Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Exitine 0.5mg/5ml Solution for IV Injection.

2. Qualitative and quantitative composition

Each 5ml contains Flumazenil 0.5mg.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for IV Infusion.

4. Clinical particulars

4.1 Therapeutic indications

Exitine® is indicated for reversal of the central sedative effects of benzodiazepines. It is therefore used in anesthesia and intensive care in the following indications:

In anesthesia:

- Termination of the anesthesia induced and maintained with benzodiazepines in hospitalised patients.
- Reversal of benzodiazepine-induced sedation in short diagnostic and therapeutic procedures in ambulant or hospitalised patients.

In intensive care:

- Exitine® is used to provide diagnostic information on or to exclude intoxication with benzodiazepines.
- As a diagnostic measure in unconsciousness of unknown cause in order to determine whether benzodiazepines or other drugs are involved or whether brain damage is present.
- As specific treatment to reverse the central effects of benzodiazepines in drug overdosage (to restore spontaneous respiration and consciousness and thereby avoid the need for intubation or to permit extubation).

4.2 Posology and method of administration

Standard dosage:

Exitine® is for intravenous use only and should be administered I.V. by an anesthetist or an experienced physician.

For administration by infusion, Exitine® can be diluted in 5% glucose (in water), or normal saline solution.

The dose should be titrated in accordance with the desired effect.

As the action of some benzodiazepines can be more prolonged than that of Exitine®, repeated doses of Exitine® may be required if sedation recurs after waking.

The drug can also be used in combination with other resuscitative measures.
In anesthesia:
The recommended initial dose is 0.2 mg I.V. and it should be administered within 15 seconds. If the desired level of consciousness is not obtained within 60 seconds of the first I.V. dose, a second dose of 0.1 mg can be injected. If necessary, this procedure can be repeated at 60-second intervals up to a total dose of 1mg. The usual dose is in the range 0.3-0.6 mg.
In the intensive care unit:
An initial dose of 0.3 mg I.V. is recommended. If the desired level of consciousness is not obtained within 60 seconds, further doses of Exitine® can be injected until the patient wakes up or a total dose of 2 mg has been administered. If drowsiness recurs, an I.V. infusion of 0.1-0.4 mg per hour can be useful. The rate of infusion should be individually adjusted to the desired level of consciousness.
In the intensive care unit, individually titrated slow injection of Exitine® should not produce withdrawal symptoms in patients who have received benzodiazepines in high doses and/or for long periods of time. If unexpected signs of overstimulation occur, 5 mg diazepam or 5 mg midazolam can be given I.V., carefully titrated to individual patient response.
If the level of consciousness or respiratory function does not improve after repeated doses of Exitine®, a non-benzodiazepine etiology must be assumed.
Special dosage instructions:
When used in anesthesia at the end of an operation, Exitine® should not be injected before the effect of peripheral muscle relaxants has worn off.
Pediatrics (children over 1 year of age):
For reversal of benzodiazepine-induced sedation, the recommended initial dose is 0.01 mg/kg body-weight (up to 0.2 mg) administered I.V. over 15 seconds. If there is no response within 45 seconds, further doses can be given at one-minute intervals. The total dose must not exceed 0.05 mg/kg body-weight or 1 mg.
Because of limited experience, Exitine® should be used with caution in the following cases:

- Children under 1 year of age for reversal of sedation.
- In all pediatric age groups to reverse the sedative properties of benzodiazepines in anesthesia, for management of overdose and for resuscitation

4.3 Contraindications

Exitine® is contraindicated in patients with known hypersensitivity to the drug.
Exitine® is contraindicated in patients who have received a benzodiazepine to treat a potentially life-threatening condition (e.g. control of intracranial pressure after severe head injury or status epilepticus

4.4 Special warnings and precautions for use

- Use of Exitine® is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although Exitine® exerts a slight intrinsic

anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

- In mixed intoxications with benzodiazepines and cyclic antidepressants, the toxicity of the antidepressants can be masked by the protective benzodiazepine effect. Therefore, in the presence of autonomic (anticholinergic), motor or cardiac manifestations of severe intoxication with tricyclics/tetracyclics, the benzodiazepine effect should not be reversed with Exitine®.
- Patients who have been given Exitine® to reverse the effect of benzodiazepines should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period of time which will depend upon the dose and duration of action of the benzodiazepines used.
- When used with muscle relaxants, Exitine® should only be injected after the effects of the neuromuscular blockade have been completely reversed.
- Exitine® is not recommended for the treatment of benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes.
- Rapid injection of Exitine® should be avoided in patients who have received benzodiazepines in high doses immediately or for up to a week before administration of Exitine® and/or over a prolonged period of time, since this can lead to withdrawal phenomena such as agitation, anxiety, emotional lability, mild confusion and sensory distortions.

4.5 Interaction with other medicinal products and other forms of interaction

- **Exitine®** blocks the central effects of benzodiazepines by competitive interaction at the receptor level. Non-benzodiazepines that act via the benzodiazepine receptor, such as zopiclone, triazolopyridazines and others, are also blocked by **Exitine®**.
- Particular caution is required when **Exitine®** is used in cases of acute mixed drug overdose, since the toxic effects (for example, convulsions and cardiac arrhythmias) of other medications also taken in overdose (especially cyclic antidepressants) may emerge after reversal of the benzodiazepine effect. The pharmacokinetics of benzodiazepine agonists is unaffected by **Exitine®** and vice versa.
- No interaction is known to occur between alcohol and flumazenil.

4.6 Pregnancy and Lactation

Pregnancy

Although studies in animals given high doses of **Flumazenil** revealed no evidence of teratogenicity, no controlled studies on pregnant women are available. The general medical principle of administering drugs in early pregnancy only if absolutely necessary should therefore be observed.

Lactation

Parenteral administration of flumazenil during lactation is not contraindicated in acute cases. It is not known whether flumazenil is excreted in human milk**.**

4.7 Effects on ability to drive and use machines

Although patients remain alert and conscious after administration of flumazenil, they should refrain from hazardous activities that demand complete mental alertness (e.g. operating dangerous machinery or driving a motor vehicle) for 24 hours after administration, since the effect of the originally ingested or administered benzodiazepine may return.

4.8 Undesirable effects

Rare cases of flushing, nausea and/or vomiting have been reported with use in anesthesia. In isolated cases patients complained of anxiety, palpitations and fearfulness after rapid injection of **flumazenil**. These undesirable effects required no specific treatment.

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

In cases of mixed drug overdose, particularly with cyclic antidepressants, reversal of the benzodiazepine effect by **Exitine®** can lead to undesirable effects (such as convulsions and cardiac arrhythmias).

Rapid injection of **Exitine®** can lead to benzodiazepine agonist withdrawal phenomena in patients who have received benzodiazepines over a prolonged period of time ending immediately or in the weeks preceding administration of **Exitine®**. These phenomena should disappear after slow I.V. injection of 5 mg diazepam or 5 mg midazolam.

Adverse events most frequently associated with flumazenil alone were dizziness, injection site pain, increased sweating, headache, and abnormal or blurred vision.

Psychiatric disorders:

Common: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation), emotional lability (abnormal weeping, depersonalisation, euphoria, increased tears, depression, dysphoria, paranoia).

Very rare: Fear, panic attacks in patients with a history of panic disorders.

Withdrawal symptoms may occur following rapid injection of **Exitine®** in patients receiving long-term treatment with benzodiazepines.

Nervous system:

Very common: Dizziness (vertigo, ataxia).

Common: Headache, paresthesia (abnormal sensation, hypoesthesia).

Rare: Confusion (poor concentration, delirium), convulsions, somnolence (stupor).

Eyes:

Common: Abnormal vision (visual field defect, diplopia).

Ear and inner ear:

Rare: Abnormal hearing (transient hearing impairment, hyperacusis, tinnitus).

Vascular disorders:

***Common*:** Cutaneous vasodilation (sweating, flushing, hot flushes).

Gastrointestinal disorders

***Very common*:** Vomiting.

***Common*:** Nausea.

General disorders:

***Common*:** Fatigue (asthenia, malaise), pain at the injection site (thrombophlebitis, skin changes, rash).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

There is limited experience of acute overdose with **Exitine®**
There is no specific antidote for overdose with **Exitine®**. Treatment of an overdose with **Exitine®** consists of general emergency medicine measures, including monitoring and stabilization of vital signs and observation of the clinical status of the patient.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Exitine® "Flumazenil" is an imidazobenzodiazepine derivative, antagonises the effect of benzodiazepines on the central nervous system. It competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. The hypnotic-sedative effects of benzodiazepines are rapidly reversed (within 1 to 2 minutes) by intravenous injection of Flumazenil and may reappear gradually within the next few hours, depending on the half-life and dose ratio of the agonist and antagonist.

5.2 Pharmacokinetic properties

After IV administration, plasma concentrations of flumazenil follow a two-exponential decay model. The pharmacokinetics of flumazenil are dose-proportional up to 100 mg.

Distribution Flumazenil is extensively distributed in the extravascular space with an initial distribution half-life of 4 to 11 minutes and a terminal half-life of 40 to 80 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. The volume of distribution at steady-state is 0.9 to 1.1 L/kg. Flumazenil is a weak lipophilic base. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells. Albumin accounts for two thirds of plasma protein binding.

Metabolism Flumazenil is completely (99%) metabolized. Very little unchanged flumazenil (less than 1%) is found in the urine. The major metabolites of flumazenil indentified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid.

Elimination Elimination of radiolabeled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in feces. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranged from 0.8 to 1.0 L/hr/kg.

5.3 Preclinical safety data

Not Applicable

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium chloride, Edetate Disodium, Glacial Acetic Acid, Sodium hydroxide &Water for injections

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage
Do not store above 30°C, do not freeze.

6.5 Nature and Content of container
Exitine® 0.5mg/5ml solution for Injection: Each 1ml contains 0.1 mg flumazenil in 5ml Vial.
Exitine is packed in Clear Tubular Glass Vial 6R stoppered with rubber stopper 20mm.

6.6 Special precautions for disposal and other handling
When **Exitine®** drawn into syringe or diluted with 5% Glucose (in water) or normal saline (0.9% Sodium chloride), any unused solution should be discarded after 24 hours.

7. Marketing Authorization Holder
MS Pharma jordan
Amman/ jordan /Sahab- street no.6, bulding no.356

8. Marketing Authorization Number

H2026/CTD8081/15839

9. Date of first authorization/renewal of the authorization

2026 March 30

10. Date of revision of the text

2026 March 30