World Health Organization

Critical review report

Carisoprodol

Expert Committee on Drug Dependence
Forty-seventh Meeting
Geneva, 14–18 October 2024

This report represents the views of an international group of experts, which do not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive summary

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 (all 3–5%). The adverse effects (typically considered to be more unexpected than side effects) are cardiovascular (such as tachycardia, postural hypotension and facial flushing), gastrointestinal (including nausea, vomiting, hiccup and epigastric distress) and haematological.

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 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. During the 1950s and 1960s, meprobamate was frequently misused, and instances of overdose were documented.

Carisoprodol has subjective effects similar to those of other central nervous system depressants such as meprobamate, pentobarbital and chlordiazepoxide. Carisoprodol produces a barbiturate-like effect at the GABA-A receptor, potentiating the neuronal inhibition produced by GABA. This inhibitory action gives rise to the sedative, anxiolytic and muscle-relaxing effects of carisoprodol and is similar to the action of meprobamate. There is some evidence, however, that carisoprodol can increase serotonergic activity, at least when administered at high doses.

The potential for misuse of carisoprodol may be related to both its sedative effects and its capacity to enhance the effects of other substances. Thus, the sedative effects of carisoprodol can be potentiated when it is combined with benzodiazepines, opioids or alcohol. 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.

Usually, ingestion of one to three 350-mg carisoprodol tablets 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 may have peaked in 2021, although this may be predominantly in one country.

Carisoprodol is actively searched online and available for online purchase from various both open and deep-web sites. According to the current social media analysis, carisoprodol may typically be ingested either on its own or in combination, especially with remaining GABAergics, gabapentinoids, opiates/opioids and tapentadol.

Carisoprodol is among frequently diverted pharmaceuticals. As of March 2011, the street value of Soma® (one brand of carisoprodol) tablets was US$ 1–5 per tablet.

According to the 2012 National Survey on Drug Use and Health, 3.69 million individuals aged ≥ 12 years 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 found 3847 items identified as carisoprodol in 2013 as compared with 1735 in 2017 and a preliminary count of 1305 in 2018. Widespread non-medical carisoprodol use has also been observed in a number of other countries.

Carisoprodol is classified under schedule IV in the US Controlled Substances Act (effective from 11 January 2012). In May 2008, it was taken off the market in Norway. In 2007, 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. 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 and 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 further known as 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate *(1)*. 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)*. Other street names include 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). Nicknames include "Lousiana trio" and "red apple" (e.g. for tapentadol + carisoprodol).

F Physical appearance

Carisoprodol is a white or almost white, fine powder *(6)* and is found 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. Carisoprodol was further presented, discussed and pre-reviewed in 2023 at the 46th ECDD meeting, where proceeding to critical review was recommended.

2 Chemistry

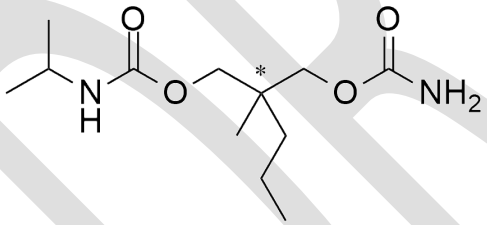
A Chemical name

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:

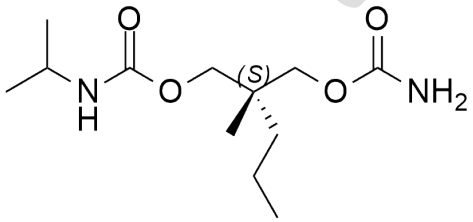


Molecular formula: $C_{12}H_{24}N_2O_4$

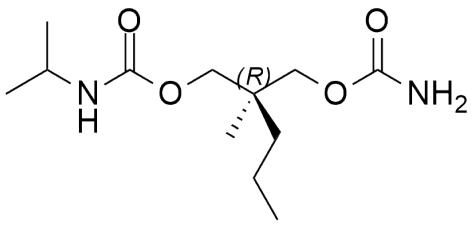
Molecular weight: 260.33 g/mol

C Stereoisomers

Carisoprodol is a racemic mixture of the 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:phosphate-buffered saline 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 a pharmaceutical ingredient is reported in the *US Pharmacopoeia (3)* and in the *European Pharmacopoeia (17)*. The latter reports tests for identification and analysis, including 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 (LC) 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 for compound identification *(22)*. Derivatization is, however, difficult and time-consuming, and alternative, sensitive methods have been developed *(23,24)*.

Currently, methods based on LC coupled to either tandem MS or high-resolution MS are the choice for 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)*. The 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 found.

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 *(1,17)*.

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 bioavailability of carisoprodol and its conversion to the metabolite meprobamate. They provided single 250-mg and 350-mg carisoprodol 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 h. For the metabolite meprobamate, the corresponding C_{max} values were 1.84 and 2.46 µg/mL. Calvo et al. *(38)* conducted a double-blind, placebo-controlled, randomized clinical trial to define the pharmacokinetics of carisoprodol and its metabolite meprobamate in 13 healthy volunteers in a crossover design. Following a single 350-mg carisoprodol dose, the values for carisoprodol were: C_{max}, 2580 ± 1214 ng/mL, $AUC_{0-\infty}$, 8072 ± 6303 h·ng/mL and $t_{1/2}$, 2 ± 0.8 h. For meprobamate, the parameters were C_{max}: 2181 ± 605 ng/mL and 34 529 ± 7747 h·ng/mL and $t_{1/2}$, 9 ± 1.9 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. For meprobamate (a steady state was reached), the parameters were C_{max}:5758 ± 1255 ng/mL and 79,699 ± 17 978 h·ng/mL and $t_{1/2}$, 8.7 ± 1.4 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

Olsen et al. *(42)* investigated the pharmacokinetics 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 (indicative of low CYP 2C19 activity), 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%.

Carisoprodol undergoes extensive metabolism in the liver, primarily by the liver enzyme CYP2C19, to form its main metabolite, meprobamate. According to Dean et al. *(43)*, 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. *(44)* enrolled 37 healthy White volunteers, of whom 2 were poor metabolizers, 11 intermediate metabolizers and 12 extensive metabolizers; the remaining 12 participants were 6 extensive 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.

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 of 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 carisoprodol 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 was most effective in augmenting the GABA response through allosteric modulation. Kumar & Dillon *(48)*, in a sequence of investigations with recombinant GABA-A 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 GABA-A receptor α subunit on the effects of carisoprodol on direct gating and allosteric modulation. By analysing 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 that separate binding sites are responsible for the distinct effects of carisoprodol in direct gating and allosteric modulation.

In a preclinical investigation, Carbonaro et al. *(50)* investigated whether the behavioural effects of carisoprodol are direct or whether conversion to meprobamate is required. Rats were conditioned to discriminate the effects of carisoprodol (100 mg/kg). The pharmacokinetics of carisoprodol and meprobamate were evaluated in vivo by microdialysis, with LC–MS–MS of samples of blood and from the nucleus accumbens. The timeline of the discriminative-stimulus effects of carisoprodol was closely aligned to its levels in blood and the nucleus accumbens, 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 (≤ 350 mg/8 h, 14 days). Muscular (electromyogram, muscular strength dynamometry) and central (sedation) effects, tolerability (psychomotor activity test, adverse events) and withdrawal symptoms were measured. No explicit indications of direct muscle relaxation were observed; however, there was evidence 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

Acute toxicity

The oral LD_{50} of carisoprodol was 1800 mg/kg in mice and 1320 mg/kg in rats *(51)*.

Subchronic toxicity

In rats given carisoprodol at < 100 mg/kg per day, the clinical signs observed were lethargy, diarrhoea, rough hair coat, prostration, urine staining in the vaginal area, ataxia and body weight changes *(52)*.

Human toxicity

Usually, ingestion of one to three carisoprodol 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)*. A 4-year-old child died after ingesting 3.5 g of carisoprodol *(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 of 9 g by one person resulted in coma. Agitation, hypertonia and myoclonic encephalopathy may be seen 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 sedatives to control agitation considered to be due to withdrawal from carisoprodol *(56)*.

According to Bramness et al. *(57)*, the symptoms and signs of carisoprodol intoxication do not fully resemble those caused by its metabolite meprobamate, a GABAergic agonist. The clinical toxicity signs and symptoms of carisoprodol intoxication are not, however, readily explained only by interaction with GABA, and a serotonin syndrome was reported in four people after ingestion of carisoprodol *(57)*. As carisoprodol is metabolized substantially 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)*. Nevertheless, meprobamate, like benzodiazepines, acts on the GABA-A receptor *(43)*. Consequently, as the overdose progresses and meprobamate accumulates, flumazenil might counteract the effects. A case study reported reversal of central nervous system depression after intravenous administration of flumazenil *(58)*. Chegondi et al. *(59)* 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.

Teratogenicity

It is not known whether carisoprodol increases the risks for miscarriage or birth defects. Briggs et al. (*60*) reported only mild sedation in a near-term infant exposed to carisoprodol throughout gestation and

during breast-feeding in the first month after birth. Both carisoprodol and its metabolite meprobamate are excreted into breastmilk (*61*).

Intake of other drugs with carisoprodol

Xu et al. *(62*) developed a preclinical in-vivo model for detecting worsening respiratory depression when various psychotropics were used in combination with oxycodone as compared with use of each opioid alone. The model is based on increased arterial partial pressure of carbon dioxide (pCO2). No changes in pCO2 were observed after co-administration of carisoprodol with oxycodone, although carisoprodol was given only at the estimated human equivalent dose of a 250-mg tablet (a small therapeutic dose). For further information on use of other drugs with carisoprodol, see sections 13 and 14.

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 (all at 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 and 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.

Pharmacological interactions: Many drugs interact with carisoprodol. Interaction of carisoprodol has been reported with virtually all opioids, other centrally acting analgesics and alcohol (*63*). People affected by porphyria and renal disease may be particularly vulnerable to the effects of carisoprodol (*63*).

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, and 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 development of tolerance. Withdrawal symptoms were elicited by both bemegride and flumazenil *(64)*.

B Studies in humans

The active metabolite of carisoprodol, meprobamate, was a frequently misused drug in the 1950s and 1960s, with reported overdoses *(65,66)*.

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 *(67–70)* such as anxiety, insomnia, tremors, muscle twitching and, in severe cases *(56),* hallucinations and seizures. The withdrawal syndrome can be treated with benzodiazepines *(70)*, a combination of carisoprodol and phenobarbital *(56)* or oral baclofen *(71)*. As with benzodiazepines, potential craving may persist.

VigiBase is the WHO global database of reported adverse events of medicinal products. It is the largest database of its kind in the world. Individual Case Safety Reports (ICSRs) have been submitted since 1968 *(72)*. The WHO Programme for International Drug Monitoring is a global

network to ensure the safety of medicines and vaccines, with 177 members.

VigiLyze, a signal detection and signal management tool that contains VigiBase data, provides additional information on dependence in humans *(72)*. A data search was conducted on 14 August 2024 of all 6015 ICSRs associated with carisoprodol as the suspected drug submitted to VigiBase in 1968–2024 *(72)*. When reports were classified by the international, clinically validated terminology in the Medical Dictionary for Regulatory Activities, the search retrieved a total of 1678/6015 entries mentioning drug abuse (643 cases, 10.7%), drug dependence (611 cases, 10.1%), drug withdrawal (201 cases, 3.3%) or intentional product misuse (223 cases, 3.7%). The peak of reporting was in 2021 (405 cases). Most patients (about 74%) were aged 18–64 years, and 57% were female; 96% of the reports were from the USA, followed by Spain (0.7%), Sweden and Norway (both at 0.5%). These data should be interpreted with caution in view of the known limitations of spontaneous adverse event reporting systems, such as underreporting, notoriety bias and missing information.

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, Gonzalez et al. *(46)* found that the GABAergic ligands pentobarbital, chlordiazepoxide and meprobamate 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 to meprobamate. Gatch et al. *(73)* conditioned Sprague-Dawley rats to differentiate propofol (10 mg/kg intraperitoneally) from vehicle and assessed carisoprodol (100 mg/kg), chlordiazepoxide and dizocilpine. Carisoprodol produced 59% and chlordiazepoxide produced 65% propofol-appropriate responses, while propofol produced 52% carisoprodol-appropriate responses. According to Gatch et al. *(73)* propofol discriminative-stimulus effects were similar to those of GABA-A receptor agonists. These preclinical findings may shed further light on the liability levels of carisoprodol abuse. (See also last paragraph of this section.)

B Studies in humans

Owens et al. *(74)* 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. People who were prescribed carisoprodol 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. *(75)* conducted a study of the subjective and psychomotor effects of carisoprodol in 15 healthy participants who received the drug at a dose of at 0, 350 or 700 mg. The higher dose led to increased scores on the visual analogue scale for descriptors associated with sedation rather than potential abuse. Nebinhani et al. *(53)* 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. Overall, subjects who use carisoprodol nonmedically may report impairment of physical or mental capability, dizziness and nausea/vomiting (*76*).

Considerations on the pharmacodynamics of carisoprodol and its abuse liability

The available preclinical and clinical evidence indicates that carisoprodol has clear GABA-A agonist pharmacodynamics, which may be more similar to those of barbiturates and/or propofol *(73)* than benzodiazepine. Bemegride (an analeptic) has shown better antagonist activities than flumazenil *(46).* In terms of the relative contribution of meprobamate, the main metabolite of carisoprodol, no data on the relative potency or efficacy of the two were available. The psychotropic effects of carisoprodol peak at 1.5 h *(39)*, probably before its full metabolic conversion to meprobamate, and the serum concentrations of meprobamate are higher than those of carisoprodol within 2.5 h of carisoprodol intake *(42).* It is also possible, however, that, at least at high or very high doses of carisoprodol, pharmacodynamics different from GABA-A agonism may play a role, and evidence of a serotonergic syndrome has been reported after overdose ingestion of carisoprodol in four subjects *(57)*. Overall, one could agree with Gatch et al. *(64)*, who suggested that the potential for addiction to carisoprodol is similar to that of other long-acting benzodiazepine and barbiturate compounds.

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 *(77)*.

There is evidence of widespread nonmedical use of carisoprodol and an increased risk of opioid overdose when it is combined with opioids, whereas other skeletal muscle relaxant drugs such as tizanidine are thought to have similar efficacy without a similar risk profile *(78)*. It is recommended that carisoprodol be avoided in the elderly population due to risks for sedation and falls *(79)*.

Extent of use for related therapeutic purposes

In 2007, Bramness et al *(80)*, analysed the Norwegian Prescription Database of information on prescription drugs dispensed to the Norwegian population. They found that 53 889 Norwegian women (2.4%) and 29 824 men (1.3%) aged ≥ 18 years had received carisoprodol at least once in 2004. Prescribing of carisoprodol was, however, skewed, some 32% of the patients having received more than 15 defined daily doses (s) of carisoprodol and > 11 000 patients (15%) received ≥ 75

DDDs in 2004. In England, the prescription cost analysis system for 2000–2005 *(81)* showed that prescriptions for carisoprodol increased over time, from 4100 prescriptions in 2000 to 5000 in 2005. In the USA, approximately 4.2 million carisoprodol prescriptions were dispensed in 2017 *(82)*, with a decrease to 3.2 million in 2018. When ranked according 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 *(83)*. 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 *(84)*.

Li et al. *(85)* evaluated the prevalence and duration of treatment with skeletal muscle relaxants in commercially insured adults in the USA from 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 disorder. 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. Data from IQVIA™ reported by the US Drug Enforcement Administration in 2019 indicated that about 4.2 million carisoprodol prescriptions were dispensed in the USA in 2017, decreasing to approximately 3.2 million in 2018 (*86*).

10 Listing on the WHO Model List of Essential Medicines

Carisoprodol is not listed on the 23rd WHO Model List of Essential Medicines *(87)*.

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; *88)*, Brazil, Ecuador, Egypt, Guatemala, Hong Kong (SAR China), Indonesia, Mexico, Nicaragua, Paraguay, Taiwan (China), Uruguay and the USA *(89)*. In Texas, USA, although carisoprodol is a prescription drug, pharmacists must access the Texas Prescription Monitoring Program for the patient's information before dispensing *(90)*. In New Zealand, carisoprodol is under part 1 of the relevant schedule (item 305) *(91)*. In Canada *(92)*, carisoprodol is a prescription drug (Schedule I) at federal level, although provincial regulations may differ; its overall use is restricted *(93)*.

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 potential misuse, it is recommended that health-care providers evaluate patients before prescribing carisoprodol, including their history of substance abuse, addiction or psychological disorders *(94)*. Monitoring of patients given carisoprodol is also recommended to identify signs of misuse or escalating doses *(95)*.

Siddiqui et al. *(96)* assessed 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. *(97)* studied 250 patients in the National Rehabilitation Centre of Abu Dhabi, United Arab Emirates. 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 *(98)* 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. *(99)* conducted a study in South Sulawesi, Indonesia, with mixed methods including interviews with 142 young people, focus group discussions and participant observation 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. *(100)* conducted a cross-sectional study of misuse of drugs in community pharmacies in Damascus, Syrian Arab Republic, and in the surrounding countryside. Data were collected from 143 community pharmacists between December 2016 and March 2017 on a structured questionnaire. Carisoprodol and tramadol were the drugs most frequently requested for misuse.

Carisoprodol is aften misused in combination with opioids *(53)*. Elarabi et al. *(101)* analysed data from a 16-week randomized controlled trial of 141 adult outpatients with opioid use disorder in the United Arab Emirates and found that carisoprodol was used nonmedically by 30 of the 141 participants. In this study, self-reported independent use of carisoprodol predicted an increased odds for nonfatal overdose (adjusted odds ratio, 4.52; 95% confidence interval [CI]: 1.81 ; 11.22). Li et al. *(102)* compared the risk of overdose associated with concomitant use of opioids and muscle relaxants with that of opioid use alone. The risk appeared to increase for misuse of carisoprodol in combination (1.84; 95% CI: 1.34 ; 2.54). In a pharmaco-epidemiological investigation, Wang et al. *(103)* 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. Concurrent use of hydrocodone, alprazolam and carisoprodol (“Houston cocktail” or “Holy Trinity”; *103*) 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)*. According to some social media-based, “netnographic” (*104*) observations, carisoprodol intake is particularly popular in combination with pregabalin, GABAergics and tapentadol (nickname: “red apple”). Carisoprodol is reportedly ingested with heroin by people who have developed a tolerance to the related benzodiazepine and pregabalin. In July 2023, in a “Google trend” research, the term “carisoprodol” was searched in Latin America (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 the number peaked in 2006. According to Google Trends in 2024, international interest in carisoprodol remained roughly the same during 2023–2024.

Reddit (a popular social media platform) included discussions on both the effects of carisoprodol at doses > 500 mg and possible alternatives to carisoprodol *(105)*. Most of the threads appeared to be older than 2 years. Some carisoprodol purchase options were also identified. Carisoprodol still appeared to be actively searched and available for online purchase from both open and deep-web sites. According to a current social media analysis, carisoprodol is typically ingested either on its own or in combination, especially with remaining GABAergics, gabapentinoids and opiates/opioids, and especially tapentadol.

Qualitative analysis

To enrich the current knowledge of carisoprodol, 3 "psychonaut" websites were qualitatively analysed *(106,107)*: Drugs-Forum (108 threads identified in 2011–2022 and 6 in 2022); Erowid (107 threads identified, most of which were quite old); and Bluelight (which contained the most recent entries, with 180 posts). Some illustrative examples are provided in Annex 3. The issues discussed included the following.

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 described as "the ultimate sedation" included the concurrent combination of tramadol, carisoprodol, pregabalin and methocarbamol.

Carisoprodol and opiates or opioids: According to some entries, *c*arisoprodol 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 use 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 *(108)* cited the findings of the National Survey on Drug Use and Health, which suggest that about 2 276 000 US residents aged ≥ 12 years 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 years reported non-medical use of Soma® at some time in their life, representing a notable rise from 3.06 million in 2011 *(109,110)*.

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 drug items (i.e. exhibits that have been analysed) identified as carisoprodol in 2013 and 1735 in 2017, with a preliminary count of 1305 in 2018 *(82)*.

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 *(71)*. 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, and 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 *(109)*.

According to Masoner et al. *(111),* who tested a range of pharmaceuticals and contaminants of emerging concern in the final leachates from 22 landfills in 12 US states, the most frequently detected contaminants were lidocaine, the nicotine derivative cotinine and carisoprodol. 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 *(82)*.

The mortality risk associated with carisoprodol may increase when it is taken in combination with other drugs *(112)*. Lee et al. *(113)* 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 than other drugs. Khan et al. *(114)* 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 with carisoprodol was 1.64 (95% CI, 0.81 ; 3.34), lower than for baclofen. More recently, Chen et al. (*115)* conducted nine retrospective cohort studies, each cohort including person-time exposure to both a skeletal muscle relaxant and hydrocodone, oxycodone or tramadol. In the oxycodone cohort, the adjusted hazard ratio (HR) for the occurrence of an injury event was 1.86 (95% CI, 1.23; 2.82). Hutchison et al. (*116*) recently confirmed the frequent occurrence of opioid + benzodiazepine + carisoprodol prescriptions, particularly in rural Texas (USA).

To assess the associations between opioids prescribed for 30 days and the risk for a fatal overdose during the subsequent 15 days, Henry et al. (*117*) designed a statewide cohort study of data for all 5.3 million patients prescribed an opioid analgesic in California (USA) in 2013. Patients prescribed benzodiazepines had a significantly greater risk for overdose, but a prescription of Z-drugs or carisoprodol was not associated with a risk for overdose.

According to the VigiLyze report for 1968–2024 report *(72;* see section 7B above for further details), which assessed 6015 reports involving carisoprodol, 93% of entries were classified as serious, which was defined as meeting the following criteria: death, life-threatening, caused or prolonged hospitalization, disabling or incapacitating and other medically important condition. The opioids most frequently reported in combination with carisoprodol were hydrocodone (27.1%) and oxycodone (25.1%), while alprazolam (21.4%) was the benzodiazepine most frequently identified in combinations. The most frequently reported terms were: completed suicide (1545 cases; 25.7%), toxicity reactions to various agents (1001 cases; 16.6%) and overdose (740 cases; 12.3%).

Illicit distribution

Carisoprodol can be diverted. In March 2011, the street price for Soma® tablets was US$ 1–5 per tablet.

Paulozzi et al. *(118)* 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

Lee et al. *(4)* investigated 80 cases involving drivers who had tested positive for hydrocodone, alprazolam or 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 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. *(119)* 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. *(120)* 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 personal injury within the first week of dispensing of a drug. People who had received a prescription for carisoprodol had a standardized incidence ratio of 3.7 (95% CI: 2.9 ; 4.8), which was comparable to the risk associated with diazepam (2.8; 95% CI: 2.2 ; 3.6).

15 Licit production, consumption and international trade

Carisoprodol is available as a medication in many countries (see section 11) but is no longer used medically in Europe since the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout the continent *(128)*.

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 *(108)*. 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 *(121)*. According to (unpublished) data from the International Narcotics Control Board, the number of incidents involving carisoprodol has increased worldwide, from 45 incidents before March 2021 from only three countries to 2416 between January 2022 and March 2023 from 23 countries.

A preliminary informal search carried out in July 2023 indicated that carisoprodol can be purchased online without a prescription on various websites, including OutlookIndia *(122)* and Westshore Women's Health *(123)*.

17 Current international controls and their impact

Carisoprodol is not currently under international control.

18 Current and past national controls

Høiseth et al. *(112)* reported that rescheduling and withdrawal of carisoprodol from the Norwegian market reduced the presence of carisoprodol in cases of 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. *(124)* conducted a prospective, longitudinal, register-based study covering a population of 4.9 million inhabitants of Norway between 1 November 2006 and 31 January 2009, before and after withdrawal of carisoprodol from the 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 people who were previously prescribed carisoprodol subsequently initiated use of opioids (11%), benzodiazepines (6.5%) and nonsteroidal anti-inflammatory drugs (12.9%).

In response to steps taken by US health-care systems to address the epidemic of opioid overdoses, Losby et al. *(125)* 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, who were 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. *(126)* compared the volume of calls to a state poison control system related to carisoprodol misuse 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. *(127)* 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 have influenced the outcomes significantly.

In 2007, the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout Europe *(128)*. 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 September 2013 due to its diversion, dependence and side-effects. Carisoprodol is not on the United Kingdom Home Office list of the 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 *(70)*. Norwegian medical regulatory authorities conducted a review of carisoprodol in March 2007 and took it off the market in May 2008 *(112)*. Carisoprodol-containing products are not available in Chile *(129)* or Peru *(130).* Carisoprodol is no longer a licensed product in Australia *(131)*.

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

No other matters were identified.

References

1. Carisoprodol. In: Buckingham R, editor. Martindale, the Extra Pharmacopoeia. 30th edition. London: Pharmaceutical Press;1993; **https://doi.org/10.1111/j.2042-7174.1993.tb00740.x** (https://onlinelibrary.wiley.com/doi/abs/10.1111/j.2042-7174.1993.tb00740.x , accessed 6 September 2024).
2. Carisoprodol. USP32-NF27. In: US Pharmacopeia. Rockville (MD): US Pharmacopeial Convention, Inc.; 2009 (https://pubchem.ncbi.nlm.nih.gov/compound/2576).
3. Horsfall JT, Sprague JE. The pharmacology and toxicology of the "Holy Trinity". Basic Clin Pharmacol Toxicol. 2016;120(2):115–9. doi:10.1111/bcpt.12655.
4. Lee JR, Stout P, Egdorf D. Houston cocktail: Driving under influence of hydrocodone, alprazolam, and carisoprodol. Forensic Sci Int. 2021;323:110819. doi:10.1016/j.forsciint.2021.110819.
5. Gupta M. Case report: Carisoprodol abuse in adolescence. Cureus. 2020;12(11):e11525. doi:10.7759/cureus.11525.
6. European Pharmacopoeia, 10th Edition (10.3-10.4-10.5). Strasbourg: European Directorate for the Quality of Medicines and Health Care; 2023 (https://cymitquimica.com/products/41-PUB200333/european-pharmacopoeia-10th-edition-103-104-105-book-english/).
7. USP 43-NF 38. US Pharmacopoeia and National Formulary. Rockville (MD): US Pharmacopeial Convention, Inc.; 2020 (https://www.usp.org/news/usp-extends-standards-implementation-for-uspnf-fcc-pubs).
8. Carisoprodol. In: O'Neil MJ, editor. The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station (NJ): Merck and Co., Inc.; 2006. (https://merckindex.rsc.org/search-results?q=carisoprodol; accessed 6 September 2024)
9. Powell LS. Method of manufacturing nu-substituted 2, 2-disubstituted-1, 3-propanediol dicarbamate. Patent number US 3092656A. Alexandria (VA): United States Patent and Trademark Office; 1963.(https://patentimages.storage.googleapis.com/07/35/4e/05427c2d8923ef/US3092656.pdf; accessed 6 September 2024)
10. Vardanyan RS, Hruby VJ. Synthesis of essential drugs. Amsterdam: Elsevier B.V; 2006 (https://www.sciencedirect.com/book/9780444521668/synthesis-of-essential-drugs).
11. Carisoprodol. Waltham (MA): Thermo Fisher Scientific; 2024 (https://www.thermofisher.com/order/catalog/product/466240050, accessed 15 August 2024)
12. Lide DR. Handbook of chemistry and physics. 88th edition. Boca Raton (FL): CRC Press; 2007 (https://pubs.acs.org/doi/10.1021/ja077011d).
13. Carisoprodol. Zhejiang: LookChem; 2023 (https://www.lookchem.com/Carisoprodol/, accessed 29 June 2023).
14. Carisoprodol (item No. 30778). Ann Arbor (MI): Cayman Chemicals Company; 2020 (https://www.caymanchem.com/product/30778/carisoprodol, accessed 28 June 2023).
15. Carisoprodol (HMDB0014539). Calgary (ALB): Human Metabolome Database; 2022 (https://hmdb.ca/metabolites/HMDB0014539, accessed 3 August 2023).
16. Coutts RT. Mass spectra of nine medicinal carbamates. J Pharmaceutical Sci. 1973;62(5):769–73. doi:10.1002/jps.2600620513.
17. Carisoprodol. In: The European Pharmacopoeia, 10th edition. Strasbourg: Council of Europe, European Directorate for the Quality of Medicines; 2020 (https://www.edqm.eu/en/european-pharmacopoeia).
18. Rabinowitz MP, Reisberg P, Bodin JI. GLC assay of meprobamate and related carbarnates. J Pharm Sci. 1972;61(12):1974–6. doi:10.1002/jps.2600611219.
19. Allen L. Quantitative determination of carisoprodol, phenacetin, and caffeine in tablets by near-IR spectrometry and their identification by TLC. J Pharm Sci. 1974;63(6:912–6. doi:10.1002/jps.2600630621.

20. Honigberg I, Stewart JT, Smith MO. Liquid chromatography in pharmaceutical analysis. IX: Determination of muscle relaxant–analgesic mixtures using normal phase chromatography. J Pharm Sci. 1978;67(5)675–9. doi:10.1002/jps.2600670528.
21. Murali D, Purna Chandra Rao P. Spectrophotometric methods for the quantification of carisoprodol using ferric chloride, o-phenanthroline, and p-nitroaniline, sodium nitrite as analytical reagents. Asian J Pharm Clin Res. 2019;384–90. doi:10.22159/ajpcr.2019.v12i2.29902.
22. Kim JY, In MK, Paeng K, Chung BC. Simultaneous determination of carisoprodol and meprobamate in human hair using solid-phase extraction and gas chromatography/mass spectrometry of the trimethylsilyl derivatives. Rapid Commun Mass Spectrom. 2005;19(21):3056_62. doi:10.1002/rcm.2173.
23. Kintz P, Mangin P, Lugnier A, Chaumont A. A rapid and sensitive gas chromatographic analysis of meprobamate or carisoprodol in urine and plasma. J Anal Toxicol. 1988;12(2):73–4. doi:10.1093/jat/12.2.73.
24. Matsumoto T, Sano T, Matsuoka T, Aoki M, Maeno Y, Nagao M. Simultaneous determination of carisoprodol and acetaminophen in an attempted suicide by liquid chromatography–mass spectrometry with positive electrospray ionization. J Anal Toxicol. 2003;27(2):118–22. doi:10.1093/jat/27.2.118.
25. Gergov M, Ojanperä I, Vuori E. Simultaneous screening for 238 drugs in blood by liquid chromatography–ion spray tandem mass spectrometry with multiple-reaction monitoring. J Chromatogr B. 2003;795(1):41–53. doi:10.1016/s1570-0232(03)00498-7.
26. Pelander A, Ojanperä I, Laks S, Rasanen I, Vuori E. Toxicological screening with formula-based metabolite identification by liquid chromatography/time-of-flight mass spectrometry. Anal Chem. 2003;75(21):5710–8. doi:10.1021/ac030162o.
27. Herrin G, McCurdy HH, Wall WH. Investigation of an LC-MS-MS (QTRAP(R)) method for the rapid screening and identification of drugs in postmortem toxicology whole blood samples. J Anal Toxicol. 2005;29(7):599–606. doi:10.1093/jat/29.7.599.
28. Mueller C, Weinmann W, Dresen S, Schreiber A, Gergov M. Development of a multi-target screening analysis for 301 drugs using a QTrap liquid chromatography/tandem mass spectrometry system and automated library searching. Rapid Commun Mass Spectrom. 2005;19(10):1332–8. doi:10.1002/rcm.1934.
29. Hegstad S, Khiabani HZ, Kristoffersen L, Kunøe N, Lobmaier P, Christophersen AS. Drug screening of hair by liquid chromatography-tandem mass spectrometry. J Anal Toxicol. 2008;32(5):364–72. doi:10.1093/jat/32.5.364.
30. Coulter C, Garnier M, Tuyay J, Orbita J, Moore C. Determination of carisoprodol and meprobamate in oral fluid. J Anal Toxicol. 2012;36(3):217–20. doi:10.1093/jat/bks009.
31. Essler S, Bruns KA, Frontz M, McCutcheon JR. A rapid quantitative method of carisoprodol and meprobamate by liquid chromatography–tandem mass spectrometry. J Chromatogr B. 2012;908:155–60. doi:10.1016/j.jchromb.2012.09.001.
32. Logan BK, Stafford DT. Direct analysis of anticonvulsant drugs in vitreous humour by HPLC using a column switching technique. Forensic Sci Int. 1989;41(1–2):125–34. doi:10.1016/0379-0738(89)90244-2.
33. Tse SA, Atayee RS, Best BM, Pesce AJ. Evaluating the relationship between carisoprodol concentrations and meprobamate formation and inter-subject and intra-subject variability in urinary excretion data of pain patients. J Anal Toxicol. 2012;36(4):221–31. doi:10.1093/jat/bks018.
34. Li Y, Delcher C, Brown JD, Wei Y, Reisfield GM, Winterstein AG. Impact of Schedule IV controlled substance classification on carisoprodol utilization in the United States: an interrupted time series analysis. Drug Alcohol Depend. 2019;202:172–7. doi:10.1016/j.drugalcdep.2019.05.025.

35. Tse SA, Atayee RS, Joseph D, Best BM. Factors affecting carisoprodol metabolism in pain patients using urinary excretion data. J Anal Toxicol. 2014;38(3):122–8. doi:10.1093/jat/bku002.
36. Wang G, Huynh K, Barhate R, Rodrigues W, Moore C, Coulter C et al. Validation of a new homogeneous immunoassay for the detection of carisoprodol in urine. J Anal Toxicol. 2011;35(2):108–12. doi:10.1093/anatox/35.2.108.
37. Lu A, Scott KS, Chan-Hosokawa A, Logan BM. Impact of expanding ELISA screening in DUID investigations to include carisoprodol/meprobamate and zolpidem. J Anal Toxicol. 2016;41(2):134–9. doi:10.1093/jat/bkw106.
38. Calvo A, Alonso S, Prieto EL, Ascaso A, Ortuño J, Fernández N et al. Single and multiple dose PK–PD characterization for carisoprodol. Part I: Pharmacokinetics, metabolites, and 2C19 phenotype influence. Double-blind, placebo-controlled clinical trial in healthy volunteers. J Clin Med. 2022;11(3):858. doi:10.3390/jcm11030858.
39. Calvo A, González-Hidalgo M, Terleira A, Fernández N, Portolés A. Carisoprodol single and multiple dose PK-PD. Part II: Pharmacodynamics evaluation method for central muscle relaxants. Double-blind placebo-controlled clinical trial in healthy volunteers. J Clin Med. 2022;11(4):1141. doi:10.3390/jcm11041141.
40. Simon S, D'Andrea C, Wheeler WJ, Sacks H. Bioavailability of oral carisoprodol 250 and 350 mg and metabolism to meprobamate: a single-dose crossover study. Curr Ther Res. 2010;1(1):50–9. doi:10.1016/j.curtheres.2010.02.003.
41. Lewandowski T. Pharmacokinetic modeling of carisoprodol and meprobamate disposition in adults. Hum Exp Toxicol. 2016;36(8):846–53. doi:10.1177/0960327116672912.
42. Olsen H, Koppang E, Alván G, Mørland J. Carisoprodol elimination in humans. Ther Drug Monit. 1994;16(4):337–40. doi:10.1097/00007691-199408000-00001.
43. Dean L. Carisoprodol therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. Medical genetics summaries. Bethesda (MD): National Center for Biotechnology Information; 2017 (https://www.ncbi.nlm.nih.gov/books/NBK425390/).
44. Bramness JG, Skurtveit S, Gulliksen M, Breilid H, Steen VM, Mørland J. The CYP2C19 genotype and the use of oral contraceptives influence the pharmacokinetics of carisoprodol in healthy human subjects. Eur J Clin Pharmacol. 2005;61(7):499–506. doi:10.1007/s00228-005-0970.
45. Gonzalez LA, Gatch MB, Taylor C, Bell-Horner CL, Forster MJ, Dillon GH. Carisoprodol-mediated modulation of $GABA_A$ receptors: in vitro and in vivo studies. J Pharmacol Exp Ther. 2009;329(2):827–37. doi:10.1124/jpet.109.151142.
46. Gonzalez LA, Gatch MB, Forster MJ, Dillon GH. Abuse potential of Soma®: the GABA(A) receptor as a target. Mol Cell Pharmacol. 2009;1(4):180–6. PMID:20419052.
47. Kumar M, Gonzalez LA, Dillon GH. Assessment of subunit-dependent direct gating and allosteric modulatory effects of carisoprodol at GABAA receptors. Neuropharmacology. 2015;97:414–25. doi:10.1016/j.neuropharm.2015.04.007.
48. Kumar M, Dillon GH. Assessment of direct gating and allosteric modulatory effects of meprobamate in recombinant GABAA receptors. Eur J Pharmacol. 2016;775:149–58. doi:10.1016/j.ejphar.2016.02.031.
49. Kumar M, Kumar M, Freund JM, Dillon GH. A single amino acid residue at transmembrane domain 4 of the α subunit influences carisoprodol direct gating efficacy at GABAA receptors. J Pharmacol Exp Ther. 2017;362(3):395–404. doi:10.1124/jpet.117.242156.
50. Carbonaro TM, Nguyen V, Forster MJ, Gatch MB, Prokai L. Carisoprodol pharmacokinetics and distribution in the nucleus accumbens correlates with behavioral effects in rats independent from its metabolism to meprobamate. Neuropharmacology. 2020;174:108152 doi:10.1016/j.neuropharm.2020.108152.
51. Carisoprodol. PubChem. 78-44-4. Bethesda (MD): National Center for Biotechnology Information,

National Library of Medicine; 2023 (https://chem.nlm.nih.gov/chemidplus/rn/78-44-4).
52. Hazard evaluation support system integrated platform. Tokyo: Safety Assessment Division, Chemical Management System, National Institute of Technology and Evaluation; 2023 (https://www.nite.go.jp/en/chem/qsar/hess-e.html).
53. Nebhinani N, Aggarwal M, Mattoo SK, Basu D. Carisoprodol: an underrecognized drug of abuse in north India. Gen Hosp Psychiatry. 2013;35(1):89–92. doi:10.1016/j.genhosppsych.2012.07.011.
54. Adams HR, Kerzee T, Morehead CD. Carisoprodol-related death in a child. J Forensic Sci. 1975 Jan;20(1):200-2. PMID: 1117271.
55. TOXBASE® (www.toxbase.org, accessed 10 July 2023).
56. Vo KT, Horng H, Smollin CG, Benowitz NL. Severe carisoprodol withdrawal after a 14-year addiction and acute overdose. J Emergency Med. 2017;52(5):680–3. doi:10.1016/j.jemermed.2016.11.015.
57. Bramness JG, Mørland J, Sørlid HK, Rudberg N, Jacobsen D. Carisoprodol intoxications and serotonergic features. Clin Toxicol. 2005;43(1):39–45. doi:10.1081/clt-45020.
58. Roberge RJ, Lin E, Krenzelok EP. Flumazenil reversal of carisoprodol (Soma®) intoxication. J Emergency Med. 2000;18(1):61–4. doi:10.1016/s0736-4679(99)00177-8.
59. Chegondi M, Badheka A, Chacham S, Kahana M. Intravenous lipid emulsion rescue therapy in a child with carisoprodol overdose. Cureus. 2019;11(11):e6250. doi:10.7759/cureus.6250.
60. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G. High-dose carisoprodol during pregnancy and lactation. Ann Pharmacother 2008;42(6):898-901. doi: 10.1345/aph.1L042.
61. Nordeng H, Zahlsen K, Spigset O. Transfer of carisoprodol to breast milk. Ther Drug Monit 2001;23(3):298-300. doi: 10.1097/00007691-200106000-00020.
62. Xu L, Krishna A, Stewart S, Shea K, Racz R, Weaver JL, Volpe DA, Pilli NR, Narayanasamy S, Florian J, Patel V, Matta MK, Stone MB, Zhu H, Davis MC, Strauss DG, Rouse R. Effects of sedative psychotropic drugs combined with oxycodone on respiratory depression in the rat. Clin Transl Sci 2021;14(6):2208-2219. doi: 10.1111/cts.13080Xu
63. Drugs.com. Carisoprodol interactions. (https://www.drugs.com/drug-interactions/carisoprodol.html; accessed 24 July 2024)
64. Gatch MB, Nguyen JD, Carbonaro TM, Forster MJ. Carisoprodol tolerance and precipitated withdrawal. Drug Alcohol Dependence. 2012;123(1–3):29–34. doi:10.1016/j.drugalcdep.2011.10.010.
65. Kamin I, Shaskan DA. Death due to massive overdose of meprobamate. Am J Psychiatry. 1959:115(12):1123–4. doi:10.1176/ajp.115.12.1123-a.
66. Ferguson MJ, Germanos S, Grace WJ. Meprobamate overdosage. Arch Intern Med. 1960:106(2):237. doi:10.1001/archinte.1960.03820020077011.
67. Reeves RR, Beddingfield JJ, Mack JE. Carisoprodol withdrawal syndrome. Pharmacotherapy. 2004;24(12):1804–6. doi:10.1592/phco.24.17.1804.52333.
68. Eleid MF, Krahn LE, Agrwal N, Goodman BP. Carisoprodol withdrawal after internet purchase. Neurologist. 2010;16(4):262–4. doi:10.1097/nrl.0b013e3181aa917e.
69. Reeves RR, Burke RS, Kose S. Carisoprodol. South Med J. 2012;105(11):619–23.
70. Carisoprodol and meprobamate: risks outweigh benefits. London: Medicines and Healthcare Products Regulatory Agency; 2014 (https://www.gov.uk/drug-safety-update/carisoprodol-and-meprobamate-risks-outweigh-benefits).
71. Paul G, Parshotam G, Garg R. Carisoprodol withdrawal syndrome resembling neuroleptic malignant syndrome: diagnostic dilemma. J Anaesthesiol Clin Pharmacol. 2016;32(3):387. doi:10.4103/0970-9185.173346.
72. VigiLyze. Uppsala: Uppsala Monitoring Centre; 2018–2023 (https://who-umc.org/pv-products/vigilyze/, accessed 22 August 2024).

73. Gatch MB, Forster MJ. Behavioral and toxicological effects of propofol. Behav Pharmacol. 2011;22(7):718–22. doi:10.1097/fbp.0b013e32834aff84.
74. Owens C, Pugmire B, Salness T, Culbertson VL, Force RW, Cady PS et al. Abuse potential of carisoprodol: a retrospective review of Idaho Medicaid pharmacy and medical claims data. Clin Ther. 2007;29(10):2222–5. doi:10.1016/j.clinthera.2007.10.003.
75. Zacny JP, Paice JA, Coalson DW. Characterizing the subjective and psychomotor effects of carisoprodol in healthy volunteers. Pharmacol Biochem Behav. 2011;100(1):138–43. doi:10.1016/j.pbb.2011.08.011.
76. Carisoprodol abuse. Brentwood (TN): American Addiction Centers; 2024 (https://drugabuse.com/drugs/carisoprodol/, accessed 24 July 2024).
77. Carisoprodol. DrugBank. Edmonton (ALB): Wishart Research Group; 2023 (https://www.drugbank.ca/drugs/DB00395, accessed 7 July 2023).
78. Zhu LL, Wang YH, Zhou Q. Tizanidine: advances in pharmacology and therapeutics and drug formulations. J Pain Res 2024;17:1257–71. doi: 10.2147/JPR.S461032.
79. Fu JL, Perloff MD. Pharmacotherapy for spine-related pain in older adults. Drugs Aging. 2022;39(7):523–50. doi:10.1007/s40266-022-00946-x.
80. Bramness JG, Furu K, Engeland A, Skurtveit S. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. Br J Clin Pharmacol. 2007;64(2):210–8. doi: 10.1111/j.1365-2125.2007.02847.x.
81. Carisoprodol. Volume 454: debated on Thursday 7 December 2006. Hansard, Parliament; 2006 (https://hansard.parliament.uk/Commons/2006-12-07/debates/0612088000010/Carisoprodol, accessed 15 August 2023).
82. Carisoprodol (Trade Name: Soma®). Springfield (VA): Drug Enforcement Administration, Diversion Control Division, Drug & Chemical Evaluation Section; 2019 (https://www.deadiversion.usdoj.gov/drug_chem_info/carisoprodol/carisoprodol.pdf).
83. Carisoprodol. Drug usage statistics, United States, 2013–2020. Arlington Heights (VA): ClinCalc LLC; 2020 (https://clincalc.com/DrugStats/Drugs/Carisoprodol, accessed 25 July 2023).
84. Carisoprodol. Inglewood (CA): The Drug Classroom; 2016 (https://thedrugclassroom.com/video/carisoprodol/).
85. Li Y, Delcher C, Reisfield GM, Wei Y, Brown JD, Winterstein AG. Utilization patterns of skeletal muscle relaxants among commercially insured adults in the United States from 2006 to 2018. Pain Med. 2021;22(10):2153–61. doi:10.1093/pm/pnab088.
86. Carisoprodol. Springfield (VA): Drug Enforcement Administration; 2019 (https://www.deadiversion.usdoj.gov/drug_chem_info/carisoprodol/carisoprodol.pdf, accessed 24 July 2024)
87. WHO Model List of Essential Medicines, 23rd List. Geneva: World Health Organization; 2023 (https://www.who.int/publications-detail-redirect/WHO-MHP-HPS-EML-2023.02).
88. Olivera ME, Uema SN, Romañuk CB, Caffaratti M, De Carvalho Mastroianni P, Varallo FR et al. Regulatory issues on pharmacovigilance in Latin American countries. Pharma Policy Law; 2014;16(3–4):289–312. doi:10.3233/ppl-140390.
89. Carisoprodol (International). Auckland: Drugs.com; 2023 (https://www.drugs.com/international/carisoprodol.html#, accessed 22 August 2024).
90. Carisoprodol. Austin (TX): Texas State Board of Pharmacy; 2023 (https://www.pharmacy.texas.gov/files_pdf/TSBP%20Rules_MASTER%20FILE.pdf, accessed 31 August 2023).
91. Medicines Amendment Regulations 2009. Wellington: New Zealand Legislation; 2009 (https://www.legislation.govt.nz/regulation/public/2009/0212/latest/whole.html; accessed 15 August 2023).
92. The Drug and Health Product Register. Ottawa: Government of Canada; 2023 (https://hpr-

rps.hres.ca/pdl.php; accessed 31 August 2023).
93. Carisoprodol. Ottawa: National Association of Pharmacy Regulatory Authorities; 2013 (https://www.napra.ca/nds/carisoprodol/, accessed 15 August 2023).
94. Conermann T, Christian D. Carisoprodol. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 31971718.
95. Preuss CV, Kalava A, King KC. Prescription of controlled substances: benefits and risks. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 30726003.
96. Siddiqui MZ, Piserchio JP, Patel M, Park J, Foster M, Desrosiers CE et al. Examination of multiple drug arrests reported to the Maine Diversion Alert Program. Forensic Sci Med Pathol. 2022;18:133–40. doi:10.1007/s12024-021-00454-1.
97. Alblooshi H, Hulse GK, Kashef AE, Hashmi HA, Shawky M, Ghaferi HA et al. The pattern of substance use disorder in the United Arab Emirates in 2015: results of a National Rehabilitation Centre cohort study. Subst Abuse Treat Prev Policy. 2016;11(1):19. doi:10.1186/s13011-016-0062-5.
98. Hardon A, Ihsan A. Somadril and edgework in South Sulawesi. Int J Drug Policy. 2014;25(4):755–61. doi:10.1016/j.drugpo.2014.05.012.
99. Hardon A, Idrus NI, Hymans TD. Chemical sexualities: the use of pharmaceutical and cosmetic products by youth in South Sulawesi, Indonesia. Reprod Health Matters. 2013;21(41):214–24. doi:10.1016/s0968-8080(13)41709-3.
100. Alaryan T, Hasan TA, Eshelli M, Alzeer S. The misuse of prescribed drugs during the Syrian crisis: a cross-sectional study. Int J Ment Health Addict. 2019;19(3):714–23. doi.org/10.1007/s11469-019-00180-4.
101. Elarabi HF, Radwan DN, Adem A, Marsden J, Lee A. Polysubstance use in adults with opioid use disorder receiving buprenorphine maintenance. J Addict Med. 2022;17(1):74–8. doi:10.1097/adm.0000000000001039.
102. Li Y, Delcher C, Wei Y, Reisfield GM, Brown JD, Tighe PJ et al. Risk of opioid overdose associated with concomitant use of opioids and skeletal muscle relaxants: a population-based cohort study. Clin Pharmacol Ther. 2020;108(1):81–9. doi:10.1002/cpt.1807.
103. Wang Y, Delcher C, Li Y, Goldberger BA, Reisfield GM. Overlapping prescriptions of opioids, benzodiazepines, and carisoprodol: "Holy Trinity" prescribing in the state of Florida. Drug Alcohol Depend. 2019;205:107693. doi:10.1016/j.drugalcdep.2019.107693.
104. Arillotta D, Guirguis A, Corkery J, Scherbaum N, Schifano F. COVID-19 pandemic impact on substance misuse: a social media listening, mixed method analysis. Brain Sci. 2021;11(7):907. doi:10.3390/brainsci11070907.
105. Carisoprodol. San Francisco (CA): Reddit, 2023 (https://www.reddit.com/r/researchchemicals/comments, accessed 15 July 2023).
106. Orsolini L, Papanti GD, Francesconi G, Schifano F. Mind navigators of chemicals' experimenters? A web-based description of e-psychonauts. Cyberpsychol Behav Soc Networking. 2015;18(5):296–300. doi:10.1089/cyber.2014.0486
107. Schifano F, Chiappini S, Corkery J, Scherbaum N, Guirguis A. The e-psychonaut drugs' psychopharmacology. Curr Opinion Pharmacol. 2021;57:165–74. doi:10.1016/j.coph.2021.02.008.
108. Soma. Fast facts. Johnstown (PA): National Drug Intelligence Center; 2006 (https://www.justice.gov/archive/ndic/pubs10/10913/index.htm; accessed 16 August 2023).
109 Estimating mental illness among adults in the United States: Revisions to 2008 estimation procedures. 2012 National Survey on Drug Use and Health. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2015 (https://www.ncbi.nlm.nih.gov/books/NBK519744/).

110. ED visits involving the muscle relaxant carisoprodol. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2011 (https://www.datafiles.samhsa.gov/study-publication/ed-visits-involving-musclerelaxant-carisoprodol-nid13834).
111. Masoner JR, Kolpin DW, Furlong ET, Cozzarelli IM, Gray JL. Landfill leachate as a mirror of today's disposable society: pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. Environ Toxicol Chem. 2016;35(4):906–18. doi:10.1002/etc.3219.
112. Høiseth G, Karinen R, Sørlid HK, Bramness JG. The effect of scheduling and withdrawal of carisoprodol on prevalence of intoxications with the drug. Basic Clin Pharmacol Toxicol. 2009;105(5):345–9. doi:10.1111/j.1742-7843.2009.00459.x.
113. Lee D, Delcher C, Maldonado-Molina MM, Thogmartin JR, Goldberger BA. Manners of death in drug-related fatalities in Florida. J Forensic Sci. 2016;61(3):735–42. doi:10.1111/1556-4029.12999.
114. Khan NF, Bykov K, Barnett ML, Glynn RJ, Vine S, Gagne JJ. Comparative risk of opioid overdose with concomitant use of prescription opioids and skeletal muscle relaxants. Neurology. 2022;99(13):e1432–42. doi:10.1212/wnl.0000000000200904.
115. Chen C, Hennessy S, Brensinger CM, Miano TA, Bilker WB, Dublin S et al. Comparative risk of injury with concurrent use of opioids and skeletal muscle relaxants. Clin Pharmacol Ther. 2024;116(1):117–27. doi:10.1002/cpt.3248.
116. Hutchison RW, Carhart J. Opioid and benzodiazepine utilization patterns in metropolitan and rural Texas. Opioid Manag. 2023;19(5):433–43. doi:10.5055/jom.0817.
117. Henry SG, Fang SY, Crawford AJ, Wintemute GJ, Tseregounis IE, Gasper JJ et al. Impact of 30-day prescribed opioid dose trajectory on fatal overdose risk: a population-based, statewide cohort study. J Gen Intern Med 2024;39(3):393–402. doi:10.1007/s11606-023-08419-6.
118. Paulozzi LJ, Strickler GK, Kreiner P, Koris CM. Controlled substance prescribing patterns – prescription behavior surveillance system, eight states, 2013. Morbid Mortal Wkly Rep. 2015;64(SS-9):1–14. doi:10.15585/mmwr.ss6409a1.
119. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. Accident Anal Prev. 2016;96:255–70. doi:10.1016/j.aap.2016.08.001.
120. Bramness JG, Skurtveit S, Mørland J, Engeland A. The risk of traffic accidents after prescriptions of carisoprodol. Accident Anal Prev. 2007;39(5):1050–5. doi:10.1016/j.aap.2007.02.002.
121. Dipa A. BNN seizes millions of “PCC” in raid on illicit Bandung pill factory. The Jakarta Post, 26 February 2020 (https://www.thejakartapost.com/news/2020/02/26/bnn-seizes-millions-of-pcc-in-raid-on-illicit-bandung-pill-factory.html).
122. Carisoprodol, Soma trial pack, buy carisoprodol 350mg & 500mg online in USA, UK. OutlookIndia, 9 September 2023 (https://www.outlookindia.com/business-spotlight/carisoprodol-soma-trial-pack-buy-carisoprodol-350mg-500mg-online-in-usa-uk-news-246259, accessed 25 July 2023).
123. Soma online. Westlake (OH): Westshore Women’s Health, 2023 (https://www.westshorewomenshealth.com/about-us/soma-online, accessed 25 July 2023).
124. Bramness JG, Furu K, Skurtveit S, Engeland A. Effect of the market withdrawal of carisoprodol on use of other prescribed drugs with abuse potential. Clin Pharmacol Ther. 2012;91(3):438–41. doi:10.1038/clpt.2011.250.
125. Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system’s comprehensive approach. J Eval Clinical Pract. 2017;23(6):1173–9. doi:10.1111/jep.12756.
126. Sun C, Hollenbach K, Cantrell FL. Trends in carisoprodol abuse and misuse after regulatory scheduling: a retrospective review of California poison control calls from 2008 to 2015. Clin Toxicol. 2017;56(7):653–5. doi:10.1080/15563650.2017.1414950.

127. Caulkins JP, Goyeneche LA, Guo L, Lenart K, Rath M. Outcomes associated with scheduling or up-scheduling controlled substances. Int J Drug Policy. 2021;91:103110. doi:10.1016/j.drugpo.2021.103110.
128. Overall summary of the scientific evaluation of medicinal products containing carisoprodol. In: Annex II. Scientific conclusions and grounds for suspension of the marketing authorisations presented by the EMEA. Amsterdam: European Medicines Agency; Committee for Medicinal Products for Human Use; 2007 (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/carisoprodol_107/WC500012425.pdf).
129. Registro Sanitario de Productos Farmacéuticos [Health Registry of Pharmaceutical Products]. Santiago: Institute of Public Health, 2023 (https://www.ispch.gob.cl/anamed/medicamentos/registro-sanitario-de-productos-farmaceuticos).
130. Prais, Pan American Health Organization and WHO for Americas Annotated Medicine and Device Lists. (https://medlistapp.paho.org/en/list/16; accessed 6 September 2024)131. Search the TGA website. Canberra: Australian Government; Department of Health and Aged Care; 2024 (https://www.tga.gov.au/search?keywords=carisoprodol&submit=Search; accessed 22 August 2024).