<table>
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<th>Title of Guideline</th>
<th>Guideline for the use of flumazenil in adults (Version 1)</th>
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<tr>
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<td>16/07/2015</td>
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<td>Date on which guideline must be reviewed</td>
<td>16/07/2020</td>
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</table>
| Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis) | All adult patients over 16 years old:  
• With benzodiazepine overdose that is associated with respiratory depression and reduced conscious level that would otherwise require mechanical ventilation.  
Excludes:  
• Where benzodiazepines have been used in the management of fitting and status epilepticus.  
• Suspected mixed overdoses especially those including tricyclic antidepressants.  
• Use as a diagnostic tool on general wards for reduced conscious levels.  
• Patients undergoing conscious sedation for radiological or endoscopic procedures (separate Patient Group Direction applies). |
| Abstract | This guideline describes the use of flumazenil boluses and infusion within the clinical context of intentional and unintentional benzodiazepine overdose. |
| Key Words | Flumazenil, Benzodiazepine Overdose |
| Statement of the evidence base of the guideline – Evidence base: | 3, 5 |
| 1a | meta analysis of randomised controlled trials |
| 1b | at least one randomised controlled trial |
| 2a | at least one well-designed controlled study without randomisation |
| 2b | at least one other type of well-designed quasi-experimental study |
| 3 | well –designed non-experimental descriptive studies (ie comparative / correlation and case studies) |
| 4 | expert committee reports or opinions and / or clinical experiences of respected authorities |
| 5 | recommended best practise based on the clinical experience of the guideline developer |
| Consultation Process | Hospital resuscitation committee  
Navin Bedi (Consultant ED)  
Mark Simmonds (Consultant Adult Critical Care Medicine)  
Gemma George (Specialist clinical pharmacist ED)  
James Parker (Specialist clinical pharmacist Critical Care) |
| Target audience | All Nursing, Medical and Pharmacy staff |

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.
Guideline for the use of flumazenil in adult patients

Background:
Flumazenil is a competitive antagonist inhibiting the activity of benzodiazepine drugs. It is used infrequently, as an UNLICENSED INDICATION in the management of deliberate or accidental benzodiazepine overdose where reduced conscious level and respiratory depression would otherwise require mechanical ventilation.

Flumazenil has limited ability to reverse respiratory depression. Reversal of sedation restores protective airway reflexes and can improve respiratory rate.

Flumazenil has a duration of action of 1 to 2 hours which is shorter than benzodiazepine drugs commonly encountered in overdose, so repeat doses, or rarely a continuous infusion may be required to maintain clinical effect.

Clinical signs of benzodiazepine overdose include:

- Reduced conscious level (usually drowsiness, occasionally coma)
- Ataxia (staggering or unsteadiness)
- Dysarthria, confusion, nystagmus
- RARELY: bradycardia, hypotension, respiratory depression

When to avoid Flumazenil:

Contra-indication to use:

1. Suspected mixed overdose especially those including tricyclic antidepressants or other pro-convulsant drugs.
2. As a diagnostic tool for patients with a reduced conscious level on general wards (excludes use in adult critical care).
3. Status epilepticus where patients may have been inadvertently oversedated by benzodiazepines given to terminate seizure activity.
4. Post cardiac arrest.
5. Head injury, unstable intracranial pressure (ICP) as flumazenil may alter cerebral blood flow causing raised ICP or seizures.

Caution to use:

1. Patients with benzodiazepine dependence. May precipitate a dose dependent withdrawal syndrome.
2. Prolonged benzodiazepine therapy for epilepsy due to the risk of convulsions.
Initial clinical management for intentional or unintentional benzodiazepine overdose:

1.1 Call Doctor to assess patient IMMEDIATELY if there is a:
- Depressed level of consciousness Neuro AVPU (alert, voice, pain, unresponsive <A), or
- Respiratory Rate (Respiratory Rate (RR) ≤ 8 bpm).

If occurring outside the Emergency or Critical Care department the Critical Care Outreach Team (CCOT) MUST also be called

1.2 Commence Oxygen
High flow oxygen (15 litres) immediately

1.3 Review Patient’s Medication
Discontinue all benzodiazepines. Review whether there has been co-ingestion of tricyclic antidepressants, carbamazepine (structure similar to tricyclics) or anti-psychotics. If yes AVOID the use of flumazenil.

1.4 Monitor Patient
Once benzodiazepine overdose has been identified, patients should have:
- Respiratory rate and consciousness level (AVPU) recorded every 15 minutes.
- Early Warning Scores (EWS) calculated every 15 minutes.

This should be continued for at least FOUR hours after the last benzodiazepine dose.

1.5 Consider need for flumazenil administration:
Indicated: following diagnosis of a benzodiazepine ONLY overdose associated with respiratory depression and reduced conscious level, that would otherwise require mechanical ventilation.

CONSIDER all CONTRA-INICATIONS to use. AVOID in suspected MIXED overdose especially with tricyclic antidepressants due to risk of convulsions and cardiac arrhythmias.

One flumazenil 500microgram ampoule is stock on all wards and departments where benzodiazepines are used in the white anaphylaxis and over-sedation boxes. A patient safety incident form MUST be completed following flumazenil administration.

See Quick reference guide in the box on ward or page 4 for initial doses
TWO INDICATIONS:

The aim of treatment is adequate conscious level, airway protection and ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect.

1. Reversal of life threatening respiratory depression and reduced conscious level from acute deliberate/unintentional large benzodiazepine overdose:

<table>
<thead>
<tr>
<th>Presentation flumazenil IV 500 micrograms in 5mls</th>
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<tr>
<td><strong>First dose:</strong></td>
</tr>
<tr>
<td>Flumazenil 500 micrograms (5ml) undiluted IV over 15 seconds</td>
</tr>
<tr>
<td>Wait 30 seconds. If unsuccessful or only partial response give:</td>
</tr>
<tr>
<td><strong>Second dose:</strong></td>
</tr>
<tr>
<td>Flumazenil 500 micrograms (5ml) undiluted IV over 15 seconds</td>
</tr>
<tr>
<td>Wait 30 seconds. If unsuccessful or only partial response give:</td>
</tr>
<tr>
<td><strong>Third dose:</strong></td>
</tr>
<tr>
<td>Flumazenil 1000 micrograms (10ml) undiluted IV over 15 seconds</td>
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<tr>
<td>If there is <strong>NO</strong> response after a total dose of 2 mg IV it is unlikely that flumazenil will reverse the CNS/respiratory depression.</td>
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<td>Where a response is seen do <strong>NOT</strong> exceed 3000 micrograms as bolus doses within one hour.</td>
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<td>If respiratory depression and / or drowsiness recur, bolus doses of flumazenil 500 – 1000micrograms can be repeated at 20-minute intervals. Alternatively an intravenous infusion may be considered (see later for administration details).</td>
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2. Reversal of severe respiratory depression and reduced conscious level from medicinal use of benzodiazepine

Consider use where the reduction in conscious level and respiratory depression would otherwise necessitate admission to critical care for mechanical ventilation; provided the use of flumazenil is not otherwise contra-indicated. To minimise potential flumazenil complications the minimum effective dose should be used for as long as is clinically indicated.

**Presentation flumazenil IV 500 micrograms in 5mls**

**First dose:**
Flumazenil 200 micrograms (2mL) undiluted IV over 15 seconds.
Wait 30 seconds

**Further doses:**
If the desired respiratory rate is not achieved further doses of flumazenil 100-200 micrograms (1 to 2mL) undiluted IV may be given every 30 seconds.

Doses above 1000 micrograms should be used cautiously in benzodiazepine dependent patients due to the risk of precipitating withdrawal.

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**Monitoring**

In the event of an adequate clinical response to flumazenil (aim for RR>10 bpm, AVPU= A), observations every 15 minutes should be maintained for 2 hours. Hourly EWS should be calculated for at least 6 hours after the last dose of flumazenil.

In event of further deterioration, further bolus doses of flumazenil at previously therapeutic doses or an infusion should be considered and close patient monitoring continued.
**Flumazenil infusion**

Flumazenil infusions SHOULD NOT ideally be started or run outside of a Critical Care area, Emergency Department area 1 or Carrel Ward (renal). If it becomes clinically necessary to start a flumazenil infusion whilst awaiting patient transfer the CCOT nurse MUST stay with the patient to monitor them. Flumazenil to make the infusion should be obtained from Critical Care on both campuses, D56 medical HDU or E12 Surgical HDU, Cardiac Critical Care, ED or the pharmacy department.

**Infusion regimen**

*Infusion preparation*

Flumazenil 2500 micrograms made up to 50ml with 5% Glucose or 0.9% Sodium Chloride *(Resulting solution 50 micrograms per ml).*

The infusion must be administered through an electronic rate controlled device (e.g. syringe pump). Preferably via a large peripheral vein (or central venous catheter) to avoid potential venous irritation due to the preparation’s low pH.

The initial starting rate for an acute intentional overdose is flumazenil 500micrograms/ hour (10ml/hr) adjusted according to individual response within the dose range of 100 – 2000microgram /hr (2- 40ml/hr)

The infusion should be discontinued every six hours to assess for continued need.

**Adverse Effects**

Anxiety, agitation and aggression. Panic attacks reported after use in patients with a history of panic disorder.

Sweating, flushing, convulsions, transient tachycardia and hypertension,

Rare cardiac dysrhythmias where a mixed overdose with potentially cardio-toxic drugs e.g. tricyclic antidepressants, carbamazepine (as structurally related to tricyclics) and chloral hydrate.
Key References


http://medusa.wales.nhs.uk/IVGuideDisplay.asp on 8/7/15
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