World Health Organization

# Pre-review report:

# Carisoprodol

**Expert Committee on Drug Dependence**
**Forty-sixth Meeting**
**Geneva, 16–20 October 2023**

*This report represents the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.*

## Contents

## Executive summary

*Clinical use*

Carisoprodol is a centrally acting muscle relaxant used in the short term as an adjunct to symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasm. Carisoprodol is prescribed in conjunction with rest, physical therapy and additional interventions to facilitate muscle relaxation. The typical dosage is 250–350 mg orally three times a day and at bedtime for a maximum duration of 2–3 weeks. At therapeutic dosages, the following side-effects are expected: drowsiness (13–17%), dizziness (7–8%), ataxia, tremor, agitation, irritability, depressive reactions, syncope, insomnia and headache (3–5%). The adverse effects are cardiovascular (such as tachycardia, postural hypotension and facial flushing), gastrointestinal (including nausea, vomiting, hiccup and epigastric distress) and haematological.

*Clinical pharmacological issues*

Carisoprodol is effectively absorbed after oral intake, with a rapid onset of action, the time to reach peak plasma concentration being within 1.5–1.7 h. Its activity typically lasts for 4–6 h. It is metabolized primarily through the liver enzyme CYP2C19, leading to formation of its primary metabolite, meprobamate. In individuals with limited or no CYP2C19 function, standard carisoprodol doses can result in exposure to four times the dose of carisoprodol and a corresponding 50% decrease in meprobamate concentration. Poor CYP2C19 metabolizers constitute 3–5% of Whites and Africans and 15–20% of Asians. The muscle relaxant properties of carisoprodol are probably associated with its sedative characteristics. Its primary metabolite, meprobamate, is thought to contribute to the therapeutic effects of the drug.

Carisoprodol has subjective effects similar to those of other central nervous system depressants such as meprobamate, pentobarbital and chlordiazepoxide. Carisoprodol is implicated in direct gating. In the GABA receptor, direct gating consists of initiation of receptor activation and subsequent unsealing of the chloride ion channel upon binding with the neurotransmitter γ-aminobutyric acid (GABA). Triggered by GABA, the GABA receptor facilitates the influx of chloride ions into a neuron or cell, leading to hyperpolarization. Hyperpolarization curbs the neuron's firing activity, diminishing its excitability and moderating overall neural function. This heightens inhibition of neural function, giving rise to sedative, anxiolytic and muscle-relaxing effects.

*Misuse, abuse and dependence*

The potential for misuse of abuse of carisoprodol may include sedative effects, enhanced effects with other substances and substance use disorder.

The sedative effects of carisoprodol may be sought by people seeking relief from anxiety, leading to dose escalation and thereby escalating the risk of misuse. Instances of seeing several prescribers to obtain larger quantities of the medication have been documented.

The sedative effects of carisoprodol can be potentiated when it is combined with benzodiazepines, opioids or alcohol. Simultaneous intake of hydrocodone, alprazolam and carisoprodol, often referred to as the "Houston Cocktail" or "Holy Trinity", could induce a euphoric state reminiscent of that induced by heroin. Such combined use might trigger a synergistic increase in dopamine in the nucleus accumbens due to interaction between activation of the μ1-opioid receptor and inhibition of GABA release. In contrast, benzodiazepines activate the GABA type A receptor, which can hinder respiration in the associated medullary centres.

During the 1950s and 1960s, the active metabolite of carisoprodol, meprobamate, was frequently

misused, and instances of overdose were documented. Prolonged or excessive use of carisoprodol can lead to dependence. Abrupt cessation of its use or a drastic reduction in the dosage after prolonged use can give rise to withdrawal symptoms similar to those of barbiturates and alcohol, including anxiety, insomnia, tremors, muscle twitching and, in severe cases, hallucinations and seizures. The withdrawal syndrome can be treated with a combination of carisoprodol and phenobarbital; benzodiazepines; or oral baclofen. As with benzodiazepines, craving might persist for an extended period.

The number of incidents involving carisoprodol recently increased worldwide, from 45 incidents before March 2021 in only from three regions to 2416 between January 2022 and March 2023 in 23 countries and territories. Usually, ingestion of one to three tablets (each containing 350 mg) produces a general feeling of well-being; taking four to ten tablets is associated with hypomania; and taking > 10 tablets may cause confusion, disorientation and partial amnesia. Reports of misuse or abuse of carisoprodol peaked in 2021. Most patients (about 44%) were aged 18–64 years; females represented 49% of the sample; 97% of the reports were from the USA and 2% from Brazil. Carisoprodol was mentioned on its own in about 94% of cases; dependence or drug dependence was identified in 440 of 1347 cases (51.5%), abuse or drug abuse in 167 (19.5%) cases and tolerance in 12 cases (1.4%).

*Social media traffic*

In July 2023, a "Google Trend" exercise was conducted. The term "carisoprodol" was searched particularly in Latin America (e.g. Guyana, Honduras, Mexico, Nicaragua, Paraguay and the Plurinational State of Bolivia). Most searches with the brand name "Soma", which is popular in the USA, originated from India and the USA, although searches by brand names represented only a small fraction of searches for carisoprodol. No peaks in searches were seen in the past 5 years, the number having peaked in 2006.

Discussions were found on Reddit (a popular social media platform) on the effects of carisoprodol at doses > 500 mg and on possible alternatives to carisoprodol. Most threads were older than 2 years, but recent opportunities to purchase carisoprodol were found. A qualitative analysis of three psychonaut websites (Drugs-Forum, Erowid and Bluelight) was conducted, and examples of the issues identified are listed.

*Diversion and illicit marketing*

Carisoprodol is among frequently diverted pharmaceuticals. As of March 2011, the street value of Soma® tablets was US$ 1–5 per tablet. Vigilant oversight of patients prescribed carisoprodol may be necessary to detect misuse or escalating dosage.

According to the 2012 National Survey on Drug Use and Health, 3.69 million individuals aged ≥ 12 reported non-medical use of Soma® at some time in their life, which represented a notable rise from 3.06 million in 2011. In 2017, the American Association of Poison Control Centers reported a total of 2236 carisoprodol-related cases, including 901 single exposures and two deaths. According to the US Laboratory Information System, federal, state and local forensic laboratories identified 3847 items identified as carisoprodol in 2013 as compared with 1735 in 2017 and a preliminary count of 1305 in 2018.

*Licensing, scheduling and possible impact*

Carisoprodol is classified under schedule IV under the US Controlled Substances Act (effective from 11 January 2012). In May 2008, it was taken off the market in Norway. The European Medicines Agency recommended that Member States suspend marketing authorization for this product in the treatment of acute (not chronic) back pain. As of November 2007, carisoprodol had been taken off the market in Sweden. In Canada, carisoprodol is a prescription drug, although provincial regulations vary, and its

overall use is restricted. Indonesia took carisoprodol off the market in September 2013. Carisoprodol is no longer a licensed product in Australia but can be accessed via the Special Access Scheme. In New Zealand, carisoprodol is a prescription drug. Published evidence suggests that rescheduling and withdrawal of carisoprodol from the Norwegian market reduced the prevalence of carisoprodol in impaired driving, deaths and contacts regarding intoxications. In the USA, the volume of calls involving carisoprodol abuse or misuse to a statewide poison control system before (2008–2011) and after (2012–2015) the 2012 scheduling change significantly decreased in the 4 years after the change as compared with the preceding 4 years.

# 1 Substance identification

## *A International Nonproprietary Name*

Carisoprodol

## *B Chemical Abstracts Service (CAS) registry number*

78-44-4

## *C Other chemical names*

Carbamic acid, (1-methylethyl)-, 2-[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester (9CI), carbamic acid, isopropyl-, 2-(hydroxymethyl)-2-methylpentyl ester carbamate (ester) (8CI), carbamic acid, isopropyl-, 2-(hydroxymethyl)-2-methylpentyl ester, carbamate (6CI), 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate
Apesan, Arusal, Atonalyt, Calenfa, Caprodat, Carisol, Carisoma, Carisoprodate, Carisoprodatum, Carisoprodol, Domarax, Flexal, Flexartal, Isobamate, Isomeprobamate, Isopropyl meprobamate, Isoprotan, Isoprotane, Isoprothane, Izoprotan, Miolisodal, Mioril, *N*-Isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, NIH 10966, NSC 172124, Rela (carbamic acid), Relasom, Sanoma, Skutamil, Soma, Somadril, Somalgit, Stialgin
*Canonical SMILES*
O=C(OCC(C)(COC(=O)NC(C)C)CCC)N
*InChI*
InChI=1S/C12H24N2O4/c1-5-6-12(4,7-17-10(13)15)8-18-11(16)14-9(2)3/h9H,5-8H2,1-4H3(H2,13,15)(H,14,16)
*InChI Key*
OFZCIYFFPZCNJE-UHFFFAOYSA-N

## D *Trade names*

Carisoprodol is sold as single-ingredient preparation under names, including *(2)*: Artifar; Caridolin; Carisoma; Chinchen; Dolaren; Flexartal; Listaflex; Mio Relax; Mioxom; Muslax; Myolax; Neotica; Rela; Rotalin; Sanoma; Scutamil-C; Soma; Somacid; Somadril; Somalgit.

It is also an ingredient of: Algiseda; Algiseda Plus; Algi-Tanderil, Beserol, Blocacid, Caridoxen, Carisoma Compound; Caritasone, Contraxen Diclofetamol, Dolaren, Dorsal, Duoflex, Dorilax Empatil Flectomas; Flexalgin, Flexicamin A, Flexicamin B12, Flexidone; Flogiatrin, Flogiatrin B12, Infralax, Lagaflex; Listaflex Forte, Mio-Citalgan, Mioflex A, Mioflex, Mionevrix, Naprontag Flex, Naprux Disten, Naxodol New Skelant Praxona Relaxibys; Rumisedan Fuerte, Sedilax, Sodol; Sodol Compound Solocam Plus, Solocam-Flex Compound; Soma Compound; Somadril Compound Somaflam Somalgesic Tandene, Tanderalgin, Tandriflan, Tandrilax, Tandrotamol, Torsilax, Trilax and Teknadone. It is also known as 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate *(1)*. Furthermore, the US Pharmacopoeia *(2)* lists carisoprodol pharmacopoeial preparations under the names Carisoprodol and Aspirin Tablets, Carisoprodol Tablets, Carisoprodol, Aspirin, and Codeine Phosphate Tablets.

## *E Street names*

The combination of an opioid, benzodiazepine and carisoprodol is commonly known by the street name of "Holy Trinity" *(3)* or "Houston cocktail" *(4)*. The drug is known by other street names, such as Ds, Dance, Las Vegas Cocktail (referring to the mixture of Soma and Vicodin) and Soma Coma (indicating the combination of Soma and codeine) *(5)*. A further street name is PCC (paracetamol–caffeine–carisoprodol).

The name "Soma", used for some carisoprodol products, is not directly linked to the hallucinogenic fungus. When carisoprodol was introduced as a medication, its relaxing and sedative effects were likened to the calming, euphoric properties associated with the ancient soma psychoactive drink.

### *F Physical appearance*

Carisoprodol is a white or almost white, fine powder *(6)* and as a white crystalline powder with a mild characteristic odour *(7)*. It has also been described as a crystalline solid with a slightly bitter taste *(8)*.

### *G WHO review history*

Carisoprodol was pre-reviewed in 2001 at the 32nd ECDD meeting. The Committee did not recommend critical review of carisoprodol at that time.

## 2 Chemistry

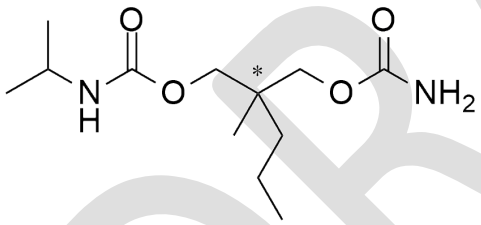
### *A Chemical name*

**IUPAC Name:** (2*RS*)-2-[(Carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)carbamate

**CA index name:** Carbamic acid, *N*-(1-methylethyl)-, 2-[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester (ACI)

### *B Chemical structure*

**Free base:**

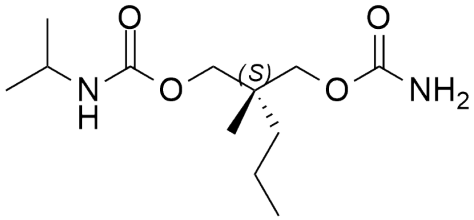


**Molecular formula:** $C_{12}H_{24}N_2O_4$

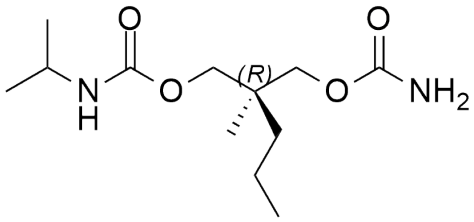
**Molecular weight:** 260.33 g/mol

### *C Stereoisomers*

Carisoprodol is a racemic mixture of enantiomers: (*R*)-carisoprodol and (*S*)-carisoprodol.



[(2*S*)-2-(carbamoyloxymethyl)-2-methylpentyl] *N*-propan-2-ylcarbamate



[(2*R*)-2-(carbamoyloxymethyl)-2-methylpentyl] *N*-propan-2-ylcarbamate

### *D Methods and ease of illicit manufacture*

Carisoprodol is an analogue of meprobamate in which one hydrogen atom is replaced by an isopropyl group on one of the carbamyl nitrogens. As the substitution makes carbon 2 a chiral centre, carisoprodol can exist as two enantiomers, (*S*)-carisoprodol and (*R*)-carisoprodol.

Carisoprodol is readily synthesized by reacting 2-methyl-2-propylpropanediol (**1**) with phosgene (**2**). The resulting chloroformate **3** is reacted with isopropylamine **4** to form 2-(hydroxymethyl)-2-methylpentyl *N*-(1-methylethyl)carbamate) **5**. The last step consists of reaction of **5** with either urethane **6**, sodium cyanate **7** or trichloroacetyl isocyanate **8** *(9,10)*.

The synthesis method reported in the literature, albeit simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

### *E Chemical properties*

*Melting-point:* 160–170 °C (2 Torr) *(11)*

*Boiling-point:* 92 °C (*12*)

423.412 °C at 760 mm Hg *(13)*

*Solubility:* In water: very slightly soluble *(6)*; one volume of carisoprodol in 2083 volumes of water according to USP31-NF26 *(1)*.

30 mg/mL at 25 °C, 140 mg/mL at 50 °C *(8)*

Feely soluble in acetone, in ethanol 96% and in methylene chloride *(6)*

One volume of carisoprodol is soluble in 2.5 volumes of alcohol and acetone and 2.3 volumes of chloroform *(7)*.

Carisoprodol is also soluble in dimethyl formamide at 20 mg/mL, in dimethyl sulfoxide at 10 mg/mL, in ethanol at 20 mg/mL, in ethanol:PBS 1:1 mixture (pH 7.2) at 0.5 mg/mL *(14)*. Carisoprodol has a logP of 2.1 *(15)***.**

### *F Identification and analysis*

Carisoprodol as a pure compound was fully characterized by nuclear magnetic resonance, infra-red spectroscopy and mass spectrometry (MS) *(16)*.

Identification and analysis of carisoprodol as pharmaceutical ingredient is reported in the US Pharmacopoeia *(3)* and in the European Pharmacopoeia *(17)*. The latter reports tests for identification and analysis, including determination of the melting-point (92–95 °C),the comparison of the infra-red spectrum with that of a reference standard, thin-layer chromatography for identification of impurities, a chemical colorimetric assay with cobalt nitrate, and quantitative determination by titration *(17).*

Several spectroscopic and chromatographic methods have been published for determination of

carisoprodol in pharmaceutical formulations *(18–21)*. As carisoprodol does not have an ultraviolet chromophore with significant absorbance, the US Pharmacopeia assay for carisoprodol tablets is based on liquid chromatography coupled to a refractive index detector *(2)*.

Numerous chromatographic methods have been reported for identification and quantification of carisoprodol in whole blood, urine, bile, muscle, liver, hair, vitreous fluid, plasma and serum. As carisoprodol is highly susceptible to thermal decomposition, methods based on gas chromatography coupled to either flame ionization detection or MS require derivatization to improve thermal stability and to form more characteristic mass spectral fragment ions, which can be used as diagnostic for compound identification *(22)*.Derivatization is, however, difficult and time-consuming, and alternative, sensitive methods have been developed *(23,24)*.

Currently, methods based on liquid chromatography coupled to either tandem MS or high-resolution MS are the choice for the quantitative determination of carisoprodol in biological fluids *(25–29)*. Qualitative and quantitative determination of carisoprodol and its primary metabolite meprobamate in biological fluids have been achieved by LC-MS *(30,31)*. Commercial availability of the deuterated reference standards of both carisoprodol and meprobamate for use as internal standards has generally facilitated development and validation of LC-MS methods *(32)*.

As carisoprodol is extensively metabolized and has a short half-life, its concentration in biological samples may be below the limit of detection. Depending on the time of sample collection, detection may be possible only of meprobamate *(33)*, which is also a prescription drug and a controlled substance in some countries (e.g. schedule IV of the Controlled Substances Act in the USA) *(34)*. Carisoprodol is metabolized to a lesser extent to hydroxy-carisoprodol *(35)*. Meprobamate and hydroxy-carisoprodol are both metabolized to hydroxy-meprobamate, then partially conjugated *(36)*. To date, no analytical method has been published on the detection of either hydroxy-carisoprodol or hydroxy-meprobamate.

Enzyme-linked immunosorbent assay kits are commercially available for the detection of carisoprodol and its major metabolite, meprobamate, in urine and blood samples. When a positive response is obtained in this assay, the result must be confirmed by LC-MS *(36,37)*.

# 3 Ease of conversion into controlled substances

No information was available on whether carisoprodol can be converted into a controlled substance.

# 4 General pharmacology

## *A Routes of administration and dosage*

Carisoprodol is typically taken orally, and it is available in tablet form. The usual recommended dosage of carisoprodol for adults is 250–350 mg taken three times a day and at bedtime. Dosages may differ according to individual factors and the instructions of the prescribing health-care professional.

## *B Pharmacokinetics*

Carisoprodol was authorized in 1959 before full characterization of its pharmacokinetics and pharmacodynamics *(38,39)*. The pharmacokinetics of carisoprodol are summarized below.

*Absorption*

Carisoprodol is well absorbed after oral administration, with a rapid onset of action (0.5–1 h) and a time to maximum plasma concentration of 1.5 h for a 250-mg tablet and 1.7 h for a 350-mg tablet. Its duration of action is generally 4–6 h. Simon et al. *(40)* quantified the relative bioavailability of carisoprodol and meprobamate. They provided single 250-mg and 350-mg tablets to 24 healthy subjects in a randomized, open-label, crossover study. The dose-adjusted $AUC_{0-\infty}$ values for carisoprodol were 5.29–5.75 µg/mL per h, depending on the dose, and the relative bioavailability was 92%. The mean $C_{max}$ values for carisoprodol were 1.24–1.78 µg/mL, depending on the dose, and the apparent terminal phase half-life ($t_{1/2}$) was 1.74–1.96 hours. Calvo et al. *(38)* conducted a double-blind, placebo-controlled, randomized clinical trial to define the pharmacokinetics of carisoprodol and meprobamate in 13 healthy volunteers in a crossover design. Following a single 350-mg dose, the values for carisoprodol were: $C_{max}$, 2580 ± 1214 ng/mL, $AUC_{0-\infty}$, 8072 ± 6303 h·ng/mL, and half-life ($t_{1/2}$), 2 ± 0.8 h. After 14 days of treatment (350 mg/8 h), the results were $C_{max}$, 2504 ± 730 ng/mL, $AUC_{0-\infty}$, 7451 ± 3615 h·ng/mL, and $t_{1/2}$, 2 ± 0.7 h. Accumulation of meprobamate, but not of carisoprodol, was seen after 14 days of treatment.

*Distribution*

Carisoprodol shows a moderate distribution capacity, signifying its presence throughout body tissues. It can cross the placenta and is also eliminated in breast milk. A proposed two-compartment pharmacokinetics model describes the metabolism of both carisoprodol and meprobamate. Lewandowski *(41)* analysed four distinct datasets and found a potential range of 0.93–1.3 L/kg for the volume of distribution of carisoprodol and 1.4–1.6 L/kg for meprobamate.

*Metabolism*

Carisoprodol undergoes extensive metabolism in the liver, primarily by the liver enzyme CYP2C19, to form its main metabolite, meprobamate. According to Dean et al. *(42)*, standard doses of carisoprodol in individuals who have little or no CYP2C19 activity can lead to four times greater exposure to carisoprodol and a concomitant 50% reduction in exposure to meprobamate. Approximately 3–5% of Whites and of Africans and 15–20% of Asians are CYP2C19 poor metabolizers. To better understand the issue, Bramness et al. *(43)* enrolled 37 healthy White volunteers, of whom 2 were poor metabolizers, 11 intermediate metabolizers and 12 extensive metabolizers; the remaining 12 participants were 6 metabolizers and 6 intermediate metabolizers who used oral contraceptives. A single oral dose of 700 mg of carisoprodol was given. Intermediate metabolizers had a longer elimination half-life (127 min) than extensive metabolizers (96 min) and a larger AUC for carisoprodol (16.3 µg.h/mL than extensive metabolizers (11.3 µg.h/mL). Overall, the authors concluded that, after a single dose of carisoprodol, the AUC was approximately 45% larger in CYP2C19 intermediate metabolizers than in extensive metabolizers. Use of oral contraceptives increased the AUC by approximately 60% in both extensive and intermediate metabolizers. Other common CYP2C19 inhibitors include omeprazole, ticlopidine, fluoxetine, fluvoxamine, topiramate, sertraline and tricyclic antidepressants. Co-administration of CYP2C19 inducers (e.g. rifampicin, carbamazepine, phenobarbital, aspirin and St John's wort) decreased the levels of carisoprodol and increased those of meprobamate.

*Elimination*

The half-life for elimination of carisoprodol is 1.7–2 h, and that of meprobamate is approximately 10 h. The kidneys are the primary route of excretion of both carisoprodol and

its metabolites. Therefore, individuals with impaired kidney function might experience prolonged elimination of carisoprodol. Carisoprodol can be removed through haemodialysis and peritoneal dialysis. Olsen et al. *(44)* investigated the elimination of carisoprodol in 10 healthy volunteers, who received 700 mg orally. Nine participants eliminated carisoprodol rapidly, with an average half-life of 99 ± 46 min, and it was extensively converted into meprobamate, the serum concentrations of meprobamate surpassing those of carisoprodol within 2.5 h of carisoprodol intake. One person, who was found to be a poor metabolizer of mephenytoin, eliminated carisoprodol with an overall half-life of 376 min, and only small amounts of meprobamate were found. Protein binding of carisoprodol was 41–67%, whereas meprobamate was bound to a lesser extent, 14–24%.

### *C Pharmacodynamics*

The muscle relaxant properties of carisoprodol are probably associated with its sedative effect. In experimental animals, the muscle relaxant properties are associated with altered interneuronal activity in the spinal cord and the descending reticular formation of the brain. Meprobamate is thought to contribute to the therapeutic effects of carisoprodol. Its subjective effects are similar to those f other central nervous system depressants, such as meprobamate, pentobarbital and chlordiazepoxide. They act primarily by enhancing the inhibitory effects of GABA *(45,46)*.

To assess these issues, Kumar et al. *(47)* used whole-cell patch clamp recordings to reveal the capacity of carisolprodol to directly control and enhance GABA-gated currents. The β1 subunit was more efficient than maximal GABA currents in direct activation, whereas the β2 subunit were the most effective in augmenting the GABA response through allosteric modulation. Kumar & Dillon *(48)*, in a sequence of investigations with recombinant GABAA receptors, showed amplification of GABA-induced current in all α subunit variations, the most significant impact being found in receptors expressing α5. Direct modulation was evident in receptors containing all α subunits, although it was diminished in receptors expressing α3.

More recently, Kumar et al*. (49)* investigated the influence of amino acids in transmembrane domain 4 of the GABAA receptor α subunit on the effects of carisoprodol on direct gating and allosteric modulatory. By analysng various mutations at the 415 position, they established a positive correlation between amino acid volume and the efficacy of carisoprodol in direct gating; no such correlation was observed with its allosteric modulatory actions. This indicates the presence of separate binding sites responsible for the distinct effects of carisoprodol in direct gating and allosteric modulation.

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In a preclinical investigation, Carbonaro et al. *(50)* investigated the behavioural effects of carisoprodol are direct or whether conversion to meprobamate is required. Rats were conditioned to differentiate the effects of carisoprodol (100 mg/kg) on the temporal pattern and alteration of discriminative effects due to administration of a CYP450 inhibitor (cimetidine) for 4 days. Furthermore, the pharmacokinetics of carisoprodol and meprobamate were evaluated in vivo by microdialysis, with LC-MS-MS of samples of blood and nucleus accumbens. The timeline of the discriminative-stimulus effects of carisoprodol was closely aligned to its levels in blood and the nucleus accumbans, while those of meprobamate were not, indicating that carisoprodol elicits behavioural effects directly, independently of meprobamate metabolism.

Calvo et al. *(39)* conducted a double-blind, placebo-controlled, randomized clinical trial involving 13 healthy participants to assess the pharmacokinetics and pharmacodynamics of carisoprodol after single (350 mg), double (700 mg) and multiple doses (up to 350 mg/8 h, 14

days). Muscular (electromyogram, muscular strength dynamometry), central (sedation) and tolerability (psychomotor activity test, adverse events) were measured, as were withdrawal symptoms. No explicit indications of direct muscle relaxation were observed; however, certain disparities in sedation were observed during the trial, implying that some of the effects of carisoprodol may be due to sedation. Notably, the impact on psychomotor impairment peaked at 1.5 h, suggesting that it originated from carisoprodol rather than meprobamate.

# 5 Toxicology

*Preclinical data; oral route*

*Acute toxicity*

The $LD_{50}$ was 1.80e+3 mg/kg in mice and 1.32e+3 mg/kg in rats *(51)*.

*Subchronic toxicity*

At < 100 mg/kg per day in rats, the clinical issues observed were lethargy, diarrhoea, rough hair coat, prostration, urine stain in the vaginal area ataxia and body weight changes *(52)*.

*Clinical data*

Usually, ingestion of one to three tablets of 350 mg produces a general feeling of well-being, 4–10 tablets are associated with hypomania, and > 10 tablets may cause confusion, disorientation and partial amnesia *(53,54)*. According to TOXBASE® *(55)*, ingestion of 21–35 g by adults has resulted in respiratory failure and coma, and ingestion of 8–10 g caused drowsiness, dizziness and impaired coordination in some patients, although ingestion 9 g by one person resulted in coma. Agitation, hypertonia and myoclonic encephalopathy can be seen with at high doses. A 34-year-old male with a history of carisoprodol abuse developed severe central nervous system and respiratory depression after acute ingestion of 7.5 g. He required high doses of multiple sedatives to control agitation considered to be due to withdrawal from carisoprodol *(56)*.

A 4-year-old child died after ingesting 3.5 g, and a 2-year-old had severe central nervous system and respiratory depression with hypoxia after ingesting 700 mg *(54)*.

Serotonin syndrome has been reported after ingestion of carisoprodol *(57)*. Because of its limited redistribution, maximum concentrations of carisoprodol appear in cardiac tissue, which, after an may induce direct cardiac toxicity *(58)*. Due to substantial metabolism of carisoprodol to meprobamate *(44)*, the concentration of meprobamate is likely to be raised after an overdose, with clinical consequences including slurred speech, ataxia, headache, weakness, hyperreflexia, clonus, convulsions, respiratory depression, hypotension, tachycardia and other dysrhythmia, hypothermia, agranulocytosis, pancreatitis, acute kidney injury, rhabdomyolysis and blisters (erythematous or haemorrhagic) *(54)*. An overdose of carisoprodol is not directly reversible with flumazenil, a GABA-A receptor antagonist *(45)*. Nevertheless, meprobamate, like benzodiazepines, acts on the GABA-A receptor *(43)*. Consequently, as the overdose progresses and meprobamate accumulates, flumazenil might counteract the effects *(59)*.

Chegondi et al. *(60)* reported the case of an adolescent girl who had overdosed with carisoprodol. She was unresponsive and had respiratory depression but recovered immediately after intravenous emulsion therapy.

*Several drugs, including carisoprodol*

Carisoprodol is often misused in combination with opiates and opioids *(53)*. Elarabi et al. *(61)* analysed data from a 16-week randomized controlled trial of 141 adult outpatients with opioid use disorder in the United Arab Emirates. Use of several substances, mainly pregabalin, was reported by 117 participants (82.9%). Self-reported independent use of carisoprodol predicted a nonfatal overdose (adjusted odds ratio, 4.52; 95% confidence interval [CI]: 1.81, 11.22). Li et al. *(62)* compared the risk of overdose associated with concomitant use of opioids and muscle relaxants with that of opioid use alone. This risk appeared to increase for misuse of carisoprodol in combination (1.84; 95% CI: 1.34, 2.54). Concurrent use of hydrocodone, alprazolam and carisoprodol ("Houston cocktail" or "Holy Trinity") may give users heroin-like euphoria, and combined use of these agents may be associated with a synergistic increase in dopamine in the nucleus accumbens *(3,4)*.

Lee et al. *(4)* investigated 80 cases involving drivers who had tested positive for hydrocodone, alprazolam and carisoprodol between 2015 and 2019. Only these three substances were found in 28% of the cases, while 28% had two of the three substances. The cases were found to have impaired driving, such as lane deviation, decreased vigilance, compromised judgement, altered speed and/or impaired braking. In a pharmaco-epidemiological investigation, Wang et al. *(63)* compared the attributes of about 17 000 patients prescribed a combination of benzodiazepines, opioids and carisoprodol with those of a group that received opioids and benzodiazepines. The recipients were predominantly young and female, who often sought care from several providers (commonly referred to as "doctor shopping"), and were given higher average daily doses of opioids.

The mortality risk associated with carisoprodol may increase when it is taken in combination with other drugs *(64)*. Lee et al. *(65)* investigated fatalities involving drugs reported to the Florida Medical Examiners Commission in the USA between 2001 and 2013. Benzodiazepines, carisoprodol, opioids and zolpidem were more often associated with unintentional fatalities and/or suicide. Khan et al. *(66)* conducted a cohort study of use of health care between 2000 and 2019 to quantify the risk of opioid overdose associated with seven prescription skeletal muscle relaxants. The weighted hazard ratio for opioid overdose relative to carisoprodol was 1.64 (95% CI: 0.81, 3.34).

# 6 Adverse reactions in humans

At therapeutic doses, common adverse effects include drowsiness (13–17%), dizziness (7–8%), ataxia, tremor, agitation, irritability, depressive reactions, syncope, insomnia and headache (3–5%) *(54)*. Cardiovascular (including tachycardia, postural hypotension and facial flushing), gastrointestinal (including nausea, vomiting, hiccup and epigastric distress) and haematological effects may occur. In post-marketing reporting and in case reports, carisoprodol has been associated with idiosyncratic reactions, including severe weakness, transient quadriplegia, euphoria, dilated pupils, disorientation and temporary vision loss *(54)*. A rare reported adverse effect is seizures.

# 7 Dependence potential

## *A Studies in experimental animals*

Swiss-Webster mice received carisoprodol intraperitoneally at 0, 100, 200, 300 or 500 mg/kg over 4 days. Loss of righting reflex was measured 20–30 min after each dose. The initial dose caused dose-dependent impairment of the righting reflex. During the 4-day exposure, the extent of impairment decreased by 75–100%, indicating the development of tolerance. Withdrawal symptoms were elicited by bemegride and flumazenil. Because of the tolerance and of the withdrawal issues

observed, the authors suggested that the potential for addiction to carisoprodol is similar to that of other long-acting benzodiazepine and barbiturate compounds *(67)*.

### *B Studies in humans*

The active metabolite of carisoprodol, meprobamate, was a frequently misused drug in the 1950s and 1960s, with reported overdoses *(68,69)*. Long-term or excessive use of carisoprodol can lead to dependence, and abrupt discontinuation or a significant reduction in dose after prolonged use can result in barbiturate- and alcohol-type withdrawal symptoms *(70–73)*, such as anxiety, insomnia, tremors, muscle twitching and, in severe cases, hallucinations and seizures. The withdrawal syndrome can be treated with benzodiazepines *(73)*, a combination of carisoprodol and phenobarbital *(56)* or oral baclofen *(74)*. Like benzodiazepines, potential cravings may persist.

VigiLyze *(75)* is a signal detection and management system for collecting information from participants in the WHO Programme for International Drug Monitoring. By integration with VigiBase, WHO's comprehensive database of potential adverse effects of medicinal products, VigiLyze allows access to national and international post-marketing data on drug safety. According to an assessment on 28 June 2023 on carisoprodol abuse and dependence in 2018–2023, the peak of reporting of carisoprodol abuse and dependence issues was in 2021. Most patients (about 44%) were aged 18–64 years, and 49% were female; 97% of the reports were from the USA and 2% from Brazil. Carisoprodol was mentioned alone in about 94% of cases. Dependence or drug dependence was identified in 440 (51.5%) of 1347 cases, abuse or drug abuse in 167 (19.5%) cases and tolerance in 12 cases (1.4%). The opioids most frequently reported in combination were oxycodone (55.7%) and hydrocodone (41.9%), while alprazolam (26.8%) was the benzodiazepine most frequently identified in combinations. Most co-reported preferred terms (n=2774) included: completed suicide (112 cases; 13.1%). suicide attempt (32 cases; 3.7%), suicidal ideation (29 cases; 3.4%), pain (80 cases; 9.1%), drug withdrawal (99 cases; 11.6%), depression (64; 7.5%), cardiorespiratory arrest (40 cases; 4.7%), death 37 cases (4.3%), and other important medical conditions (591; 69.2%).

## 8 Abuse potential

### *A Studies in experimental animals*

Gonzalez et al. *(46)* used both electrophysiological and behavioural methods to demonstrate that carisoprodol elicited picrotoxin-sensitive inward currents surpassing those generated by meprobamate, suggesting that carisoprodol can directly induce GABAergic effects in vivo.

In further drug discrimination studies involving rats trained with carisoprodol, pentobarbital, chlordiazepoxide and meprobamate, Gonzalez et al. *(46)* found that the GABAergic ligands substituted for carisoprodol in a dose-dependent manner. The discriminative stimulus effects of carisoprodol were effectively countered by bemegride, a barbiturate antagonist, but not by flumazenil, a benzodiazepine antagonist. They concluded that the barbiturate-like effects of carisoprodol are not due solely stem to meprobamate. Gatch et al. *(76)* conditioned Sprague-Dawley rats to differentiate propofol (10 mg/kg intraperitoneally) from substances including vehicle, carisoprodol (100 mg/kg), chlordiazepoxide and dizocilpine. The proportion of responses similar to those of propofol was 59% with carisoprodol and 65% with chlordiazepoxide.

### *B Studies in humans*

Owens et al. *(77)* identified individuals with prolonged use of carisoprodol (n = 340) and other

skeletal muscle relaxants (n = 453) in a dataset of 130 000 individuals in the Idaho Medicaid pharmacy and medical claims database in the USA in 2005. Carisoprodol users had a higher incidence of concurrent opioid use (81.5% vs 59.8%; $P < 0.01$) and were more likely to have had previous diagnoses suggesting other substance abuse (34.1% vs 21.4%; $P < 0.01$); 80% continued to self-finance carisoprodol when third-party coverage was terminated. The researcher considered that the data support potential abuse of carisoprodol. Zacny et al. *(78)* conducted a study involving 15 healthy participants who received carisoprodol at 0, 350 and 700 mg in order to evaluate its subjective and psychomotor effects. The higher dose led to increased scores on the visual analogue scale for descriptors associated with sedation rather than potential abuse. Nebinhani et al. *(54)* investigated a group of 34 individuals, most of whom described an overall sense of wellness after consuming up to three tablets. After 4–10 tablets, a hypomanic state was reported, with feelings of confusion. When more than 10 tablets were taken at once, they experienced sensations of disorientation and drowsiness.

# 9 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

*Indications for which the substance is approved for therapeutic use*

Carisoprodol is a centrally acting muscle relaxant used in the short term as an adjunct in symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasm. Carisoprodol is prescribed to relieve symptoms of muscle pain in people ≥ 16 years of age at a dosage of 250–350 mg orally three times a day and at bedtime, for a maximum duration of 2–3 weeks *(55)*. Its main clinical and therapeutic use is therefore to relieve muscle spasms and restricted movement due to strains, sprains and injuries. Carisoprodol is intended to be used with rest, physical therapy and other measures to relax muscles. Muscle relaxants such as carisoprodol have also been used in the management of diverse clinical conditions marked by heightened skeletal muscle activity, including in multiple sclerosis *(79)*.

*Extent of use for related therapeutic purposes*

In England, the prescription cost analysis system for 2000–2005 *(80)* showed that prescriptions for carisoprodol increased over time, from 4100 prescriptions in 2000 to 5000 prescriptions in 2005. In the USA, approximately 4.2 million carisoprodol prescriptions were dispensed in 2017 *(81)*, with a decrease to 3.2 million in 2018. With "rank" referring to the frequency with which a given medication is prescribed in a calendar year, carisoprodol prescriptions in the USA gradually decreased over time, from 175 in 2013 to 343 in 2019 *(82)*. Despite restrictions, carisoprodol is still widely prescribed, with over 3 million prescriptions (a decrease from 10 million in 2008) written in the USA in 2016 *(83)*.

Li et al. *(84)* evaluated the prevalence and duration of treatment with skeletal muscle relaxants in commercially insured adults in the USA, using the MarketScan Research Database for 2005–2018, covering approximately 49 million individuals. The prevalence of skeletal muscle relaxant treatment varied from 61.5 to 68.3 per 1000 individuals. About one third of users did not have a diagnosis of musculoskeletal disorders. When compared with other skeletal muscle relaxants, such as cyclobenzaprine, baclofen, tizanidine and methocarbamol, use of carisoprodol decreased over time. Individuals prescribed carisoprodol tended to have longer treatment than those treated with other skeletal muscle relaxants.

# 10 Listing on the WHO Model List of Essential Medicines

Carisoprodol is not listed on the 23rd WHO Model List of Essential Medicines *(85)*.

## 11 Marketing authorizations (as a medicinal product)

Carisoprodol is a prescription medication, which was introduced onto the market in 1959. At present, carisoprodol (either on its own or in combination) appears to be a licensed drug in several countries and territories, including Argentina (dispensing possible, but the drug is dispensed under the condition of an archived prescription and is subject to intensive pharmacovigilance *(86)*), Brazil, Ecuador, Egypt, Guatemala, Hong Kong (SAR China), Indonesia, Mexico, Nicaragua, Paraguay, Taiwan (China), Uruguay and the USA *(87)*. In Texas, USA, although carisoprodol is a prescription drug, pharmacists must access the Texas Prescription Monitoring Program for the patient's information before dispensing *(88)*. In New Zealand, carisoprodol is under part 1 of the relevant schedule (item 305) *(89)*. In Canada *(90)*, carisoprodol is a prescription drug (Schedule I) at federal level, although provincial regulations may differ, and its overall use is restricted *(91)*.

## 12 Industrial use

No industrial use was identified.

## 13 Non-medical use, abuse and dependence

According to Gupta *(6)*, carisoprodol is usually ingested orally; however, snorting of the substance induces euphoria more rapidly.

Carisoprodol may be diverted from legitimate medical channels and enter the illicit market *(65)* to be sold without proper medical supervision, increasing potential abuse and adverse consequences. To mitigate the potential for misuse, health-care providers should evaluate patients before prescribing carisoprodol, including their history of substance abuse, addiction or psychological disorders *(92)*. Monitoring of patients given carisoprodol is recommended to identify signs of misuse or escalating doses *(93)*.

Siddiqui et al. *(94)* assessed the drug arrests reported to the Diversion Alert Program in Maine, USA. Of the 9216 arrests for drugs, 64% involved a single drug. Carisoprodol, amitriptyline and quetiapine were those most likely to be found in misuse intoxications.

Alblooshi et al. *(95)* studied 250 patients in the National Rehabilitation Centre of Abu Dhabi. While opioid and alcohol were the most common substances used, carisoprodol (4.2 ± 0.4 tablets per day) was one of the most popular drugs reported in combinations, especially among people aged < 30 years. Hardon & Ihsan *(96)* assessed use of psychoactive prescription drugs by sex workers in Makassar, Indonesia, and particularly carisoprodol, which is available over the counter. Sex workers reportedly used most of their earnings to purchase carisoprodol, which was alleged to make them feel more confident and to make their work more acceptable. Hardon et al. *(97)* conducted a study in South Sulawesi, Indonesia, with mixed methods including interviews with 142 young people, with focus group discussions and participant observation. The objective was to understand how young people in the region engage with pharmaceuticals and cosmetics for sexual health. Some participants expressed interest in a blend of carisoprodol, paracetamol and caffeine, which they used to stimulate their libido and enhance their sexual confidence.

Alaryan et al. *(98)* conducted a cross-sectional study of misuse of drugs in community pharmacies in Damascus and in the surrounding countryside. Data were collected from 143 community pharmacists between December 2016 and March 2017 with a structured questionnaire. The study showed notable differences between the two areas, with higher instances of drug misuse among adolescents in the

countryside than those in Damascus. Carisoprodol and tramadol were the drugs most frequently requested by misusers. These individuals sought the medications without a valid prescription and used various strategies to obtain the drugs: 81% resorted to emotional appeal and 51% attempted to use irregular prescriptions.

In July 2023, "Google trend" research was conducted. The term "carisoprodol" was searched particularly in Latin America (e.g. Guyana, Honduras, Mexico, Nicaragua, Paraguay and the Plurinational State of Bolivia). Most searches with the brand name Soma®, which is popular in the USA, originated from India and the USA, although searches by brand names comprised only a small fraction of those for carisoprodol. No peaks in searches were identified during the past 5 years but peaked in 2006.

Reddit (a popular social media platform) included discussions on both the effects of carisoprodol at doses > 500 mg and possible alternatives to carisoprodol *(99)*. Most of the threads appeared to be older than 2 years. Some carisoprodol purchase options were also identified.

*Qualitative analysis*

Three "psychonaut" websites have been analysed *(100;101)*: Drugs-Forum (108 threads identified in 2011–2022 and 6 in 2022); Erowid (107 threads identified, most of which were quite old); and Bluelight (whuch contained the most recent entries, with 180 posts). Some illustrative examples are provided in Annex 3. The issues discussed included:

*Carisoprodol as a recreational drug:* Carisoprodol enthusiasts noted that, from the recreational point of view, the drug may be closest to both "old barbiturates" and methaqualone and may be "pretty popular" with people who are "drug nerds".

*Carisoprodol potentiation techniques:* According to some entries, the effects of carisoprodol can be potentiated by aspirin, while others recommended concurrent use of the *N*-methyl-D-aspartate antagonists, ketamine-like dextromethorphan of methoxetamine. Other possible combinations mentioned as "the ultimate sedation" were tramadol, carisoprodol, pregabalin and methocarbamol.

*Carisoprodol and opiates or opioids:* According to some entries, carisoprodol is "the only thing that categorically potentiates" the opiate high. All opiates and opioids were described as appropriate, although tramadol was noted specifically.

*"Coming off" carisoprodol:* Possible anecdotal suggestions for self-detoxification included tapering off of usage and taking further GABAergics, such as benzodiazepines and phenibut.

# 14 Nature and magnitude of public health problems related to misuse, abuse and dependence

The National Drug Intelligence Center in the USA *(102)* cited the findings of the National Survey on Drug Use and Health, which suggest that about 2 276 000 US residents aged ≥ 12 had used carisoprodol or Soma® nonmedically at least once in their lifetime. The prevalence increased over time; according to the 2012 National Survey on Drug Use and Health, 3.69 million people aged ≥ 12 reported non-medical use of Soma® at some time in their life, representing a notable rise from 3.06 million in 2011 *(103,104)*.

According to the Laboratory Information System, a database managed by the Drug Enforcement Administration in the USA, federal, state and local forensic laboratories identified 3847 items identified as carisoprodol in 2013 and 1735 in 2017, with a preliminary count of 1305 in 2018 *(81)*.

Between 1996 and 2005, the number of emergency department visits due to carisoprodol in the USA increased from 6569 to 19 513, the drug being listed at that time as one of the 25 most dangerous in the

country *(83)*. Gupta *(6)* reported that the number of emergency room visits linked to inappropriate use or abuse of carisoprodol increased from 15 830 visits in 2004 to 31 763 visits in 2009. The number of patients aged ≥ 50 years tripled (from 2070 to 7115), and the number of patients aged 35–49 doubled (from 6345 to 12 048). Although carisoprodol misuse by adolescents has been documented since 2007 *(6)*, the number of younger patients remained largely unchanged, while 77% of visits involved other medications, primarily narcotic pain relievers (55%) and benzodiazepines (47%). Hospitalization related to carisoprodol was required for 35% of emergency room visits between 2004 and 2009 *(103)*.

*Illicit distribution*

Carisoprodol is a drug that can be diverted. In March 2011, the street price for Soma® tablets was US$ 1–5 per tablet. In 2017, the American Association of Poison Control Centers reported a total of 2236 cases related to carisoprodol, including 901 single exposures and 2 deaths *(81)*.

Paulozzi et al. *(105)* in 2013 analysed data extracted from the Prescription Behavior Surveillance System, a public health monitoring mechanism for assessment and quantification of appropriate and inappropriate use of prescribed controlled substances in eight states in the USA. Substantial differences were found between states in the rates of prescription, with a twofold difference for opioids and an eightfold difference for carisoprodol. While the factors that contributed to such variation were unknown, the authors recommended that states use their prescription drug monitoring programmes for quantification at population level to measure the efficacy of policies to curtail misuse of prescription drugs.

*Driving*

In the USA, Lu et al. *(37)* analysed the results of 1672 tests of driving under the influence of drugs to determine the frequency of the involvement of carisoprodol or meprobamate. These substances were found in 99 samples (5.9%).

Rudisill et al. *(106)* conducted a literature review to identify medications that were associated with an elevated risk of motor vehicle collisions. Of the 53 medications assessed, 15 (28.3%) were associated with an increased risk, including carisoprodol. Bramness et al. *(107)* in Norway used data from three population-based registries covering the period April 2004–September 2005 to determine the risk of an accident associated with a personal injury within the first week of dispensing of a drug. People who had received a prescription for carisoprodol had a standardized incidence ratio (IRR) of 3.7 (95% CI: 2.9, 4.8), which was comparable to the risk associated with diazepam (IRR 2.8; 95% CI: 2.2, 3.6).

## 15 Licit production, consumption and international trade

Carisoprodol is available as a medication in many countries.

## 16 Illicit manufacture and traffic and related information

Law enforcement officers reported that young people living in Arizona and California, USA, often obtained carisoprodol at pharmacies in Mexico *(102)*. In February 2020, the National Narcotics Agency in Indonesia seized a reported four million pills of carisoprodol during a raid on four houses running an illicit drug manufacturing operation in West Java *(108)*. See Appendix 1 for additional unpublished information.

A preliminary informal search carried out in July 2023 indicated that it is possible to purchase carisoprodol online without a prescription on various websites, including OutlookIndia *(109)* and Westshore Women's Health *(110)*.

## 17 Current international controls and their impact

Høiseth et al. *(64)* reported that the rescheduling and withdrawal of carisoprodol from the Norwegian market reduced the prevalence of carisoprodol in impaired driving, deaths and intoxications. They also reported that sales decreased from 2 defined daily doses/1000 inhabitants per day in 2007 to 0.5 in May 2008 and then further to 0.09 after withdrawal from the market.

Bramness et al. *(111)* conducted a prospective, longitudinal, register-based study covering a population of 4.9 million inhabitants between 1 November 2006 and 31 January 2009, before and after withdrawal of carisoprodol from the Norwegian market in 2008. The participants, who had been using opioids and/or benzodiazepines at the same time as carisoprodol increased their consumption of these substances after withdrawal of carisoprodol. The authors noted that 11% of former carisoprodol users initiated use of opioids, 6.5% began to use benzodiazepine, and 12.9% initiated use of nonsteroidal anti-inflammatory drugs.

In response to steps being taken by US health-care systems to address the epidemic of opioid overdoses, Losby et al. *(112)* conducted a retrospective pre- and post-evaluation study of outcomes before and after a comprehensive initiative to transform the way in which chronic pain is viewed and treated. The study population comprised 3 203 880 adults observed between 2010 and 2015. All the observed outcomes were reduced, including a 90% decrease in use of the combination of a prescribed opioid with benzodiazepines and carisoprodol.

Also in the USA, Sun et al. *(113)* compared the volume of calls related to carisoprodol abuse or misuse to a state poison control system before (2008–2011) and after (2012–2015) the change in scheduling of carisoprodol. The number of calls decreased significantly, leading the authors to conclude that government regulation can reduce potential drug abuse.

Li et al. *(34)* observed a reduction of 20% in carisoprodol dispensing after its scheduling in the USA. The decrease was particularly large among younger people and among patients with injuries. Caulkins et al. *(114)* reported that, while certain states had implemented measures to limit the availability of carisoprodol before its federal scheduling, the impact of those measures did not appear to influence the outcomes significantly.

## 18 Current and past national controls

In 2007, the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout Europe *(115)*. Norwegian medical regulatory authorities conducted a review of carisoprodol in March 2007 and took it off the market in that country in May 2008. Carisoprodol was taken off the market in Sweden in November 2007. Carisoprodol has been classified under Schedule IV of the US Controlled Substances Act since January 2012. Carisoprodol was taken off the market in Indonesia in n September 2013 due to its diversion, dependence and side-effects. Carisoprodol is no longer a licensed product in Australia but can be accessed via the Special Access Scheme *(84)*. Carisoprodol is not on the United Kingdom Home Office list of most commonly encountered drugs currently controlled under the legislation on misuse of drugs; however, it was reported in 2014 that marketing authorization for carisoprodol was to be suspended *(73)*. Carisoprodol-containing products are not available in Chile *(116)* or Peru.

## 19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

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