



# Classification of Rilmazafone

Submission to the Medicines Classification Committee

**Medsafe**  
**January 2018**

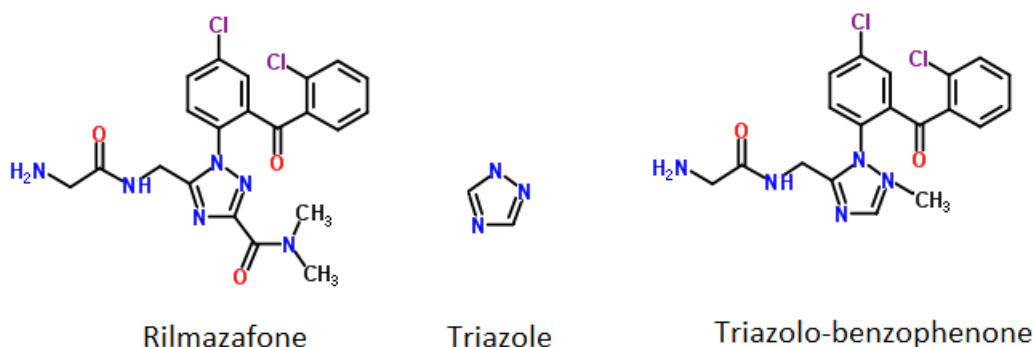


New Zealand Government

## 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 Rilmazafone. Customs has asked Medsafe whether there should be restrictions on importing rilmazafone into New Zealand.

Rilmazafone is known as one of the 'Japanese benzos' because it was first developed in Japan. It is a substituted heterocyclic 1,2,4 triazole of the class triazolyl benzophenones.



Rilmazafone is considered to be a benzodiazepine pro-drug, and in Japan, is used for the short-term treatment of insomnia. Benzodiazepines are scheduled as Prescription Medicines in Schedule 1 of the Medicines Regulations 1984. However, rilmazafone is itself not a benzodiazepine.

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

Rilmazafone (recommended INN)

### Chemical names

1H-1,2,4-Triazole-3-carboxamide, 5-(((aminoacetyl)amino)methyl)-1-(4-chloro-2-(2-chlorobenzoyl)phenyl)-N,N-dimethyl-

1-[4-Chloro-2-(2-chlorobenzoyl)phenyl]-5-[(glycolamino)methyl]-N,N-dimethyl-1H-1,2,4-triazole-3-carboxamide

2',5-Dichloro-2-(3-dimethylcarbamoyl-5-glycylaminomethyl-1H-1,2,4-triazol-1-yl)benzophenone

5-((2-Aminoacetamido)methyl)-1-(4-chloro-2-(o-chlorobenzoyl)phenyl)-N,N-dimethyl-1H-1,2,4-triazole-3-carboxamide

5-[(2-Aminoacetamido)methyl]-1-[4-chloro-2-(o-chlorobenzoyl)phenyl]-N,N-dimethyl-1H-1,2,4-triazole-3-carboxamide

5-[[[(Aminoacetyl)amino]methyl]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-N,N-dimethyl-1H-1,2,4-triazole-3-carboxamide

### Other names

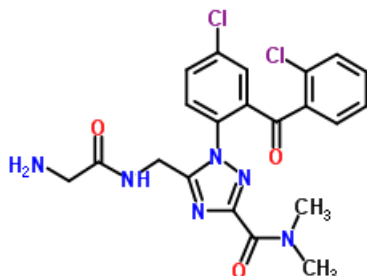
Rhythmy

**Chemical formula**

C<sub>21</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>3</sub>

**Molecular weight**

475.33 gmol<sup>-1</sup>

**Chemical structure****CAS Registry Number**

99593-25-6

**3. Classification sought**

Prescription medicine

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

Australia – not scheduled. In Australia, benzodiazepines and benzodiazepine derivatives are Schedule 4 – Prescription Only Medicine.

USA – Unscheduled.

Europe – Unscheduled.

Canada – Unscheduled.

Japan – Rilmazafone appears to have been approved in Japan as a prescription medicine.

**5. Reasons for requesting the classification**

The active metabolite of Rilmazafone has been reported to be 8-chloro-6-(2-chlorophenyl)-N,N-dimethyl-4H-1,2,4-triazolo [1,5-a][1,4]benzodiazepine-2-carboxamide (also known as M1). (Yamamoto et al, Yoshimura et al, Ibi et al, Yamaguchi et al, Koike et al in a series of papers).

Other metabolites of M1 are:

M4 - major metabolite in plasma and urine = 8-chloro-6-(2-chlorophenyl)-4H-1,2,4-triazolo [1,5-a][1,4]benzodiazepine-2-carboxylic acid

M3 - N,N-didesmethyl-M1 = 8-chloro-6-(o-chlorophenyl)-4H-1,2,4-triazolo-[1,5-a] [1,4] benzodiazepine-2-carboxamide

M2 - N-desmethyl-M1 = 8-chloro-6-(o-chlorophenyl)-N-methyl-4H-1,2,4-triazolo[1,5-a] [1,4] benzodiazepine-2-carboxamide

MA - 8-chloro-6-(o-chlorophenyl)-N-hydroxymethyl-4H-1,2,4-triazolo [1,5-a] [1,4]benzodiazepine-2-carboxamide

MD - 8-chloro-6-(o-chlorophenyl)-N-hydroxymethyl-N-methyl-4H-1,2,4-triazolo [1,5-a] [1,4]benzodiazepine-2-carboxamide.

There is no information available on the extent of usage of Rilmazfone in New Zealand. It does not appear to be a commonly accessed drug in the Western world.

The Japanese Pharmaceuticals and Medical Devices Agency has recently required the precautions for Rhythmy to be revised to add the risk of drug dependency, irritable excitation and confusion (JPMDA 2017).

The FDA's Adverse Events Reporting System (FAERS 2017) has 35 cases reported between 1999 and 2017 for rilmafazone and 23 cases for rilmazafone hydrochloride. The majority of events were associated with general disorders, nervous system disorders and psychiatric disorders. In all cases, rilmazafone (or the hydrochloride) had been taken with other medications, particularly other anxiolytics.

The WHO's Vigilyze database has 61 Individual Case Safety Reports (ICSRs) between 1991 and 2018. The data shows a trend in number of reports increasing from about 2012. About half the reports were in people aged 18-44 years, and the majority of reports were from the Asia region. The most frequent reported effects were drug interaction, somnolence, anxiety, headache, hepatic function and loss of consciousness.

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

## 6. Published literature

A number of studies conducted by Yamamoto et al, Yoshimura et al, Ibbi et al, Yamaguchi et al, Koike et al. between 1984 and 1988 elucidated the pharmacokinetic, pharmacodynamics, physiologic effects of Rilmazafone and its metabolites, M1, M2, M3 and M4, MA and MD in various animals.

Matsubara et al (1987) showed that plasma levels of rilmazafone and its metabolites are regulated by drug-metabolising enzymes in the liver and are also affected by cytochrome P-450.

These studies established that the substance had benzodiazepine-like effects. The effect was considered to be less than that of diazepam, triazolam or nitrazepam.

Uemura et al (2015) investigated next-day residual effects in healthy elderly patients administered zolpidem, triazolam or rilmazafone and concluded that the latter appeared to be more favourable. (Uemura et al, 2015).

Sugaya et al (2007) investigated rilmazafone in the treatment of nocturia, where it was found to be as effective as melatonin but did not increase mean serum melatonin levels.

Tsutsui et al (2009) examined rimazafone, diphenhydramine and kavain on the sleep-wake cycle of sleep-disturbed rats, and concluded that all three had sleep quality-enhancement effects.

Nishino et al (2008) examined the anxiolytic effect of short-acting benzodiazepine hypnotics, including rilmazafone, in mice using an elevated plus-maze. They concluded that these were more potent, with smaller doses, than diazepam used as a control.

Rilmazafone has been considered to have a high potential to influence performance in the equine athlete (Kentucky Horse Racing Commission, 2015).

## **7. Discussion and conclusions**

There is some discussion of rilmazafone as a recreational drug on various user forums and websites such as Tripsit.me, Erowid.org, and Reddit.com.

Rilmazafone 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 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.

Rilmazafone has also been reported by users to have a balance of anxiolytic and sedating effects (Reddit.com: R/Benzos). It has an onset of action of about 30-60 minutes, presumably because it is a pro-drug, and lasts about 6-8 hours (Tripsit.com). Other effects that have also been reported are muscle relaxant and mild euphoria. Rilmazafone is soluble in water, which has been seen by users as an advantage for its use over most other benzodiazepines.

Benzodiazepines are scheduled as prescription medicines under the Medicines Act 1981, and are also scheduled as Controlled Drug Class C1 under the Misuse of Drugs Act 1975.

While Rilmazafone is not a benzodiazepine, the literature indicates that it does have benzodiazepine-like effects. Rilmazafone does not appear to have the same extent of effect (either beneficial or adverse) as benzodiazepines, and would not justify scheduling as a controlled drug.

According to the Japanese Pharmaceuticals and Medical Devices, there appears to be a risk of dependency, irritable excitation and confusion with use. The legitimate use of rilmazafone is a therapeutic use, which is the treatment of insomnia. The classification of rilmazafone as a prescription medicine would be consistent with the classification of other anxiolytics and sedatives, and are in line with the risks and use of rilmazafone.

## **References**

FAERS (2017). FDA Adverse Event Reporting System (FAERS) Public Dashboard. Search on Rilmazafone and Rilmazafone hydrochloride. Data as at 31 August 2017. <https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis>

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<https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/6b5a135f-f451-45be-893d-20aaee34e28e/state/analysis>

Vigilyze database (2018). Search on Rilmazafone. Data as at 25 January 2018. <https://vigilyze.who-umc.org/#/>

Ibii N, Yamamoto K. (1984). Pharmacology of a 1H-1, 2, 4-triazolyl benzophenone derivative (450191-S), a new sleep-inducer (III). Behavioral study on interactions of 450191-S and other drugs in mice. *Nihon Yakurigaku Zasshi*. 84(2):155-73. [abstract only; article in Japanese]. <https://www.ncbi.nlm.nih.gov/pubmed/6149177>

JPMDA (2017). Japanese Pharmaceuticals and Medical Devices Agency. Revision of Precautions. Rilmazafone Hydrochloride Hydrate. March 21, 2017. <http://www.pmda.go.jp/files/000219606.pdf>

Kentucky Horse Racing Commission. Uniform Drug, Medication and Substance Classification Schedule. August 2015. Accessed 30 October 2017. <http://khrc.ky.gov/Documents/DrugandMedicationClassificationSchedule.pdf>

Koike M, Norikura R, Yoshimori T, Futaguchi S, Sugeno K. (1986). Biopharmaceutical characterization of 450191-S, a ringopened derivative of 1,4-benzodiazepine. I. Active metabolite levels in rat plasma. *Journal of Pharmacobio-Dynamics* 9(7):563-69. [https://www.jstage.jst.go.jp/article/bpb1978/9/7/9\\_7\\_563/article](https://www.jstage.jst.go.jp/article/bpb1978/9/7/9_7_563/article)

Koike M, Futaguchi S, Takahashi, S, Sugeno K. (1988). Biopharmaceutical characterization of 450191-S, a ring-opened derivative of 1,4-benzodiazepine. II. Evidence for reduced first-pass extraction by rat liver. *Drug Metabolism and Disposition* 16(4):609-615. <https://www.ncbi.nlm.nih.gov/pubmed/2903031>

Koike M, Norikura R, Sugeno K. (1986). Intestinal activation of a new sleep inducer 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative, in rats. *Journal of Pharmacobio-Dynamics* 9(3):315-20. <http://www.ncbi.nlm.nih.gov/pubmed/3454653>

Koike M, Futaguchi S, Sugeno K, Touchi A, Matsubara T. (1986). Autoinduction of 450191-S, a new sleep inducer of 1H-1,2,4-triazolyl benzophenone derivative, in dogs. *Journal of Pharmacobio-Dynamics* 9(11):909-16. [https://www.jstage.jst.go.jp/article/bpb1978/9/11/9\\_11\\_909/article/-char/ja/](https://www.jstage.jst.go.jp/article/bpb1978/9/11/9_11_909/article/-char/ja/)

Koike M, Norikura R, Sugeno K. (1986). Effect of food on absorption of 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative from rat small intestine. *Journal of Pharmacobio-Dynamics* 9:447-452. [https://www.jstage.jst.go.jp/article/bpb1978/9/5/9\\_5\\_447/article/-char/ja/](https://www.jstage.jst.go.jp/article/bpb1978/9/5/9_5_447/article/-char/ja/)

Koike M, Norikura R, Futaguchi S, Yamaguchi T, Sugeno K, Iwatani K, Ikenishi Y, Nakagawa Y. (1987). N-hydroxymethyl metabolites of 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative, in dog plasma. *Drug Metabolism and Disposition* 15(3):426-428. <http://dmd.aspetjournals.org/content/15/3/426.short>

Koike M, Norikura R, Iwatani K, Sugeno K, Takahashi S, Nakagawa Y. (1988). Structure determination of metabolites of rilmazafone, a 1H-1,2,4-triazolyl benzophenone derivative in monkey urine. *Xenobiotica* 18(3):257-268. <http://www.tandfonline.com/doi/abs/10.3109/00498258809041662>

Matsubara T, Touchi A, Yamada N. (1987). Effect of change of hepatic drug-metabolizing activity on plasma concentrations of major metabolites of the new sleep inducer 450191-S, a 1H-1,2,4-triazolyl benzophenone derivative. *Japanese Journal of Pharmacology* 44(4):429-36. <https://www.ncbi.nlm.nih.gov/pubmed/3682408>

Nishino T, Takeuchi T, Takechi K, Kamei C. (2008). Evaluation of anxiolytic-like effects of some short-acting benzodiazepine hypnotics in mice. *Journal of Pharmacological Science* 107(3):349-54. <https://www.ncbi.nlm.nih.gov/pubmed/18603828>

Reddit.com. R/Benzos. Accessed 26 October 2017. [https://www.reddit.com/r/benzodiazepines/comments/6ybbcr/japanese\\_benzos/](https://www.reddit.com/r/benzodiazepines/comments/6ybbcr/japanese_benzos/)

Sugaya K, Nishijima S, Miyazato M, Kadekawa K, Ogawa Y. (2007). Effects of Melatonin and Rilmazafone on Nocturia in the Elderly. *Journal of International Medical Research*, 35(5): 685-691. <http://journals.sagepub.com/doi/pdf/10.1177/147323000703500513>

Tripsit factsheet: Rilmazafone. Accessed 26 October 2017. <http://drugs.tripsit.me/rilmazafone>

Tsutsui R, Shinomiya K, Takeda Y, Kitamura Y, Kamei C. (2009). Hypnotic and sleep quality-enhancing properties of kavain in sleep-disturbed rats. *Journal of Pharmacological Science* 111(3):298-8. <https://www.ncbi.nlm.nih.gov/pubmed/19881224>

Uemura SI, Kanbayashi T, Wakasa M, Satake M, Ito W, Shimizu K, Shimizu T, Nishino S, Shioya T. (2015). Residual effects of zolpidem, triazolam, rilmazafone and placebo in healthy elderly subjects: A randomized double-blind study. *Sleep Medicine* 16(11):1395-1402. <http://www.sciencedirect.com/science/article/pii/S1389945715008357>

Yamaguchi T, Nakanishi M, Yamashita M, Matsumoto H, Nakamura M, Kominami G, Iwatani K, Nakagawa Y, Kono M, Sugeno K, Fukuda H. (1987). Pharmacology of a new sleep-inducer, a 1H-1,2,4-triazolyl benzophenone derivative, 450191-S (VIII). Examination and determination of metabolites in human plasma and urine. *Folia Pharmacologica Japonica* Vol. 90(4):239-247. [abstract only; article in Japanese]. [https://www.istage.jst.go.jp/article/fpj1944/90/4/90\\_4\\_239/article](https://www.istage.jst.go.jp/article/fpj1944/90/4/90_4_239/article)

Yamamoto K, Hirose K, Matsushita A, Yoshimura K, Sawada T, Eigyo M, Jyoyama H, Fujita A, Matsubara K, Tsukinoki Y. (1984). Pharmacology of a new sleep-inducer, 1H-1, 2, 4-triazolyl benzophenone derivative, 450191-S (I). Behavioural analysis. *Nihon Yakurigaku Zasshi*. 84(1):109-54. [abstract only; article in Japanese]. <http://europepmc.org/abstract/med/6149174>

Yamamoto K, Matsushita A, Sawada T, Naito Y, Yoshimura K, Takesue H, Utsumi S, Kawasaki K, Hirono S, Koshida H, Tazaki T. (1984). Pharmacology of a new sleep-inducer, a 1H-1,2,4-triazolyl benzophenone derivative, 450191-S (II). Sleep-inducing activity and effect on the motor system. *Folia Pharmacologica Japonica* 84(1):25-89. [abstract only; article in Japanese]. [https://www.istage.jst.go.jp/article/fpj1944/84/1/84\\_1\\_25/article](https://www.istage.jst.go.jp/article/fpj1944/84/1/84_1_25/article)

Yamamoto K, Ueda M, Kurosawa A, Hirose K, Doteuchi M, Nakamura M, Ozaki S, Matsumura S, Matsuda S, Satoh H, Miyata K, Masui M, Hirose F, Tatsumi K, Hirono S, Utsumi S. (1984). Pharmacological studies of a new sleep-inducer, 1H-1,2,4-

triazolyl benzophenone derivative (450191-S) (V). General pharmacological activities. Nihon Yakurigaku Zasshi. Aug;84(2):175-212. [abstract only; article in Japanese]. <https://www.ncbi.nlm.nih.gov/pubmed/6149178>

Yamamoto K, Naito Y, Sawada T. (1987). Pharmacological studies of a new sleep inducer; 1H-1,2,4-triazolyl benzophenone derivatives (450191-S, rilmazafone hydrochloride) (VII). Comparison of sleep-inducing activities between young and elderly rhesus monkeys. Folia Pharmacologica Japonica 90(3):155-62. [abstract only; article in Japanese]. [https://www.researchgate.net/publication/197271111\\_Pharmacological\\_studies\\_of\\_a\\_new\\_sleep\\_inducer\\_1H-124-triazolyl\\_benzophenone\\_derivatives\\_450191-S\\_rilmazafone\\_hydrochloride\\_VII\\_Comparison\\_of\\_sleep-inducing\\_activities\\_between\\_young\\_and\\_elderly\\_rhesus](https://www.researchgate.net/publication/197271111_Pharmacological_studies_of_a_new_sleep_inducer_1H-124-triazolyl_benzophenone_derivatives_450191-S_rilmazafone_hydrochloride_VII_Comparison_of_sleep-inducing_activities_between_young_and_elderly_rhesus)

Yoshimura K, Horiuchi M, Inoue Y, Yamamoto K. (1984). Pharmacological studies on drug dependence. (III): Intravenous self-administration of some CNS-affecting drugs and a new sleep-inducer, 1H-1, 2, 4-triazolyl benzophenone derivative (450191-S), in rats. Folia Pharmacologica Japonica 83(1):39-67. [abstract only; article in Japanese] <http://europepmc.org/abstract/med/6538866>