

ACMD

Advisory Council on the Misuse of Drugs

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Sarah Newton MP
Minister for Vulnerability, Safeguarding and Countering Extremism
Home Office
2 Marsham Street
London SW1P 4DF

2 December 2016

Dear Minister,

I am writing to recommend that you lay a temporary class drug order (TCDO) pursuant to section 2A of the Misuse of Drugs Act 1971 (MDA) for the following substances:

- U-47,700
- Etizolam and other designer benzodiazepines.

Please find enclosed two reports containing the Advisory Council on the Misuse of Drugs' (ACMD) consideration of the evidence of harms on these substances.

U-47,700

U-47,700 is a synthetic opioid, originally developed as a research chemical but with no legitimate use. Reportedly 7.5 times more potent than morphine it is a structural analogue of AH-7921. AH-7921 was controlled as a Class A drug in January 2015 following ACMD advice, particularly regarding its high addiction potential.

The ACMD is concerned that abuse of U-47,700 has the potential for severe harms, particularly following reports from the USA of more than 80 deaths attributed to this substance and that the patterns of abuse are mirroring those of heroin.

The US Drug Enforcement Administration has consequently subjected U-47,700 to temporary emergency scheduling under the Controlled Substances Act.

Designer Benzodiazepines

Benzodiazepines such as diazepam and chlordiazepoxide have had medical applications for more than 50 years, particularly as sedatives. Many of these are contained in Class C of the

MDA due to their potential for tolerance and dependence resulting in severe withdrawal symptoms.

Benzodiazepines also have a long history of abuse, frequently illicitly sourced by diversion from the legitimate supply chain.

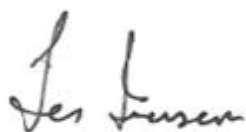
The ACMD is aware of increasing reports of harms associated with designer benzodiazepines. These are substances which are not licensed medicines in the United Kingdom, but are imported specifically for abuse as Novel Psychoactive Substances (NPS).

Of particular concern is **Etizolam**, which has reportedly become the predominant benzodiazepine abused within the illicit drug market across Scotland and has been implicated in several deaths across the UK.

In addition, the ACMD wish to include several other designer benzodiazepines in their TCDO recommendation: **Adinazolam, Bromazolam, 4'-Chlorodiazepam, Clonazolam, Deschloroetizolam, Diclazepam, Flubromazepam, Flubromazolam, Fonazepam, 3-Hydroxyphenazepam, Meclonazepam, Metizolam, Nifoxipam, Nitrazolam and Pyrazolam**, to reduce the displacement from Etizolam to other related substances with similar associated harms.

The ACMD is convinced that due to the severity of the potential harms caused by abuse of these substances, immediate TCDO action is necessary to prevent further deaths.

Yours sincerely,



Professor Les Iversen
ACMD Chair



Professor Simon Gibbons
Chair of the ACMD's NPS Committee

CC:

Rt Hon. Amber Rudd MP (Home Secretary)

Rt Hon. Jeremy Hunt MP (Secretary of State for Health)

Nicola Blackwood MP (Parliamentary Under Secretary of State for Public Health and Innovation)

Minister for Health and Social Services, Wales

Minister for Public Health, Scotland

Minister for Health, Social Services & Public Safety, Northern Ireland

ACMD

Advisory Council on the Misuse of Drugs

U-47,700

A review of the evidence of use and harm

Background

1. U-47,700 is a research drug that was developed and patented by the Upjohn Company in the 1970's³. The Advisory Council on the Misuse of Drugs (ACMD) was alerted to this substance in 2016 following reports of its increasing abuse and potent effects, similar to Class A substances. This report also follows the recent decision by the United States Drug Enforcement Administration (DEA) to subject U-47,700 to temporary control in Schedule 1 of the Controlled Substances Act, following tens of deaths associated with the substance.

Chemistry and Pharmacology

2. U-47,700 (*Annex A*) is a derivative of dimethylaminocyclohexane with a 3,4-dichlorobenzoylamide moiety attached.
3. The IUPAC name is 2-(3,4-dichlorophenyl)-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylacetamide¹.
4. It is an analogue of AH-7921, a Class A substance under the Misuse of Drugs Act 1971.
5. U-47,700 is described by the EMCDDA as a potent opioid¹.
6. It is reportedly 7.5 times more potent than morphine (in animal studies), but has a shorter duration of action (reported to last between 60 to 90 minutes)¹.
7. U-47,700 is a selective μ -opioid receptor agonist ($K_d = 5.3$ and 910 nM for μ and K -opioid receptors respectively)¹.
8. U-47,700 has not been studied in humans, however it may have abuse liability and dependence potential, based on users' reported experiences¹.
9. Users report the effects of U-47,700 to be similar to those of other opioids⁴. Reported positive effects include feelings of euphoria and a general lift in mood⁷.
10. Negative effects include respiratory depression and a strong urge to re-dose⁷.

Legitimate Uses

11. The ACMD consulted with the Medicines and Healthcare products Regulatory Agency (MHRA) and found no UK marketing authorisations for U-47,700 as a medicine.

Misuse and Abuse

12. U-47,700 was first notified as an NPS in Europe to the EMCDDA in 2015, following a seizure by Swedish customs¹. It has since been identified in Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Lithuania, Poland, Slovenia, Spain and the United Kingdom².

13. U-47,700 can be inhaled, insufflated, taken orally as tablets and injected¹.
14. In the US, the patterns of abuse of U-47,700 mimic those of heroin and other opioids: the clandestine forms of distribution include ‘deals’ contained in knotted plastic and stamped with logos⁴.
15. This substance is therefore likely to be sought as a legal substitute by users of illicit opioids such as heroin and/or prescription opioids.
16. U-47,700 is being obtained as a ‘research substance’ from unregulated sources, particularly online. Therefore the purity, identity and quality are inconsistent⁴.
17. The DEA reports that U-47,700 may act as a precursor to opioid use and dependence⁴.

Acute Harms

18. Users of U-47,700, particularly those who are using it for the first time, are likely to be at risk of developing substance use disorders, overdose and death⁴.
19. The EMCDDA reported three deaths in Europe in 2016 where U-47,700 has contributed or been the cause (Belgium, Sweden and the United Kingdom).
20. With regards to the death in the UK¹, Brandt *et al.* noted that there was no information or evidence of prior opioid use in the individual involved⁷.
21. The public health risks posed by U-47,700 are therefore the same as heroin, fentanyl and other opioid analgesics⁴.
22. In the US, the DEA have received reports of at least 46 confirmed deaths related to U-47,700⁴.

Chronic Harms

23. As this substance has only appeared as an NPS in 2015, there are no data on its long term effects.

Prevalence

24. The EMCDDA reported an increase in detection of U-47,700 since the end of 2015¹.
25. The EMCDDA reported several notable seizures of U-47,700 in Europe including over 1 kg in powder form and 260 ml of liquid. The largest single seizure of U-47,700 in powder form was 1.054 kg, which was seized in Spain, en route from China to Barcelona in January 2016¹.
26. In the US, seizures of U-47,700 have been encountered in the form of counterfeit tablets that mimic pharmaceutical opioids⁴.

27. Information from the National Poisons Information Service (NPIS) recorded a total of four accesses to the TOXBASE[®] database regarding U-47,700 (from 17 November 2015 until 13 July 2016)⁵.
28. Police Scotland made a total of six seizures of tablets containing U-47,700 which had the appearance of Diazepam tablets⁶. Three of these seizures amounted to a total of 2,626 tablets between January and March 2016.
29. On the 1st June 2016, Police Scotland reported one further seizure in Lanarkshire, found to contain three bags of 50 tablets (150 tablets in total).

International Data

30. U-47,700 is controlled in several European countries including Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Latvia, Sweden and Turkey².
31. The US DEA published their intentions to temporarily control U-47,700 as a Schedule 1 substance under the Controlled Substances Act, with effect from November 2016, citing “U-47,700 poses an imminent hazard to public safety”⁴.

Social Harms

32. It is too early to document any social harms associated with the use of U-47,700. However, extensive knowledge of the dangers of other opioids suggest the potential for social harm. Opioid use can lead to addiction, acquisitive crime, family disruption and loss of employment and these could be predicted as possible consequences if U-47,700 were to gain widespread use.

Polysubstance Use

33. In the USA there is association between the presence of U-47,700 and fentanyl/fentanyl derivatives in post-mortem tests¹.

Conclusion

34. Given the serious adverse effects and deaths already reported in the short period U-47,700 has been available in the UK and given our knowledge of the abuse characteristics of other potent opioid drugs, the ACMD believes that U-47,700 should be subject to control in the UK.

Recommendation

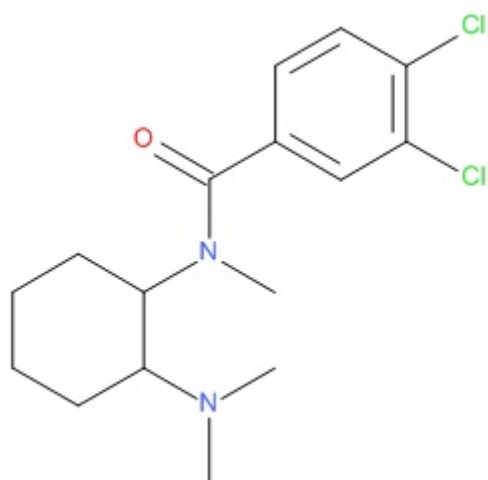
35. The ACMD has reviewed the evidence and, pursuant to Section 2B(6) of the Misuse of Drugs Act 1971, it considers that, in the case of U-47,700, it is a drug that is being, or is likely to be, misused, and that misuse is having, or is capable of having, harmful effects. **The ACMD therefore recommends that 2-(3,4-dichlorophenyl)-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylacetamide (U-47,700) be subject to a Temporary Class Drug Order (TCDO).** This is the quickest route to some level of control.

36. The control of the compound should extend to include any stereoisomeric forms, any salts of such compounds and any preparation or product containing such compounds.
37. The Council has found no evidence that U-47,700 has a recognised medicinal use and therefore advise that it is treated as a Schedule 1 drug in applying the provisions of the Misuse of Drugs Regulations (as amended).

References

1. EU EARLY WARNING SYSTEM ALERT: EU-EWS-RCS-AL-2016-0003, U-47,700 in Europe.
2. EMCDDA: EDND: European information and database on new drugs.
3. <https://patents.google.com/patent/US4098904>
4. Department of Justice, Drug Enforcement Administration, 21 CFR Part 1308; Schedules of Controlled Substances: Temporary Placement of U-47700 into Schedule 1.
5. National Poisons Information Service (NPIS): Report on enquiries from UK healthcare professionals relating to Etizolam and U-47700.
6. Police Scotland: Paper to ACMD (July to October 2016).
7. The first reported fatality associated with the synthetic opioid 3,4-dichloro-N-[2-(dimethylamino) cyclohexyl]-N-methylbenzamide (U-47700) and implications for forensic analysis; Elliott SP, Brandt SD and Smith C; Drug Test Anal. 2016 Aug;8(8):875-9. doi: 10.1002/dta.1984. Epub 2016 May 27.

Annex A: U-47,700



IUPAC name: 2-(3,4-dichlorophenyl)-N-[(1R,2R)-2-(dimethylamino)cyclohexyl]-N-methylacetamide¹.

CAS Registry number: 82657-23-6 (HCl salt); 121348-98-9 (free base)¹.

ACMD

Advisory Council on the Misuse of Drugs

Designer Benzodiazepines

A review of the evidence of use and harms

Designer Benzodiazepines

1. Benzodiazepines refer to a group of drugs which were first synthesised in the 1950's. Originally popular and widely available as sedatives, most notably 'Valium' (Diazepam), it became apparent that this class of drugs caused tolerance and dependence with severe withdrawal symptoms in its users¹.
2. Benzodiazepines take their name from the core component six-membered benzene ring that is fused to a seven-membered diazepine ring which contains two nitrogen atoms. The core benzodiazepine structure can be modified in a variety of ways to produce a range of materials with different potencies and modes of action⁸.
3. Many benzodiazepines are controlled under the Misuse of Drugs Act as Class C substances (*Annex A*). The materials listed are essentially those which are named in the 1971 UN Convention and many are not approved for use in the UK⁸.
4. There have been increasing reports of 'designer benzodiazepines'- substances which evade the MDA and have no legitimate medicinal use in the UK, being created or imported specifically for the psychoactive effect they induce.
5. The Advisory Council on the Misuse of Drugs (ACMD) have been alerted to the problematic use of these designer benzodiazepines, in particular Etizolam. This has led the ACMD to review the harms associated with the misuse of these substances. Police Scotland have reported that the situation in Scotland is particularly problematic, with Etizolam having been recovered in all police divisions across Scotland⁷.
6. This report focuses on Etizolam as a 'model' or 'typical' designer benzodiazepine, yet the ACMD's final recommendations also extend to several other designer benzodiazepines: *Diclazepam*, *Flubromazepam*, *Pyrazolam*, *Deschloroetizolam*, *Flubromazolam*, *Nitrazolam*, *Nifoxipam*, *Clonazolam*, *4'-Chlorodiazepam* and *Bromazolam*, *Meclonazepam*, *Adinazolam*, *Metizolam*, *3-Hydroxyphenazepam* and *Fonazepam*, due to their increasing prevalence, similar associated harms and to reduce the potential displacement to these from Etizolam, should a TCDO be invoked.

Chemistry and Pharmacology

7. Etizolam (4-(2-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine) (*Annex B*) in pure form is a white crystalline powder, which is soluble in methanol and chloroform but not in water².
8. Etizolam is a 'thienotriazolodiazepine' which acts on the benzodiazepine site of the GABA-A receptor.
9. In animal studies Etizolam is similar pharmacologically to diazepam². It reportedly causes similar adverse effects, such as sedation, sleepiness, muscle relaxation, ataxia, slurred speech and loss of consciousness².
10. There is a range of possible modifications which are applicable to several different benzodiazepine core structures, so there is a potential for the development of families

of novel, closely-related benzodiazepine NPS. This position is similar to that of the synthetic cannabinoids.

Medicinal Use

11. The ACMD consulted with the Medicines and Healthcare products Regulatory Agency (MHRA) and found no UK marketing authorisations for the substances in Annex F as medicines.
12. Etizolam is not registered as a medicinal product in the UK but is a recognised medicine in Japan, Italy and India. The primary application of Etizolam is for the treatment of generalised anxiety disorder with depressive symptoms². Additional medical applications include treatments for sleep problems and convulsions, as well as replacement therapies for alcohol addiction.
13. Trade names for Etizolam include: Depas, Etilaam, Etizest, Etizola, Etizolan, Pasaden and Sedekopan².
14. The recommended dosage of Etizolam for medicinal use is approximately 1 mg to 1.5 mg per day but can be up to 4 mg. This is in the form of the free base in 0.5-1 mg tablets for oral administration².

Misuse and Abuse

15. Benzodiazepines can be misused in a variety of ways. Their effects are alcohol-like and they can be used instead of alcohol; more commonly they are used with alcohol to potentiate its effects. They can also be used to 'come down' from stimulants, for example by clubbers wishing to sleep after a night out. Large overdoses and overdoses in combination with alcohol are used in suicide attempts⁸.
16. As well as being self-administered, benzodiazepines have potential for use in drug-facilitated crimes, particularly as some are known to cause amnesia⁸.
17. Etizolam was first notified as an NPS in 2011 and has reportedly been imported from Europe, the Far East and India as tablets in blister packs¹².
18. Street names for Etizolam include: Etiz, Etizzy².
19. The EMCDDA have received reports of seizures of Etizolam in the form of tablets and powders.
20. Recently, Etizolam has appeared in the form of 'blotters' (similar to LSD paper doses). Its high potency ($\approx 5x$ diazepam) allows an effective dose of a few milligrams to be present on a paper dose⁸.

Prevalence

21. The EMCDDA have received notifications that Etizolam has been detected in several European countries including Cyprus, Denmark, Finland, France, Germany, Hungary,

Norway, Lithuania, Luxembourg, Spain, Sweden and the United Kingdom often in transit from China¹².

22. Intelligence from Police Scotland shows a general decrease in the prominence of Diazepam, an exponential increase in Etizolam and a more gradual increase in Diclazepam. Current trends, as identified by forensic services in Scotland, suggest that Etizolam has become the predominant benzodiazepine abused within the illicit drug market across Scotland⁴.
23. The ACMD is concerned with Police Scotland's report that a number of benzodiazepines are being sold as "street valium". When analysed, tablets with the appearance of diazepam tablets were found to contain diclazepam, diazepam, a mixture of etizolam and the synthetic opiate U-47,700 or U-47,700 on its own.
24. The Forensic Early Warning System (FEWS) project detected Etizolam in their prison collection plan in 2015 to 2016 and Diclazepam in their head shop collection plan for the same period¹⁰.
25. Information from the National Poisons Information Service (NPIS) record a total of 1257 accesses to the TOXBASE[®] database regarding Etizolam (from 18 June 2013 until 13 July 2016). There were an additional 93 telephone enquiries during the same time period¹¹.

Acute Harms

26. Etizolam has been detected regularly in post-mortem cases since October 2013. Drug-related deaths evidence from Police Scotland indicates that there has been a spike in the presence of Etizolam in post-mortem toxicology results since the end of 2015, with projection data suggesting this could increase to 50 drug-related deaths per month in Scotland³ (*Annex C*).
27. There has also been a 113% increase in Section 4 Road Traffic Act 1988 cases, as tested by Scottish Police Authority Forensic Services and an 800% increase in those involving Etizolam³.
28. In Glasgow, one NHS hospital has reported that the number of presentations of patients presenting at Accident and Emergency with benzodiazepine overdoses hit a peak of six patients per day³.
29. The EU-MADNESS project collates drug-related deaths data from Scotland and Northern Ireland. There have been 46 deaths in 2016 registered in Scotland during the first six months of 2016 where Etizolam has been implicated and 22 deaths involving Diclazepam⁹ (*Annex D*).

Chronic Harms

30. Prolonged use of benzodiazepines can lead to tolerance and dependence which can be difficult to resolve⁸.

Social Harms

31. It is too early to document any social harms associated with the use of Etizolam.

Polysubstance Use

32. The misuse of benzodiazepines by high-risk opioid users is common and associated with morbidity and mortality among this group⁴.
33. Data from the National Programme on Substance Abuse Deaths (NPSAD) indicated that in 2015 there were a total of 25 instances where an uncontrolled benzodiazepine was implicated in the cause of death. In all cases, these substances were found in combination with other drugs, and over half were combined with other NPS. Heroin or morphine was found in twelve cases and methadone in two⁵.
34. NPSAD data showed 32 instances where a non-controlled benzodiazepine was found in post-mortem toxicology (*Annex E*). These uncontrolled benzodiazepines were implicated with other drugs in 21 cases (11 of which were other NPS)⁵.

International Control

35. Etizolam is controlled in several European countries including Denmark, Estonia, Finland, Germany, Italy, Sweden and Turkey¹².

Conclusion

36. The risks associated with the designer benzodiazepines are very similar to those of the currently controlled benzodiazepines, and some are highly potent. Etizolam has been implicated in drug related deaths in the UK this year and reports from different sources also indicate harms and death. There has also been a report of Etizolam being mixed with a potent opiate. There is therefore an imminent case for control.
37. There is a risk that controlling one benzodiazepine could lead to displacement to other benzodiazepines which have the potential to cause harms. Therefore ACMD consider that control should apply to a **group of listed** benzodiazepines (*Annex F*).
38. There is also the potential that other designer variants could emerge in the future as the structures can be easily modified.

Recommendation

39. The ACMD has reviewed the evidence and, pursuant to Section 2B(6) of the Misuse of Drugs Act 1971, it considers that, in the case of the Etizolam, this is a drug that is being, or is likely to be, misused, and that misuse is having, or is capable of having, harmful effects.
40. **The ACMD therefore recommends that 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (Etizolam) be subject to a TCDO.**

41. The ACMD also recommends that the following closely-related compounds be subject to a Temporary Class Drug Order (TCDO):

- **7-Chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (Diazepam)**
- **7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (Flubromazepam)**
- **8-Bromo-1-methyl-6-(2-pyridinyl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (Pyrazolam)**
- **2-Ethyl-9-methyl-4-phenyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (Deschloroetizolam)**
- **8-Bromo-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (Flubromazolam)**
- **1-Methyl-8-nitro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (Nitrazolam)**
- **5-(2-Fluorophenyl)-3-hydroxy-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (Nifoxipam)**
- **6-(2-Chlorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (Clonazolam)**
- **7-Chloro-5-(4-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (4'-Chlorodiazepam)**
- **8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (Bromazolam)**
- **(3S)-5-(2-Chlorophenyl)-3-methyl-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (Meclonazepam)**
- **1-(8-Chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-1-yl)-N,N-dimethylmethanamine (Adinazolam)**
- **4-(2-Chlorophenyl)-2-ethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine (Metizolam)**
- **7-Bromo-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one (3-Hydroxyphenazepam)**
- **5-(2-Fluorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (Fonazepam)**

42. The control of the compounds should extend to include any stereoisomeric forms, any salts of such compounds and any preparation or product containing such compounds.
43. The Council has found no evidence that Etizolam, or any other of the listed compounds, has a recognised medicinal use in the United Kingdom and therefore advise that it is treated as a Schedule 1 drug in applying the provisions of the Misuse of Drugs Regulations (as amended).
44. The ACMD will continue to monitor for any potential displacement to other benzodiazepines and other compounds and keep the situation under review and provide further advice accordingly.

References

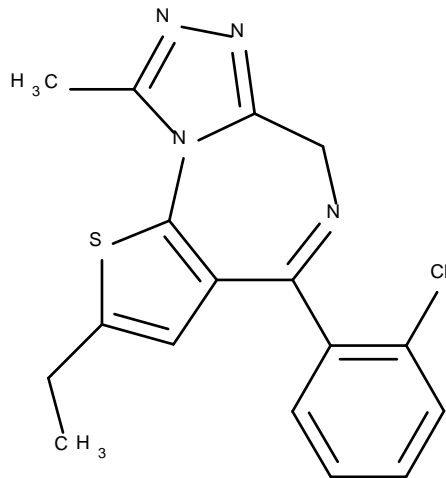
1. The Pharmaceutical Journal, Vol. 283, p305 | URI: 10978453
2. WHO Expert Committee on Drug Dependence: Etizolam (INN) Pre-Review Report
3. Police Scotland: Paper to ACMD (July to October 2016)
4. European Monitoring Centre for Drugs and Drug Addiction: Perspectives on Drugs; The Misuse of Benzodiazepines among high-risk opioid users in Europe
5. National Program on Substance Abuse Deaths (NPSAD): Update (Nov 2016)
6. NICE: <https://www.nice.org.uk/search?q=benzodiazepines>
7. Police Scotland presentation to NPS Committee (14 November 2016)
8. ACMD NPS Committee meeting paper: Benzodiazepines: 2015.
9. EU-MADNESS Project: Drug related deaths 2016, Scotland and Northern Ireland.
10. FEWS Collection Plans for Head Shops and Prisons
11. National Poisons Information Service (NPIS): Report on enquiries from UK healthcare professionals relating to Etizolam and U-47700.
12. EMCDDA: EDND: European information and database on new drugs.

Annex A: List of benzodiazepines named within the Misuse of Drugs Act

Alprazolam
Bromazepam
Brotizolam
Camazepam
Chlordiazepoxide
Clobazam
Clonazepam
Chlorazepic acid
Clotiazepam
Cloxazolam
Delorazepam
Diazepam
Estazolam
Fludiazepam
Flunitrazepam
Flurazepam
Halazepam
Haloxazolam
Ketazolam
Loprazolam
Lorazepam
Lormetazepam
Medazepam
Midazolam
Nimetazepam
Nitrazepam
Nordazepam
Oxazepam
Oxazolam
Phenazepam (added 2012)
Pinazepam
Prazepam
Temazepam
Tetraazepam
Triazolam

Annex B – Etizolam

Structure



Chemical (IUPAC name)¹⁴

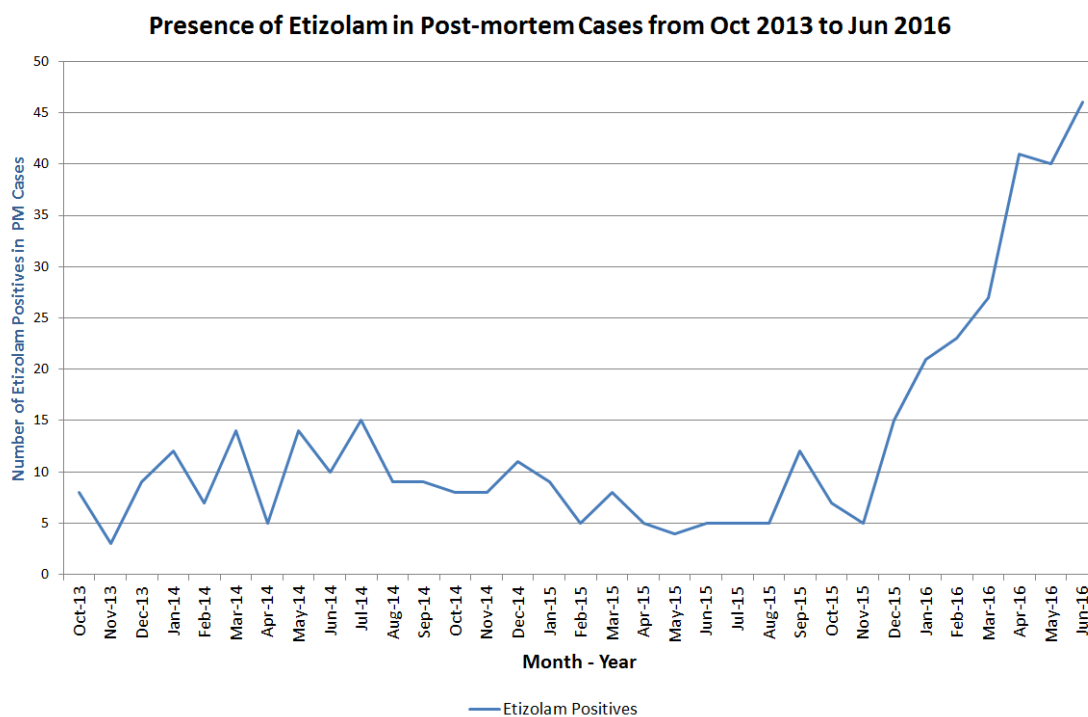
4-(2-Chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine

CAS number

40054-69-1

Annex C: Police Scotland Data

Post-mortem cases where Etizolam was detected:



Annex D: EU-MADNESS Data from National Records of Scotland

Selected benzodiazepine analogue deaths registered in Scotland (<i>Some deaths may involve both substances</i>)				
	2013	2014	2015	2016 Q1 & Q2
Diclozepam	1	6	9	22
Etizolam	8	39	47	46

Annex E: Data from NPSAD on Uncontrolled Benzodiazepines

i. Number of instances where implicated in cause of death

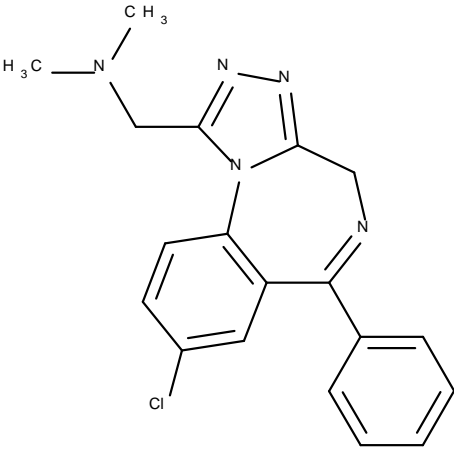
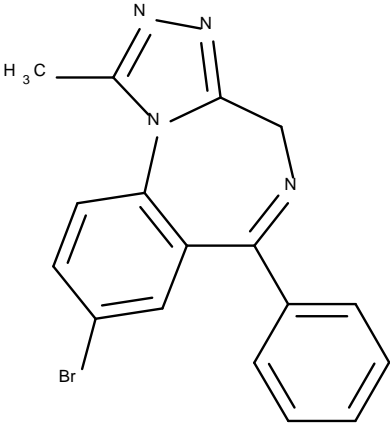
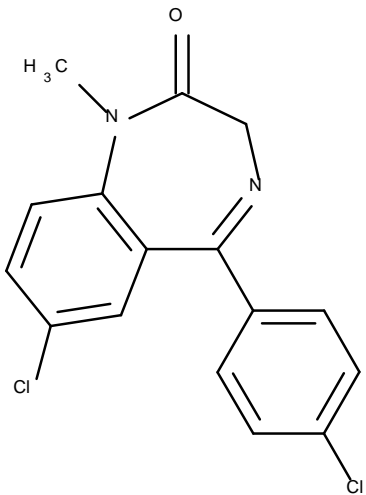
Substance	2013	2014	2015	2016
Diclozepam	0	0	3	0
Etizolam	2	8	2	1
Flubromazepam	0	3	3	1
Flubromazolam	0	0	1	0
Pyrazolam	1	0	0	0

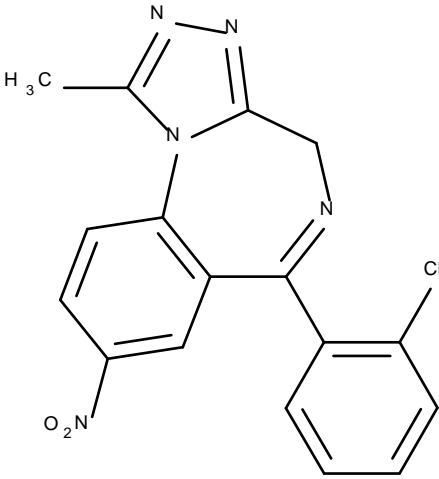
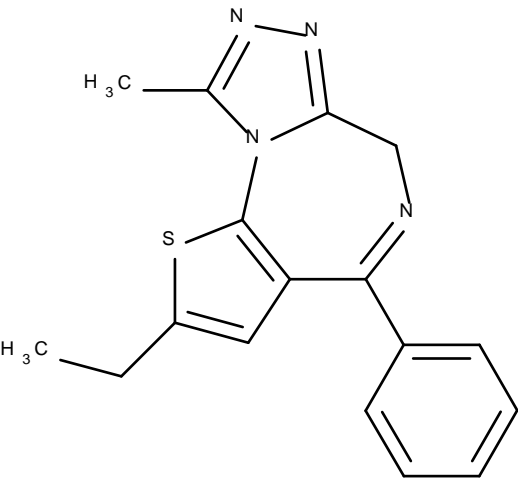
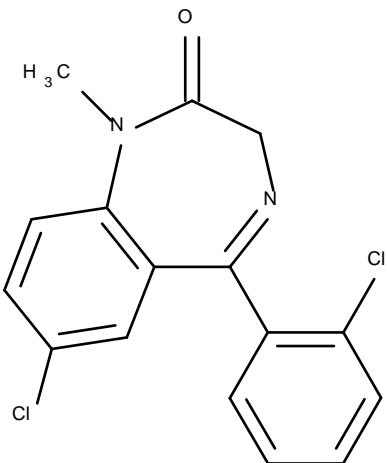
ii. Number of instances where found in post-mortem toxicology

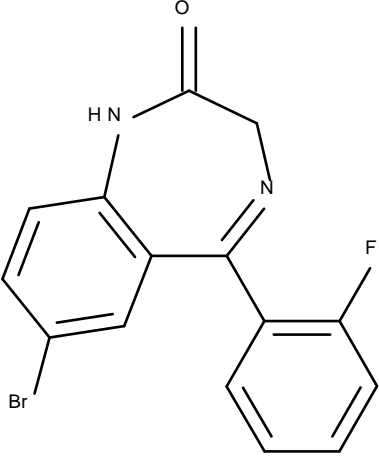
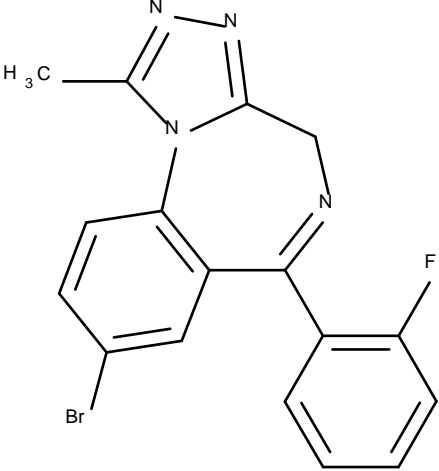
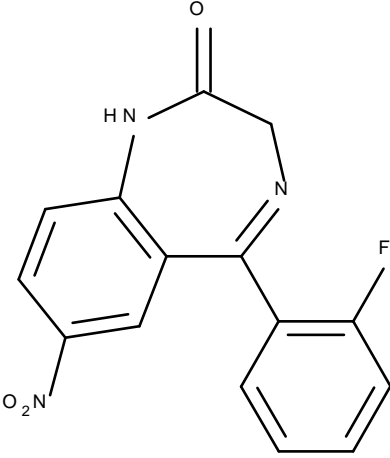
Substance	2013	2014	2015	2016
Diclozepam	0	0	4	0
Etizolam	3	9	3	2
Flubromazepam	0	3	3	1
Flubromazolam	0	0	1	0
Pyrazolam	2	0	1	0

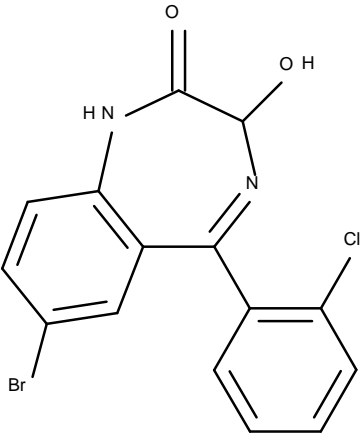
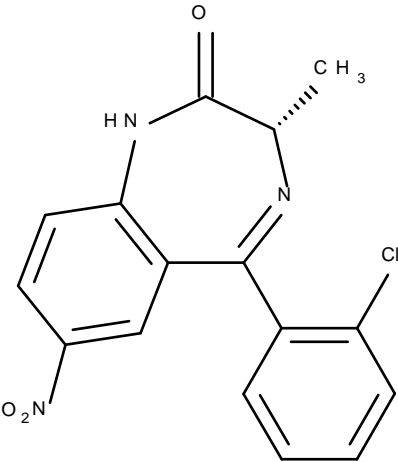
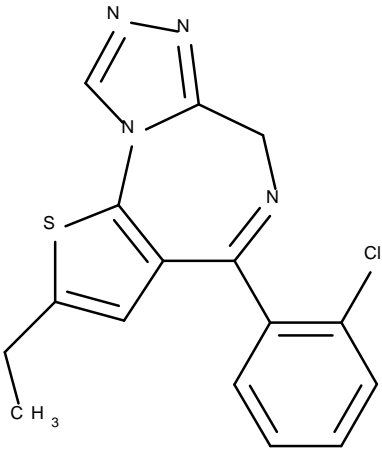
NPSAD collects data that is voluntarily submitted by coroners in England. Data collection for 2016 is not yet completed. The data presented here are based on official notifications received by NPSAD up to 11th November 2016, submitted voluntarily by Coroners in England, Wales and Northern Ireland. Due to the procedures undertaken during an inquest, there is often a significant delay between the death occurring and the inquest being concluded, and as such we anticipate receiving many more cases for 2016 and to a lesser extent 2015. Data are submitted voluntarily by Coroners and as such there may be variable and incomplete geographic coverage.

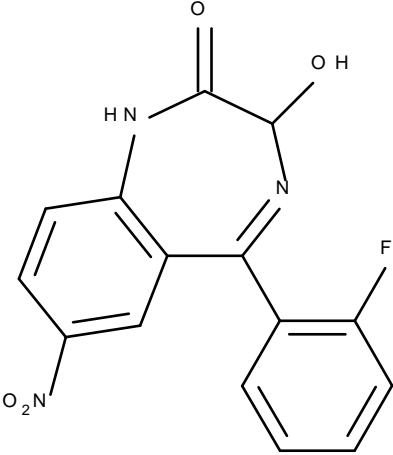
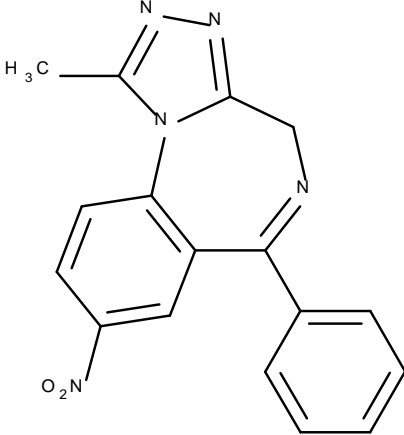
Annex F: Table of benzodiazepines with IUPAC nomenclature

Common Name	IUPAC name	Structure
Adinazolam	1-(8-Chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-1-yl)-N,N-dimethylmethanamine	
Bromazolam	8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	
4'-Chlorodiazepam	7-Chloro-5-(4-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one	

<p>Clonazolam</p>	<p>6-(2-Chlorophenyl)-1-methyl-8-nitro-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine</p>	
<p>Deschloroetizolam</p>	<p>2-Ethyl-9-methyl-4-phenyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine</p>	
<p>Diclazepam</p>	<p>7-Chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	

<p>Flubromazepam</p>	<p>7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	
<p>Flubromazolam</p>	<p>8-Bromo-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine</p>	
<p>Fonazepam</p>	<p>5-(2-Fluorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	

<p>3-Hydroxyphenazepam</p>	<p>7-Bromo-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	
<p>Meclonazepam</p>	<p>(3S)-5-(2-Chlorophenyl)-3-methyl-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	
<p>Metizolam</p>	<p>4-(2-Chlorophenyl)-2-ethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine</p>	

<p>Nifoxipam</p>	<p>5-(2-Fluorophenyl)-3-hydroxy-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one</p>	
<p>Nitrazolam</p>	<p>1-Methyl-8-nitro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine</p>	
<p>Pyrazolam</p>	<p>8-Bromo-1-methyl-6-(2-pyridinyl)-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine</p>	