annex 2.

- Gidazepam
- Desalkylgidazepam
- Methylclonazepam
- Cloniprazepam
- Difludiazepam
- Thionordazepam
- Clobromazolam
- 4'-Chloro-deschloroalprazolam
- Fluclotizolam
- Deschloroclotizolam
- Flubrotizolam
- Fluetizolam
- Bentazepam
- Bretazenil,
- Rilmazafone

Leads: Home Office

Measure of outcome: The inclusion of these compounds in Class C of the Misuse of Drugs Act 1971.

Recommendation 2: The ACMD recommends that the following should be added to Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) because they have no medicinal use in the UK. They should also be designated as controlled drugs to which section 7(4) of the 1971 Act applies.

- Gidazepam
- Desalkylgidazepam
- Methylclonazepam
- Cloniprazepam
- Difludiazepam
- Thionordazepam
- Clobromazolam
- 4'-Chloro-deschloroalprazolam
- Fluclotizolam
- Deschloroclotizolam
- Flubrotizolam
- Fluetizolam
- Bentazepam
- Bretazenil,
- Rilmazafone

Leads: Home Office

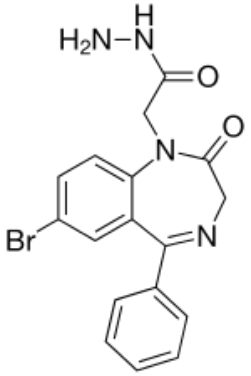
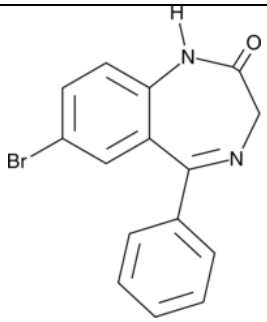
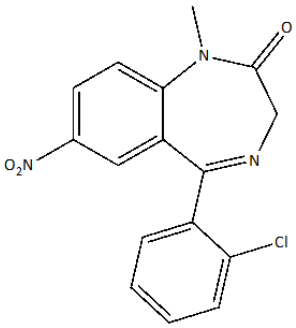
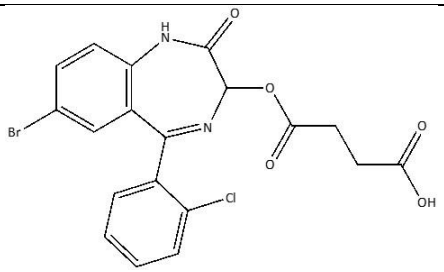
Measure of outcome: The inclusion of these compounds in Schedule 1 of the Misuse of Drugs Regulations 2001 and designation as controlled drugs to which section 7(4) of the 1971 Act applies

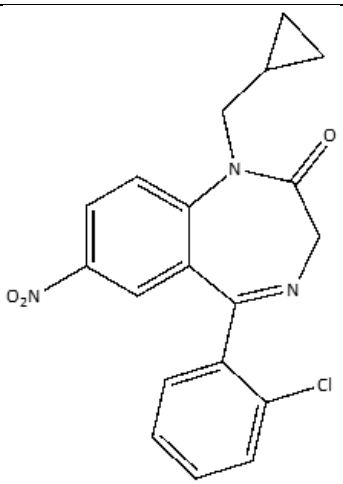
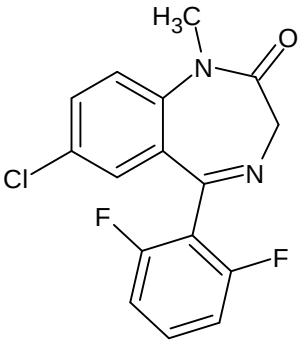
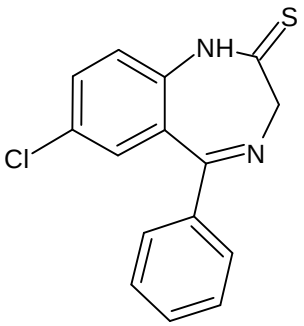
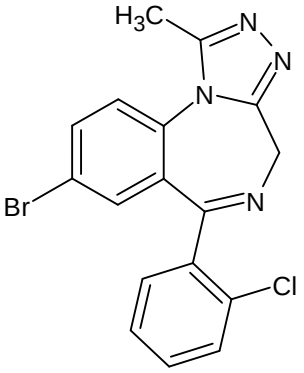
Annex A: List of benzodiazepines controlled under the Misuse of Drugs Act 1971 and Misuse of Drugs Regulations 2001

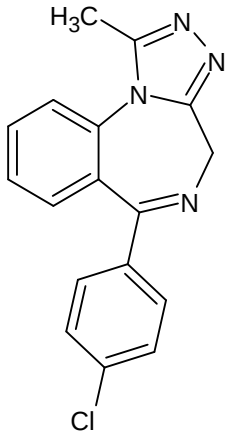
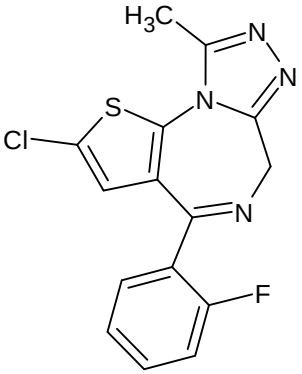
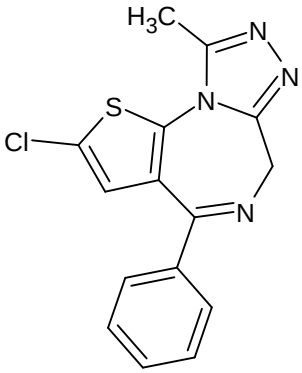
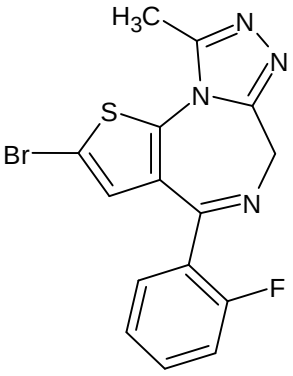
Category	**Licensed as medicines in the UK**		**Not licensed as medicines in the UK**		
MDA status	**Class C**	**Class C**	**Class C**	**Class C**	**Class C**
MDR Schedule	**Schedule 4 Pt 1**	**Schedule 3**	**Schedule 4 Pt 1**	**Schedule 3**	**Schedule 1**
Examples	Alprazolam Chlordiazepoxide Clobazam Clonazepam Diazepam Flurazepam Loprazolam Lorazepam Lormetazepam Nitrazepam Oxazepam	Midazolam Temazepam	Bromazepam Brotizolam Camazepam Clorazepic acid Clotiazepam Cloxazolam Delorazepam Estazolam Fludiazepam Halazepam Haloxazolam Ketazolam Medazepam Nimetazepam Nordazepam Oxazepam Oxazolam Pinazepam Prazepam Remimazolam Tetrazepam Triazolam	Flunitrazepam Phenazepam	Adinazolam Bromazolam 4'-Chlorodiazepam Clonazolam Deschloroetizolam Diclazepam Etizolam Flubromazepam Flubromazolam Fonazepam 3-Hydroxyphenazepam Meclonazepam Metizolam Nifoxipam Nitrazolam Pyrazolam Flualprazolam* Flunitrazolam* Norfludiazepam*

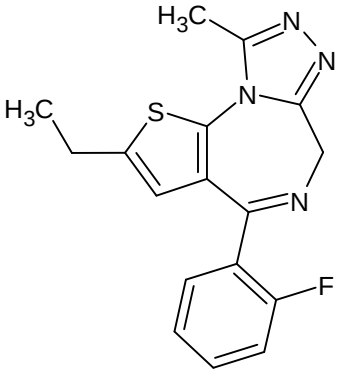
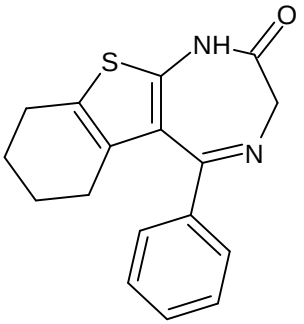
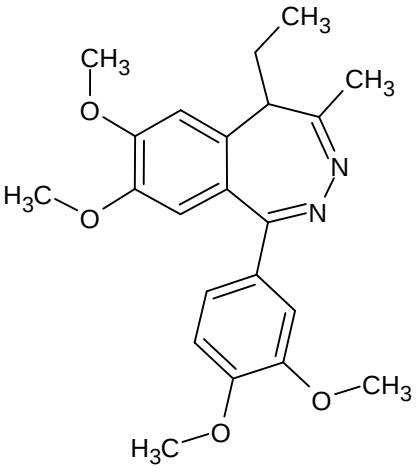
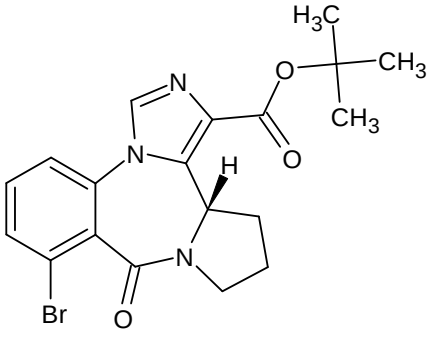
*3 substances most recently controlled following recommendations made by the ACMD in the 2020 report.

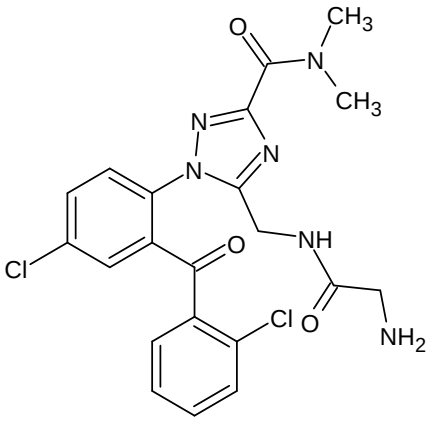
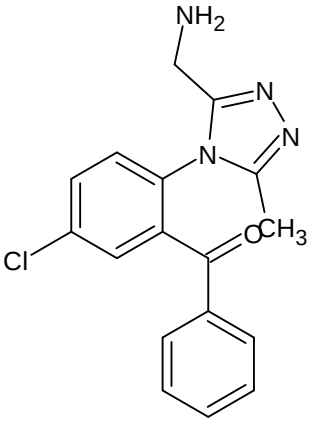
Annex B: Chemical structures and synonyms of compounds considered in this report.

	Name	Synonyms	Structure
1,4 benzodiazepines			
#1	Gidazepam	Hidazepam Hydazepam 7-bromo-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-acetic acid, hydrazide	
#2	Desalkylgidazepam (Metabolite of gidazepam)	Bromonordiazepam Bromo-nordazepam 7-bromo-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one	
#3	Methylclonazepam	ID 690 Ro 05-4082 5-(2-chlorophenyl)-1-methyl-7-nitro-3*H*-1,4-benzodiazepin-2-one	
#4	Cinazepam	BD-798 Levana® 4-[[7-bromo-5-(2-chlorophenyl)-2-oxo-1,3-dihydro-2*H*-1,4-benzodiazepin-3-yl]oxy]-4-oxo-butanoic acid	

#5	Cloniprazepam	Kloniprazepam 1-Cyclopropylmethyl clonazepam 5-(2-chlorophenyl)-1-(cyclopropylmethyl)-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one	
#6	Difludiazepam	Ro 07-4065 7-chloro-5-(2,6-difluorophenyl)-1-methyl-3*H*-1,4-benzodiazepin-2-one	
#7	Thionordazepam	Thionordiazepam 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-thione	
Triazolobenzodiazepines			
#8	Clobromazolam	Phenazolam 8-bromo-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	

#9	4'-Chloro-deschloroalprazolam	6-(4-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	
Thienotriazolodiazepines			
#10	Fluclotizolam	2-chloro-4-(2-fluorophenyl)-9-methyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine	
#11	Deschloroclotizolam	Thienodiazepine 2-Chloro-9-methyl-4-phenyl-6*H*-thieno(3,2-f)(1,2,4)triazolo(4,3-a)(1,4)diazepine	
#12	Flubrotizolam	2-Bromo-4-(2-fluorophenyl)-9-methyl-6*H*-thieno(3,2f)(1,2,4)triazolo(4,3a)(1,4)diazepine	

#13	Fluetizolam	2'-Fluorodeschloroetizolam 2-ethyl-4-(2-fluorophenyl)-9-methyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine	
Thienodiazepine (modified 1,4 benzodiazepine)			
#14	Bentazepam	Thiadipone Tiadipone 5-phenyl-1,3,6,7,8,9-hexahydro-2*H*-[1]benzothieno[2,3-e][1,4]diazepin-2-one	
2,3 Benzodiazepine			
#15	Tofisopam	1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3- benzodiazepine	
Imidazopyrrolobenzodiazepine			
#16	Bretazenil,	Ro 16-6028 Bretazenilum *tert*-butyl-8-bromo-11,12,13,13a-tetrahydro-oxo-9*H*-imidazo(1,5-a)-pyrrolo(2,1-c)(1,4)benzodiazepine-1-carboxylate	

Benzodiazepine pro-drug			
#17	Rilmazafone	Rhythmy 450191-S 5-([(2-aminoacetyl)amino]methyl)-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-*N,N*-dimethyl-1,2,4-triazole-3-carboxamide	
Other			
#18	Alprazolam triazolobenzophenone	[2-[3-(aminomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]-5-chlorophenyl] phenyl-methanone	

Annex C: Sources and quality of evidence

This report has been written in accordance with the ACMD Standard Operating Procedure for using evidence in ACMD reports [ACMD, 2021).

To evidence the identification and prevalence of novel benzodiazepines in the UK, the ACMD's NPS Committee wrote to stakeholders requesting available data on the 18 substances listed in Annex B in July 2023. Responses were received from the following (which may include submissions of 'no data held')

External agencies:

- Office for Health Improvement and Disparities (law enforcement drug seizure data)
- Eurofins (law enforcement drug seizure data)
- EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS (EU-MADNESS)
- Forensic Service of Northern Ireland (law enforcement drug seizure data)
- Northern Ireland Statistics and Research Agency (post mortem toxicology data)
- National Programme on Substance Abuse Deaths (post mortem toxicology data)
- National Poisons Information Service (enquiries from health professionals about patients with suspected poisoning)
- Rapid Action Drug Alerts and Response study (toxicology data from hospital patients in Scotland)
- Scottish Police Authority Forensic Services (law enforcement drug seizure data, toxicology analysis of biological samples from complainers and accused in relation to criminal or traffic offences, post mortem toxicology data)
- NHS Grampian/Crown Office and Procurator Fiscal Service (post mortem toxicology data)
- Leverhulme Research Centre for Forensic Science, University of Dundee (non-judicial seized samples from Scottish prisons)
- SOCOTEC UK (law enforcement drug seizure data)
- Welsh Emerging Drug & Identification of Novel Substances (WEDINOS, submitted sample analysis)

Government agencies:

- Forensic Early Warning System (DSTL)
- Medicines and Healthcare products Regulatory Agency (MHRA)

The report also draws on evidence from peer-reviewed literature (UK and international publications) and government reports. The ACMD considered international approaches when drafting its recommendations.

Quality of evidence (design, limitations, bias)

For many of the recently-encountered compounds considered in this report, there was limited direct evidence of their availability and harms. The ACMD has therefore made recommendations on their classification and schedule based on the known harms of other similar compounds for which more evidence is available.

It is important to note that owing to the ‘novelty’ of all of these substances, forensic testing is limited and inconsistent across the UK and as a result, compounds of interest may not be detected. This is especially likely for those compounds for which reference standards have been unavailable. As a result their prevalence in UK drug markets may be unrecognised or underestimated.

Annex D: List of abbreviations used in this report

ACMD	Advisory Council on the Misuse of Drugs
4-ANPP	4-anilino-N-phenethylpiperidine
CFSRE	Center for Forensic Science Research & Education
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU-MADNESS	EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS
GABA	Gamma amino butyric acid
HRMS	High-Resolution Mass Spectrometry
IONA	Identification of Novel Psychoactive Substances
IUPAC	International Union of Pure and Applied Chemistry
Ki	Inhibition constant (concentration of drug needed to occupy 50% of receptors)
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
NADDI	National Association of Drug Diversion Investigators
NDEWS	National Drug Early Warning System
NHS	National Health Service
NMR	Nuclear Magnetic Resonance
NPSAD	National Programme on Substance Abuse Deaths
NPS	Novel Psychoactive Substances
PDE	Phosphodiesterase
PSA	Psychoactive Substances Act 2016
QSAR	Quantitative structure-activity relationship analysis (QSAR)
THC	Tetrahydrocannabinol
UK	United Kingdom
USA	United States of America
WEDINOS	Welsh Emerging Drug & Identification of Novel Substances

Annex E: ACMD membership, at time of publication

Dr Ann Sullivan	Consultant physician in HIV and sexual health
Dr Anne Campbell	Reader in substance use and mental health and co-director of the Drug and Alcohol Research Network at Queens University Belfast
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services at NHS Greater Glasgow and Clyde
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust
Professor David Taylor	Professor of psychopharmacology, King's College, London
Dr Derek Tracy	Medical director of West London NHS Trust
Dr Emily Finch	Clinical director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Professor Graeme Henderson	Professor of pharmacology at the University of Bristol
Mr Harry Shapiro	Director – DrugWise
Dr Hilary Hamnett	Senior lecturer in forensic science, University of Lincoln
Professor Judith Aldridge	Professor of criminology at the University of Manchester
Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Mr Lawrence Gibbons	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Mr Mohammed Fessal	Chief pharmacist, Change Grow Live
Professor Owen Bowden-Jones	Chair of Advisory Council on the Misuse of Drugs, Consultant psychiatrist, Central North-West London NHS Foundation Trust

Dr Paul Stokes	Senior clinical lecturer in mood disorders, King's College, London
Dr Richard Stevenson	Emergency medicine consultant, Glasgow Royal Infirmary
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Ms Rosalie Weetman	Public health lead (alcohol, drugs and tobacco), Derbyshire County Council - (currently on secondment to Office for Health Improvement and Disparities, as programme manager, Drug and Alcohol Improvement Support Team)
Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and professor of clinical pharmacology and therapeutics, Newcastle University

Annex F: ACMD NPS Committee membership, at time of publication

Dr Ann Sullivan	Consultant physician in HIV and sexual health
Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Mr Paul Bunt	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Mr Peter Cain	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Mr Lawrence Gibbons	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	Senior lecturer in forensic science, University of Lincoln
Professor Graeme Henderson	Professor of Pharmacology at the University of Bristol
Professor Stephen Husbands	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson*	Emergency Medicine Consultant, Glasgow Royal Infirmary
Professor Simon Thomas*	NPS Committee Chair, Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical

	Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble*	Retired Laboratory of the Government Chemist (LGC) expert
Dr David Wood	Consultant physician and clinical toxicologist at Guy's and St Thomas' and reader in clinical toxicology at King's College London

In addition to members of the NPS committee listed, significant contributions were made by the following co-opted member of the Working Group:

Dr Peter Maskell*	Senior Forensic Toxicologist, Scottish Police Authority Forensic Services and Honorary Associate Professor, University of Glasgow

*Novel benzodiazepine working group members

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