Classification of Phenibut

Submission to the Medicines Classification Committee

Medsafe
January 2018

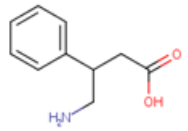
1. Background

The Ministry of Health has received queries from the New Zealand Customs Service (Customs) regarding the regulatory position of cognitive enhancing products, including the substance Phenibut. Customs has asked Medsafe whether there should be restrictions on their importation into New Zealand.

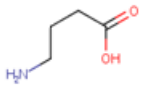
Phenibut can be described as a phenyl derivative of gamma-aminobutyric acid (γ-aminobutyric acid, or GABA). The compound's name "pheni-but" is based on its origin of synthesis and its structure, which was first reported by Perekalin et al in the 1960s (Lapin, 2001).

The addition of a phenyl ring to butyric acid enables the compound to cross the blood-brain barrier. Phenibut acts as a GABA agonist, primarily at GABA*b* receptors, stimulating dopamine release. In contrast, GABA itself does not cross the blood-brain barrier, limiting its use as a viable therapeutic drug to treat anxiety. However, GABA also occurs naturally in the human nervous system.

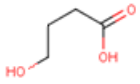
At this time, GABA is a Controlled Drug B1 under the Misuse of Drugs Act 1975, as it is a substance from which gamma-hydroxybutyrate or GHB (commonly known as Fantasy) can be derived. GHB is a Controlled Drug B1 under the Misuse of Drugs Act 1975.



Phenibut

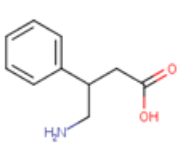


Gamma-aminobutyric acid (GABA)

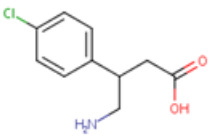


Gamma-hydroxybutyrate (GHB)

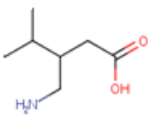
Phenibut is classified as a GABApentinoid. GABApentinoids are a class of drugs that binds to and blocks the α2δ subunit-containing voltage-dependent calcium channels. This class includes Baclofen which is indicated for skeletal muscle spasticity (eg, Lioresal), Pregabalin which is indicated for neuropathic pain and for the control of epileptic seizures, (eg, Lyrica) and Gabapentin an anticonvulsant, analgesic and anxiolytic for the treatment of anxiety disorders (eg, Neurontin). Baclofen, Pregabalin and Gabapentin are all currently scheduled as Prescription Medicines in Schedule 1 of the Medicines Regulations 1984.



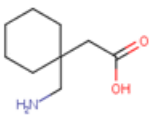
Phenibut



Baclofen



Pregabalin



Gabapentin

The most common uses expounded for phenibut are as a nootropic (a drug used to enhance memory or other cognitive functions), to reduce anxiety, to improve sleep, increase sexual drive, and increase production of human growth hormone. These last two appear to be academically unsubstantiated.

2. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

None.

Chemical names

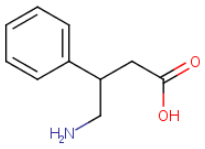
4-Amino-3-phenylbutyric acid
4-Amino-3-phenylbutanoic acid [IUPAC name]
beta-(Aminomethyl)benzenepropanoic acid
beta-(Aminomethyl)hydrocinnamic acid
beta-Phenyl-gamma-aminobutyrate
beta-Phenyl-gamma-aminobutyric acid
beta-phenyl-GABA
β-Phenyl-γ-aminobutyrate
β-Phenyl-γ-aminobutyric acid

Other names

Fenibut / Fenigam
Phenigam / Phenigama / Phenygam
Phenylgamma
PhGaba / Pgaba
Noofen

Chemical formula	Molecular weight
$C_{10}H_{13}NO_2$	179.2 $gmol^{-1}$

Chemical structure



CAS Registry Number

1078-21-3

3. Classification sought

Prescription medicine

4. Classification status in other countries (especially Australia, UK, USA, Canada)

Australia – The Advisory Committee on Medicines Scheduling (July 2017) recommended that phenibut be classified as a Schedule 9 prohibited substance, only to be used for research purposes. The TGA's report on the Committee's recommendation is included as an attachment to this submission.

USA – Unscheduled. Phenibut is available as a nutritional supplement as it meets the criteria of the Dietary Supplement Health and Education Act 1994 (DSHEA) as a synthetic amino acid derivative. It is usually promoted with health maintenance claims (eg, helps to keep you calm) instead of disease state or condition claims (eg, reduces anxiety) (Cutter 2016, Owen et al, 2016).

United Kingdom – Unscheduled. In 2014, the MHRA seized a large range of cognitive enhancers, including phenibut, on the basis that these were unlicensed medicinal products being supplied for sale (MHRA 2014).

It is unclear if phenibut is caught under the UK's Psychoactive Substances Act 2016. Some of the reported activities of the substance fall into categories of effects regulated under this Act, such as changes in alertness, mood, empathy, and drowsiness (effects which would apply to many nootropics). Possession of cognitive enhancers is not illegal, although the MHRA's action indicates that sale without a licence is prohibited (for example, if phenibut was indeed determined to be a cognitive enhancer substance).

Canada – Unscheduled. The Natural and Non-prescription Health Products Directorate of Health Canada has noted that this does not fit their criteria for consideration as a natural health substance as it is not a naturally occurring substance (NHPID 2017). It is available as an unscheduled substance, usually from on-line retailers, health food shops and body-building forums.

Europe – Unscheduled. It is not regulated by the European Medicines Agency. However, some nootropic substances such as piracetam are available only on prescription in some European Union countries and are freely available in others.

Russia – Phenibut is a licensed prescription medication used for a variety of conditions including anxiety, insomnia, post-traumatic stress disorders, depression, stuttering, tics, attention deficit disorders, and vestibular disorders. Russian cosmonauts were reported to have been supplied with the substance to help relieve tension, anxiety and fear (Buckley 2006).

Latvia – as for Russia.

There is no information on the FDA's Adverse Events Reporting System (FAERS) on Phenibut.

There is no information on phenibut CARM's adverse reaction database.

On the WHO's Vigilyze database, there have been 19 ICSRs (Individual Case Safety Report) reported on phenibut since 2012, with a jump in numbers since 2016. The majority of the reports were in people aged 18-44 years from the Americas, and the majority of events were associated with general, nervous system or psychiatric disorders.

5. Reasons for requesting the classification

Phenibut acts as a full agonist of the GABA*b* receptor, which is responsible for its sedating effects. At higher doses, phenibut also acts as a GABA*a* agonist (Shulgina 1986).

Users from various websites and on-line forums (for example Reddit.com, Social Anxiety Support.com, Brain Pro Tips.com, Bluelight.com, Erowid.org, Corpina.com) reported positive effects:

- extreme calm
- increased sociability
- increased sense of “well-being”
- mild euphoria
- variable increase in alertness
- improved cognition and memory retention

Negative effects reported by users and researchers (Samokhvalov et al 2013; Sankary et al 2017; Joshi et al 2017) are:

- hangover
- dependence
- headache
- depression, anxiety
- sedation, particularly from excessive dose or overuse
- lethargy
- agitation
- delirium
- confusion
- rarely, tonic-clonic seizures

Most on-line articles and discussions refer to tolerance (reduced effect) with long-term use, and escalating doses are necessary to achieve the effect previously experienced. There are also withdrawal effects, which may include agitation, anger, anxiety, depression, dizziness, hallucination, insomnia, irritability, nausea, tremors. Withdrawal from phenibut is expected to present like baclofen withdrawal (Alvis and Sobey, 2017) and that of other GABA*b* agonists and managed with benzodiazepines and supportive care (Maryland Poison Center 2017; O’Connell 2017; American Addiction Centers 2017, Mental Health Daily 2016).

The extent of phenibut use in New Zealand is unknown. However, it is available for sale from on-line retailers such as Trademe.co.nz, supplements.co.nz, iherbs.co.nz, tripme.co.nz, biovea.com, evitamins.com, nootsupply.co.nz.

Most commercially available phenibut appears to be in the form of the hydrochloride salt, phenibut HCl. Ingestion of phenibut hydrochloride on either an empty stomach or with caffeine (which stimulates gastric secretion) increases the rate of absorption. Phenibut is also commercially available as the free amino acid, which is slower to dissolve and is slightly bitter to the taste. Unlike the hydrochloride salt, the free amino acid can be absorbed intranasally, sublingually, and rectally (Psychonautwiki 2017).

Starting doses vary significantly on the various web user forums (for example, Reddit.com, LiftMode.com, Bluelight.com, Corpina.com, Nootrohacker.com). 200-500 mg has been suggested for nootropic effect. For other effects, including as an anxiolytic, anti-depressant, sleep aid for insomnia, recreational drug, doses of 250-750 mg up to three times daily have been recommended. Use of up to 3000 mg per day have been reported in some athletes (Tomen, 2017).

Phenibut is reported to also potentiate or improve the effects of tranquilisers, narcotics and neuroleptic medications (Psychonautwiki 2017).

6. Published literature

PubMed lists 203 entries relating to phenibut. Many are either case reports on incidents, commentaries from health practitioners on the effects or availability of phenibut, or are pharmacokinetic or chemical activity studies in various situations. See: https://www.ncbi.nlm.nih.gov/pubmed/?term=phenibut

There are also several on-line user forums (some as mentioned above) on the use of phenibut.

7. Discussion and conclusions

Nootropic (and other therapeutic) claims are associated with phenibut.

Phenibut has psychoactive effect and could be considered a psychoactive substance under the Psychoactive Substances Act 2013 when sold for the purpose of inducing a psychoactive effect, and its importation could be stopped under that Act. However, the real purpose behind an importation is often difficult to establish when shipments are stopped at the border by Customs. As it is currently an unscheduled substance, the importer may claim that it is being imported for personal therapeutic use.

From the literature, there appear to be some risks associated with its use, most commonly headache, lethargy, dependency and withdrawal symptoms including agitation, irritability, anger. In extreme instances, seizures have been reported.

Phenibut does not meet the moderate risk of harm threshold necessary to be controlled under the Misuse of Drugs Act 1975. Nevertheless, its use and availability should be controlled because of the risk of adverse effects.

The Medicines Classification Committee discussed the nootropic and cognitive enhancing substances racetam and racetam-like structures at the 53rd and 54th meetings and advised that they be classified as prescription medicines. Hence, the classification of phenibut as a prescription medicine would be consistent with the Committee's approach to nootropic substances, the scheduling of the GABApentinoid class of substances, and the uses and risks associated with the substance.

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Attachment

Excerpt from:
(https://www.tga.gov.au/sites/default/files/public_notice_-_interim_decision_and_reasons_for_decision_-_accs_acms_and_joint_-final_0.pdf)

Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health

15 September 2017

(ACMS, Joint ACCS-ACMS, and ACCS meetings – March and July 2017)

Notice under subsection 42ZCZN/42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations)

2.3 Phenibut

Referred scheduling proposal
A delegate from the Therapeutic Goods Administration has referred a scheduling proposal to create a new Schedule 9 or Schedule 4 with an Appendix D, Part 5 entry for phenibut in the Poisons Standard.

Scheduling application
This was a delegate initiated application. The delegate's proposed amendments to the Poisons Standard are:

Schedule 9 – New Entry

PHENIBUT.

OR

Schedule 4 – New Entry

PHENIBUT.

Appendix D, Part 5 – New Entry

PHENIBUT.

AND

Index – New Entry

PHENIBUT
cross reference: BETA-PHENYL-GAMMA-AMINOBUTYRIC ACID

Schedule 4/9
Appendix D, Part 1

The reasons for the request are:

- Case reports of significant toxicity have emerged, as well as evidence of dependence; and
- One state has raised concerns regarding the potential for tolerance and withdrawal symptoms from the use of Phenibut. Specific toxicity is related to these symptoms.

Current scheduling status and relevant scheduling history

Phenibut is currently not captured by any schedule entry in the current Poisons Standard.

The pharmacologically similar substance, Baclofen, is in Schedule 4 and Appendix K of the current Poisons Standard.

Phenibut has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulatory information

Phenibut is not listed as an ingredient in products on the ARTG (link is external) and cannot be legally sold in Australia as a Therapeutic Good. However, information received from one Australian state health department indicates that phenibut is marketed to relieve anxiety and depression, improve sleep and enhance cognition.

Despite phenibut not being in products on the ARTG, the Database of Adverse Events Notification (DAEN) - Medicines (link is external) has returned 1 report of an adverse event suspected to be related to phenibut in an unregistered product.

Phenibut is not listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2017.

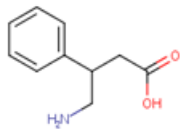
International regulations

No evidence of scheduling in New Zealand, EMA, US FDA or Canada.

Substance summary

Phenibut is a neuropsychotropic drug with anxiolytic and nootropic (cognition enhancing) effects. It acts as a GABA mimetic, primarily at GABA*b* and to some extent at GABA*a* receptors.

Table 2.3.1: Chemical information for phenibut

Property	Phenibut
Chemical structure	
Molecular formula	$C_{10}H_{13}NO_2$
Molecular weight	179.2 g/mol
CAS number	1078-21-3
IUPAC and/or common and/or other names	4-amino-3-phenylbutanoic acid (IUPAC); Commonly known as beta-phenyl-gamma-aminobutyric acid.

Pre-meeting public submissions

Eleven (11) public submissions were received, two (2) in support, eight (8) opposed (four (4) to the Schedule 9 proposal and four (4) showing some agreement with a Schedule 4 entry to allow access via a prescription) and one (1) did not state their position.

Main points in support:

- There are no established therapeutic uses for phenibut.
- In Australia there are confirmed cases of phenibut poisoning and an increase in the number of suspected cases of phenibut use, misuse and harm.
- Phenibut is marketed on the internet as a dietary supplement to treat anxiety and sleep disorders. However, there is strong evidence to indicate that it is predominantly used as a recreational drug.
- The medical conditions phenibut is reportedly being used to treat (including anxiety and sleep disorders) are better managed by a medical practitioner.
- Phenibut represents a significant risk of harm, including overdose (intentional and accidental). Complications of overdose include coma requiring admission to an Intensive Care Unit (ICU) for advanced life support.
- Withdrawal symptoms result when phenibut is stopped.
- No preference between Schedule 4/Appendix D or Schedule 9 was indicated in the submissions.

Main points opposed:

- Personal stories indicate that where other medicines have failed phenibut has:
  - provided improvement to sleep and symptoms of anxiety, depression, idiopathic hypersomnia and Post-Traumatic Stress Disorder (PTSD); and
  - been used to treat addiction to alcohol and benzodiazepine use.
- Claims that suppliers of phenibut provide adequate information on its safe use.
- Consumers have had no problems with toxicity or dependence and believe phenibut is very safe.
- Scheduling phenibut may cause an increase in alcohol consumption, use of stronger anti-anxiety medicines or black-market drug purchasing.
- Internationally phenibut is only regulated in Russia. No evidence for scheduling in other countries.
- Submissions indicate some preference for:
  - Schedule 4 without an appendix entry to allow access via a prescription; and
  - Schedule 3 to allow access by a pharmacist.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee recommended that new Schedule 9 and index entries be created in the Poisons Standard for phenibut as follows:

Schedule 9 – New Entry

PHENIBUT.

Index – New Entry

PHENIBUT

cross reference: BETA-PHENYL-GAMMA-AMINOBUTYRIC ACID

Schedule 9

The committee also recommended an implementation date of 1 February 2018.

Members agreed that the relevant matters under Section 52E(1) of the Therapeutic Goods Act 1989 included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Risks of phenibut include tolerance, dependence, abuse, accidental and intentional overdose resulting in significant toxicity requiring hospitalisation, with severity potentially requiring ICU admission.
- There are anecdotal reports of the therapeutic benefit of phenibut based on public submissions.
- Although phenibut is used therapeutically in Russia, the associated clinical trial literature is unable to be evaluated critically at this time due to translation issues. Furthermore, there has been no established therapeutic benefit of phenibut in regulatory comparable countries.
- Taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of phenibut and the high risk of dependency, abuse, misuse and illicit, the perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.
- The substance is not currently permitted in Australia to be marketed for therapeutic reasons but is widely available on the internet for purchase. International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders. Prevalence of use is not established but is clearly across the country and increasing.
- Phenibut is a neuropsychotropic drug with anxiolytic and cognition enhancing effects. It acts as a GABA mimetic, primarily at GABA*b* and to some extent at GABA*a* receptors. Published reports of ED presentations, acute intoxication with delirium, and dependence treated with baclofen. These reports include reports from Australia. Descriptions of withdrawal include tremors, anxiety, insomnia, hypertension, hyperhidrosis, psychosis, tachycardia, widening of QRS complex and convulsions. There is significant risk of harm. Effects include CNS depression, delirium, seizures – potentially requiring intubation and ventilation.
- Rapid development of tolerance and dependence with a withdrawal syndrome consisting of hallucinations, agitation, tremor, insomnia, abdominal pain, vomiting.
- The availability as a powder increases risks of toxicity.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- Scheduling Policy Framework (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Schedule 9 and index entry in the Poisons Standard for phenibut. The proposed Schedule entry is as follows:

Schedule 9 – New Entry
PHENIBUT.

Index – New Entry
PHENIBUT
cross reference: BETA-PHENYL-GAMMA-AMINOBUTYRIC ACID

Schedule 9

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the Therapeutic Goods Act 1989 considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- There are anecdotal reports of the therapeutic benefit of phenibut based on public submissions.
- Although phenibut is used therapeutically in Russia, the associated clinical trial literature is unable to be evaluated critically at this time due to translation issues. Furthermore, there has been no established therapeutic benefit of phenibut in regulatory comparable countries.
- International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders.
- Risks of phenibut include tolerance, dependence, abuse, accidental and intentional overdose resulting in significant toxicity requiring hospitalisation, with severity potentially requiring ICU admission.
- The perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- The substance is not currently permitted in Australia to be marketed for therapeutic reasons but is widely available on the internet for purchase. International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders. Prevalence of use is not established but is clearly across the country and increasing.
- Prevalence of use is not established but is clearly across the country and increasing.

(c) the toxicity of a substance:

- Phenibut is a neuropsychotropic drug with anxiolytic and cognition enhancing effects. It acts as a GABA mimetic, primarily at GABA*b* and to some extent at GABA*a* receptors.

- Published reports of ED presentations, acute intoxication with delirium, and dependence treated with baclofen. These reports include reports from Australia.
- Descriptions of withdrawal include tremors, anxiety, insomnia, hypertension, hyperhidrosis, psychosis, tachycardia, widening of QRS complex and convulsions. There is significant risk of harm.
- Effects include CNS depression, delirium, seizures – potentially requiring intubation and ventilation.
- The availability as a powder increases risks of toxicity.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Packaged as a supplement in 250 and 500mg capsules.
- No restrictions at present, currently available in powder and capsules with variable labelling.
- The availability as a powder increases risks of toxicity. Loose powders pose particular risk of accidental overdose.

(e) the potential for abuse of a substance:

- Rapid development of tolerance and dependence with a withdrawal syndrome consisting of hallucinations, agitation, tremor, insomnia, abdominal pain, vomiting.
- Cases of recreational abuse have been described.
- Rapid development of tolerance is established.

(f) any other matters that the Secretary considers necessary to protect public health:

- Taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of phenibut and the high risk of dependency, abuse, misuse and illicit, the perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.