European Monitoring Centre for Drugs and Drug Addiction

EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	20 December 2022	RCS ID	EU-EWS-RCS-FN-2022-0037
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of 5-[[(2-aminoacetyl)amino]methyl]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide (rilmazafone) as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA		

1. Read me first

This document provides formal notification of the analytical identification of 5-[[(2-aminoacetyl)amino]methyl]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide (rilmazafone) for the first time in Europe.

Please report any additional data you have on this substance to: ews@emcdda.europa.eu

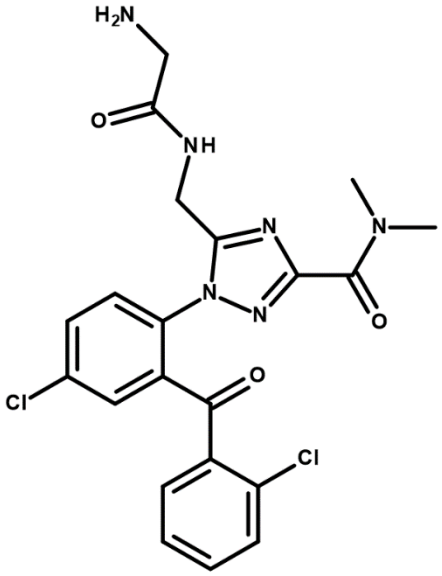
2. Data use restrictions

As with all formal notifications issued by the EU EWS remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this notification to other groups we would ask that you exercise your best judgment on what information needs to be provided. If you have any questions in this respect, please contact us.

3. Names of substance and other identifiers

- IUPAC name: 5-[[(2-aminoacetyl)amino]methyl]-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide
- Chemical names: 5-((2-aminoacetamido)methyl)-1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide; 5-[[(2-amino-1-oxoethyl)amino]methyl]-1-[4-chloro-2-[(2-chlorophenyl)-oxomethyl]phenyl]-*N*,*N*-dimethyl-1,2,4-triazole-3-carboxamide; 1-[4-chloro-2-(2-chlorobenzoyl)phenyl]-5-[(glycylamino)methyl]-*N*,*N*-dimethyl-1,2,4-triazole-3-carboxamide; 5-[(2-aminoethanoylamino)methyl]-1-[4-chloro-2-(2-chlorophenyl)carbonyl-phenyl]-*N*,*N*-dimethyl-1,2,4-triazole-3-carboxamide; 5-((2-aminoacetamido)methyl)-1-(4-chloro-2-(*o*-chlorobenzoyl)phenyl)-*N*,*N*-dimethyl-1*H*-1,2,4-triazole-3-carboxamide
- Common name: rilmazafone
- Other names: 450191-S; Rhythmy®
- Chemical formula: $C_{21}H_{20}Cl_2N_6O_3$
- Molecular weight: 475.33
- CAS Registry number: 99593-25-6 (base); 85815-37-8 (hydrochloride salt)
- InChIKey: KYHFRCPLIGODFH-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Other

5. Detection

Type: Collected sample

6. Chemistry and Analysis

Chemical classification: azacyclic; azole; other azole

Rilmazafone is a substituted heterocyclic 1,2,4-triazole of the triazolyl benzophenones class and a ring-opened derivative of 1,4-benzodiazepine [1,2]. While not classified as a benzodiazepine, rilmazafone exhibits benzodiazepine-like effects [1]. The hydrochloride salt of rilmazafone was originally mentioned in the scientific literature in 1982 [3]. Rilmazafone seems to be referred to as one of the ‘Japanese benzos’ because it was first developed in Japan [1].

Rilmazafone shares some structural similarities with the cyclopyrrolones zopiclone and pagoclone, formally notified in 2012 and 2019, respectively.

According to the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, rilmazafone hydrochloride hydrate is a white to pale yellow-white crystalline powder and is very soluble in methanol, soluble in water and slightly soluble in ethanol [4].

7. Pharmacology and toxicology

Pharmacological classification: anxiolytic or sedative-hypnotic

Rilmazafone is reported to be a short acting hypnotic with a half-life of 10 hours [5-7] and a benzodiazepine prodrug [1,7]. The benzodiazepine receptor 1 (BZ1) selectiveness of rilmazafone is not

considered high [7]. It is metabolised to several pharmacologically active compounds, including 8-chloro-6-(2-chlorophenyl)-*N*,*N*-dimethyl-4*H*-1,2,4-triazolo [1,5-*a*][1,4]benzodiazepine-2-carboxamide (also known as M-1) which is reported to be the primary active metabolite of rilmazafone [1,2]. Unlike the parent compound, active metabolites of rilmazafone contain a benzodiazepine ring structure and are considered to have potent affinities for the benzodiazepine receptors, with the sleep-inducing effect of rilmazafone attributed to them [2].

Rilmazafone has been reported to show an anxiolytic-like effect in mice with a significant effect observed at a dose of 0.1 mg/kg, p.o. [5]. In a study of the effects of some benzodiazepines on the retrieval process of spatial memory using an eight-arm radial maze in mice, it was found that rilmazafone, at a dose of 2.0 mg/ kg, caused a significant increase in total error, when used orally [8]. The potentiation effect of ethanol on benzodiazepine-induced memory deficits was also investigated and coadministration of rilmazafone (0.5 mg/kg) with ethanol caused a significant increase in total error [8].

Rilmazafone has been approved in Japan as a prescription medicine under the trade name Rhythmy [1]. The regular clinical dose of rilmazafone is 1–2 mg per day according to the package insert in Japan [9]. According to a regional survey in Japan in 2008 rilmazafone was recorded as the fourth most-prescribed hypnotic [7]. It is ‘often used for elder patients with insomnia in Japan’ [10] because ‘the muscle relaxation effect is weak’ [7]. It is reported that the PMDA has required the precautions for Rhythmy to be revised to add the risk of drug dependency, irritable excitation and confusion [1].

In an investigation of the early morning effects and residual effects on the physical and cognitive functions after hypnotic administration, rilmazafone administration (rilmazafone hydrochloride 1 mg) led to better results in the Functional Reach Test and Body Sway Test compared to placebo or other hypnotics tested [7]. Rilmazafone is reported to have ‘carry-over effects compared to placebo and other hypnotics’ in humans, which Uemura *et al*. suggest is likely due to the longer half-life of the substance [7].

Adverse effects associated with rilmazafone (35 cases between 1999 and 2017) and rilmazafone hydrochloride (23 cases) have been recorded in the FDA’s Adverse Events Reporting System (FAERS 2017) [1]. In all cases, rilmazafone (or the hydrochloride) had been taken with other medications, particularly other anxiolytics and the majority of events were associated with general disorders, nervous system disorders and psychiatric disorders [1]. In addition, 61 Individual Case Safety Reports (ICSRs), between 1991 and 2018, associated with rilmazafone, have been recorded in the World Health Organisation’s Vigilyze database [1]. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) noted that ‘the data shows a trend in number of reports increasing from about 2012’, with half the reports in people aged 18-44 years, the majority of reports were from the Asia region and the most frequent reported effects were drug interaction, somnolence, anxiety, headache, hepatic function and loss of consciousness [1].

The antifungal medication, itraconazole, was found to have been mistakenly contaminated with rilmazafone hydrochloride hydrate following a “human error in operations” in the manufacturing process, in Japan, in December 2020 [9,11]. The administration of contaminated tablets could have resulted in an intake of up to 20 times the recommended daily doses of rilmazafone [9]. Several cases of adverse reactions, which included dizziness, lightheadedness, loss of consciousness and intense drowsiness, were reported by pharmacies following administration of itraconazole [9]. Contaminated tablets were prescribed to 344 patients (324 administered) and of these, 245 people reported health implications, including two fatalities, 38 traffic accident cases, and 41 emergency transport and hospital admission cases [9].

8. References

[1] Medsafe (2018), Classification of Rilmazafone - Submission to the Medicines Classification Committee. https://www.medsafe.govt.nz/profs/class/Agendas/Agen60/5.6.1-Rilmazafone.pdf
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[3] Hirai K, et al. Synthesis and biological activity of (3, 5-disubstituted-1H-1, 2, 4-triazol-1-yl) benzophenone derivatives. Journal of Heterocyclic Chemistry. 1982;19(6):1363-9.
[4] https://www.pmda.go.jp/files/000231284.pdf
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