Remimazolam. A New Drug With Potential Applications in Anaesthesia and Critical Care

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KEY POINTS

- Remimazolam is a new benzodiazepine.
- Remimazolam has properties of midazolam and remifentanil, offering rapid onset and offset.
- Remimazolam has clinical uses in procedural and intensive care sedation as well as general anaesthesia.
- Flumazenil can be used to reverse the effects of remimazolam.

INTRODUCTION

Remimazolam is an intravenous sedative agent that combines the pharmacodynamic effects of midazolam with the pharmacokinetic properties of remifentanil. It shows potential for use in procedures where rapid onset and offset of action are required.[1,2]

In the following tutorial, we aim to present available evidence on clinical uses, pharmacology, and future clinical applications of remimazolam as both a sedative and anaesthetic agent.

CLINICAL USES OF REMIMAZOLAM

Remimazolam is currently used as a sedative agent for short cardioversion procedures at University Hospitals of Leicester NHS Trust.

It has been proposed for use across the following varied clinical settings:

1. Procedural sedation: endoscopic, diagnostic, and minor surgical procedures.
2. General anaesthesia: Induction and maintenance of anaesthesia in combination with other agents.
3. Intensive care sedation.

Table 1 outlines dosing guidelines for adults for procedural sedation.[3]

Procedural Sedation

From 2015 to 2022, authors of 4 trials[4-7] investigated the effectiveness of remimazolam as a sedative agent for upper gastrointestinal endoscopy (UGIE) in a total of 731 individuals aged between 18 and 60 years of age. These trials are outlined in Table 2.

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TAKE ONLINE TEST

	Adults <65 years of age	Elderly ≥65 years of age and/or with ASA-PS III-IV and/or body weight <50kg
Procedural sedation **with opioid****	Induction Administer opioid.* Wait 1 to 2 minutes. Initial dose of remimazolam injection: 5mg (2mL) over 1 minute. Wait 2 minutes. Maintenance / titration Remimazolam injection: 2.5mg (1mL) over 15 seconds. Maximal total dose administrated in the clinical trials was 33mg.	Induction Administer opioid.* Wait 1 to 2 minutes. Initial dose of remimazolam injection: 2.5 to 5mg (1 to 2mL) over 1 minute. Wait 2 minutes. Maintenance / titration Remimazolam injection: 1.25 to 2.5mg (0.5 to 1mL) over 15 seconds. Maximal total dose administrated in the clinical trials was 17.5mg.
Procedural sedation **without opioid**	Induction Remimazolam injection: 7mg (2.8mL) over 1 minute. Wait 2 minutes. Maintenance / titration Remimazolam injection: 2.5mg (1mL) over 15 seconds. Maximal total dose administrated in the clinical trials was 33mg.	Induction Remimazolam injection: 2.5 to 5mg (1 to 2mL) over 1 minute. Wait 2 minutes. Maintenance / titration Remimazolam injection: 1.25 to 2.5mg (0.5 to 1mL) over 15 seconds. Maximal total dose administrated in the clinical trials was 17.5mg.

ASA-PS = American Society of Anesthesiologists Physical Status. * For administration to patients concomitantly taking opioids, central nervous system depressants, alcohol or benzodiazepines, refer to the Summary of Product Characteristics. ** For example: 50 micrograms of fentanyl or a suitably reduced dose for elderly or debilitated patients.

Table 1. Dosing Guidelines of Remimazolam in Adults for Procedural Sedation With and Without Opioids[3]

Collectively, the authors of these trials concluded that remimazolam, either with or without adjunctive therapy, can achieve satisfactory sedation levels in healthy individuals and those with liver cirrhosis undergoing UGIE, without causing significant haemodynamic disturbances or respiratory depression in comparison with other commonly used agents.

Authors of recent studies comparing remimazolam with midazolam for moderate sedation during bronchoscopy have shown remimazolam to be safe and effective,[8] with authors of 1 study concluding that remimazolam achieves adequate sedation with shorter onset time and faster cognitive recovery than midazolam.[9]

General Anaesthesia

Remimazolam has been licensed for general anaesthesia in Japan, China, and South Korea.[1] Authors of a recent study comparing remimazolam to propofol as general anaesthetic agents in ASA 1 or 2 patients showed both agents to be efficacious, with a total absence of intraoperative awakening or recall, body movement, and need for rescue sedative medication.[10] The time to loss of consciousness and extubation was longer for the remimazolam groups than the propofol group; however, the remimazolam groups had a more favourable side-effect profile, with less hypotension and injection site pain, than the propofol group.

Doi et al. (2020) evaluated remimazolam's efficacy and safety in higher-risk ASA 3 surgical patients. They found similar recovery, efficacy, and safety profiles to those in ASA 1 and 2 patients. However, a higher dose (12 mg/kg/h) resulted in a significantly shorter time to achieve loss of consciousness than a lower dose (6 mg/kg/h).[11]

Shi et al. (2022) compared remimazolam tosilate with propofol for general anaesthesia in liver cirrhosis ASA 2 and 3 patients undergoing endoscopic variceal ligation.[12] Participants received either a 0.2-mg/kg remimazolam bolus for induction, followed by a 1.0–2.0-mg/kg/h infusion for maintenance, or a propofol bolus of 2 mg/kg for induction, followed by infusion of 4–10 mg/kg/h, until surgery ended. Flumazenil was routinely administered to the remimazolam group, and the same volume of saline was given to the propofol group immediately after surgery. While remimazolam had a longer time to loss of consciousness, it had significantly shorter times to return to consciousness and extubation, with lower incidences of intraoperative hypotension and postoperative hypoxia.

Intensive Care Sedation

Remimazolam was approved in August 2020 for compassionate use in intensive care sedation in Europe.[1] It possesses desirable characteristics for an ideal sedative drug in the intensive care setting. For example, it is short-acting and is metabolised by first-order pharmacokinetics, in which it is swiftly hydrolysed by tissue esterase enzymes into inactive metabolites. Prolonged sedation with propofol can lead to propofol infusion syndrome (PRIS). Remimazolam may be a more suitable hypnotic agent for patients at risk of PRIS, such as those with hypertriglyceridaemia. In a Phase II study[13] conducted by Peterson (2017), all 49 Japanese patients

Author	Trial Phase, No., Age	Dose of Remimazolam	Primary Endpoint	Comparator; Co-Treatment	Results
Borkett et al. 2019	IIa, 100 participants, 18–60 y	3 groups with different doses: 0.10, 0.15, and 0.20 mg/kg	Compare efficacy and safety of different single remimazolam doses with midazolam for sedation in UGIE	Midazolam 0.075 mg/kg IV; no co-treatment	A single dose of remimazolam (0.1–0.2 mg/kg) induced quicker sedation and faster recovery than midazolam in UGIE patients.
Chen et al. 2021	III	5.0 mg plus 2.5 mg top-ups	Efficacy and safety of remimazolam tosilate for sedation in UGIE	Propofol 1.5 mg/kg plus 0.5 mg/kg top-ups; co-treatment: fentanyl (0.5 mcg/kg), lidocaine viscous oral liquid 10 g	1. The successful sedation rate in the remimazolam group was not inferior to propofol. 2. The remimazolam group took longer to achieve sedation (2 min versus 1.3 min; $P < .0001$) but had a shorter recovery time (5.75 min versus 6.71 min; $P < .0001$). 3. The remimazolam group had significantly lower rates of hypotension, treatment-related hypotension, and respiratory depression ($P < .001$, $P < .0001$, $P = .0064$).
Tan et al. 2022	III, 99 participants, >60 y	Initial dose: 2 groups with different doses: 0.1 and 0.2 mg/kg); extra dose: 0.05 mg/kg	Efficacy and safety of remimazolam in patients requiring bronchoscopy	Propofol 1–1.5 mg/kg with 0.5 mg/kg top ups; no co-treatment	1. No significant difference in postoperative cognitive function, sedation, and recovery times between the lower-dose remimazolam group and the propofol group. 2. Higher-dose remimazolam group demonstrated poorer immediate recall and shorter delay recall than their base line ($P < .05$) and scored worse than the propofol group for attention ($P < .05$). 3. Lower-dose remimazolam group had the lowest incidence of hypotension (3.0%) compared with the higher remimazolam group (21.2%) and the propofol group (48.55%; $P < .05$).
Cao et al. 2022	III, 148 participants, 18–65 y	0.1 mg/kg	Efficacy and safety of remimazolam sedation for patients with liver cirrhosis undergoing UGIE	Propofol 2 mg/kg; co-treatment: sufentanil 0.15 μg/kg	1. Remimazolam group took a longer time to sedate than the propofol group (88.3 s versus 62.7 s, respectively; $P < .001$). 2. Remimazolam group had a faster recovery period than the propofol group (44.7 s versus 64.6 s; $P < .001$) 3. Incidence of adverse events, such as respiratory depression (2.7% versus 17.6%, $P = .003$) and hypotension (4.1% versus 14.9%, $P = .025$) was lower in the remimazolam group than in the propofol group.

Table 2. Outline of 4 Trials[4-7] From 2015–2022 in Which Authors Investigated the Effectiveness of Remimazolam as a Sedative Agent for Upper Gastrointestinal Endoscopy (UGIE)

admitted to the intensive care unit (ICU) were successfully sedated with remimazolam without experiencing any adverse events, although a subgroup that received continuous infusion of the drug for more than 24 hours displayed higher plasma concentrations than expected, the significance of which was unknown at the time. The safety profile of remimazolam for long-term sedation in critically ill patients, however, is yet to be established.

PHARMACOLOGICAL CHARACTERISTICS

Chemical Structure and Mechanism of Action

Remimazolam is presented as a 20-mg powder which is reconstituted with 8.2 mL of 0.9% sodium chloride and delivered via the intravenous route as a bolus dose, followed by an infusion if necessary.[2] It is soluble in slightly acidic environments and can precipitate in lactated or acetated solutions, such as Ringer's or Plasma-Lyte 148,[2] as shown in Figure 1.

Remimazolam has been shown to be compatible with the administration of common anaesthetic drugs such as remifentanil, fentanyl, midazolam, and common neuromuscular blocking agents.[2]

Remimazolam contains the carboxylic ester group present in remifentanil, which is integrated into its benzodiazepine core, as shown in Figure 2. Figure 3 shows how this carboxylic ester group enables remimazolam to be rapidly hydrolysed into its inactive metabolite, CNS 7054, by carboxylesterase-1, which is mainly located in the liver. Like other benzodiazepines, remimazolam enhances the γ-aminobutyric acid Type A inhibitory receptor with increased frequency of opening ligand-gated chloride ion channels.

Pharmacokinetics

The intranasal route is painful with low bioavailability (50%). The oral route has very poor bioavailability (1%–2%). For 100% bioavailability, remimazolam is administered as an intravenous bolus or as a continuous infusion.

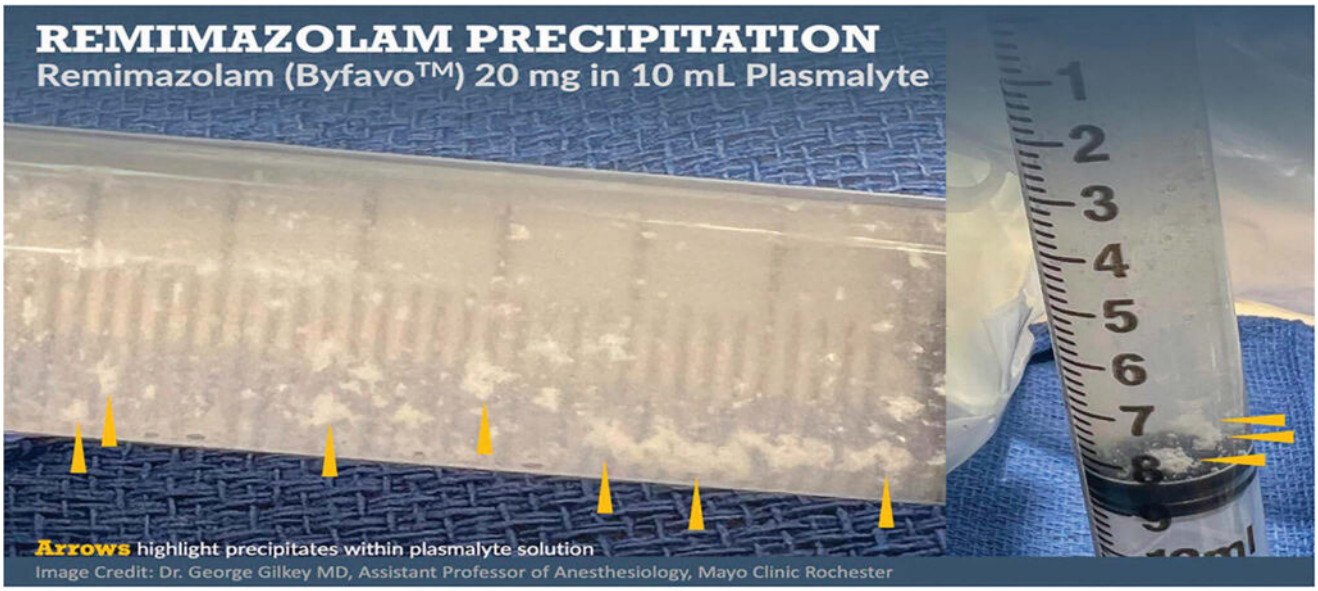

Figure 1. Photograph of 20 mg remimazolam (ByFavo) drawn into 12 mL syringe of 10 mL Plasma-Lyte. Yellow arrows highlight precipitate formation.[2]

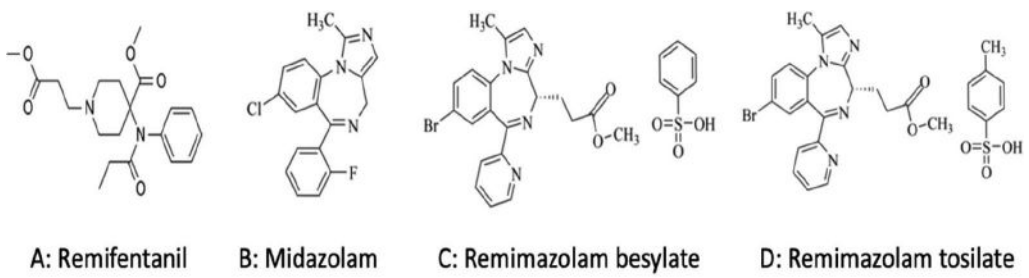

Figure 2. Chemical structures of (A) remifentanil, (B) midazolam, (C) remimazolam besylate, and (D) remimazolam tosilate.[1] (C) and (D) are different salt forms of remimazolam.

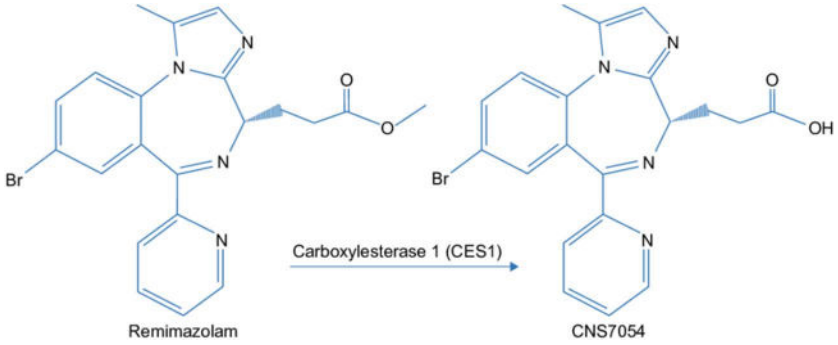

Figure 3. Metabolism of remimazolam to its inactive metabolite (CNS 7054) by carboxylesterases such as carboxylesterase 1.[1]

Figure 4 illustrates how peak effect site concentration over time of remimazolam compares with other commonly used opioids and sedatives. Notably, remimazolam has a faster onset and offset than midazolam.[14] Figure 5 shows that its context sensitive half-life is shorter (<10 minutes) than the other agents it was compared with.[1]

Remimazolam is highly protein bound, 91% being primarily bound to albumin. Table 3 shows that, when administered intravenously, the volume of distribution for midazolam is greater than that of remimazolam. The elimination clearance of remimazolam is greater than that of midazolam contributing to its significantly shorter terminal half-life.

As mentioned above, carboxylesterase-1 is the enzyme primarily responsible for metabolising remimazolam into its pharmacologically inactive metabolite CNS 7054. This metabolic pathway does not involve cytochrome-dependent hepatic pathways; therefore, the likelihood of significant drug interactions with remimazolam is low.

Authors of several trials have investigated the pharmacokinetic properties of remimazolam in different populations. No significant pharmacokinetic differences were observed with age or renal function.[15] However, a significantly higher remimazolam exposure and decreased drug elimination was found in individuals with severe hepatic impairment (Child-Pugh class C) than those with normal hepatic function and those with mild/moderate hepatic function (Child Pugh Class A and B).[15] Remimazolam undergoes hepatic metabolism, primarily through tissue esterases, and to a lesser extent through liver enzymes (CYP3A4). The metabolising enzyme, carboxylesterase-1, is predominantly located in the liver, and the clearance of remimazolam is affected by increasing stages of hepatic impairment. Clinical effects may be more pronounced and last longer in patients with severe hepatic impairment due to decreased clearance and altered drug binding in the presence of hypoalbuminaemia. Lower initial doses and careful titration would, therefore, seem prudent in patients with severe hepatic impairment.

Pharmacodynamics

Remimazolam causes no injection site pain. Its effects of sedation and anaesthesia have been evaluated through methods such as electroencephalogram (EEG), β ratio, bispectral index, Modified Observer's Assessment of Alertness/Sedation, and Narcotrend index. Authors of studies have concluded that remimazolam is a fast-acting, well-tolerated, safe drug with dose-dependent pharmacodynamic properties.[1] Remimazolam was shown not to cause any significant ECG changes. It did not affect respiratory rate, heart rate, or blood pressure. A dose of 0.10-mg/kg bolus of remimazolam produces sedation within 60 seconds, which peaks at 1–4 minutes. A patient is likely to be alert at 10 minutes after this.[2]

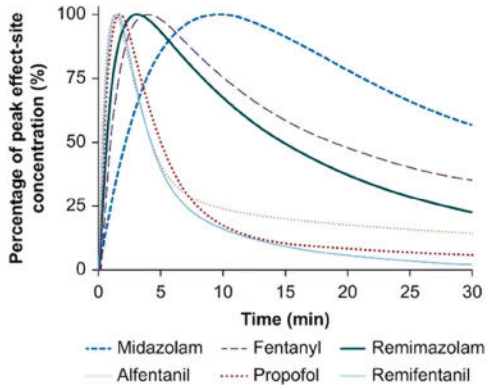

Figure 4. Effect site opioid and hypnotic concentrations over time as a proportion of the peak effect site concentration. Simulated using STANPUMP.[14]

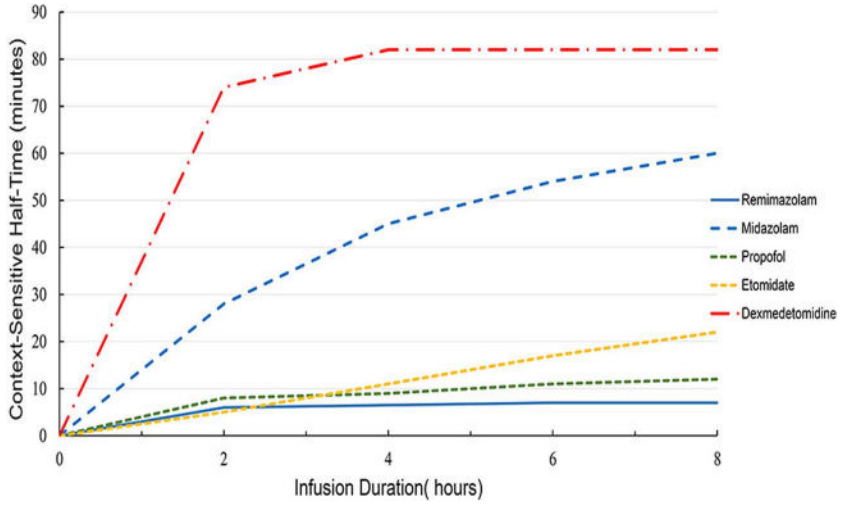

Figure 5. The context-sensitive half-times for the sedatives remimazolam, midazolam, propofol, etomidate, and dexmedetomidine.[1]

Drug	Onset (min)	Recovery (min)	Duration (min)	Volume Distribution (L)	Clearance (L/h)	Terminal Half-Life (h)
Midazolam	3–5	40	12	81.8 ± 27.1	23 ± 4.5	2.89 ± 0.65
Remimazolam	1–3	5.5–20	8	34.8 ± 9.4	70 ± 13.9	0.75 ± 0.15

Table 3. Comparison of the Pharmacokinetic Properties of Midazolam With Remimazolam[1]

SAFETY DATA

Adverse events related to remimazolam during procedural sedation and general anaesthesia are limited and consistent with those observed with other benzodiazepines. Such events include changes in blood pressure and heart rate as well as nausea, vomiting, and headaches.[10,11] As the use of remimazolam becomes more prevalent, case reports of anaphylaxis, delayed emergence, and resedation after reversal with flumazenil have appeared. In a recent review on serious adverse events, 36 case reports and 73 trials were found involving a total of 6740 patients who received remimazolam.[16] Hypotension was present in 911 cases, delayed emergence in 68, anaphylaxis in 10, and resedation in 8. The incidence of hypotension was noted to be lower than other anaesthetics, even in higher-risk patients. Remimazolam is contraindicated in patients with known hypersensitivity reactions to Dextran 40 due to cross-reactivity.[2] Remimazolam itself may not be directly allergenic; however, the presence of Dextran 40 in the formulation can result in an immune response in susceptible individuals.

Although remimazolam has a potential risk of abuse and misuse,[5] the risk is akin to that of midazolam, a drug known to have a low potential for intravenous abuse. The safety and efficacy of remimazolam in paediatric patients are yet to be established, despite ongoing trials for potential use in this population. As a result, remimazolam is not currently licensed in the UK for use in the paediatric population.

Kilpatrick et al. conducted a preclinical trial to investigate the efficacy of flumazenil in reversing the actions of remimazolam.[17] In a later Phase III trial by Doi et al. (2020), flumazenil was found to be effective in reversing the effects of remimazolam in only 10% of individuals who had not awoken 30 minutes after infusion.[11] Patients can become resedated if remimazolam effects outlast the flumazenil antagonism, like other benzodiazepines. The availability of a reliable reversal agent provides a safety feature for overdose cases and in the event of adverse effects.

SUMMARY

Remimazolam is characterised by its fast onset of action, ultrashort duration, and quick recovery time. Further research, however, is necessary to evaluate the efficacy and safety of long-term sedation with remimazolam in the ICU and its use in paediatric populations. Future developments include developing target-controlled infusion models for plasma and effect sites, investigating synergy with specific opiates like remifentanil, and elucidating EEG signatures to facilitate use in general anaesthesia. Remimazolam has already found clinical use as a sedative agent in out-of-theatre settings for dentistry, endoscopic procedures, cardiac catheterization, magnetic resonance imaging, and interventional radiological procedures.

Cost is an issue to this novel agent becoming common in clinical practice in the developed and developing world, especially when established generic agents like propofol and midazolam work very well. Faster recovery times may help to increase procedure throughput, countering increased costs. Remimazolam may find a role in procedural sedation, in which it could be administered by non-anaesthetists. Its fast onset, offset, haemodynamic stability and the ability to administer extra doses without prolonged sedative effects offer advantages over current agents. Adaption to a primary remimazolam from a primary midazolam practice, however, would take time, training, and cultural shifts, which are likely to require significant resources.

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