

Applicable area: **ICU, HDU**

These guidelines are intended for and to be used only by experienced critical care staff under direct supervision of HNELHN Intensive Care Specialists in designated HNE Intensive Care Area Clinical Stream units. The authors are not responsible for inappropriate use of these guidelines.

ADULT	Flumazenil IV for Reversal of Benzodiazepine Overdose	
Authorised prescribers	Infusion: Under the direction of an ICU Specialist or Fellow or Clinical Toxicologist only	
Indication for use^{1,2}	Reversal of sedation due to isolated benzodiazepine deliberate or iatrogenic overdose	
Background²⁻⁵	<ul style="list-style-type: none"> • Flumazenil is a competitive antagonist at benzodiazepine receptors. • Onset: 1 – 3 mins Peak effect: 6 – 10 mins Half life: 1 hour • Pharmacokinetics of benzodiazepines are unaffected by flumazenil 	
	<ul style="list-style-type: none"> • Benzodiazepine overdose is common and while it can cause coma, respiratory depression and death, most cases are not of major clinical significance. • With rapid development of tolerance, patients frequently wake from their sedation or coma while high concentrations of the benzodiazepine persist. The administration of a benzodiazepine antagonist such as flumazenil in the presence of a benzodiazepine prevents the development of this tolerance. This can result in a prolongation of the effect of the benzodiazepine manifesting as a prolonged requirement for the antagonist and increased hospital length of stay. • Thus, for routine management of uncomplicated benzodiazepine overdose, there is no indication for flumazenil. Very occasionally, flumazenil treatment may be indicated to avoid intubation and/or intensive care admission particularly after iatrogenic overdose. 	
Contra-indications^{1,2}	<ol style="list-style-type: none"> 1. Benzodiazepine-dependent pregnant women; risk of precipitating withdrawal in foetus; ADEC category B3. 2. Use of benzodiazepines for control of a potentially life threatening condition e.g., status epilepticus 3. Mixed overdoses – using flumazenil to reverse benzodiazepine induced sedation in mixed overdoses of benzodiazepines and proconvulsant or proarrhythmic drugs (e.g. TCAs, chloral hydrate, theophylline, antihistamines, amphetamines etc) may be dangerous, resulting in uncontrollable seizures and death. A negative history of ingestion of proconvulsant or proarrhythmic drugs, normal ECG and no physical signs of anticholinergic or sympathomimetic drug overdose make such co-ingestion less likely. 	
Precautions^{1,2}	<ol style="list-style-type: none"> 1. Benzodiazepine dependence – rapid reversal of benzodiazepine effects may be undesirable as it may precipitate severe withdrawal symptoms and seizures. 2. Severe head injury, unstable intracranial pressure – treatment with flumazenil may alter cerebral blood flow, causing raised intracranial pressure or seizures. 	

Dosage ²⁻⁴	<p>IV bolus Initial dose 0.2 mg IV over 15 seconds Repeat doses If there is no response after 45 seconds, titrate 0.1 mg doses IV every minute until there is response or a 2 mg total dose has been administered. If there is no response at this point reconsider diagnosis.</p> <p>IV continuous infusion If indicated, i.e., if drowsiness recurs: give half the total IV bolus dose needed to wake the patient, hourly. Dose range: 0.1 – 1 mg/hour (= 2.5 – 25 mL/hour of 2 mg in 50 mL strength)</p>																																								
Duration of therapy	Until estimated elimination time of benzodiazepine																																								
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Preparation and administration ⁶	<p>IV bolus: Freely running IV infusion line into a large vein (minimise pain at injection site) IV continuous infusion: Peripheral or Central Venous Line</p> <p>IV bolus: Undiluted IV continuous infusion: Dilute 2 mg up to 50 mL with sodium chloride 0.9% or glucose 5%</p>																																								
Compatibilities	See Australian Injectable Drugs Handbook via CIAP or hard copy on the ward																																								
Important drug interactions ⁷	<ul style="list-style-type: none"> Non-benzodiazepine agonists at benzodiazepine receptors <i>e.g.</i>, zopiclone, zolpidem are also blocked by flumazenil 																																								
Monitoring requirements	<ul style="list-style-type: none"> Closely monitor patients for re-sedation, benzodiazepine withdrawal symptoms and seizures. Monitor for at least 2 hours after last flumazenil dose Continuous cardiac monitoring, blood pressure, heart rate, respiratory and neurological observations 																																								
Management of complications ¹	Hyperacute withdrawal precipitated by flumazenil in severely benzodiazepine dependent patients may need very high doses of benzodiazepines to control																																								
Basis of guideline	<ol style="list-style-type: none"> JHH QUM Flumazenil Nov 2009 Australian Medicines Handbook – online July 2010 Whyte IM. Benzodiazepines. In: <i>Medical Toxicology</i> Dart RC (ed) 3rd ed. Lippincott Williams & Wilkins, Baltimore, USA 2004:811–823 Martin Caravati E. Flumazenil. In: <i>Medical Toxicology</i> Dart RC (ed) 3rd ed. Lippincott Williams & Wilkins, Baltimore, USA 2004:199 – 203 Flumazenil Drug Information – Up To Date online 2011 Australian Injectable Handbook 4th ed 2008 MIMS Online 2010 																																								
Groups consulted	Staff specialists, trainees, senior nursing and pharmacists (or relevant directors of pharmacy) of the Intensive Care Area Clinical Stream																																								
Keywords	HNE Intensive Care Area Clinical Stream, ICU, flumazenil, benzodiazepine overdose, prescribing guideline																																								

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