

## Esketamine hydrochloride

### Approved indication: treatment-resistant depression

#### Spravato (Janssen-Cilag) nasal spray containing 32.3 mg/0.2 mL

Some patients with major depressive disorder will not respond to antidepressant therapy, even if they have adhered to treatment with an adequate dose for an adequate duration. These patients then need to switch to another antidepressant.<sup>1</sup> In such treatment-resistant cases augmentation of antidepressant therapy may also be considered. One drug that has been used, off label, for augmentation is the anaesthetic drug ketamine.

The effect of ketamine in depression is thought to be related to its action on the N-methyl-D-aspartate (NMDA) receptor. By antagonising the NMDA receptor, ketamine may increase glutamate release and improve synaptic functioning.

Esketamine is the S-enantiomer of ketamine. It has a higher affinity for the NMDA receptor and can be given in a nasal spray. The bioavailability of an intranasal dose is approximately 48% with a peak plasma concentration 20–40 minutes later. Most of the dose is metabolised in the liver with most of the metabolites being excreted in the urine. The terminal half-life is 7–12 hours. Esketamine metabolism includes the cytochrome (CYP) P450 system, particularly CYP2B6 and CYP3A4. There are potential interactions with other drugs metabolised by these enzymes. No dose adjustment is needed in renal impairment or mild–moderate hepatic impairment.

Animal studies show that ketamine can cause developmental neurotoxicity during pregnancy. Women taking esketamine should use effective contraception during treatment and for six weeks afterwards. The risk of harm during breastfeeding is unknown.

Esketamine is a Schedule 8 drug and must be taken in the presence of a health professional. One spray is given into each nostril. When starting the drug, a dose determined by age is given twice weekly. After four weeks esketamine can be reduced to once weekly. Depending on the response, insufflation can possibly be reduced to fortnightly from week nine. If the patient improves, the recommendation is to continue treatment for at least six months.

The main clinical trials supporting the approval of esketamine have been included in a meta-analysis.<sup>2</sup> These five trials used changes in the 60-point Montgomery-Asberg Depression Rating

Scale (MADRS) to assess efficacy. They involved 774 patients with major depressive disorder. In this pooled sample there was a response to augmentation of antidepressant treatment in 53.2% of the 442 patients who took esketamine and 38.5% achieved remission. For the 332 patients in the placebo group the response rate was 36.4% with 24.7% achieving remission. For patients starting a new antidepressant, approximately six need to be treated with esketamine for four weeks for one to benefit.<sup>2</sup>

In addition to the trials in the meta-analysis, the safety of esketamine was assessed in a long-term open-label study. This enrolled 802 patients with treatment-resistant depression and followed them for up to one year. The median treatment with esketamine was approximately 23 weeks. Most patients had adverse events with the most frequent being dizziness, dissociation, nausea, headache and somnolence. Adverse events led to 9.5% of the patients stopping esketamine.<sup>3</sup>

Esketamine can temporarily increase blood pressure so this should be measured before insufflation and about 40 minutes afterwards. The blood pressure usually returns towards pre-dose levels after about 90 minutes.<sup>4</sup> Emergency care is needed if there is a hypertensive crisis. Esketamine is contraindicated in patients with a history of aneurysm or intracerebral haemorrhage. After each dose patients should also be monitored for sedation and dissociation for at least two hours. They should not eat for at least two hours before a dose and should not drive or operate machinery until the following day.

Caution will be needed if prescribing for a patient with a history of substance abuse, including alcohol. Ketamine has been misused, but this may be less likely with esketamine. The risk of dependence with esketamine is uncertain.

While the meta-analysis showed a benefit, not all of the trials of esketamine have reported a clear advantage in treatment-resistant depression. In a study of 138 patients over the age of 65 years the MADRS score had declined after 28 days by 10 points with esketamine and by 6.3 points with placebo.<sup>4</sup> The rapid action of esketamine may be an advantage in managing patients with an imminent risk of suicide. A placebo-controlled trial involving 66 of these patients reported a mean decrease of 13.4 points in the MADRS score four hours after a dose of esketamine. The reduction in the placebo group was 9.1 points, but by 24 hours there was no difference between the groups in suicidal thoughts.<sup>5</sup>

**T** manufacturer provided the product information

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## REFERENCES

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The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27](#).

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration in the USA](#) and the [European Medicines Agency](#).