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ADIS DRUG EVALUATION

Remimazolam: A Review in Procedural Sedation

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Abstract

Remimazolam (Byfavo™) is a benzodiazepine sedative that is indicated for the induction and maintenance of procedural sedation in adults. Remimazolam was efficacious in three phase III trials in patients requiring endoscopies. Significantly higher procedure success rates (composite of the completion of the procedure, top-up doses of study drug within predefined limits and no requirement for rescue therapy) were observed with remimazolam than with placebo, with the majority of placebo recipients requiring rescue midazolam. Furthermore, remimazolam significantly reduced times to onset of sedation and recovery in comparison with placebo (plus rescue). Remimazolam is generally well tolerated, with hypotension and hypertension the most common adverse drug reactions. Higher doses of concomitant fentanyl with remimazolam may increase the incidence of adverse drug reactions and deep sedation events. However, no correlation was observed between depth of sedation and vital signs. In summary, remimazolam is a useful option for the induction and maintenance of procedural sedation. Although pharmacoeconomic analyses for remimazolam are not yet available, the rapid induction of sedation and short recovery times with remimazolam may be beneficial in improving patient throughput in clinics.

Plain Language Summary

Procedural sedation may be administered to patients to improve their comfort during diagnostic or therapeutic procedures. Remimazolam (Byfavo™) is a rapidly metabolised, intravenously administered benzodiazepine sedative, which induces sedation by binding to specific neurotransmitter receptors in the brain. It is approved for the induction and maintenance of procedural sedation in adults. Remimazolam had superior efficacy to placebo in three clinical trials in patients requiring an endoscopy. Most (> 80%) remimazolam recipients successfully completed their endoscopy (≥ 97% of patients) within a predefined dosage regimen of remimazolam (≥ 84%), without requiring midazolam as a rescue sedative (≥ 90%). Conversely, the vast majority (≥ 90%) of placebo recipients required rescue sedation. Times until the onset of sedation and until the patient was ready for discharge post procedure were significantly shorter with remimazolam than with placebo plus rescue. Remimazolam is generally well tolerated, with hypotension and hypertension being the most common adverse drug reactions. Overall, remimazolam is a fast-acting option for procedural sedation and is associated with short recovery times, which has the potential to improve patient throughput in clinics.

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Remimazolam: Clinical Considerations

Benzodiazepine sedative which is rapidly metabolised by tissue esterases into an inactive metabolite.
Superior to placebo plus midazolam rescue in pivotal trials of endoscopy patients, with high (> 80%) procedure success rates.
Clinically significant reductions in onset of sedation and recovery times vs placebo plus rescue sedation.
Generally well tolerated, including in patients with ASA-PS scores 3 or 4.

1 Introduction

Procedural sedation is the administration of hypnotic agents or techniques to enable the effective completion of a diagnostic or therapeutic procedure, which may be otherwise painful or uncomfortable for patients [1, 2]. The target depth of sedation is consistent with the American Society of Anesthesiologists' definition of moderate sedation, where sedated patients are capable of purposeful response to verbal or tactile stimulation. Furthermore, cardiovascular function and spontaneous ventilation are typically maintained in patients, and no airway intervention is required [3]. Procedural sedation may be performed in inpatient or outpatient settings [3], and may be administered by trained personnel who are not anaesthetists [1].

The ideal properties of sedatives for procedural sedation include ease of use, rapid onset of action, quick recovery and minimal residual sedation [4]. In particular, short onset of action and recovery times may result in reduced costs and increased utilisation of procedure and recovery rooms [5]. Benzodiazepine sedatives, of which midazolam is considered to be the gold standard [6], have been utilised for procedural sedation [1, 3, 7]. Although many benzodiazepines may be considered for procedural sedation, including diazepam and lorazepam [3], midazolam is preferred due to its shorter onset to sedation and duration of sedation times, reduced risk of thrombophlebitis and high amnestic potential [7]. Despite the advantages of midazolam as a sedative, the active metabolite of midazolam is a potent sedative [6], which may contribute to elongated sedation times [1].

Remimazolam (Byfavo™) is a benzodiazepine sedative that contains a rapidly hydrolysed ester linkage [4], which subsequently results in the production of an inactive metabolite [8]. As such, remimazolam is classified as a 'soft drug', which have been investigated to create fast-acting sedatives with a predictable recovery [9]. Remimazolam is approved in the USA for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 min or less [10]. In the EU, remimazolam is approved for procedural sedation in adults, with no specified duration for the procedure [11]. This review summarises the pharmacological properties of remimazolam, and discusses relevant clinical efficacy and tolerability data for its use in the induction and maintenance of procedural sedation.

2 Pharmacodynamic Properties

Remimazolam produces sedative effects by binding to the benzodiazepine binding site on γ-aminobutyric acid (GABA) receptors in the brain [10]; it binds selectively to $GABA_A$ receptors with undetectable affinity for other receptors or ion channels [12]. As with other benzodiazepines, remimazolam does not show clear selectivity to any specific $GABA_A$ receptor subtype [10]. Animal studies with remimazolam demonstrated inhibition of cell firing in the substantia nigra pars reticulata and loss of righting reflex, indicative of sedative activity [12].

In a thorough QT study in 57 healthy subjects, peak mean placebo-corrected change-from-baseline (ΔΔ) QT intervals from an electrocardiogram were +6.7 and +10.7 ms with intravenous (IV) bolus doses of remimazolam 10 and 20 mg, and +4.5 and +8.1 ms with IV midazolam 2.5 and 7.5 mg [10]. Peak mean ΔΔ heart rates were +12.3 and +15.2 bpm with IV bolus remimazolam 10 and 20 mg [10]. However, the results in the thorough QT study were confounded by rapid changes in heart rate, and these results may be due to QT/RR hysteresis [13]. A subsequent study with IV infusion of remimazolam 1–5 mg/min for 35 min in 20 healthy male subjects resulted in a peak mean ΔΔ QT interval of +3.4 ms, and the upper limit of the 90% confidence interval was < 10 ms at all timepoints [13]. The EU SPC includes a warning that a small increase in QTc interval may occur with remimazolam due to a transient increase in heart rate [11].

2.1 Abuse Potential

As with other benzodiazepines, remimazolam has the potential for misuse. In the USA, remimazolam is categorised as a Schedule IV controlled substance [10], and its potential for abuse and dependence is recognised in the EU [11]. The desirability of remimazolam for recreational use was broadly comparable to midazolam in a crossover trial in recreational drug users. In total, 39 subjects evaluated single IV doses of remimazolam 5 and 10 mg, midazolam 2.5 mg and 5 mg or placebo. Comparable abuse-relevant positive effect scores on visual analogue scales were reported between remimazolam and midazolam. Both benzodiazepines were rated higher than placebo, and no clear preference for the higher dose as compared with the lower dose of remimazolam or midazolam was observed [14].

Remimazolam has a low potential for misuse as an oral sedative for drug-facilitated sexual assaults, owing to its low oral bioavailability and oral activity with or without alcohol [15]. The oral bioavailability of remimazolam was low in healthy subjects (1.2–2.2% absolute bioavailability), and the oral minimum biologically active dose was beyond the highest tested dose of remimazolam 480 mg as no subjects reached a score < 3 on the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S; 0–5 scale where 5 indicates fully awake). This quantity is equivalent to 24 vials of remimazolam 20 mg. Remimazolam is not a predictable sedative for drug-facilitated sexual assaults when taken with alcohol. Remimazolam 360 mg taken orally with 125 mL of 40% v/v alcohol induced a significant state of sedation (MOAA/S score 1) in 1 in 10 subjects. Additionally, the

bitter taste of remimazolam is difficult to mask, which decreases its potential for covert use [15].

3 Pharmacokinetic Properties

Remimazolam is rapidly distributed following IV administration (mean distribution half-life 0.5–2 min), with an approximately dose-proportional relationship between cumulative dose and the area under the plasma-time curve from time 0 to infinity [10]. The volume of distribution of remimazolam during the terminal phase is 0.76–0.98 L/kg, and the extent of plasma protein binding is > 91%, predominantly to serum albumin. The terminal half-life of remimazolam in plasma is 37–53 min, and its clearance (54–75 L/h) is not linked to body weight. Remimazolam is mainly metabolised by tissue carboxylesterases (predominantly type 1A) to CNS7054, which is subsequently metabolised by hydroxylation and glucuronidation. Less than 1% of the original dose is excreted in the urine as unchanged remimazolam in colonoscopy patients, and 50–60% of the dose is excreted in the urine as CNS7054 [10]. CNS7054 is considered to be an inactive metabolite [8, 10]; the affinity of CNS7054 was 410-fold lower than remimazolam in binding to human brain homogenates [12].

The pharmacokinetics of remimazolam are altered in patients with hepatic impairment, despite the limited metabolism by cytochrome P450 (CYP) enzymes [10]. The volume of distribution increased during the terminal phase (33% increase with moderate hepatic impairment and 41% increase with severe hepatic impairment) and at steady state (50% and 115% increase). Half-life was increased to 60 min with moderate hepatic impairment and 105 min with severe hepatic impairment compared with 42 min with no impairment. The loss of consciousness (1.6 min in healthy subjects vs 3.2 and 2.0 min with moderate and severe impairment) and recovery times (8.0 min vs 12.1 and 16.7 min) were also extended with hepatic impairment. Warnings for the use of remimazolam in patients with severe hepatic impairment are summarised in Sect. 6. Pharmacokinetics of remimazolam were not affected by chronic kidney disease, age, sex, race or body weight [10].

Remimazolam has a low potential for pharmacokinetic drug interactions [10]. Neither remimazolam nor CNS7054 cause relevant inhibition of the CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 enzymes, or induction of the CYP 1A2, 2B6 and 3A4 enzymes. Similarly, neither remimazolam nor CNS7054 are inhibitors of human drug transporters OAT3, OCT2, OATP1B1, OATP1B3, OAT1 and BCRP, and remimazolam is not a substrate for OATP1B1, OATP1B3 and BCRP. The hydrolysis of remimazolam by human liver S9 fractions is not affected by remifentanil, which suggests low competition for liver carboxylesterases [10].

4 Therapeutic Efficacy

The efficacy of remimazolam in the induction and maintenance of procedural sedation was evaluated in three, randomised, double-blind, multicentre phase III trials [16–18]. In addition to the pivotal phase III trials, the efficacy of remimazolam is supported by two phase II dose-ranging trials; one trial with 162 patients requiring a colonoscopy [19], and one trial with 100 patients requiring upper gastrointestinal endoscopy [20]. The phase II trials are not discussed further.

In all phase III trials, patients were randomised to one of three treatment groups, blinded remimazolam, blinded placebo or open-label midazolam (Fig. 1); with fentanyl administered to all patients for analgesia. As ≥ 90% of placebo recipients required rescue sedation with midazolam (Table 1), this group will hereafter be referred to as placebo plus rescue, though rescue sedation was available to patients in any group. Two trials were conducted in patients requiring colonoscopies; one trial enrolled low-risk patients with American Society of Anesthesiologists Physical Status (ASA-PS) scores 1–3 (1–6 scale where lower scores indicates lower risk), hereafter referred to as colonoscopy trial 1 [17], the other trial enrolled higher-risk patients with ASA-PS scores 3 or 4, hereafter referred to as colonoscopy trial 2 [18]. A third trial, hereafter referred to as the bronchoscopy trial, enrolled patients requiring bronchoscopies with ASA-PS scores 1–3 [16] (Fig. 1). Baseline patient demographics were generally well balanced between groups in each trial [16–18].

Dosing regimens were generally similar across the phase III trials. Patients in the remimazolam groups received an IV dose of remimazolam 5 mg (2.5–5.0 mg at the investigator's discretion in colonoscopy trial 2), with top-up doses of remimazolam 2.5 mg (1.25–2.5 mg in colonoscopy trial 2) to a maximum of five doses permitted in any 15-min window [16–18]. Patients randomised to the placebo plus rescue group received equivalent volumes of saline solution, including top-up doses; Patients randomised to open-label midazolam received IV doses of midazolam 1 mg or 1.75 mg (in accordance with the US label) with top-up doses of midazolam 0.5–1 mg to a maximum of three doses in any 12-min window. Rescue therapy with midazolam dosed at the investigators' discretion was available for all patients. The dosage of fentanyl is summarised in Table 1, with top-up doses permitted to a maximum cumulative dose of 200 µg. Procedures were started once patients achieved an MOAA/S score ≤ 3 [16–18].

The primary endpoint in the colonoscopy 1 and bronchoscopy trials was procedure success, which was a composite endpoint defined as the successful completion of the procedure, not exceeding the number of permitted top-up doses, and completion of the procedure without rescue therapy [16,

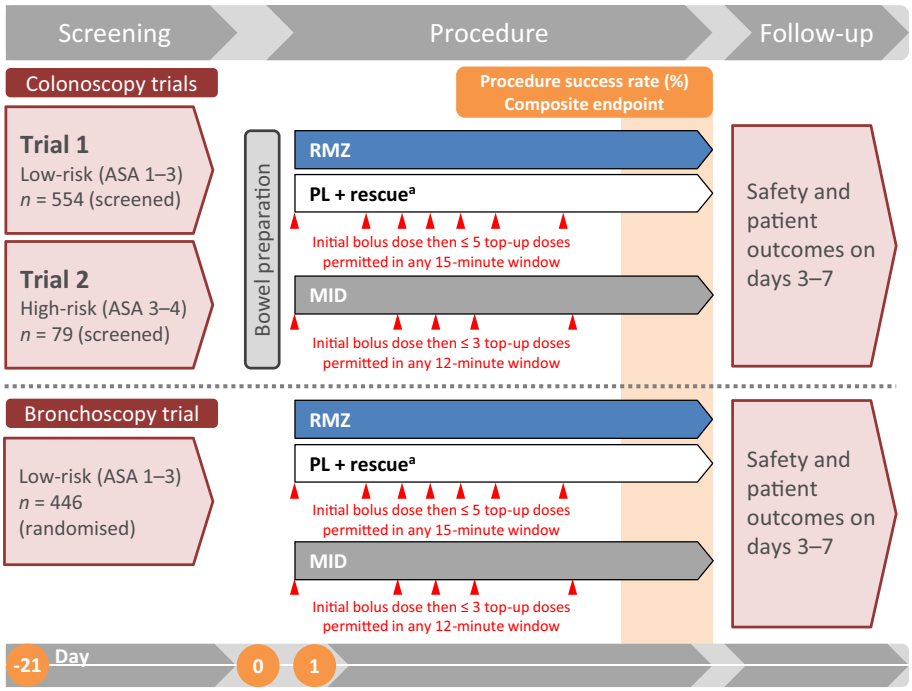

Fig. 1 Trial design of the pivotal phase III trials of remimazolam, with key efficacy results reported in the animated figure (available online). Procedure success was defined as completion of the procedure, no use of rescue sedation with midazolam and not exceeding permitted top-up dosages. RMZ initial bolus dose was 2.5–5.0 mg and top up doses were 1.25–2.5 mg. MID initial bolus dose was 1 mg or 1.75 mg and top up doses were 0.5–1 mg. All patients received fentanyl for analgesia. *ASA* American Society of Anesthesiologists Physical Status scores, *MID* midazolam, *PL* placebo, *RMZ* remimazolam. *$p < 0.0001$ vs PL (in the online figure). [a]Rescue sedation with midazolam was required in ≥ 90 % of placebo recipients; rescue sedation was available to all groups

17]. The primary analysis was the comparison of procedure success rates between the remimazolam and placebo plus rescue groups; testing of other endpoints and comparisons with midazolam were exploratory analyses [16, 17]. The primary objective of colonoscopy trial 2 was to assess the safety of remimazolam in higher risk patients; evaluation of remimazolam efficacy was a secondary objective. In this trial, procedure success rates and other efficacy endpoints were exploratory analyses [18].

All three phase III trials supported the efficacy of remimazolam in procedural sedation [16–18]. High (> 80%) procedure success rates were observed in remimazolam groups in all trials, with the rates being significantly higher than the rates observed in the corresponding placebo plus rescue groups (Table 1). No consistent reason for treatment failure was observed in the remimazolam groups across trials, whereas rescue therapy was required in ≥ 90% of patients in the placebo plus rescue groups across all trials (Table 1) [16–18].

Rapid onset of action and recovery from sedation were observed with remimazolam in exploratory analyses (Table 2). Across the phase III trials, the mean time required to begin the procedure was 5.1–8.0 min [16–18], which was significantly shorter in remimazolam-treated patients than in placebo (plus rescue)-treated patients in colonoscopy trial 2 and the bronchoscopy trial [16, 18]. MOAA/S scores plotted against time showed a steep decline for remimazolam recipients, with peak sedation reached in a median of 3–5 min after the start of medication [16–18]. Recovery from sedation was assessed as the time required for patients to be fully alert (three consecutive MOAA/S scores of 5), the time until patients were ready for discharge and the time to return to normal (Table 2). Most recovery times were significantly shorter with remimazolam than with placebo plus rescue in colonoscopy trial 1 and the bronchoscopy trial; limited data are available from colonoscopy trial 2 [16–18].

Patient-reported outcomes were generally consistent between groups in colonoscopy trials 1 and 2. At a follow-up assessment between day 3 and day 7, recall of the procedure was assessed on a 0–10 scale using the Brice questionnaire, where higher scores indicate higher recall. Mean recall scores in colonoscopy trial 1 were 1.9, 1.7 and 1.6 in the remimazolam, placebo plus rescue and midazolam groups, respectively [17], and 2.2, 1.8 and 1.1, respectively, in colonoscopy trial 2 [18]. Patient satisfaction in colonoscopy trial 1 was assessed using a visual analogue scale (0–10 scale, higher scores indicate greater satisfaction), and satisfaction scores were high (9.4–9.6) in all groups [17].

5 Tolerability

Remimazolam was generally well tolerated in pivotal phase III trials. In these trials (Sect. 4), the tolerability of remimazolam (cumulative dose 5–30 mg [10]) was compared with placebo (with midazolam rescue in ≥ 90% of patients) or midazolam in patients requiring a colonoscopy [17, 18] or a bronchoscopy [16]. Overall, no significant differences in heart rate, oxygen saturation levels or respiration rate were reported between groups in each of the pivotal trials [16–18],

Table 1 Efficacy of remimazolam in phase III trials of procedural sedation

Endpoints, % of patients	Colonoscopy Trial 1 [17]			Colonoscopy Trial 2 [18]			Bronchoscopy [16]		
	RMZ ($n = 298$)	PL + rescue ($n = 60$)	MID ($n = 103$)	RMZ ($n = 31$)	PL + rescue ($n = 16$)	MID ($n = 30$)	RMZ ($n = 310$)	PL + rescue ($n = 63$)	MID ($n = 73$)
Procedure success[a]	91.3*	1.7	25.2	87.1*	0.0	13.3	80.6*	4.8	32.9
Completion of procedure	97.7	98.3	98.1	100.0	100.0	100.0	97.1	95.2	93.2
Rescue therapy[b] not required	96.6	5.0	35.9	90.3	0.0	20.0	84.2	9.5	46.6
Top-up doses within limits[c]	94.0	26.7	45.6	90.3	12.5	13.3	95.5	84.1	86.3

Results in ITT populations in colonoscopy trial 1 and the bronchoscopy trial and in the modified ITT population in colonoscopy trial 2. Dosages are reported in the text. All patients also received fentanyl for analgesia at an initial dose of 50–75 µg [subsequently reduced to 50 µg maximum following a safety review (see Sect. 5)] with top-up doses of 25 µg every 5–10 min permitted to a maximum cumulative dose of 200 µg

ITT intent-to-treat, *MID* midazolam, *PL* placebo, *RMZ* remimazolam

*$p < 0.0001$ vs PL

[a]Primary endpoint in colonoscopy trial 1 and the bronchoscopy trial

[b]Rescue therapy was MID dosed at investigators' discretion

[c]Predefined limits of up to five total doses in an 15-min interval (RMZ and PL) or up to three total doses in any 12-min interval (MID)

Table 2 Mean times to outcomes across three phase III trials

Outcomes	Colonoscopy Trial 1 [17]			Colonoscopy Trial 2 [18]			Bronchoscopy [16]		
	RMZ ($n = 298$)	PL + rescue ($n = 60$)	MID ($n = 103$)	RMZ ($n = 31$)	PL + rescue ($n = 16$)	MID ($n = 30$)	RMZ ($n = 310$)	PL + rescue ($n = 63$)	MID ($n = 73$)
Start of procedure (min)	5.1[a]	20.3	16.9	8.0**[†]	20.0	18.6	6.4**	17.2	16.3
Fully alert[b] after end of procedure (min)	7.35**	21.95	15.84	3.0[a]	5.3	7.0	6.0**	13.6	12
Fully alert[b] after last dose (min)	14.36**	31.93	25.19	11.0[a]	18.0	18.8	11.6**	20	18
Ready for discharge after end of procedure (min)	42.65**	53.18	47.92	NR	NR	NR	60*	81	66
Ready for discharge after last dose (min)	49.78**	63.78	57.44	NR	NR	NR	64*	93	70
Back to normal[c] after last dose (h)	5.51*	9.54	9.22	NR	NR	NR	6.7	15.6	7.4

Statistical testing of these outcomes were exploratory. RMZ and PL administration was double-blinded, MID was open-label. MID dosed at investigators' discretion was available as rescue therapy in all groups; rescue therapy was required in ≥ 90% of placebo recipients

MID midazolam, *NR* not reported *PL* placebo, *RMZ* remimazolam

*$p \leq 0.001$, **$p \leq 0.0001$ vs PL, [†]$p < 0.00001$ vs MID

[a]Statistical testing for this outcome was not reported

[b]Fully alert defined as the first of three consecutive MOAA/S scores of 5

[c]Patient-reported

and no deaths were reported across all trials [10]. The most commonly reported adverse reactions (incidence ≥ 10 %) in remimazolam recipients across the phase III trials were hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia and diastolic hypotension (Fig. 2) [21]. A post-hoc analysis in colonoscopy trial 1 showed the incidence of treatment-emergent adverse events (TEAEs) was lower with remimazolam than with midazolam ($p < 0.0001$), which was mainly due to differences in the incidence of hypotension (38.9% with remimazolam vs 61.8% with midazolam) [17]. In a pooled analysis of all phase III trials, the incidences of serious TEAEs were 2.7%, 0.5% and 3.0% of patients in the remimazolam, placebo plus rescue and midazolam groups, respectively, and the incidences of individual events were all < 1% [21]. Two patients discontinued the study drug across the phase III trials as a result of adverse drug reactions (ADRs); one remimazolam-treated patient in the bronchoscopy trial due to bradycardia, hypertension, hypotension, hypoxia and respiratory rate increase, and one midazolam-treated patient in colonoscopy trial 2 due to respiratory acidosis [10]. Reversal of sedation with flumazenil was not required in any remimazolam recipients

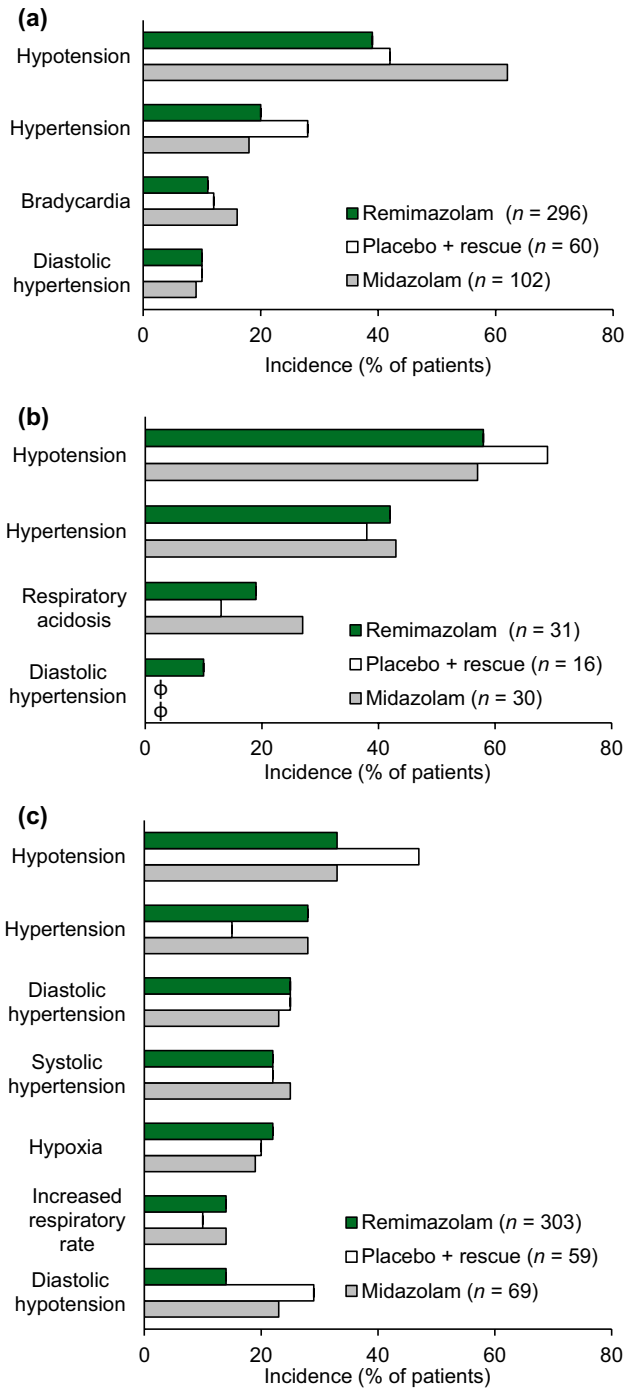

Fig. 2 Adverse reactions with an incidence ≥ 10% in remimazolam treatment groups in **a** colonoscopy trial 1, **b** colonoscopy trial 2 or **c** the bronchoscopy trial [10]. ϕ indicates an incidence of 0%

across the phase III trials, one patient in the placebo plus rescue group in the bronchoscopy trial received flumazenil to shorten procedure time [21]. Remimazolam administration was not associated with clinically meaningful injection-site pain (mean scores of ≈ 5 on a 1–100 visual analogue scale) in colonoscopy trials 1 and 2 [17, 18].

The incidence of TEAEs in the remimazolam group was comparable to the incidences in the placebo plus rescue and midazolam groups in higher risk patients (ASA-PS scores 3 or 4) during colonoscopy study 2 [18]. The primary endpoint of this trial was the comparison of safety in the remimazolam group versus the placebo plus rescue and open-label midazolam groups (Sect. 4). TEAEs were reported in 28, 13 and 26 patients in the remimazolam, placebo plus rescue and midazolam groups, respectively, (90.3, 81.3 and 86.7% of patients, respectively); the differences between the remimazolam group versus the placebo plus rescue and midazolam groups were not statistically significant. No significant differences ($p > 0.05$) were detected in the incidence of cardiovascular and respiratory TEAEs between the remimazolam group versus the placebo plus rescue and midazolam groups. Drug-related TEAEs were reported in 3, 2 and 2 patients, respectively (10.8%, 12.5% and 6.7%, respectively), with no significant differences reported between the remimazolam group versus the placebo plus rescue and midazolam groups [18].

Higher cumulative doses of fentanyl administered with remimazolam may increase the incidence of ADRs [10]. In colonoscopy trial 1 and the bronchoscopy trial, the incidence of ADRs were analysed in patients stratified by cumulative fentanyl dose. The analysis suggested a higher incidence of some ADRs with higher cumulative fentanyl doses, including hypotension, hypertension, bradycardia, hypoxia and increased respiratory rate [10]. Furthermore, a numerically higher rate of remimazolam-administered patients receiving an initial fentanyl dose of 75 µg reached a MOAA/S score of 0 in colonoscopy trial 1 (patient numbers were not reported) [17], or 0 or 1 in the bronchoscopy trial (12% with 75 µg fentanyl, 3.5% with 50 µg fentanyl and 4.2% with 25 µg fentanyl) [16]. Thus, the initial dose of fentanyl was reduced to 50 µg following a safety review [16, 17]. Despite the higher incidence of deep sedation events with higher fentanyl doses, no correlation between MOAA/S score and vital signs were detected in exploratory analyses in colonoscopy trial 1 and the bronchoscopy trial [17, 22].

6 Dosage and Administration

For the induction and maintenance of procedural sedation in adults in the USA and the EU, the dosage of remimazolam should be individualised and titrated to the desired clinical response [10, 11]. In the USA, the recommended dose of remimazolam for the induction of procedural sedation is 5 mg via an IV push injection over 1 min. If required, supplemental IV doses of remimazolam 2.5 mg over 15 s may be given with ≥ 2 min between doses. In patients with ASA-PS scores 3 or 4, the induction dose of remimazolam is 2.5–5 mg and supplemental doses of 1.25–2.5 mg at the discretion of the physician and based on the general condition of the

patient [10]. In the EU, the recommended remimazolam dose regimen in adults aged < 65 years receiving concomitant opioids (e.g. fentanyl 50 μg) is consistent with the recommended US dosage (i.e. remimazolam 5 mg for the induction of procedural sedation and remimazolam 2.5 mg maintenance doses) [11]. In the EU, in patients who are not receiving a concomitant opioid, an initial remimazolam dose of 7 mg is recommended for the induction of procedural sedation. In patients with ASA-PS scores 3 or 4, aged ≥ 65 years and/or who have a body weight < 50 kg, regardless of concomitant opioid administration a 2.5–5 mg induction dose is recommended with supplemental doses of 1.25–2.5 mg [11].

Like other agents used for procedural sedation (e.g. midazolam [23]), the prescribing information for remimazolam includes warnings related to sedation, which is associated with hypoxia, bradycardia and hypotension (Sect. 5) [10, 11]. Vital signs should be continuously monitored during sedation and through the recovery period in patients administered remimazolam. The sedative effects of remimazolam may be increased in patients with severe hepatic impairment (Sect. 3) [10, 11]. In the EU, particular care is required in patients with myasthenia gravis and remimazolam is contraindicated with unstable myasthenia gravis [11].

Consult local prescribing information for other warnings, precautions, contraindications, personnel and equipment requirements for monitoring and resuscitation of patients and detailed instructions on the preparation and administration of remimazolam.

7 Place of Remimazolam in Procedural Sedation

Remimazolam is an effective sedative for the induction and maintenance of procedural sedation. The efficacy of remimazolam was demonstrated across three pivotal trials in patients undergoing endoscopies (Sect. 4). High (> 80%) procedure success rates were achieved with remimazolam, which were significantly higher than with placebo (with the majority of placebo recipients requiring midazolam rescue). The observed efficacy can be attributed to remimazolam, rather than the sedative effects of concomitant fentanyl administration, based on the findings of these placebo (plus rescue)-controlled trials [16]. The coadministration of fentanyl for analgesia is consistent with standard practice [18].

Guidelines for procedural sedation in the USA [3, 7] and Europe [1] recommended the choice of agent be appropriate to the procedure and patient [3] or selected for their ease of dosing to achieve and maintain sedation while minimising adverse events [1]. Benzodiazepine agents were identified as a treatment option [1, 3, 7], of which midazolam was preferred due to its faster onset of action than other benzodiazepines [1, 7]. Other recommended options include anaesthetic agents, such as propofol [1, 3, 7] or ketamine [1, 3]. These guidelines were published prior to the availability of remimazolam, and specific guidance for remimazolam is awaited with interest.

Clinically significant improvements in the times until the start of procedure and until ready for discharge were observed with remimazolam relative to placebo plus rescue (Sect. 4) [21]. Adequate sedation was induced in 5.1–8.0 min in remimazolam groups, with ready to discharge times of 49.8–64 min after last dose (where reported); compared with 17.2–20.3 min and 63.8–93 min across the placebo plus rescue groups, and 16.3–18.6 min and 57.4–70 min in the midazolam groups. One possible explanation for the longer recovery times with midazolam may be due to the formation of an active metabolite [1], whereas the main metabolite of remimazolam is inactive (Sect. 3). Another potential explanation is the elimination half-life of midazolam is 1.8–6.4 h [23], while the terminal half-life of remimazolam is 37–53 min [10]. Shorter sedation and recovery periods may be appealing to surgical centres for reducing costs and increasing patient throughput [21]. However, as placebo (plus rescue) recipients were required to demonstrate treatment failure prior to receiving midazolam rescue, the rapidity of the onset of sedation with remimazolam may be overstated [17]. Other pharmacokinetic advantages with remimazolam includes the low potential for pharmacokinetic drug interactions (Sect. 3), whereas sedation with midazolam, which is metabolised by CYP3A4, may be prolonged with concomitant CYP3A4 inhibitors [23]. Furthermore, the clearance of remimazolam is consistently high across patients, as it is predominantly metabolised by ubiquitous tissue esterases [9]. In contrast, the clearance of midazolam varies by ≈ 30% between patients [9]. The potential for recreational abuse with remimazolam was comparable to midazolam, and remimazolam has limited potential in facilitating sexual assaults due to its low oral bioavailability (Sect. 2.1).

Remimazolam was generally well tolerated in clinical trials (including in higher-risk patients with ASA-PS scores of 3 or 4), with the most common ADRs being hypotension and hypertension (Sect. 4). Across the three pivotal trials, treatment discontinuation due to ADRs was required in one remimazolam recipient, and one midazolam recipient [10]; and the reversal of sedation was required in one patient receiving placebo plus rescue [21]. No significant differences in vital signs were observed between the remimazolam, placebo plus rescue and midazolam groups. The effect of higher concomitant doses of fentanyl with remimazolam is unclear; higher doses may increase the incidence of some ADRs [10], as well as increasing the incidence of deep sedation [16, 17]. However, no correlation between vital signs and MOAA/S scores were observed [17, 22]. Monitoring of vital signs during sedation and recovery is required. Concomitant administration of remimazolam and opioids may deepen sedation [10].

Currently, no direct comparisons of efficacy are available between remimazolam and propofol, which is the most common sedative in Europe for its short onset of action and

context-sensitive half-time and predictable duration [1]. Although propofol in procedural sedation is generally well tolerated, serious morbidity has been reported [24]; including the risk for hypotension as propofol causes vasodilation that reduces systemic resistance, particularly in older patients or patients with cardiovascular disease [25]. The administration of propofol by non-anaesthetists is controversial due to safety concerns [9, 24]. In contrast, remimazolam, which is a benzodiazepine sedative, appears less likely to induce significant respiratory depression [25]. Other potential advantages with remimazolam may include low pain on injection, as mean pain scores were < 5 on a scale of 100 (Sect. 5); in contrast, injection site pain is a known issue with propofol [1]. Additionally, flumazenil is available as a reversal agent against remimazolam overdose [10], whereas no specific reversal agents are available for propofol [7]. Although remimazolam alone may not supplant the use of propofol in procedural sedation [26], remimazolam is regarded a potential option with short recovery times [9, 26]. Direct comparisons in onset of action and recovery times between remimazolam and propofol may be of interest, as well as pharmacoeconomic analyses between remimazolam and other sedatives. Other studies which may be of interest include the evaluation of remimazolam in non-endoscopic procedures, such as emergency medicine, dentistry or radiology [2].

In conclusion, remimazolam is a useful option for the induction and maintenance of procedural sedation. High procedure success rates were observed in patients undergoing endoscopic procedures, and remimazolam was generally well tolerated. Clinically significant improvements in onset of action and recovery times were achieved with remimazolam compared with placebo plus rescue, which may be valuable for increasing patient throughput in clinics. However, pharmacoeconomic analyses are required to determine the cost optimisation that may be achieved with remimazolam.

Data Selection Remimazolam: 132 records identified	
Duplicates removed	46
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	57
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	3
Cited efficacy/tolerability articles	8
Cited articles not efficacy/tolerability	18
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were remimazolam besylate, Byfavo, procedural sedation Records were limited to those in English language. Searches last updated 21 May 2021.	

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