

January 2023

Gabapentin (Neurontin®)

2-[1-(aminomethyl) cyclohexyl] acetic acid

Introduction:

Gabapentin is a prescription medication approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain and epileptic disorders. It is currently marketed in capsule, tablet and oral solution formulations. In recent years however, gabapentin has been increasingly encountered by law enforcement, documented in national crime lab reports, reported to poison control centers and diverted for illicit use.

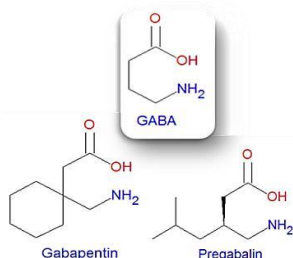
Licit Uses:

According to the FDA-approved product label, gabapentin is used clinically in the management of postherpetic neuralgia in adults and as an adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy.

Between 2011 and 2021, the annual total prescriptions dispensed for gabapentin steadily increased, roughly two-fold. According to IQVIA National Prescription Audit™, total prescriptions dispensed for gabapentin were approximately 33.4 million in 2011, 56.9 million in 2015, 68.3 million in 2019, 69.0 million in 2020, and 70.9 million in 2021. Gabapentin is available in various dosage forms and strengths including capsule strengths of 100, 300 and 400 milligrams, tablet strengths of 600 and 800 milligrams and the oral liquid form is typically produced as a 250 milligrams/5 mL solution.

Chemistry:

The chemical structures for gabapentin [1-(aminomethyl) cyclohexaneacetic acid], gamma-aminobutyric acid (GABA) and pregabalin are shown below. Gabapentin closely resembles pregabalin, a schedule V drug under the Controlled Substances Act in its chemical structure and pharmacological activity.



The chemical structure of gabapentin is derived from the addition of a lipophilic cyclohexyl group to the backbone of GABA. Gabapentin is a crystalline substance and freely soluble in water, alkaline and acidic solutions.

Pharmacology:

The exact mechanisms through which gabapentin exerts its analgesic and antiepileptic actions are unknown. However, according to the information from the FDA-approved label for the gabapentin drug product, gabapentin has no effect on GABA binding, uptake or degradation. In-vitro studies have shown gabapentin binds to auxiliary $\alpha 2-\delta$ subunits of voltage-gated Ca^{2+} channels on neurons thereby resulting in a decrease in neuronal excitability.

At clinically therapeutic doses (900-3600 mg/day), gabapentin does not bind to GABA_A or GABA_B receptors, nor does it bind to benzodiazepine sites.

The FDA-approved product label for gabapentin mentions adverse reactions such as dizziness, somnolence (drowsiness), peripheral edema (swelling), ataxia (incoordination), fatigue and nystagmus (involuntary rapid eye movement). According to a published study which

analyzed online information from 32 websites, gabapentin use, similar to pregabalin, is associated with sedative and/or psychedelic effects.

Illicit Uses:

Gabapentin has been encountered in postmortem toxicology reports as indicated by data from the American Association of Poison Control Centers (AAPCC). According to the 2020 annual report of AAPCC's National Poison Data System (NPDS), gabapentin was detected in a total of 135 fatalities in 2020 alone, compared to 168 total fatalities between 2012 and 2016 combined. Of those cases, gabapentin was the primary cause of death in 23 individuals. According to this report, gabapentin was amongst one of the most frequent analytes detected in 1,547 tissue samples. Of the 154 analytes detected, gabapentin accounted for 25 samples. Total exposure calls as a result of gabapentin stayed largely the same between 2017 and 2020 with 22,088 calls made in 2017 and 21,423 in 2020. Among cases classified as single substance pharmaceutical exposures (AAPCC defines single exposures as the number of human exposure cases that identified only one substance), gabapentin was identified as a single substance in 7,214 cases in 2020. With respect to medical outcomes associated with gabapentin calls to poison control centers in 2020, gabapentin was associated with 7 deaths, 178 outcomes classified as "major", 832 outcomes classified as "moderate", and 1,441 outcomes classified as "minor".

User Population:

The population likely to abuse gabapentin appears to be the same as those abusing sedative hypnotic substances. In a cohort of 503 adults reporting nonmedical use of pharmaceuticals (and not enrolled in treatment facilities for such illicit use) in Appalachian Kentucky, 15% of respondents reported using gabapentin specifically to "get high." This number represented a 165% increase compared to one year prior and a 2,950% increase from 2008 respondents within the same cohort. In a 2013 online survey distributed to 1,500 respondents from the United Kingdom aged 16 to 59 years, 1.1% self-reported lifetime prevalence of gabapentin misuse.

Illicit Distribution:

The National Forensic Laboratory Information System (NFLIS) is a system that collects drug analysis information from state, local, and other federal forensic laboratories. According to NFLIS-Drug, gabapentin annual reports were 3,251, 3,605, and 3,267 in 2018, 2019, and 2020, respectively. In 2021, 2,931 gabapentin drug reports were reported to NFLIS-Drug, which still remains a nearly 2-fold increase in cases reported in 2012 (1,028 drug reports). Additionally, the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system, a prescription drug abuse/misuse and diversion monitoring system that collects geographically- specific data, indicate that 407 cases of gabapentin diversion were reported in 41 states between 2002 and 2015. The rates of diversion steadily increased from 0.0 in 2002 to 0.027 cases per 100,000 population in 2015. Recent data from the United States Food and Drug Administration Adverse Event Reporting System (FAERS) found abuse-related reports associated with gabapentin found a higher proportion of abuse-related reports for pregabalin (10.2% of 571 reports and 26.1% of 97,813 reports) when compared to gabapentin (5.7% of 10,038 reports and 22.9% of 99,977 reports).

Control Status

Gabapentin is not currently controlled under the Controlled Substances Act of 1970.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@dea.gov.

