PRODUCT MONOGRAPH

JAMP-FLUMAZENIL

FLUMAZENIL INJECTION, USP

(Flumazenil)

0.1 mg/mL

THERAPEUTIC CLASSIFICATION

Benzodiazepine Antagonist

Date of Preparation :

October 9, 2014

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Submission Control No: 178046

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ACTION AND CLINICAL PHARMACOLOGY

JAMP-Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which blocks the central effects of agents that act via the benzodiazepine receptor, by competitive inhibition. The antagonism is specific, since in animal experiments the effects of compounds which have no affinity for the benzodiazepine receptor (e.g. barbiturates, meprobamate, ethanol, GABA-mimetics, and adenosine receptor agonists) were not affected by flumazenil. Flumazenil does not reverse the central effects of opioids.

Following the intravenous administration of radiolabelled flumazenil to human volunteers, the distribution of radioactivity corresponded closely to the distribution of benzodiazepine receptors as determined by positron emission tomography.

The hypnotic-sedative effects of benzodiazepines are rapidly reversed by flumazenil. However, the residual effects may reappear gradually within a few hours, depending on the dose and plasma concentration of flumazenil, the time elapsed since the benzodiazepine agonist was given, and the dose and elimination half-life of the previously administered benzodiazepine agonist. Flumazenil has shown some weak intrinsic agonistic (e.g. anticonvulsant) activity without therapeutic relevance.

Pharmacokinetics

In young male volunteers, the pharmacokinetics of intravenous flumazenil were linear over a dose range of 2-100 mg. Increasing doses of flumazenil were accompanied by a corresponding increase in the area under the plasma concentration-time curve (AUC: 37 ng/mL•hr at 2 mg and 1906 ng/mL•hr at 100 mg), and maximum plasma concentration (C_{max}: 55 ng/mL at 2 mg and 3332 ng/mL at 100 mg). However, elimination half-life, volume of distribution at steady state, and plasma clearance were independent of dose over the entire range studied. The mean elimination half-life of flumazenil following the administration of single intravenous doses to healthy subjects

was approximately one hour.

Plasma protein binding is low. Over a concentration range of 24 to 570 ng/mL, flumazenil was found to be 50% bound to human plasma proteins. Albumin accounts for approximately two- thirds of the plasma protein binding. The binding of flumazenil was not affected by a high concentration of diazepam (10 mcg/mL), and flumazenil did not interfere with the binding of diazepam.

Flumazenil undergoes rapid and extensive hepatic metabolism; less than 0.2% of the administered dose is eliminated unchanged in the urine. The major metabolites of flumazenil identified in the urine are the free acid and its glucuronide conjugate.

In healthy volunteers, approximately 70% of an intravenous dose of flumazenil was excreted within the first two hours after dosing and another 16% during the next two hours. Elimination was essentially complete within 72 hours, with 90 to 95% of the total radioactivity appearing in the urine and 5 to 10 % in the feces. Ingestion of food during an intravenous infusion of flumazenil results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal.

The following table summarizes the ranges of mean pharmacokinetic parameters reported in a series of studies, after single intravenous doses of flumazenil.

Subjects	**Dose (mg)**	**Elimination Half-life ($t_{2\beta}$) (min)**	**Volume of Distribution at Steady State (Vd_{SS}) (L/kg)**	**Plasma Clearance (CI_{pl}) (L/hr)**
Male volunteers 23-26 years	2-100	48-55	0.83-0.86	55-57
Male volunteers 28-42 years	2.5	42-72	0.63	41
Volunteers 39 years	2	46	0.62	74
Cirrhosis				
- moderate 45 years	2	76	0.68	29
- severe 45 years	2	142	0.85	19
Volunteers 37 years	1	51	0.91	60
Chronic renal failure				
- without dialysis 36 years	1	38	0.94	75
- with dialysis 55 years	1	43	1.07	75
Age Volunteers:				
Male:				
20-28 years	2	54	0.87	56
65-77 years	2	66	0.93	56
Female:				
24-30 years	2	48	0.96	66
63-67 years	2	54	0.78	44

There were no statistically significant differences between the distribution and elimination parameters of 12 elderly (8 males and 4 females) and 6 young (4 males and 2 females) healthy volunteers, following the administration of a 2 mg intravenous dose.

When administered together with the benzodiazepines midazolam, flunitrazepam or lormetazepam,

the pharmacokinetic parameters of flumazenil were not affected. Similarly, the pharmacokinetics of benzodiazepines remained unaltered in the presence of the antagonist flumazenil.

Hepatic Impairment
In patients with cirrhosis, the pharmacokinetics of flumazenil were altered, particularly in patients with severely impaired liver function. Elimination half-life was prolonged and plasma clearance markedly decreased. Since plasma protein binding is lower in cirrhotic patients than in healthy subjects, the levels of free drug are substantially increased, namely from 55% in controls

to 64% and 79% in patients with moderate and severe liver dysfunction, respectively. Caution should be exercised with initial and/or repeated dosing to patients with liver disease.

Renal Impairment
In patients with chronic stabilized renal failure (creatinine clearance - 10 mL/min) in the absence and presence of dialysis, the pharmacokinetics of flumazenil remained essentially unaltered.

INDICATIONS AND CLINICAL USE

JAMP-Flumazenil is indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anesthesia and intensive care in the following situations:

- Termination of general anesthesia induced and/or maintained with benzodiazepines.
- Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures.
- For the diagnosis and/or as an adjunct to supportive measures used for the management of deliberate or accidental benzodiazepine overdosage.

Geriatrics (> 65 years of age):
Elderly patients may be more sensitive to the effects of flumazenil. For a brief description, see PRECAUTIONS-Use in the Elderly

Pediatrics (< 18 years of age):
The safety and effectiveness of flumazenil in children below the age of 18 has not been established.

CONTRAINDICATIONS

JAMP-Flumazenil is contraindicated:
- In patients with known hypersensitivity to flumazenil or to benzodiazepines.
- In epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. The abrupt suppression of the protective effect of benzodiazepines may induce

convulsions in epileptic patients.

- In patients who are showing signs of serious cyclic antidepressant overdose (see PRECAUTIONS).
- In patients who have been given a benzodiazepine for a potentially life threatening condition (e.g. intracraniapressure).

WARNINGS

IN VIEW OF THE SHORT DURATION OF ACTION OF JAMP-FLUMAZENIL AND THE POSSIBLE NEED FOR REPEAT DOSES, THE PATIENT SHOULD REMAIN CLOSELY MONITORED UNTIL ALL POSSIBLE CENTRAL BENZODIAZEPINE EFFECTS HAVE SUBSIDED.

THE IMMEDIATE AVAILABILITY OF OXYGEN, RESUSCITATIVE EQUIPMENT AND SKILLED PERSONNEL FOR THE MAINTENANCE OF AIRWAY, VENTILATION AND CARDIAC FUNCTION SHOULD BE ENSURED BEFORE THE ADMINISTRATION OF ANY BENZODIAZEPINE OR JAMP-FLUMAZENIL.

Resedation: Flumazenil is a competitive inhibitor of benzodiazepines at the receptor site and does not affect the pharmacokinetics of benzodiazepines. Thus, when the effect of flumazenil wears off, the patient returns to the point of residual sedation that would have been present at that time had flumazenil not been given. In patients administered large doses of long-acting benzodiazepines or in critically ill patients, this could be deep sedation. In a US clinical study in patients with benzodiazepine intoxication, 90/133 (67.7%) patients became resedated.
Therefore, JAMP-Flumazenil should be administered only when the continued observation of patients for recurrence of sedation, respiratory depression, or residual benzodiazepine effects can be assured.

Respiration: When used in anesthesiology at the end of surgery, JAMP-Flumazenil should not be given until the effects of neuromuscular blockade have been completely antagonized and careful monitoring of the respiratory depressant effect of opiate analgesics has been assured.
After the benzodiazepine has been antagonized with JAMP-Flumazenil, any residual respiratory depressant effect of benzodiazepines and other agents, such as opiates, may require interventions such as establishing an airway and assisted ventilation.

The ability of flumazenil to reverse benzodiazepine-induced respiratory depression is equivocal; in some studies residual effects of benzodiazepines on respiration were still present despite reversal of sedation.

Seizures: Rapid intravenous injections should be avoided in patients treated for long periods of time and/or with high doses of benzodiazepines, as JAMP-Flumazenil may trigger withdrawal symptoms (e.g. convulsions, agitation, anxiety, emotional lability as well as mild confusion and sensory distortions). Seizures have been reported in patients known to suffer from epilepsy, or

severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed-drug overdose. Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates.

PRECAUTIONS

General: In high-risk patients (e.g., patients treated with benzodiazepines for long periods of time, overdose with signs of cyclic antidepressant overdosage), the advantages of counteracting benzodiazepine-related sedation should be weighed against the drawbacks of rapid awakening.

Postoperative pain must be taken into account. Following a major intervention, it may be preferable to maintain a moderate degree of sedation.

JAMP-Flumazenil is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.

Anxiety and Panic Disorder: The dosage of JAMP-Flumazenil should be adjusted carefully in patients suffering from preoperative anxiety or having a history of chronic or episodic anxiety. In anxious patients, particularly those with coronary heart disease, it is preferable to maintain a degree of sedation throughout the early postoperative period rather than bring about complete arousal.

Flumazenil has been reported to provoke panic attacks in patients with history of panic disorders.

Instructions to Patients Upon Discharge: Patients who have received JAMP-Flumazenil to reverse the effects of benzodiazepine sedation should be instructed, if possible in writing, not to drive, to operate machinery or to engage in any other physically or mentally demanding activity for 24 hours or until the effects of the benzodiazepine have subsided, since the effect of the benzodiazepine may return. Patients should also be warned not to take alcohol, or drugs not prescribed by their physician, until the effects of the benzodiazepines have subsided.

Use in Children: The safety and effectiveness of flumazenil in children below the age of 18 has not been established.

Use in the Elderly: In the absence of data on the use of flumazenil in elderly patients, it should be born in mind that this population is generally more sensitive to the effects of drugs and should be treated with due caution.

Use in Pregnancy and Lactation: Although studies in animals have not shown evidence of embryotoxicity or teratogenicity (see REPRODUCTION AND TERATOLOGY), JAMP-Flumazenil should be used during pregnancy only, if in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risks to the fetus.

It is not known whether flumazenil is excreted in human milk. For this reason, breast feeding should be interrupted for 24 hours when JAMP-Flumazenil is used during lactation.

Use in Hepatic Impairment: In patients with liver insufficiency, the elimination of flumazenil can be delayed. Caution should be exercised with initial and/or repeated dosing to patients with liver disease. (see ACTION AND CLINICAL PHARMACOLOGY-Hepatic Impairment, DOSAGE AND ADMINISTRATION).

Seizures have been reported in patients known to suffer from severe hepatic impairment, particularly after long-term treatment with benzodiazepines or in cases of mixed-drug overdose.

Use in Renal Impairment
No dosage adjustments are necessary in patients with renal impairment.

Use in Respiratory Disease
The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be given appropriate ventilatory support, rather than administration of flumazenil.

Use in Acute Myocardial Infarction or Cardiac Arrhythmias: Flumazenil abruptly terminates the effects of benzodiazepines. As a result, sympathetic tone may be increased and thus, cardiac electrical instability enhanced. Consequently, caution is advised when administering JAMP-Flumazenil to patients with myocardial infarction or cardiac arrhythmias.

Use in Patients with Increased Intracranial Pressure Receiving Benzodiazepines (e.g. head injury, brain tumour, intracranial hemorrhage): In patients with increased intracranial pressure, flumazenil may further increase intracranial pressure, cerebral perfusion pressure, or precipitate convulsions. In such patients, flumazenil should be used with extreme caution and only by practitioners prepared to manage such complications, should they occur.

Multiple Drug Overdosage: Particular caution is necessary when using JAMP-Flumazenil in cases of multiple drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside.

Patients should be evaluated for the signs and symptoms (autonomic, neurological or cardiovascular) of a cyclic antidepressant overdose. A diagnostic ECG can be used to confirm the presence of these agents; a QRS duration of 0.1 seconds or greater indicates a serious overdosage with cyclic antidepressants, which should be treated with appropriate measures. Depending on the extent of involvement of benzodiazepines in the multiple drug overdose, this may or may not include JAMP-Flumazenil.

Use in the ICU: JAMP-Flumazenil should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. Flumazenil may produce convulsions in patients physically dependent on benzodiazepine (see WARNINGS-Seizures).

DRUG INTERACTIONS

Interactions with central nervous system depressants other than benzodiazepines have not been studied specifically.

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level; the effects of non-benzodiazepines which act via the benzodiazepine receptor, such as zopiclone, triazolopyridazines and others, are also blocked. However, flumazenil does not reverse the effects of drugs that do not act via this route, such as opioids.

The pharmacokinetics of flumazenil are unaltered in the presence of benzodiazepines, and similarly, flumazenil does not affect the kinetics of benzodiazepines.

There is no pharmacokinetic interaction between ethanol and flumazenil.

ADVERSE REACTIONS

Flumazenil is generally well tolerated. In postoperative use, nausea and/or vomiting are observed, particularly if opiates have also been employed. Flushing has also been noted. If patients are awakened too rapidly, they may become agitated, anxious or fearful. Transient increases in blood pressure and heart rate may also occur.

Excessively and/or rapidly injected doses of flumazenil may induce benzodiazepine withdrawal symptoms such as anxiety attacks, tachycardia, dizziness and sweating in patients on long-term benzodiazepine treatment.

Although clinical experience with flumazenil is limited, seizures and/or cardiac arrhythmias have been observed in patients who are physically dependent on benzodiazepines, and in multiple drug overdose, particularly in the presence of tricyclic antidepressants.

Flumazenil has been reported to provoke panic attacks in patients with a history of panic disorders.

The following table summarizes the adverse reactions which occurred with an incidence of >1%.

Clinical Adverse Events >1%

Organ System	Adverse Event	Frequency (%)	
		General Anesthesia/ Sedation n=7365	Known or Suspected Benzodiazepine Overdose n=764
Central Nervous System	Agitation	0.2	5.8
	Crying/Tears Headache	0.5	3.5
	Anxiety/Anxious Feeling	0.5	1.6
	Seizures/Convulsions	0.3	1.4
	Dizziness	–	1.3
		1.4	1.2
Gastrointestinal	Nausea	4.3	2.2
	Vomiting	2.6	2.0
Cardiovascular	Hypertension	0.1	1.4
	Tachycardia	0.1	1.2
Miscellaneous	Shivering/Cold Sensation/Chills	0.5	1.2

Other clinical adverse events which occurred with an incidence of <1% are as follows:

Cardiovascular
Ventricular premature beats, arrhythmia, palpitations, bradycardia, flush, hypotension, chest pain.

Respiratory
Dyspnea, hypopnea, nasal congestion, cough, subjective suffocation.

CNS/Neuromuscular
Startle reaction, fear, nervousness, restlessness, excitation, aggressiveness, anger; euphoria, hallucinations, vertigo, confusion, tiredness/drowsiness, depression; involuntary/spontaneous movement, tremor, mouth movement, tetany, speech disorder.

Gastrointestinal
Salivation, dry mouth, hiccoughs.

Dermatological
Urticaria, pruritus.

Miscellaneous
Pain, allergic reaction, strabismus, sweating.

Local Tolerance
Slight to moderate pain at the site of injection occurred in 2.5% of patients and redness was observed in 1.3% of patients in clinical trials one hour after the administration of flumazenil.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

~~For management of a suspected drug overdose, contact~~ your regional Poison Control Centre.

Flumazenil, administered intravenously to healthy volunteers at a dosage of 100 mg, did not produce symptoms of overdosage. Reversal of sedation or general anesthesia with excessively high doses of JAMP-Flumazenil may produce symptoms of benzodiazepine withdrawal, such as anxiety, agitation, increased muscle tone, hyperesthesia, and possible convulsions.

There is very limited experience of acute overdose in humans with flumazenil. There is no specific antidote for overdose with flumazenil. Treatment of an overdose with JAMP-Flumazenil should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Convulsions associated with the flumazenil administration have been successfully managed with benzodiazepines; phenytoin or barbiturates (see WARNINGS-Seizures).

DOSAGE AND ADMINISTRATION

JAMP-FLUMAZENIL SHOULD BE ADMINISTERED INTRAVENOUSLY BY A PHYSICIAN WITH EXPERIENCE IN ANESTHESIOLOGY.

JAMP-Flumazenil is not indicated for epileptic patients who have been treated with benzodiazepines for a prolonged period. The abrupt cessation of the protective effect of benzodiazepines may induce convulsions in epileptic patients.

Caution should be exercised with initial and repeated dosing to patients with hepatic insufficiency as elimination of flumazenil can be delayed in these patients (see ACTION AND CLINICAL PHARMACOLOGY-Hepatic Impairment).

The dose of JAMP-Flumazenil should always be individually titrated to the desired response to avoid abrupt awakening. Particular care is needed with patients who are physically dependent on benzodiazepines, patients who have ingested multiple drugs, and patients who are prone to anxiety. In the intensive care unit, in patients treated with high doses of benzodiazepines and/or for long periods of time, the individually titrated injections of JAMP-Flumazenil, slowly administered, should not produce withdrawal syndromes (see PRECAUTIONS). If unexpected symptoms occur, diazepam or midazolam could be carefully titrated intravenously according to patient's response.

JAMP-Flumazenil may be used concurrently with other resuscitative procedures (see Known or Suspected Benzodiazepine Overdose).

JAMP-Flumazenil is compatible with 5% dextrose in water and normal saline solutions. If JAMP-Flumazenil is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours (see PHARMACEUTICAL INFORMATION).

Reversal of General Anesthesia/Sedation

The recommended initial dose is 0.2 mg administered intravenously over 15 seconds. If the desired level of consciousness is not obtained within 60 seconds, a further dose of 0.1 mg can be injected and repeated at 60 second intervals, up to a maximum total dose of 1 mg. The usual dose is between 0.3 and 0.6 mg.

Known or Suspected Benzodiazepine Overdose

Necessary measures should be taken to monitor the patient's vital signs and institute supportive treatment as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects. JAMP-Flumazenil is intended as an adjunct to, not as a substitute for, supportive measures used to manage overdose (e.g., proper management of airway, assisted breathing, circulatory access and support, internal decontamination by charcoal and possibly lavage, and adequate clinical evaluation).

For the reversal of excessive sedative effects of benzodiazepines in overdose cases, titrate flumazenil as described below, until the patient clearly responds or until the maximum recommended dose has been reached.

The recommended initial dose is 0.3 mg administered intravenously over 30 seconds, followed by a series of 0.3 mg injections, each administered over a 30-second period, at 60 second intervals. The maximum recommended dose is 2.0 mg.

If a significant improvement in the level of consciousness and respiratory function is not achieved after repeated injections of flumazenil, a non-benzodiazepine aetiology must be assumed.

If drowsiness recurs, an intravenous infusion of 0.1-0.4 mg/hr may be useful. The rate of the infusion should be individually adjusted to the desired level of arousal.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Flumazenil

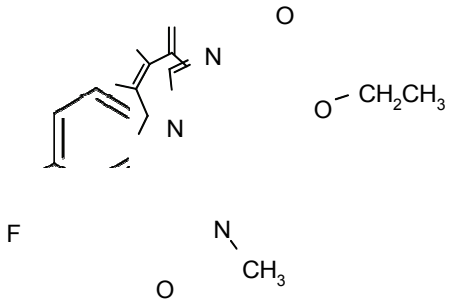
Code: Ro 15-1788

Chemical Names:

(1) 4H-Imidazo [1, 5-α][1, 4] benzodiazepine-3-carboxylic acid, 8-fluoro-5, 6-dihydro-5-methyl-6-oxo, ethyl ester

(2) Ethyl 8-fluoro-5, 6-dihydro-5-methyl-6-oxo-4*H*-imidazo [1,5-α][1,4] benzodiazepine-3-carboxylate

Structural Formula:



Molecular Formula: $C_{15}H_{14}FN_3O_3$

Molecular Weight: 303.29 g/mol

Description: White or almost white crystalline powder

Solubility: Freely soluble in dichloromethane, sparingly soluble in methanol, slightly soluble in hydrochloric acid 0.1N and very slightly soluble in water.

Melting Range: 198-202ºC

pH: Flumazenil is very slightly soluble in water, therefore pH cannot be measured.

pKa: 1.7 (in weak base)

Composition

Each mL of JAMP-Flumazenil contains: flumazenil 0.1 mg, methylparaben 1.8 mg and propylparaben 0.2 mg as preservatives, sodium chloride for isotonicity, Edetate disodium 0.1 mg, acetic

acid 0.1 mg, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

Stability and Storage Recommendations
JAMP-Flumazenil should be stored at 15°C-30°C. Protect from light. Discard unused portion 28 days after the initial puncture.

Stability and Storage of Diluted Solutions
JAMP-Flumazenil may be diluted with dextrose 5% solution or sodium chloride 0.9%. If flumazenil is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours.

AVAILABILITY OF DOSAGE FORMS

Description of dosage form:

Flumazenil Injection USP 0.1 mg/mL-5 ml fill is a clear colorless solution free from visible particles filled in 5 ml USP Type I flint tubular vials with 20 mm Grey bromobutyl omniflex coated rubber closure [Ready for sterilization] and 20 mm red flip off aluminum seal.

Flumazenil Injection USP 0.1 mg/mL- 10 ml Fill is a clear colorless solution free from visible particles filled in 10 ml USP Type I flint tubular vials with 20 mm Grey bromobutyl omniflex coated rubber closure [Ready for sterilization] and 20 mm red flip off aluminum seal.

Flumazenil Injection 0.1 mg/mL is available in multidose vials of 5 mL and 10 mL, boxes of 5.

Latex-Free Stopper – Stopper contains no dry natural rubber.

PHARMACOLOGY

Receptor Studies

Using ^{3}H-flumazenil, a benzodiazepine antagonist or ^{3}H-clonazepam, a benzodiazepine agonist as radioligands in *in vitro* binding studies, a variety of receptor agonists showed very similar potency in inhibiting the binding of either ligand.

Ligand	IC_{50} (nmol/l)	
	^{3}H-Flumazenil binding	^{3}H-Clonazepam binding
Agonists		
Clonazepam	1.4	1.2
Flunitrazepam	4.8	5.1
Diazepam	19.5	13.5
Zopiclone	50	46
Antagonist		
Flumazenil	1.3	2.0

Flumazenil also displaced ^{3}H-flunitrazepam under *in vivo* conditions. The ED_{50} was 4.0 mg/kg PO when mice were sacrificed 15 minutes after the administration of flumazenil. Autoradiography studies have revealed that while ^{3}H-flunitrazepam binds to both central and peripheral benzodiazepine receptor sites, ^{3}H-flumazenil binds only to central receptor sites. This suggests that flumazenil will antagonize only those effects of the benzodiazepines that are mediated via the central nervous system.

While flumazenil interacts with the same number of benzodiazepine receptor sites as the benzodiazepines, the mode of interaction of the antagonist and agonists differs. Under conditions which alter receptor affinity for agonists, no change is seen in ^{3}H-flumazenil binding specifically, (a) in the presence of GABA, benzodiazepine receptor affinity is enhanced for agonists, but remains unchanged for flumazenil; (b) in the presence of photoaffinity labelling, benzodiazepine receptor affinity is attenuated for agonists, but remains unchanged for flumazenil.

In conclusion, similar to benzodiazepine agonists, flumazenil interacts with central benzodiazepine receptors in nanomolar concentrations, the inhibition of agonist binding by flumazenil being competitive. Unlike the agonists, flumazenil is insensitive to GABA or photoaffinity labelling induced changes in receptor affinity.

Benzodiazepine Antagonist Activity

Flumazenil potently antagonizes the centrally-mediated pharmacological effects of various benzodiazepines. In the table below, only the minimal effective doses are described, but flumazenil exerts its effects in a dose-dependent fashion.

Antagonism of Benzodiazepines in Neurological and Behavioural Studies

Test Performed (species)	Benzodiazepine		Flumazenil	
	Effect	Dose mg/kg	Effect	Minimal Effective Dose mg/kg
Traction test (mice)	muscle relaxation	diazepam 3 IP	reversal	0.2 PO (ED_{50})
Pentylenetetrazole-induced Convulsions (mice)	antagonism of convulsions	diazepam 5 IP	reversal	2.8 PO (ED_{50} at 15 minutes) 7.0 PO (ED_{50} at 45 minutes)
Hexobarbital-induced loss of righting reflex (mice)	potentiation	meclonazepam 1 IP	reversal	3 PO
Locomotor activity (rats)	hypomotility	diazepam 30 PO	reversal	30 PO
Open field behaviour (rats)	reduced exploration and rearing	meclonazepam 10 PO	reversal	1 PO
Conflict behaviour (rats)	attenuation of conflict	diazepam 5 PO	reversal	10 PO
Behavioural observation (dogs)	ataxia	meclonazepam 3 PO meclonazepam 10 PO	prevention reversal	10 PO 30 PO
Behavioural observation (squirrel monkeys)	sedation, anesthesia	flunitrazepam 3 IV. midazolam 10 IV	reversal reversal	1 PO 0.3 IV
Cognition (mice)	induction of anterograde amnesia	triazolam 1 PO.	reversal	10 PO
Electrophysiological studies "encéphale isolé" (rats)	reduced cell firing in several central regions	midazolam 0.1-10 mcmol/kg IV (0.3-3 mg/kg)	recovery of cell firing	10 mcmol/kg IV (3 mg/kg)
Acute spinal (cats)	enhancement & prolongation of dorsal root potentials	meclonazepam 0.1 IV	prevention & reversal	1 IV
Respiratory study (rabbits)	reduced respiratory min. volume & rate of respiration	diazepam 0.1 IV flunitrazepam 0.03 IV	reversal reversal	0.1 IV 0.1 IV

The ability of flumazenil to antagonize benzodiazepine agonists is specific for this class of drugs. The muscle relaxant, anticonvulsant, and anti-conflict effects of phenobarbital, meprobamate, and ethanol were not antagonized by flumazenil. Flumazenil was also inactive against scopolamine or hypercapnia-induced anterograde amnesia and morphine-induced respiratory depression.

Flumazenil-Induced Withdrawal

Flumazenil, administered IV, IM, or PO, elicited typical benzodiazepine withdrawal signs in mice, rats, cats and squirrel monkeys, following chronic administration of benzodiazepines (12 to 35 days). The symptoms included emesis, vocalization, tremors, rigidity, and convulsions. The type of withdrawal symptoms and their intensity depended upon the dose and duration of benzodiazepine treatment, as well as the time of flumazenil administration vis-à-vis the last dose of the benzodiazepine.

Intrinsic Activity

Flumazenil did not affect normal behaviour in rats, dogs, or squirrel monkeys in doses of up to 100 mg/kg. Similarly, motor activity, conditioned avoidance behaviour, conflict behaviour in rats and continuous avoidance behaviour in squirrel monkeys remained unchanged when flumazenil was given in doses of up to 100 mg/kg PO. These findings indicate that flumazenil is devoid of benzodiazepine agonist activity at doses that are substantially higher than those which exert antagonist activity.

Inverse Agonist Activity

A group of benzodiazepine receptor ligands, classified as "inverse agonists" cause opposite effects to those of the benzodiazepine receptor agonists, namely they produce convulsions and anxiety in appropriate animal models.

Flumazenil did not induce convulsions, except at sublethal doses. However, it did exert weak anxiogenic activity in several behavioural animal models, namely in the "social interaction" and "conditioned spatial aversion" tests, as well as in various conflict situations. Active doses ranged from 4 to 30 mg/kg IP or PO.

Cardiovascular Effects

Flumazenil did not affect blood pressure or heart rate either in spontaneously-hypersensitive rats (maximum dose 100 mg/kg PO) or in renal hypertensive dogs (maximum dose 30 mg/kg PO).

TOXICOLOGY

Acute Toxicity

Route of Administration	Species	Sex	LD_{50} (mg/kg)	Symptoms
IV	Mice	Male Female	159-168 132-159	Deaths, preceded by tonic-clonic convulsions, occurred within 30 minutes of dosing. Surviving animals were hypoactive, and manifested respiratory depression and increased muscle tone.
	Rats	Male Female	119-134 161-182	
IP	Mice	Male Female	>2000 1500	Deaths occurred within three days of dosing. Most animals were hypoactive, and manifested catatonia, tremors, salivation, lacrimation and respiratory depression.
	Rats	Male & Female	2200	
SC	Mice	Male & Female	>1000	
PO	Mice	Male Female	2500 1300	
	Rats	Male & Female	4200	
	Rabbits	Male & Female	2000	

Intravenous Pyramiding Dose Toxicity in Dogs

Three groups of four dogs each (2/sex) received (a) flumazenil at doses of 0.01, 0.03, 0.1 and 0.3 mg/kg; (b) pyramiding doses of the vehicle (0.1, 0.3, 1.0 and 3.0 mL/kg) and; (c) equivalent volumes of physiological saline. The dogs were dosed twice a week over a two-week period. All dogs survived the pyramiding doses of flumazenil and were essentially asymptomatic throughout the study. Flumazenil did not affect body weight, food intake, hematological or clinical chemical parameters.

Long-Term Toxicity Studies

1. Two-Week Intravenous–Rats

Flumazenil was injected IV into the tail vein of rats (8/sex/group) at doses of 0, 1, 3 and 10 mg/kg/day.

Tissue irritation at the injection site was pronounced and dose-related. At the low dose, local tolerance was acceptable. At the mid-dose, all rats had swollen and reddened tails beginning with the third dose and continuing to the end of the study. At the high dose, intolerance at the injection site was severe. Hematomas occurred in five of eight males and one female rat. Two of eight male rats in the high-dose group also showed ulceration of the tail and in three male rats the administration of the drug had to be performed intraperitoneally on the fifth day. In general, female rats tolerated the treatment better than male animals. Pronounced bleeding at the injection site was also observed in most of the mid- and high-dose animals beginning about the fifth day of the study.

At the 10 mg/kg dose, male rats gained weight at a slower rate than male controls, this effect was considered to be treatment-related. A similar effect in female rats was equivocal.

2. Two-Week Oral–Rats

Flumazenil was administered by gavage to rats (8/sex/group) at doses of 0, 5, 25 and150 mg/kg/day. The drug was given for 15 or 16 consecutive days to female and male rats, respectively.

Flumazenil was devoid of toxic effects at the doses studied.

3. Two-Week Intravenous–Dogs

Flumazenil was injected IV to beagle dogs (2/sex/group) at doses of 0, 1, 3 and 10 mg/kg/day.

The mid-dose produced drowsiness and the high-dose produced drowsiness and ataxia; both effects were observed following dosing. In the course of the study, a slight tolerance did develop to these effects.

Injections were poorly tolerated in the dogs receiving 10 mg/kg of flumazenil, due to hardened and thrombosed veins and a strong defence reaction from the animals.

In the high-dose group, reticulocytes were significantly increased in the second week of the study in comparison to the control group. Platelets were decreased in all treated groups *vis-à- vis* baseline values, but the changes were not dose-related. A statistically significant increase in the relative liver weights was noted in the high-dose group, this effect was considered to be treatment-related.

4. Two-Week Oral–Dogs

Flumazenil was administered in capsules to beagle dogs (2/sex/group) at doses of 0, 5, 20 and 80 mg/kg/day for 15 consecutive days.

Slight diarrhea was noted at the 20 mg/kg dose and marked diarrhea (sometimes bloody) at the 80 mg/kg dose. Mean spleen weights were decreased and mean liver weights increased in all flumazenil-treated dogs. At necropsy, the tunica mucosa of the colon was more convoluted in high-dose animals than in controls.

5. Four-Week Intravenous–Rats

Flumazenil was injected IV into the tail vein of rats (12/sex/group) at doses of 0, 1, 3 and 10 mg/kg/day.

Local tolerance to the IV injections was poor and the degree of swelling and pain was dose-related. At the high dose, the route of administration had to be switched from intravenous to intraperitoneal about 15 days after the beginning of the study.

In male rats, there was a dose-related weight gain deficit. Although the mean values remained within the normal range, WBC counts decreased in male rats in a dose-related fashion at week 4. The

decrease seen in the high-dose group was statistically significant. Both absolute and relative liver weights were increased in high-dose female rats. Peri lymphadenitis was seen in high-dose males and females; this might have been due to the intraperitoneal injections. One high-dose female rat had a moderate degenerative change in the retina.

6. Four-Week Intravenous–Dogs

Flumazenil was injected IV to beagle dogs (2/sex/group) at doses of 0, 1, 3 and 10 mg/kg/day.

Mid-dose dogs were sedated and high-dose dogs showed both sedation and ataxia. Tolerance did not develop to these effects. WBC counts decreased slightly. While the mean values were within normal range, in a few dogs they fell below normal. Local tolerance (injection site) was poor in the high-dose groups as also shown by high inflammation scores.

7. Thirteen-Week Oral–Rats

Flumazenil was administered in the diet to rats (18/sex/group) at doses of 0, 5, 25 and 125 mg/kg/day.

In female rats, liver weights were somewhat elevated in the high-dose group, and thyroid weights slightly decreased in a dose-related fashion.

8. Thirteen-Week Oral–Dogs

Flumazenil was administered in capsules to beagle dogs, (3/sex/group), seven days/week, at doses of 0, 5, 20 and 80 mg/kg/day.

Slight sedation, lasting 1-3 hours following dosing was noted in the high-dose group; tolerance did not develop to this effect. Weight gain in high-dose animals was somewhat attenuated when compared to controls. At week 12, heart rate was increased in high-dose dogs, *vis-à-vis* both baseline and control dogs. There was a dose-related decrease in both absolute and relative spleen weights.

9. Twelve-Month Oral–Rats

Flumazenil was administered in the diet to rats (20-30/sex/group) at doses of 0, 6, 20 and 125 mg/kg/day. An interim sacrifice of ten control rats (5/sex) and ten rats from the high- dose group (5/sex) was carried out at six months.

Hemoglobin, erythrocyte and hematocrit values were slightly lower in treated male animals than in controls, throughout the study. In females, these parameters were reduced only at six months.

At six months, both absolute and relative thyroid weights in high-dose males, and liver weights in high-dose females were significantly increased. Histopathological evaluation revealed a slight to moderate congestion in the liver of all females treated with the high dose. At twelve months, absolute and relative thyroid weights were slightly decreased in low- and mid-dose males, but increased in high-dose animals. Liver weights and histopathological findings were similar in treated

and control rats.

Mutagenicity
Flumazenil had no mutagenic activity in six out of seven mutagenicity assays (Ames test, Treat and Plate test, gene mutation, *in vivo* and *in vitro* clastogenicity and *in vivo* DNA repair). In a UDS assay, there was a dose-dependent unscheduled incorporation of ^{3}H-thymidine in nuclear DNA of rat hepatocytes after treatment with flumazenil concentrations of 252, 504 and 1010 mcg/mL for eighteen hours. However, the increase could only be shown at substance concentrations that were also cytotoxic. Since there were no effects in the absence of cytotoxicity, interactions between cytotoxic and DNA-damaging effects, resulting in repair processes, cannot be excluded.

Reproduction and Teratology
1. Fertility and General Reproductive Performance
In a Segment I study, flumazenil was administered by gavage to rats in doses of 0, 15, 45 and 125 mg/kg/day. Thirty-two males per group were treated for 10 weeks prior to mating and during the mating period. The treatment of 32 females per group started two weeks prior to mating and continued through the gestation and lactation periods. No mortality or adverse effects were observed on parental animals.

Mating success, gestation length and outcome of pregnancy was not influenced by treatment either in the parental or in the F1 generation.

Gestational parameters such as the number of corpora lutea, implantations, resorptions and number of pups born alive were comparable to concurrent and historical control data in the parental as well as in the F1 generation.

Weight gain of F1-pups was normal in the low- and mid-dose groups but slightly decreased in the high-dose group. This decrease became statistically significant at weaning (lactation day 23). The viability of pups from the F1 and F2 generation was not affected by treatment.

2. Teratology–Rats
In a Segment II study, flumazenil was administered by gavage to rats at doses of 0, 15, 50 and 150 mg/kg/day. The test drug was administered to 40 mated female rats/dose from day 7 to day 16 of gestation inclusively; control rats received a similar volume of the vehicle. The study included rearing of the offspring until weaning in order to determine the postnatal effects of prenatally administered flumazenil.

Weight gain by the dams was not impaired and there was no evidence for an adverse effect on the various reproductive parameters (i.e. resorption rate, number of dead fetuses, mean body weight of fetuses, mean crown/rump length and duration of the gestation period). During the postnatal period, the body weight of pups increased uniformly in all dose groups and the incidence of pup mortality was not increased in any of the treatment groups.

External, skeletal, and soft tissue examinations of the fetuses gave no indication of treatment- related teratogenicity. Five fetuses from a single litter in the high-dose group showed multiple skeletal abnormalities (i.e. shortened, poorly ossified and deformed long bones in fore and hind limbs, missing toes and enlarged heads).

3.Teratology–Rabbits

In a Segment II study, flumazenil was administered by gavage to rabbits at doses of 0, 15, 50 and 150 mg/kg/day. The test drug was administered to 20 mated female rabbits/dose from day 7 to day 19 of gestation, inclusively; control rabbits received a similar volume of the vehicle. Weight gain of the does during the gestation period, mating success, mean number of corpora lutea and mean number of implantations were not impaired in any of the groups.

The resorption rate noted in the high-dose group (1.6 per pregnant female), was significantly greater than that for the concurrent control (0.7 per pregnant female), but was within the range for historical controls. Examinations of fetuses for malformations revealed no evidence for a teratogenic effect of flumazenil up to a dose of 150 mg/kg/day.

4. Perinatal and Postnatal–Rats

In a Segment III study, flumazenil was administered by gavage to rats at doses of 0, 5, 25 and 125 mg/kg. The test drug was administered to 24 mated females/group from day 16 of gestation until weaning, on day 22 of lactation. A control group received the vehicle.

There were no significant dose or drug-related differences between the groups in the number of intrauterine and perinatal deaths. Mortality during lactation was increased in the high-dose group (14% versus 7.8% in the control group). From the weanlings in which the organs were weighed, a slight but dose-related increase of liver weights was noted in the mid- and high- dose groups. The physical and functional development of neonates was normal, although there was a slight but statistically significant delay of incisor eruption, ear opening and auditory startle response in the offsprings of high-dose-treated dams.

Irritation Studies

1. Venous Irritation–Rabbits

A single injection of 1.0 mL of flumazenil (1 mg/mL, mixed micelles formulation) into the marginal ear vein of 6 New Zealand rabbits did not cause significant irritation of the veins.

2. Local Tolerance–Rabbits

Five rabbits were given an IV injection of 0.5 mL of flumazenil (0.5 mg/5 mL, aqueous formulation) in the direction of the venous flow for the marginal ear veins. IV tolerance was rated as good; only one animal had some reddening in the vicinity of the injection site (without any effect on the vein) on days 1 and 2.

3. Local Tolerance–Rat Hindquarter Muscle

Intramuscular tolerance was rated as good in 10 rats receiving 0.1 mL of flumazenil (0.5 mg/5mL,

aqueous formulation) into the gastrocnemius muscle of each hind limb. Creatinine phosphokinase was elevated relative to baseline at 24 hours after injection in both treated and control animals. The elevations seen in treated rats were somewhat larger than those observed in the control group.

4. Hemolysis Testing–Dogs

Intravenous administration of 1.0 mL of flumazenil (1 mg/mL, mixed micelles formulation) to 12 dogs did not produce any significant hemolysis.

REFERENCES

Pharmacology

1. Barrett JE, et al. Behavioral studies with anxiolytic drugs II. Interactions of zopiclone with ethyl-beta-carboline-3-carboxylate and Ro 15-1788 in squirrel monkeys. J Pharmacol Exp Ther 1986; 236:313-9.

2. D'Argy R, Persson A, Sedvall G. A quantitative cerebral and whole body autoradiographic study of an intravenously administered benzodiazepine antagonist ^{3}H- Ro 15-1788 in mice. Psychopharmacology 1987;92:8-13.

3. Haefely WE. Pharmacology of the benzodiazepine receptor. Eur Arch Psychiatr Neurol Sci 1989;238:294-301.

4. Hunkler W, et al. Selective antagonists of benzodiazepines.Nature 1981; 290:514-6.

5. Samson Y, et al. Kinetics and displacement of [^{11}C] Ro 15-1788, a benzodiazepine antagonist, studied in human brain in vivo by positron tomography. Eur J Pharmacol 1985;110:247-51.

6. Wettstein JG, Spealman RD. Behavioural effects of zopiclone, CL 218,872 and diazepam in squirrel monkeys: antagonism by Ro 15-1788 and CGS 8216. J Pharmacol Exp Ther 1986; 238:522-8.

Human Pharmacokinetics

7. Klotz U, Ziegler G, Reimann IW. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. Eur J Clin Pharmacol 1984;27:115-7.

8. Massarella J, Schwam E, Pitman V, et al. Food increases the clearance of flumazenil during intravenous infusion. Clin Pharmacol Ther 1990;47:182.

9. O'Boyle C, et al. Ro 15-1788 antagonizes the effects of diazepam in man without affecting its bioavailability. Br J Anæsth 1983;55:349-55.

10. Pomier-Layrargues G, et al. Pharmacokinetics of benzodiazepine antagonist Ro 15-1788 in cirrhotic patients with moderate or severe liver dysfunction. Hepatology 1989;10:969-72.

Clinical Pharmacology

11. Barakat T, et al. Ventilatory effects of flumazenil on midazolam-induced sedation Anesthesiology 1988;69:A817.

12. Carter AS, et al. Speed of reversal of midazolam-induced respiratory depression by flumazenil–a study in patients undergoing upper GI endoscopy. Acta Anæsthesiol Scand 1990;34:59-64.

13. Croughwell ND, et al. Safety of rapid administration of flumazenil in patients with ischæmic heart disease. Acta Anæsthesiol Scand 1990;34(suppl 92):55-8.

14. Dailland PH, et al. Effect of Ro 15-1788 (flumazenil) on the CO_2 responsiveness after midazolam-fentanyl anesthesia. Anesthesiology 1988;69:A815.

15. Forster A, et al. Double-blind randomized, study evaluating the effects of a specific benzodiazepine antagonist on cerebral blood flow. Anesthesiology 1984;61:A248.

16. Geller E, et al. Cardiorespiratory effects of antagonism of diazepam sedation with flumazenil in patients with cardiac disease. Anesth Analg 1991;72:207-11.

17. Klotz U, et al. Pharmacodynamic interaction between midazolam and a specific benzodiazepine antagonist in humans. J Clin Pharmacol 1985;25:400-6.

18. Louis M, et al. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery. Anesthesiology 1984,61:A61.

19. Marty J, et al. Coronary and left ventricular hemodynamic responses following reversal of flunitrazepam-induced sedation with flumazenil in patients with coronary artery disease. Anesthesiology 1991;74:71-6.

20. Mora CT, Torjman M, White PF. Effects of diazepam and flumazenil on sedation and hypoxic ventilatory response. Anesth Analg 1989;68:473-8.

21. Weinbrum A, Geller E. The respiratory effects of reversing midazolam sedation with flumazenil in the presence or absence of narcotics. Acta Anæsthesiol Scand 1990;34 (suppl 92):65-9.

22. Whitwam JG. Resedation. Acta Anæsthesiol Scand 1990;34(suppl 92):70-4.

23. Wolff J, et al. The effect of the benzodiazepine antagonist flumazenil on regional cerebral

blood flow in human volunteers. Acta Anæsthesiol Scand 1990;34:628-31.

Clinical Use

24. Alon E, et al. Double-blind study of the reversal of midazolam-supplemented general anæsthesia with Ro 15-1788. Br J Anæsth 1987;59:455-8.

25. Birch BRP. Cardiac arrest associated with flumazenil. Br Med J 1992;305:180-1.

26. Duvaldestin P, et al. Efficacy of flumazenil reversal after midazolam-induced anesthesia. Anesthesiology 1988;69:A560.

27 Fisher GC, Clapham MCC. Flumazenil in intensive care. Anæsthesia 1991;46:413-6.

28. Geller E, et al. Risks and benefits of therapy with flumazenil ('Anexate') in mixed drug intoxications. Eur Neurol 1991;31:241-50.

29. Hoejer J, Baehrendtz S. The effect of flumazenil (Ro 15-1788) in the management of self-induced benzodiazepine poisoning. Acta Med Scand 1988;224:357-64.

30. Hoejer J, et al. Diagnostic utility of flumazenil in coma with suspected poisoning: a double-blind, randomized controlled study. Br Med J 1990;301:1308-11.

31. Katz Y, et al. Cardiac arrest associated with flumazenil. Br Med J 1992;304:1415.

32. Kirkegaard L, et al. Antagonism of diazepam sedation in outpatients undergoing gastroscopy. Anæsthesia 1986;41:1184-8.

33. O'Sullivan GF, Wade DN. Flumazenil in the management of acute drug overdosage with benzodiazepines and other agents. Clin Pharmacol Ther 1987;42:254-9.

34. Philip BK, Simpson TH, Hauch MA. Flumazenil reverses sedation after midazolam-induced general anesthesia in ambulatory surgery patients Anesth Analg 1990;71:371-6.

35. Rodrigo MRC, Rosenquist JB. The effect of Ro 15-1788 ('Anexate') on conscious sedation produced with midazolam. Anæsth Intensive Care 1987;15:185-92.

36. Skielboe M, Andersen P, Weber M. Antagonism of diazepam sedation by flumazenil. Br J Anæsth 1989;63:554-7.

37. Wolff J, et al. Ro 15-1788 for postoperative recovery: a randomized clinical trial in patients

undergoing minor surgical procedures under midazolam anæsthesia. Anæsthesia 1986;41:1001-6.

Reviews

38. Amrein R, et al. Clinical pharmacology of flumazenil. Eur J Anæsthesiol1988;(suppl 2): 65-80.

39. Brogden RN, Goa KL. Flumazenil: A preliminary review of its benzodiazepine antagonist properties, intrinsic activity and therapeutic use. Drugs 1988;35:448-67.

40. Dunton AW, et al. Flumazenil: U.S. clinical pharmacology studies. Eur J Anæsthesiol 1988;2:81-95.

41. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). Clin Pharmacokinet 1988;14:1-12.

42. Prischl F, et al. Value of flumazenil in benzodiazepine self-poisoning. Med Toxicol 1988;3:334-9.

43. Sandoz Canada Inc. Product Monograph: Flumazenil Injection SDZ. Control# 154070, July 4, 2012

CONSUMER INFORMATION

JAMP-Flumazenil
(flumazenil)

This leaflet is a part of the "Product Monograph" published for JAMP-Flumazenil and is designed specifically for Consumers.
Please read this information before you start to take your medicine. Keep this leaflet until you have finished all of your JAMP-Flumazenil, as you may need to read it again. If you are helping someone else to take JAMP-Flumazenil, read this leaflet before the first dose is given.
This leaflet is a summary and will not tell you everything about JAMP-Flumazenil. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Reversing drowsiness, sedation, and other effects caused by a medicine within a group of medicines called benzodiazepines. It may be used to wake you up after anesthesia or if you have been in intensive care.

What it does:

JAMP-Flumazenil contains the active ingredient flumazenil. Flumazenil is a benzodiazepine antagonist. It works by blocking receptors in the brain and central nervous system that benzodiazepines need to reach to be active, which helps reduce drowsiness and sedation caused by benzodiazepines.

When it should not be used:

- If you have had an allergic reaction to Flumazenil or to benzodiazepines in the past
- If you are allergic to any of the ingredients it contains (see '**What the nonmedicinal ingredients are**')
- If you are taking a benzodiazepine for control of a life-threatening condition (eg. Increased pressure in the head, seizures).
- If you are experiencing side effects due to an overdose of a medicine used to treat depression

What the medicinal ingredient is:
Flumazenil

What the nonmedicinal ingredients are: methylparaben, propylparaben, sodium chloride, edetate disodium, acetic acid 0.1 mg, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

What dosage forms it comes in:
Flumazenil Injection 0.1 mg/mL is available in multidose vials of 5 mL and 10 mL, boxes of 5.

Latex-Free Stopper – Stopper contains no dry natural rubber.

WARNINGS AND PRECAUTIONS

- JAMP-Flumazenil may affect your ability to be alert. Driving, operating machinery and other hazardous activities should therefore be avoided altogether for at least 24 hours.
- You must not consume alcohol or other drugs that affect your central nervous system.
- Although JAMP-Flumazenil is given to reverse drowsiness, you may experience a return of drowsiness for up to 24 hours after JAMP-Flumazenil is given. If you notice a return of drowsiness or experience shortness of breath, contact your doctor as soon as possible.

BEFORE you use JAMP-Flumazenil talk to your doctor or pharmacist if you:

- have liver problems
- have anxiety or panic disorders
- have heart problems or irregular heart beat
- Are pregnant or planning to become pregnant, discuss with your doctor the benefits and risks of using JAMP-Flumazenil during pregnancy.
- Are breastfeeding as flumazenil may pass into breast milk. Therefore, breast feeding should be interrupted for 24 hours when JAMP-Flumazenil is used.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or healthfood store without a prescription.

Some medicines may interfere with JAMP-Flumazenil. These medicines include:

- medicines within the benzodiazepine group (examples: clonazepam, chlordiazepoxide, diazepam, flurazepam or bromazepam)

These medicines are affected by JAMP-Flumazenil. Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

If you have not told your doctor about any of the above, tell him/her before you start taking JAMP-Flumazenil.

PROPER USE OF THIS MEDICATION

Usual dose:
JAMP-Flumazenil should be administered intravenously by a physician with experienced in anaesthesiology at your doctor's office, hospital or clinic. Your doctor will decide what dose you will receive which will depend on your particular condition.

Overdose:

In case of drug overdose, contact a health care

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications JAMP-Flumazenil can cause some side effects. For most patients these side effects are likely to be minor and temporary as your body adjusts to the medicine. However, some may be serious. Consult your doctor or pharmacist as soon as you can if you do not feel well while taking JAMP-Flumazenil.

Seek urgent medical attention if you experience:

- **Allergic reactions** (very rare)

If you have an allergic reaction, see a doctor straight away. The signs may include: sudden swelling of the throat, face, lips or mouth. This can make it difficult to breathe or swallow; sudden swelling of the hands, feet or ankles; skin rash or itching.

- **Convulsions (seizures)**

These are more likely to happen in people who already have epilepsy or severe liver problems or people who have taken medicines called benzodiazepines for a long time.

The most common side effects are:

- Nausea
- Vomiting

Less common possible side effects are:

- Feeling of anxiousness, fear or panic
- Dizziness and sweating
- Increase of blood pressure (flushing) and heart rate
- Headaches, mood swings and chills
- Rash, blurred vision, tremors, low blood pressure, urinary incontinence, and constipation
- Panic attacks in patients that have a history of panic disorders

Withdrawal symptoms

- If you have recently been taking a benzodiazepine (for example to help you sleep or to treat anxiety), you may get withdrawal symptoms after having JAMP-Flumazenil. This may happen even if you stopped taking these medicines a few days or weeks before having JAMP-Flumazenil. Withdrawal symptoms include disturbed sleep, depression, feeling nervous, feeling irritable, feeling dizzy, a rapid heartbeat, diarrhea and sweating.

This is not a complete list of side effects. For any unexpected effects while taking JAMP-Flumazenil, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- Keep JAMP-Flumazenil in a cool dry place stored at room temperature (15-30°C). Protect from light. Discard unused portion 28 days after the initial puncture.
- JAMP-Flumazenil may be diluted with dextrose 5% solution or sodium chloride 0.9%. If flumazenil is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours.
- Keep this medicine out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor.

This leaflet was prepared by JAMP Pharma Corporation.

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