ACMD

Advisory Council on the Misuse of Drugs

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Rt Hon Dame Diana Johnson DBE MP
Minister for Policing and Crime Prevention
2 Marsham Street
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13th August 2025

Dear Minister

RE: ACMD advice on ganaxolone

The Advisory Council on the Misuse of Drugs (ACMD) is grateful to the Medicines and Healthcare products Regulatory Agency (MHRA) for providing a written submission and oral presentation on the neuroactive steroid ganaxolone (Ztalmy®). Further to these representations, the ACMD is able to provide advice on whether ganaxolone warrants control under the Misuse of Drugs Act 1971.

Ganaxolone was approved for marketing in the UK on 7th March 2024 for the treatment of the rare epileptic seizure disorder 'Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder', for patients from 2 to 17 years of age, with the potential to continue use in patients aged 18 years and above if required. As CDKL5 deficiency disorder is a rare condition, ganaxolone was designated an orphan drug, a scheme that offers incentives for developing medicines intended for small numbers of patients. Ganaxolone is a prescription-only medicine, which will be prescribed by specialist paediatric neurologists.

Ganaxolone is a methyl analogue of the endogenous neurosteroid, allopregnanolone, that positively and allosterically modulates gamma-aminobutyric acid A (GABA-A) receptors in the central nervous system (CNS) by interacting with a recognition site that is distinct from other allosteric GABA-A receptor modulators. The precise mechanism by which ganaxolone exerts its therapeutic effects in the treatment of seizures associated with CDKL5 deficiency disorder is unknown.

Animal studies found that ganaxolone shares an internal/subjective interoceptive cue with benzodiazepines and dose-dependently supports self-administration, suggesting ganaxolone has reinforcing characteristics similar to those of benzodiazepines. Abrupt discontinuation of ganaxolone in animal studies led to some experiencing withdrawal symptoms.

In human studies, ganaxolone is associated with CNS-effects, particularly somnolence and sedation. Adverse CNS effects associated with misuse (e.g., euphoria) have been reported with ganaxolone treatment. In a clinical study to evaluate the abuse potential of single oral doses of ganaxolone in healthy recreational CNS depressant users, supratherapeutic doses showed significantly less abuse potential compared with lorazepam. It was not possible to assess physical dependence with ganaxolone during clinical trials. No intentional overdose or misuse of ganaxolone in clinical studies has been reported to date. As ganaxolone is primarily administered to young people, there is the chance of diversion, although there is no evidence of this at present.

Classification

Ganaxolone has potential for misuse due to its CNS effects. However, due to the rarity of CDKL5 deficiency disorder, it is likely that use of ganaxolone will be highly limited. Due to the limited and restricted setting in which ganaxolone will be used, the ACMD considers the potential for misuse to be very low. In the United States, after an eight-factor analysis by the Department of Health and Human Services, ganaxolone was placed under the control of the Controlled Substances Act in 2022, but only as a Schedule V drug, indicating the lowest level of misuse potential. Ganaxolone is currently unclassified in European countries.

Recommendation 1

The ACMD recommends that ganaxolone should not be controlled under the Misuse of Drugs Act 1971 nor scheduled under the Misuse of Drugs Regulations 2001 at this time.

Recommendation 2

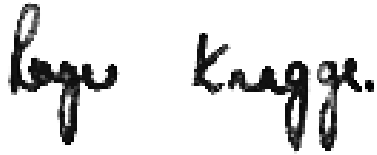
The ACMD recommends that the MHRA incorporate consideration of misuse, abuse and diversion into their risk management plan for ganaxolone, and that the MHRA, in collaboration with the licence holder, monitor misuse in their post-marketing surveillance. If the surveillance shows evidence of misuse, the MHRA should resubmit evidence to the ACMD for further consideration.

Lead department
MHRA.

Measure of implementation

Monitoring of misuse in post-marketing surveillance report and risk management plan, and resubmission of evidence to the ACMD if misuse is reported.

Yours sincerely,



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