Wafermine™- Prescriber Information

Wafermine™ is a lyophilised ketamine wafer administered sublingually. It incorporates the propriety Waferix™ wafer technology which results in rapid disintegration of the hydrophilic wafer matrix and release of the active drug upon contact with saliva.

Wafermine™ is manufactured by Syrinx Pharmaceuticals, a Therapeutic Goods Administration ("TGA") approved and current Good Manufacturing Practices ("cGMP") compliant manufacturer in Croydon, Victoria.

1 Indications and Availability

Wafermine™ is currently under clinical development for the indication of moderate to severe acute postoperative and procedural pain. Therefore, it is not currently listed on the Australian Therapeutics Goods Register.

Wafermine™ is currently available to prescribers under exemption Schedule 5A (item 5) of the Australian Therapeutic Goods Regulations for use in patients.

2 Dosage and Administration

Wafermine™ dosage should be titrated to analgesic response. To date, the typical dose of Wafermine™ prescribed under Schedule 5A is 25-50 mg. For example, in one Australian Tertiary Hospital, Wafermine™ is prescribed for the management of procedural pain secondary to burn dressing changes as 25-50mg, 10 minutely PRN. A maximum dose per procedure has not been established.

The absolute bioavailability of the drug was observed to be 29% in a clinical study of 8 healthy males. This suggests that a dose of Wafermine™ 50mg would produce a similar drug exposure (i.e. AUC∞) to approximately Ketamine 15mg administered intravenously.

Duration of action after a single dose is up to 2-3 hours [data on file].

Wafermine™ is administered sublingually. To ensure the sublingual mucosa is moist prior to wafer administration, patients should be instructed to rinse their mouth with approximately 20 mls of water and then to swallow completely. The wafer should be placed posteriorly towards the base of the tongue and medially on either side of the frenulum in the sublingual space. The wafer dissolves within 1-2 minutes of being placed sublingually.
Dosage Forms and Strengths

Wafermine™ is supplied as 25mg and 50mg sublingual wafers.

Clinical Pharmacology

4.1 Pharmacodynamics: Ketamine is a competitive antagonist at the NMDA receptor, which is believed to be the principal mechanism of its analgesic action.

4.2 Pharmacokinetics: Wafermine™ contains racemic ketamine. The pharmacokinetics of the two isomers are similar. The time to peak concentration (Tmax) occurred at 30 minutes post dose. The elimination half-life is between 2.0-2.5 hours. Dose linearity was established across the dose range (35mg to 100mg) for both Cmax and AUCinf. The absolute bioavailability of ketamine from Wafermine™ is 29%. Some sublingual ketamine is swallowed and absorbed. Swallowed ketamine undergoes hepatic first-pass metabolism. Ketamine is principally eliminated by hepatic metabolism, with the major pathways being CYP3A4 and 2B6. The principal metabolite is norketamine which, which has activity as an NMDA antagonist, but with lower potency than ketamine.

Clinical Studies

To date six clinical studies with Wafermine™ have been completed. This includes three pharmacokinetic studies conducted in healthy volunteers and three studies managing acute pain in patients who have undergone dental and bunionectomy surgery.

Safety:

Wafermine™ has been administered to 302 participants across the clinical trial program including 210 patients for the management of acute post-operative pain. Wafermine™ has also been prescribed since 2014 to a large number of patients (>40,000 wafers) in hospitals throughout Australia under exemption Schedule 5A of the Australian Therapeutics Regulations.

Wafermine™ has been well-tolerated in both single and multiple dose trials. Single dose studies investigated Wafermine™ doses between 25mg to 100mg whereas the multiple dose study in patients undergoing bunionectomy were administered up to 315mg in divided doses (35mg or 70mg) over a 14 hour period.

The most common treatment-emergent adverse events across all completed studies were as follows: dizziness (27%), nausea (26%), oral discomfort (10%), headache (9%), somnolence (7%), vomiting (7%), euphoric mood (6%) and feeling abnormal (5%). The majority (66%) of these events were of mild severity and were of limited duration. There were no serious adverse events.

Efficacy:

All studies showed a rapid analgesic response with a reduction in pain intensity scores within 10 minutes. Peak analgesic response occurred between 20-30 minutes post dosing with a median reduction of 1.75 points on a 11 point numerical scale (0-10). The duration of action was up to 2-3 hours with the higher doses trialled [data on file].
6 Precautions

6.1. The elimination of ketamine could potentially be delayed in patients with significant renal or hepatic impairment. Dose reduction should be considered in patients with cirrhosis or other types of liver impairment.

6.2. Ketamine may affect your ability to drive or operate a machinery. If affected advise patients not to drive or operate a machinery.

6.3. Use with caution in patients with increased intraocular pressure (eg. glaucoma), neurotic traits or psychiatric illness, seizures, hyperthyroidism or patients receiving thyroid hormone replacement, pulmonary or upper respiratory infection, acute intermittent porphyria, intracranial mass lesions, a presence of head injury, globe injuries or hydrocephalus.

7 Contraindication

7.1. Ketamine is contraindicated in patients with any condition in which a significant elevation of blood pressure would be hazardous such as: severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or haemorrhage.

7.2. Ketamine is also contraindicated in those who have shown hypersensitivity to the drug or its components.

8 Supply, Storage and Handling

Wafermine™ is presented in foil backed blister strips of 10 wafers at either 25mg or 50 mg dose. The foil is marked with either “Wafermine 25” or “Wafermine 50”. Wafermine™ supplies should be stored as per requirements for Schedule 8 controlled drugs. Wafermine™ may be stored at room temperature and has a shelf life of 24 months.

9 Manufacturer

Syrinx Pharmaceuticals
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10 Reference