Remimazolam (BYFAVO)
National Drug Monograph Addendum
August 2024

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Indication(s) Under Review in This Document

- Induction of general anesthesia (off-label)

Remimazolam is FDA approved for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

Dosage Form(s) Under Review

- Injection, for intravenous use, 20 mg remimazolam (equivalent to 27.2 mg remimazolam besylate) in 12 mL vial, lyophilized powder for reconstitution (2.5mg/mL).
- Induction of Procedural Sedation For adult patients: (FDA Approved)
  - Administer 5 mg intravenously over a 1-minute.
  - For ASA* III and IV patients: Administer 2.5 mg to 5 mg intravenously over 1 minute based on the general condition of the patient.
- Maintenance of Procedural Sedation (as needed) For adult patients: (FDA Approved)
  - Administer 2.5 mg intravenously over 15 seconds. At least 2 minutes must elapse prior to administration of any supplemental dose.
  - For ASA III and IV patients: Administer 1.25 mg to 2.5 mg intravenously over 15 seconds. At least 2 minutes must elapse prior to administration of any supplemental dose.
- Induction and maintenance of general anesthesia: (Off-Label)
  - Doses used for induction and maintenance of anesthesia vary across studies as well as the route of administration for induction (intravenous bolus or infusion). *However, optimal dosing has not been established*.
    - Approved dosing in Japan and South Korea includes an initial infusion of 6-12 mg/kg/h for induction followed by 1 mg/kg/h for maintenance of anesthesia (maximum rate of 2 mg/kg/h).[2]

*ASA = American Society of Anesthesiologists Physical Status Classification System

Clinical Evidence Summary

Efficacy Considerations

- Twenty-one studies comparing induction or induction and maintenance of general anesthesia with remimazolam vs. propofol in patients undergoing a variety of surgical procedures were reviewed for this addendum. Most of the studies included less than 100 patients; were conducted at a single center outside of the United States; and were single-blinded due to challenges (e.g., drug color, need to administer appropriately, etc.) in blinding the anesthesiologist to the study drug.[3-23] Patients classified as American Society of Anesthesiologists physical status I-III (ASA I-III) were included in most trials.
- Several of the studies compared remimazolam to propofol in non-inferiority designed clinical trials. Two studies compared remimazolam plus flumazenil to propofol in time to recovery from anesthesia.
- Primary outcome measures include comparison of the efficacy of anesthesia induction, maintenance of the appropriate depth of anesthesia, adverse hemodynamic effects, use of vasoactive drugs, recovery from anesthesia and adverse events between remimazolam and propofol.
- Dosing of remimazolam for induction and maintenance of anesthesia varied across studies and included use of bolus or infusion for induction and different infusion rates for maintaining an appropriate depth of anesthesia (bispectral or BIS index between 40-60) until the surgery was over.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Design	Results	Adverse Events/Comments
Doi, etal.[3] 2020 Phase IIb/III Elective Surgery ASA I-II Trial conducted Nov 2012-Mar 2013	MC, R, SB (patient blinded) (Non-inferiority) N=391 (≥ 20 years) Induction: Rem 6 or 12 mg/kg/h vs. Pro 2-2.5 mg/kg slow bolus until LOC Maintenance: Rem 1mg/kg/h (adjusted prn) VS. Pro 4-10 mg/kg/h until surgery ends. Combined endpoint: No intraoperative awakening/recall, no need for rescue sedatives and no body movements	N-375 (16 did not receive study med of the original 391) Primary Endpoint Efficacy: 100% in all groups, Rem non-inferior to Pro as sedative for GA. Mean time to LOC: Rem 6: 102 s Rem 12: 88.7 s Pro: 78.7, p<0.0001 (Rem 6) and p=0.0149 (Rem 12) Mean time to 1) eye opening-Rem 6-12: 14.9-14.5 vs. Pro 10.3 min, 2) extubation-Rem 6-12: 19.2 vs. Pro 13.1 min, 3) ability to state DOB-Rem 6-12:	80% of patients in each group reported adverse events including decreased BP, injection site pain (18.7% Pro only) N/V and pyrexia. Statistically significant, more patients in Pro vs. Rem required vasopressors (64% Pro vs. Rem 40-42.7%) Mean surgical duration >2 hours; longer in the 6 mg/kg/h Rem group vs. Pro (155 min vs. 123.4 min, p=0.006, respectively); NS Rem 12 mg/kg/h vs. Pro The mean cumulative dose to achieve LOC was lower in

		24.8-24.1 vs. Pro 15.6 min, and 4) discharge from the OR-Rem 6-12: 28.7-27.9 vs. Pro 19.1 min were all statistically shorter in the Pro vs. both Rem groups. Flumazenil use/mean time to wake after use: Rem 6: 9.3%/ 1.8 min Rem 12: 8.7%/ 0.9 min	the Rem 6 vs. 12 group (0.17 mg/kg vs. 0.29 mg/kg, respectively) The optimal infusion rate for maintenance ranged 0.8-1 mg/kg/h (Rem); mean dose received: 3.47 mg/kg in both Rem groups.
Doi, et al.[4] 2020 Rem dose ranging comparison in GA in elective surgery. ASA III Trial conducted Nov 2012-Mar 2013	MC, DB, R; N=67 (>20 years); high-risk patients Induction: Rem 6 or 12 mg/kg/h until LOC, Maintenance: up to 2 mg/kg/h (adjusted prn) until surgery ends. "Optimal infusion rate" during the anesthesia maintenance period was "when the optimal anesthetic state is maintained" left to clinical judgement. Combined endpoint: No intraoperative awakening/recall, no need for rescue sedatives and no body movements	N=62 full analysis set (4 withdrew prior to study; 7 treatment violation) N=55 per protocol set Primary Endpoint Efficacy: 100% in both Rem groups Mean time to LOC: Rem 6: 97 s Rem 12: 82 s, p=0.0139 Mean dose to LOC: Rem 6: 0.16 mg/kg Rem 12: 0.27 mg/kg Mean optimal infusion rate: Rem 6: 0.56 mg/kg/h Rem 12: 0.57 mg/kg/h Mean time to: 1) awareness, 2) extubation, 3) ability to state DOB, 4) discharge from the OR did not differ between groups. Anesthetic effect of Rem is independent of the induction rate. Flumazenil was given to 2 patients (low dose group) who did not wake 30 min after the last dose of Rem.	Decrease in BP was reported less often in the 6 mg (54.8%) vs. 12 mg (67.7%). Over the trial period, decreased BP occurred in 25.8% Rem 6 mg vs. 41.9% Rem 12 mg. ADEs were reported in 45.2% Rem 6 mg vs. 54.8% Rem 12 mg Mean optimal infusion rate in this trial (ASA III) less than in Doe, et al.[2] ASA I-II physical status of 0.8-1 mg/kg/h
Dai, et al.[5] 2021 Elective noncardiac surgery ASA I-II Single bolus dose	R, N=190 (18-65 years) Induction: Rem 0.2 mg/kg (R1), Rem 0.3 mg/kg (R2), Rem 0.4 mg/kg (R3) or Pro 2 mg/kg. If LOC was not achieved in 1 min with Rem (MOAA/S score >1), Rem	N=190 (1 excluded-protocol violation) Successful induction: R1: 89% R2: 94% R3: 100% Pro: 100% (p<0.05 vs. R1)	Injection site pain: Pro 27% vs. 0% R1,2,3 Hypotension: R1: 13% R2: 24% R3: 34% Pro: 44%, p<0.05 R1, R2

	0.05 mg/kg was given each time score >1 until LOC. If LOC was not achieved in 1 min with Pro, one additional Pro 0.5 mg/kg was given until LOC. Primary Outcome: "Efficacy and safety of induction anesthesia between Rem and Pro. 1) completed induction without recall, 2) no need for rescue sedation, 3) supplemental doses of Rem or Pro <1 during induction Safety Endpoint: No serious ADEs during induction	Rescue sedation: R1: 11% R2: 6% R3: 0 Pro: 0 (p< 0.05 vs. R1) BIS "significant drop" vs. R1, R2, R3, p<0.01 vs Pro	**NS Pro vs. R3** **R1 vs. R3, p<0.05** ***No mention of use of vasoactive agents.*** Authors indicate trial of single injection for induction vs. infusion due to anesthesiologist preference and faster onset of LOC with bolus vs. infusion. Study limitations: 1) Characteristics and color of Rem vs. Pro are different so blinding may be impacted. 2) Rem not used for maintenance so more studies are needed 3) ASA III not included.
Liu, et al.[6] 2021 Double Cardiac valve replacement surgery (MVR/AVR) NYHA II-III; ASA III Single center	R, DB; single-center, N=60 (35-65 years) Induction: Rem 0.3 mg/kg (rate 1.8 mg/kg/h) vs. Pro target-controlled infusion: 2.5 mcg/mL BIS index maintained 40-60 Primary outcomes: Change in hemodynamics (HR, MAP) and cardiac events (hypotension, bradycardia) and cumulative dose of norepinephrine needed/patient during induction. Hypotension=MAP <60 and 50 mg norepi was given	N=60 Primary Outcomes: Change in: -HR-NS -MAP: Rem 19.5 mmHg vs. Pro 26.7 mmHg; p=0.0016 -Hypotension: Rem 16.7% vs. 43.3%, p=0.0242 -Bradycardia: NS -Norepi: Rem 8.3 mcg vs. Pro 33.3 mcg, p=0.0123 Other: NS difference in MAP, HR, BIS index during other timepoints	NA
Zhang, et al.[7] 2021 Hysteroscopy ASA I-II Single center	R, N=82 (18-65 years) Induction: Rem 0.2 mg/kg vs. Pro 1.5-2 mg/kg until LOC Maintenance: Rem 1 mg/kg/hr vs. Pro 1.5-2 mg/kg until LOC Hysteroscopy was started after MOAA/S score was ≤ 2. Primary outcome: ADEs	N=82 Injection site pain: 33/41 (80.5%) was > in Pro vs. Rem 1/41 (2.4%); p<0.001 SpO_2 ≤ 95% 4/41 (9.8%) Rem vs. 21/41 (51.2%) Pro, p<0.001 No significant difference in bradycardia or hypotension.	Total Rem dose: 0.4 mg/kg, supplemental dose of Rem 10.8 mg Duration of operation 12-13 min; time to awake was longer in the Rem vs. Pro (199 vs. 59 s, respectively, p<0.05; time in PACU shorter in Rem vs. Pro 5.44 vs. 6.3 min, p<0.05
Mao, et al.[8] 2022	R, Single-blind; N=136 (18-84 years)	N=128 (8 d/c intervention-4 in each group)	Reported ADEs did not differ statistically during

Urological surgery ASA I-III	Induction: Rem 0.2-0.3 mg/kg vs. Pro 2-3 mg/kg and both received sufentanil. Maintenance: Rem 1-2 mg/kg/hr vs. Pro 4-10 mg/kg/hr both received remifentanil Primary Outcomes: Quality of Life-15 [QoL-15] scale (quality of post-op recovery: physical comfort, emotional state, physical independence and psychological support and pain)-measured 1 day prior to and 1 and 3 days post-op Other important endpoints: SpO_2, HR, mean BP and frequency of vasoactive drugs during anesthesia (to maintain the BP and HR to within 20% of preinduction values)	Primary Outcome: QoL-15 POD 1, p=0.004 in favor of Rem POD 3: NS Physical comfort and emotional state were statistically superior in Pro vs. Rem on POD 1 and 3. Mean BP was higher in Rem vs. Pro after induction, p=0.002, but became similar after intubation, likely due to vasoactive drugs in Pro. HR faster in Rem vs. Pro during induction, p<0.001, but became similar during surgery. Vasoactive drugs: Pro 56.3% vs. Rem 28.1%, p<0.001	surgery. Nausea, vomiting, somnolence and emergency delirium were reported numerically more often in Rem vs. Pro and BP fluctuation more often in Pro vs. Rem. Anesthesiologists were not blinded. Authors comment that post-op recovery, use of lower doses in elderly patients and use in other surgeries should be confirmed in clinical trials before widespread use.
Gao, et al.[9] 2023 Carotid endarterectomy ASA II-III single center	R, N=43 (60-75 years) Induction: Rem 0.3 mg/kg vs. Pro 1.5-2 mg/kg Primary Outcome: Regional cerebral oxygen saturation (SrO_2)	N=40 (1 Rem, 2 Pro) Primary Outcome: SrO_2 NS difference between groups Of the hemodynamic indexes measured (HR, Cardiac Index), only MAP was significantly lower in Pro vs. Rem, p<0.05 but remained >80 mmHg in both groups.	No difference in SrO_2 between groups Vascular resistance index remained stable with no differences between groups. Authors recommend further research due to small study population.
Woo Song, et al.[10] 2023 Surgery with GA and receiving ACE or ARB inhibitors. ASA I-III Single center	R, single-blind; N=82 (19-65 years) Induction: Rem 6 mg/kg/h vs. Pro 2 mg/kg until LOC Maintenance: Rem 1 mg/kg/h was infused in both groups. Up to 2 mg/kg/h was permitted for BIS >60 BIS index maintained 40-60 Primary Outcome: Incidence of hypotension following induction. Hypotension=mean BP reduced ≥	N=81 Primary Outcome: Rem 62.5% Pro 82.9%, p=0.04 Rem resulted in lesser BP reduction vs. Pro (<10 mmHg drop in BP vs. Pro) After intubation, changes in mean BP, SBP and DBP (NS) *Use of vasoactive agents not reported.*	ADEs minimal including tachychardia and HTN in 2 patients in Pro, Flu was given to one Rem patient due to delayed emergence. Anesthesia was administered >2 hours in both groups. Authors note that incidence of hypotension post-induction was higher than observed in other trials and

	30% from baseline or MAP <65 mmHg		that patients receiving ACE or ARB inhibitors are at a higher risk.
Yang, et al.[11] 2023 Orthopedic surgery in older patients. ASA I-III single center	R, N=320 Induction: Rem 0.2-0.3 mg/kg vs. Pro 1-1.5 mg/kg, both received alfentanil for amnesia and analgesia Maintenance: Rem and Pro given as infusion (no dose range listed) and adjusted to maintain BIS index between 40-60 and with inhaled desflurane. Primary Outcome: Post-op delirium during 3 days post-op. (Assessed by CAM-tool assessing features of delirium=acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness) Other Outcomes: emergence agitation, extubation time, PACU stay	N=300 (20 dropped from analysis Primary Outcome: NS difference between groups in post-op delirium or in onset or duration of delirium Statistically more use of vasoactive meds in Pro vs. Rem (26 vs. 17 mcg, respectively, p<0.01) Other Outcomes: NS except time to extubate and length of PACU stay longer in Rem vs. Pro, both p<0.001 Although not statistically different, emergence agitation occurred more in the Rem vs. Pro group (10.9% vs. 6.6%, respectively) Total Dose: Rem 67 mg Pro 435 mg	Hypotension after induction: Rem 17.1% Pro 43%, p <0.001 PACU hypoxia, nausea and vomiting were reported more in the Rem vs. Pro, differences were NS. Unplanned transfer to ICU (NS) occurred in 1 Rem and 4 Pro patients. Surgery just over 2 hours in each group. Evaluator blinded. Authors conclude Rem is not associated with post-op delirium vs. Pro; patients receiving Pro had more induction hypotension and received vasoactive drugs; but Rem had longer time to extubation and time in PACU vs. Pro
Sekiguchi, et al.[12] 2023 Surgery under GA ASA I-II single center	R, N=40 (40-80 years) Induction: Rem 12 mg/kg/h vs. Pro (effect site target conc.) 3 mcg/mL, both received remifentanil Maintenance: Rem 1-2 mg/kg/h vs. Pro 2-5 mcg/mL to maintain BIS index 40-60 after LOC Primary Outcome: Max change in MAP after induction. Other outcomes: max change in HR, CO, SV and hypotension (defined as MAP <65 mm/Hg over 2.5 min) Patients monitored from start of induction to 10 min after intubation	N=40 Primary Outcome: Changes in MAP, HR, CO and SV=NS between groups Hypotension: Rem 35% Pro 55%, NS Mean dose until LOC: Rem 0.34 mg/kg Pro 1.21 mg/kg	No differences in ADEs reported. Anesthesiologists unblinded Mean dose until LOC: Rem 0.34 mg/kg Pro 1.21 mg/kg Authors acknowledge use of lower doses of Pro due to effect site target conc dosing vs. bolus which may explain the longer time to LOC with Pro vs. Rem (3.5 min vs. 1.7, respectively, p<0.001)

Shimizu, et al.[13] 2023 Endoscopic sinus surgery (TIVA) Rem + Flu ASA I-II	R, N=66 Induction: Rem 12 mg/kg/h or an "effect site target concentration": Pro 3-4 mcg/ml Maintenance: Rem 1-2 mg/kg/h or Pro 2-5 mcg/min "effect site target conc." Anesthetics were adjusted to BIS values between 40-60. All patients in the Rem group received 0.2-0.5 mg Flu Primary Outcome: Quality of psychomotor recovery, as assessed by Trieger Dot Test (done prior to induction and at 30, 60, 90, 120, 150 and 180 min after d/c from the OR. Number of dots missed (NDM) and max distance of dots missed (MDDM) measured. Other endpoints: 1) time to eye opening, 2) response to verbal commands, 3) extubation, 4) discharge from the OR were reported.	N=64 (1 excluded from analysis in each group due to post operative delirium) Primary Outcome: Psychomotor Recovery: NDM and MDDM favored Pro vs. Rem (time periods starting 30 min after surgery and through 2 hours were statistically significant). Other outcome measures: Time to eye opening, response to verbal commands, extubation and d/c from the OR were statistically shorter in Rem vs. Pro. $p<0.05$	One patient in each group excluded from analysis due to post-op delirium. No significant differences in HR, SBP, DBP, and SpO_2 between groups throughout study. Authors caution that the immediate benefit/recovery of Rem vs. Pro is attributed to use of Flu in the Rem group and that late recovery was superior for Pro vs. Rem suggesting that a moderate to lasting residual Rem effect is possible, even a day after anesthesia and that a longer observation period for psychomotor function is recommended, especially when reversed by Flu. Authors recommend further studies without flu to clarify the safety and efficacy of Rem.
Luo, et al.[14] 2023 Differing doses of Rem vs. Pro in short (30-60 min) Laparoscopic Surgery ASA I-II	R, N=192 Induction: Rem 6 mg/kg/h (low); Rem 9 mg/kg/h (median); Rem 12 mg/kg/h (high) vs. Pro 2 mg/kg Maintenance: Rem 1 (low), 2 (median), 3 mg/kg/h (high) vs. Pro 6 mg/kg/h Primary Outcome: Time to extubation after surgery Other Outcomes: time to LOC, duration of PACU stay, passive eye-opening, BIS values after induction, operation time, etc.	N=192 Primary Outcome: Rem low: 12.7 min Rem median: 13.17 min Rem high: 15.21 min Pro: 12.24 min; NS between Rem low and Pro Significant difference in favor of: Rem low vs Rem high Pro vs. Rem median and High Rem median vs. Rem high Other Outcomes: 1-Time to consciousness: superior in Pro vs. all Rem groups 2-Use of norepi: > in Pro vs. all Rem groups (Pro 53% vs. 23%, 31% and 37.5%- appears dose related)	No differences in ADEs, excerpt hypotension in Pro vs. all Rem groups (Pro 30.6% vs. Rem 8.5%, 22.5%, 16.7%) Intraoperative Dose of Pro and Rem: Rem low: 93.5 mg Rem median: 188 mg Rem high: 255.37 mg Pro: 580.95 mg Authors calculated costs and commented that cost was greater in the Rem group vs. Pro and the cost increased with higher Rem doses. BIS values were higher in Rem vs. Pro at all doses and authors question using BIS

		3-all other outcomes, NS	value to accurately monitor depth of anesthesia with Rem. Other studies have reported similar findings. Authors comment that the induction effect of Rem has not been compared to midazolam.
So, et al.[15] 2023 Laparoscopic cholecystectomy (TIVA) ASA I-III	R, Single-Blind, N=84 (>65 years) Induction: Rem 6 mg/kg/h vs. Pro 1-1.5 mg/kg until LOC Maintenance: Rem 1 mg/kg/h up to max of 2 mg/kg/h vs. Pro 100 mcg/kg/min, adjusted as appropriate until the end of surgery. Appropriate depth of anesthesia defined as BIS index 40-60 Primary Outcome: Time to LOC Other Outcomes: Depth of anesthesia score (ADS), time to extubation and discharge from the OR and hemodynamic parameters.	N=81 (3 excluded in Pro) Primary Outcome: Rem 120 s Pro 60 s, p<0.001 Other Outcomes: 1-Time to extubation: Rem 12 min Pro 10 mg, p=0.007 2-D/C from the OR: Rem 15 min Pro 12 min, p=0.018 3-NS differences in incidence of hemodynamic changes (SBP, DBP, mean BP, HR), time from end of anesthesia to eye opening, or depth of anesthesia	No difference in ADEs reported. **All patients received pre-op Mid 0.05 mg/kg IM** Mean dose of Rem to LOC=0.2 mg/kg Authors noted the cost difference between Rem and Pro exceeded 20-fold. Authors conclude that Rem was inferior to Pro in anesthesia induction and recovery but question the clinical significance of the small differences. Anesthesiologist unblinded.
Choi, et al.[16] 2023 Hypertensive patients having elective surgery with GA. ASA II Single center	R, DB, N=96 (20-64 years) Induction: Rem 6 mg/kg/h vs. Pro 1.5-2 mg/kg infused over 1 min Rem 1 mg/kg/h or Pro 3-6 mg/kg/h was infused for 5 min after intubation. Primary Outcome: Change in hemodynamic parameters during induction at various timepoints (mean BP, SBP, DBP, HR)-if change in mean BP was >30% of baseline or MAP <65, vasoactive agents were given.	N=96 Primary Outcome: Hypotension: Rem 37.5% Pro 64.6%, p=0.14 Bradycardia: Rem 0% Pro 2.1%, NS Percent change in mean BP, SBP, DBP and HR did not differ at most time points except % change in SBP was > in Pro vs. Rem pre-induction and after LOC	Authors conclude more stable hemodynamics in Rem vs. Pro in patients with hypertension
Duan, et al.[17] 2023 Elderly patients having hip replacement surgery	R, single-blind, single-center, N=60 (60-75 years) Induction: Rem 2-4 mg/kg vs. Pro 15-2 mg/kg	N=60 Primary Outcome: Rem 3 (10%) Pro 10 (33%), p=0.028	No difference in ADEs between groups Unclear if MAP <65 at any timepoint but fluctuation in

ASA I-III Single center	Maintenance: Rem 0.3-0.5 mg/kg/h vs. Pro 4-8 mg/kg/h Ondansetron was given post-op to all patients. Primary Outcome: Emergence agitation (measured by Riker Sedation-Agitation Scale [RSAS]-score of ≥5 indications agitation.) Other Outcomes: HR, MAP, time to awake, extubation, ADEs.	Other Outcomes: Duration of anesthesia, time to awake, extubation similar between groups	MAP and HR appeared less in Rem vs. Pro
Toyota, et al.[18] 2023 Spinal surgery in elderly patients Rem + Flu ASA I-III Single center	R, single-blind, single center, N=44 (>75 years) Induction: Rem 12 mg/kg/h vs. Pro (target-controlled infusion of 3 mcg/mL Maintenance: Rem up to 2 mg/kg/h vs. Pro, both adjusted to BIS index between 40-60 Flu 0.5 mg administered upon D/C of anesthetic to Rem group. Primary Outcome: Time elapsed from anesthetic D/C to extubation Other Outcomes: Elapsed time from D/C of anesthetic to eye opening, obey commands and WFTS score of ≥12 (defined as ability to be D/C from the OR)	N-39 (5 patients not included) Primary Outcome: Rem + Flu 4 min Pro 8 min, p<0.001 Other Outcomes: time to eye opening, obey commands and time to achieve WFTS of 12 all statistically shorter in Rem + Flu vs. Pro	Average rate of Rem 0.93 mcg/kg/min (0.056 mg/kg/hr) vs. Pro 3.99 mg/kg/hr 5/20 Rem + Flu patients did not achieve full recovery after Flu admin. Authors note that dosing of Rem and Pro was based on electroencephalogram monitoring, minimal doses were not established and could have been reduced. Adequate dose and timing of Flu for Rem has not been established. Anesthesiologist unblinded Authors note lack of experience with Rem leading to questions of optimal dosing, dose of Flu and additional studies and several years of clinical use are necessary.
Huang, et al.[19] 2023 Hypertensive patients having surgery for breast cancer.	R, DB, single center, N=120 (40-86 years) Induction: Rem 0.3 mg/kg vs. Pro 2 mg/kg Maintenance: Rem 0.3 mg/kg/h vs. Pro 2 mg/kg/h to BIS index 40-60	N=120 Primary Outcome: Overall: Rem 36.7% Pro 58.3%, p=0.017 Elderly: Rem 45.9%	No difference in ADEs

ASA II-III Single center	<u>Primary Outcome:</u> Incidence of post-induction hypotension during the first 20 min after induction (defined as reduction >30% from baseline or MAP <60 mmHg	Pro 60.5%, p=0.206 Adult: Rem 21.7 Pro 54.5, p=0.023 Hypotension during maintenance: Rem 51.7 Pro 51.7, p>0.99 Minimum MAP was lower in the Rem (71 mmHg) vs. Pro (66 mmHg) group but did not meet threshold for hypotension. No difference in minimal MAP during maintenance anesthesia or in the PACU **No difference in use of vasoactive drugs during induction or maintenance anesthesia.	
Zhang, et al.[20] 2024 Cerebral endovascular procedure ASA I-III Single center	R, DB, non-inferiority trial, N=142 (<u>≥</u> 18 years Induction: Rem 0.1/kg vs. Pro 1-1.5 mg/kg Maintenance: Rem 0.3-0.7 mg/kg/h vs. Pro 4-10 mg/kg/h BIS index maintained 40-60 <u>Primary Outcome:</u> Time to emergence from GA (defined as eye opening verbal command) <u>Secondary Outcomes:</u> Time to LOC, induction hypotension, post-op delirium, etc.	N=129 completed trial <u>Primary Outcome</u>: Rem 16.1 min Pro 19 min, p=0.003 for noninferiority (NS) <u>Secondary Outcomes:</u> -Rem had shorter time to response to verbal command and to spontaneous breath but time to extubation and to orientation was NS -Only other diff was PIH and use of vasopressors: Rem 11.3% vs. Pro 25.4%, p=0.03 (PIH) Rem 29.6% vs. Pro 62%, p<0.001 (vasopressors)	Approx. mean duration of surgery 90 min, duration of anesthesia 2+ hours Authors conclude Rem is non-inferior to Pro for emergence from GA
Kim, et al.[21] 2024 Major spine surgery (TIVA) GA in prone position ASA I-III Single center	R, single center, N=94 (19-80 years) Induction: Rem 6 mg/kg/h vs. Pro target-controlled infusion 2-3.5 mcg/mL Maintenance: Rem 1-2 mg/kg/h vs. Pro target controlled 2-3 mcg/mL	N=94 <u>Primary Outcome:</u> Rem 95.7% Pro 83%, p=0.091 <u>Other Outcomes:</u> -Hypotension event/pt	Mean operative time: 135-137 min NS Mean anesthetic time: 186-189 min, NS Total amount of remifentanil 1562-1600 mg, NS

	TIVA: remifentanil target-controlled 3-5 ng/mL Primary Outcome: Incidence of hypotensive episodes during 1st hour of prone positioning Other Outcomes: Incidence of severe hypotension, and use of inotropic and vasoactive agents	Rem 4.7 vs. Pro 4.1, p=0.366 -Pts with severe hypotension: Rem 76.6% Pro 66%, p=0.254 -Inotropes or vasopressors: 5 mg ephedrine give Pro, none in Rem. Norepinephrine was not given in either group. NS in amount of phenylephrine given p=0.239	Authors conclude no differences in incidence of hypotension in prone position between groups within 1st hour. Although the mean MAP value or incidence of MAP <65 mmHg was not found, authors noted that Rem had a higher MAP (p=0.003) and heart rate (p<0.001) vs. Pro but stroke volume was higher in Pro vs. Rem (p=0.029) in the first 10 min after prone positioning.
Fechner, et al.[22] 2024 Elective surgery in ASA III-IV (TIVA with Rem or Pro and remifentanil)	R (3:1), MC, single-blind, non-inferiority trial, N=365 (≥ 18 years) Induction: Rem 6 mg/min vs. Pro 30 mg/kg/h Maintenance: Rem 0.7-2.5 mg/min vs. Pro 4-10 mg/kg/h Primary Outcome: Anesthetic efficacy (defined as % of time NCI values ≤ 60 after incision to closure) Other Outcomes: PIH to 15 min after incision defined as MAP <65 mmHg for ≥ 1 min, decrease in MAP >20% or >30% from baseline for 1 min or need for norepinephrine.	N=365 Primary Outcome: Rem 93% Pro 99%, p=0.0003 -Rescue anesthetic was used in 1.9% Rem vs. 0% Pro (no stats) -More remifenanil was given to Rem vs. Pro during surgery, p=0.0001 Other Outcomes: -MAP <65 mmHg (events): Rem 6.6 Pro 8.6, p=0.036 -Norepinephrine bolus or infusion: (events) Rem 14.1 Pro 19.9, p=<0.001 -MAP reduction >20 or 30% NS difference -HR <45 and/or need for atropine or glycopyrrolate: Rem 1.68 Pro 3.88, p=0.003 -Time to extubation: Rem 12 min Pro 11 min, p=0.008 -Time to orientation: Rem 54 min Pro 30 min, p=<0.001	ADEs related to study drug did not differ between groups, including N/V. Although "clinically apparent" post-op delirium did not differ, post-op delirium, as assessed by Nu-DESC score, indicated higher delirium in Rem 19% vs. Pro 7%, p=0.001 Trial drug doses: Rem 0.53 mg/kg Pro 2.9mg/kg
Liu, et al.[23] 2024 Elderly patients undergoing radical	R, single center, N=100 (≥ 65 years) Induction: Rem 0.1-0.2 mcg/kg vs. Pro 0.1-0.2 mcg/kg	N=100 Primary Outcome: Incidence: Rem N=15	No difference in ADEs. Authors conclude that Rem did not increase the incidence of post-op

resection of colon cancer ASA I-III Single center	Maintenance: Rem 0.4-1.2 mg/kg/h vs. Pro 4-10 mg/kg/h Primary Outcome: Incidence and duration of post-op delirium within 7 days of surgery	Pro N=11, p=0.362 No difference in cumulative duration of delirium between groups.	delirium in elderly patients having radical resection for colon cancer.

ASA=American Society of Anesthesiologists Physical Status, AVR=aortic valve replacement, BP=blood pressure, BIS=bispectral index, dBP=diastolic blood pressure, CAM=confusion assessment method, CO=cardiac output, DOB=date or birth, Flu=flumazenil, GA=general anesthesia, HR=heart rate, LOC=loss of consciousness, MC=multicenter, Mid=midazolam, MDDM=maximum distance of dots missed, MOAA/S=Modified Observer's Assessment of Alertness/Sedation, MVR=mitral valve replacement, NCI=Narcotrend Index, NDM=number of dots missed, NS=nonsignificant, N/V=nausea and vomiting, P=placebo, PACU=post anesthesia care unit, PIH=post-induction hypotension, POD=post-op day, Pro=propofol, R=randomized, Rem=remimazolam, s=seconds, SB=single-blind, sBP=systolic blood pressure, SV=stroke volume, TIVA=total intravenous anesthesia, WFTS=white fast track score

Summary of Efficacy:

- Overall, the time to loss of consciousness (LOC), depth of anesthesia during maintenance and recovery from anesthesia were similar between remimazolam and propofol. However, there were some differences in favor of propofol for time to LOC, depth of anesthesia (measured by bispectral index or BIS maintained between 40-60), and recovery from anesthesia.
    - There are questions of whether use of the BIS index and and/or BIS index target values of 40-60 are reliable when measuring appropriate depth of anesthesia with remimazolam or other benzodiazepines since the index was originally developed for propofol-based anesthesia.[14-15]
- Variation in efficacy may be explained by use of different doses and methods of administering remimazolam (bolus vs. infusion). Since remimazolam is not FDA approved for the management of induction or induction and maintenance of anesthesia, optimal dosing has not been established.
    - Several investigators reported mean dose of remimazolam to LOC:
        - Doi, et al.[3]: 6-12 mg/kg/hr=0.17 mg/kg and 0.29 mg/kg, respectively.
        - Doi, et al.[4]: 6-12 mg/kg/hr=0.16 mg/kg and 0.27 mg/kg, respectively.
        - Dai, et al.[5]: 0.2-0.4 mg/kg (0.3 and 0.4 mg/kg vs. propofol NS)
        - Sekiguchi, et al.[12]: Rem 12 mg/kg/hr=0.34 mg/kg vs. propofol 1.21 mg/kg
        - So, et al.[15]: Rem 6 mg/kg/hr=0.2 mg/kg
    - There have been several studies to determine the 50% and 90-95% effective induction dose (ED_{50} and ED_{90} or ED_{95}) based upon dose-response LOC, respiratory depression and hemodynamic variables.
        - Chae, et al. 2022 (IV bolus dose; N=120): Reported the optimal doses of remimazolam depending upon age: 0.25-0.33 mg/kg (age <40 years); 0.19-0.25 mg/kg (age 60-80 years); and 0.14-0.19 mg/kg (age >80 years).[28]
        - Tan, et al. 2023 (IV bolus dose; N=100): Administered varied bolus doses to determine ED_{50} and ED_{95}: ED_{50}=0.09 (0.08-0.11) mg/kg and ED_{95}=0.21 mg/kg (0.16-0.35 mg/kg). Anesthesia was maintained with propofol. Authors recommend a combination of remimazolam for induction and propofol for maintenance to produce more stable sedation, reduce total doses and have less effect on cardiovascular and respiratory depression.[29]

        - Jeong et al. 2023 (IV Infusion; N=20 until 6 cross-over pairs were observed): Infusion starting at 0.1 mg/kg/min and increased or decreased by 0.02 mg/kg/min, depending upon response of prior patient, to determine the ED_{50} and ED_{90} for loss of responsiveness at 2 minutes. ED_{50}=0.07 mg/kg/min and ED_{90}=0.10 mg/kg/min (equal to 6 mg/kg/h).[30]
    - In three trials, comparing induction doses of remimazolam 6, 9 or 12 mg/kg/hr, there was a small reduction in time to LOC in the higher dose groups. Additionally, the time to recovery was longer in the higher dose remimazolam groups vs. lower doses and vs. propofol. The incidence of post-induction hypotension was numerically higher in the high dose groups and similar to propofol.[3-4,14]
    - In one study, comparing bolus induction doses of remimazolam (0.2, 0.3 and 0.4 mg/kg) vs. propofol, investigators observed successful induction with higher doses and similar to propofol. The incidence of hypotension increased with higher doses of remimazolam and was similar to propofol.[5]
    - In 2 studies, flumazenil was given to all patients in the remimazolam groups after stopping anesthesia.[13,18] In one of the studies, investigators observed a potential for rebound sedation and suggested caution be used for up to one day after stopping anesthesia.[13] In the other study, authors commented that the appropriate dose of flumazenil is unclear and additional studies are needed.[18]
- Four systematic reviews and/or meta-analyses of the safety and efficacy of remimazolam for induction or induction and maintenance of anesthesia were reviewed.[24-27] Although the number of studies and sample sizes were small, authors reported a significantly lower risk for post-induction hypotension, hemodynamic changes and injection site pain with remimazolam vs. propofol. The systematic review by Ko, et al., reported shorter time to LOC and better anesthesia depth with propofol vs. remimazolam. **Each of the authors recommended additional studies be conducted to confirm their findings.** *(Refer to table 2 for details)*
- Aside from post-induction hypotension and injection site pain, there were no consistent differences in adverse events (e.g., PONV, post-op delirium, respiratory depression, dizziness, etc.) between remimazolam and propofol.

Table 2: Efficacy results from systematic reviews/meta-analyses

Study	Design	Results	Authors Conclusion
Ko, et al.[24] 2023	To compare the risk of hypotension and characteristics of induction and recovery Rem vs. Pro in GA N= 8 studies (738 patients) (Evidence to March 2022)	-PIH significantly lower for Rem vs. Pro (RR 0.57, 0.43-0.75, p<0.001 (I2=12%, 5 studies-564 pts) -Anesthesia depth (BIS index) "lighter" with Rem vs. Pro (MD 9.26, 3.06-25.47, p=0.003, I^2=94%, 5 studies, 490 pts) -Time to LOC shorter in Pro vs. Rem (MD 15.49 s, 6.53-24.46, p=0.0007, I^2=61%, 3 studies, 331 patients) -NS difference in time to eye opening, extubation and risk of PONV	Rem was associated with lower risk for PIH vs. Pro and similar recovery. **Further studies are required to support findings.**
Peng, et al.[25]	To compare the hemodynamic effects of Rem	Changes in HR and MAP represented more stable hemodynamic characteristics of Rem vs. Pro	Evidence suggests Rem has a lesser effect on hemodynamics during GA.

	vs. Pro during induction of GA N=8 studies (964 patients) (Evidence to September 2022)	-HR: MD -4.99, -7.98 to -2, I^2=41.6%, p=0.001 -MAP: MD -5.91, -8.57 to -3.24, I^2=0, p<0.001	However, quality of recovery is inconclusive. **Additional RCTs with larger sample sizes are needed to assess the benefit-risk ratio with this new medication.**
Wu, et al.[26]	To determine if safety related outcomes are in GA are superior with Rem vs. Pro. N=8 studies (998 patients)	Lower risk of hypotension in Rem vs. Pro: (RR 0.43, 0.34-0.55, I^2=0%, p<0.00001) Higher pre and post intubation MAP in Rem vs. Pro Higher incidence of hypoxemia, N/V, dizziness and injection site pain in Pro vs. Rem	A higher incidence of the ADEs reported here are not consistently reported as a higher rate for Pro vs. Rem, except injection site pain. **A large sample size is needed to validate the findings.**
Huang, et al.[27]	To compare the ADEs between Rem and Pro for GA in surgical patients. N=16 studies (1897 patients) (Evidence to December 2023)	The rate of the following higher in Pro vs. Rem: -Hypotension (RR 0.5, 0.43-0.58, P=0.00001) -Bradycardia (RR 0.53, 0.36-0.78, p=0.001) -Injection site pain No significant difference for the following: PONV, dizziness, psychiatric symptoms or respiratory depression.	Bradycardia was reported to be more prevalent in Pro vs. Rem but p=0.05 **This new drug should be further studied and more research with larger population sizes should be carried out to confirm this hypothesis that Rem has few ADEs vs. Pro in GA**

ADEs=adverse drug events, GA=general anesthesia, LOC=loss of consciousness, MD=mean difference, N/V=nausea and vomiting, PONV-post-op nausea and vomiting, Pro=propofol, Rem=remimazolam, RR=relative risk

Summary of Safety:

- Of the twenty-one studies reviewed, comparing induction of anesthesia with remimazolam vs. propofol, most reported a lower incidence of post-induction hypotension and need for vasoactive medications in favor of remimazolam. However, several studies did not report statistically significant differences in hemodynamic measures (HR, MAP, mean BP, or systolic or diastolic BP) or use of vasoactive agents between groups.[7,9,12-13,15-17,21] In the studies, post-induction hypotension was generally defined as mean arterial pressure (MAP) <60-65 mmHg, >30% change from baseline and need for vasoactive medications.
- When reported, changes in hemodynamic parameters were not statistically different between remimazolam and propofol during anesthesia maintenance and therefore, the advantage of replacing propofol maintenance anesthesia with remimazolam is not supported by the evidence.[10,19,21]
- There are several serious adverse events discussed in a review of the safety of remimazolam.[35]
    - Potential for delayed emergence: Remimazolam is metabolized by nonspecific tissue carboxylesterase 1 (CES1) located in the liver but extra-hepatic metabolism can also occur in the lung. There is significant variation in CES1 activity due to inter-ethnic variability and genetic polymorphisms may contribute to differences in the pharmacokinetics of remimazolam. For example, there are two single-nucleotide polymorphisms of CES1 showing lesser enzymatic activity in Caucasian populations

which are not present in the Korean population. Other factors that may contribute to delayed emergence, especially with continuous infusion of remimazolam, include sensitivity to benzodiazepines, flavonoids, fatty acids and alcohol can inhibit CES1 activity, hepatic impairment, increased body mass index (BMI), age and low plasma albumin levels. Lower doses of remimazolam may reduce the risk for delayed emergence in susceptible patients.

- Re-sedation after reversal with flumazenil: Flumazenil is a competitive benzodiazepine receptor antagonist and is used to reverse the effect of benzodiazepines, including remimazolam. However, there is a risk for re-sedation with remimazolam when flumazenil is used. Flumazenil administration reduces the occupancy rate of remimazolam at the receptor site, resulting in recovery from sedation. However, as the occupancy rate of flumazenil at the receptor site decreases, there is the potential for an increase in the concentration of remimazolam at the receptor, especially in patients with reduced metabolism of remimazolam. This increase in concentration of remimazolam increases the risk for re-sedation. It is recommended that flumazenil be reserved for patients with delayed emergence or awakening after anesthesia or sedation to reduce the risk. It is hypothesized that the risk of re-sedation is increased when higher bolus doses of flumazenil are administered and recommend initial doses of 0.2 mg be given and patients monitored for two hours after reversal.
- Anaphylaxis: There have been ten reported cases of anaphylaxis associated with the use of remimazolam. Although the mechanism for anaphylaxis has yet to be determined, remimazolam is contraindicated in patients with known hypersensitivity to Dextran 40. There is a rare possibility that patients may have an allergy to remimazolam or be at increased risk for anaphylaxis due to a prior exposure to midazolam.

Other Considerations

Midazolam is FDA approved for the induction of general anesthesia, but its longer half-life and active metabolites may lead to delayed recovery vs. propofol and remimazolam. Remimazolam is a short acting benzodiazepine analog modified by adding an ester linkage which is quickly metabolized by non-specific plasma tissue esterases into inactive metabolites. Although the metabolism of remimazolam is not affected by age, renal impairment, body weight, gender or race, use in hepatic impairment may significantly increase the half-life. Remimazolam is not FDA approved for induction of general anesthesia. Although there are several older studies using midazolam as a co-induction agent with propofol for general anesthesia, there are no comparative trials with remimazolam.[31-33]

	Mean Residence Time	Terminal Half-Life
Midazolam	3.62 hour	4.29 hour
Remimazolam	0.51 hour	0.75 hour

Kim, et al.[2]

There are several medications/fluids that are commonly used during the perioperative period that are incompatible with remimazolam, resulting in precipitation of remimazolam.[1,36] See product labeling for compatible fluids.

Other Therapeutic Options

Alternative treatments for **induction of general anesthesia**, procedural sedation and ICU sedation are listed in table 3 below.

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Remimazolam[1] (BYFAVO) IV bolus	NF	FDA Approved: Induction and maintenance of procedural sedation in adults undergoing procedures lasting ≤ 30 minutes. Sedative, amnestic, anxiolytic Off-Label: Request use for induction of anesthesia to reduce the risk and complications of post-induction hypotension (optimal dosing unclear, has been studied as IV bolus or infusion)	Onset: 1-2 min Peak sedation: 3-3.5 min after IV injection of 2.5-5 mg bolus for induction; At least 2 minutes must elapse before supplemental doses 1.25-2.5 mg IV can be given Duration of action: 11-14 min Dose in trials range 5-30 mg (Mean 9-11 mg) Induction of anesthesia: 0.3-0.4 mg/kg or 6-12 mg/kg/h; Maintenance: 1-2 mg/kg/h (*optimal dosing has not been established*) Similar to midazolam, excessive sedation can be reversed by flumazenil
Midazolam[1] IV, IM, PO	F	FDA approved for pre-op sedation, procedural sedation, induction of anesthesia, sedation in the OR or ICU in mechanically ventilated patients Sedative, amnestic, anxiolytic	Onset: 1-2 min Peak sedation: 3-5 min Duration of action: 10-60 min *Excessive sedation can be reversed by flumazenil Usual max dose is 5 mg/procedure Induction: 3-4 mg given once[31-33]
Propofol[1] IV bolus or infusion	F	FDA approved for induction and maintenance of anesthesia or sedation, monitored anesthesia care for procedures and sedation in the ICU Sedative, amnestic, no analgesic properties	Onset: <1 min; Duration: 3-10 min; injection is painful Contraindicated in patients with allergies to eggs, egg products, soybeans or soy products.
Ketamine IV bolus or infusion	F	FDA approved as anesthetic agent for diagnostic or surgical procedures, for induction of anesthesia as a supplement to other anesthetics. Dissociative, amnestic	Onset:<1 min Duration: 5-10 min (IV) Need to pretreat with glycopyrrolate to reduce excessive salivation Potential for emergence delirium
Dexmedetomidine IV infusion	PA-F	FDA approved for sedation of mechanically ventilated patients in the ICU, and in non-intubated patients prior to and during surgical or other procedures. Sedation, anxiolytic, analgesia	VA CFU-2018: ICU setting for short or intermediate-term sedation as an alternative to propofol or benzodiazepines Onset of action: <1 min Duration: 5 min Little to no respiratory depression occurs

Etomidate IV	F	Approved for anesthesia induction and maintenance of anesthesia for short procedures. Hypnotic, no analgesic properties	Onset: <1 min Duration: 3-5 min Can cause myoclonus, pain on injection, lower seizure threshold. May be useful in trauma or hypotension

[1]Reduced doses may be necessary when combined with other agents or in elderly patients and/or with ASA physical status score III/IV

Projected Place in Therapy

- There are several drugs that can be used for induction of anesthesia including propofol, etomidate and ketamine each with their unique set of advantages and disadvantages.[34]
    - Propofol has a quick onset and offset, antiemetic, antipruritic and anticonvulsant properties. It can be useful in patients with bronchospasm and asthma because of its upper airway and bronchodilator effects, reducing airway resistance. Also, in patients with brain injury because of its central nervous system effects and can be used in patients with renal or hepatic impairment. However, it is associated with dose-dependent hypotension, respiratory depression and injection site pain. Post-induction hypotension may be reduced with use of lower doses, especially in the elderly, in patients with hypovolemia due to sepsis, myocardial infarction or use of one or more adjuvant anesthetic medications that may exaggerate its effects.
    - Etomidate has a quick onset and offset, hemodynamic stability and anticonvulsant properties. It may be selected in less stable patients or used in those with head injuries because of its lack of hemodynamic effects. Disadvantages include high incidence of postoperative nausea and vomiting, injection site pain and involuntary myoclonic movements.
    - Ketamine has a rapid onset and may be selected in patients with or a potential to develop hypotension from any cause (e.g., hypovolemia, sepsis, hemorrhage, etc.). It has analgesic and bronchodilation properties and does not impact airway reflexes and respiratory drive. Disadvantages include increased oxygen demand, pulmonary artery pressure, increased intracranial pressure and salivation and the potential for developing hallucinations, nightmares and vivid dreams.
- In the same review of "General Anesthesia: Intravenous Induction Agents" from UpToDate, midazolam is listed as an "adjuvant induction agent". The authors indicate that although a small dose of midazolam can be given to reduce anxiety, routine use for premedication or for induction is not consistent with Enhance Recovery After Surgery (ERAS) protocols. The authors note that although evidence supporting remimazolam for induction are limited, it may have the potential to avoid the adverse events associated with longer-acting benzodiazepines, like midazolam.[34]
- Twenty-one clinical trials comparing remimazolam (as a bolus or infusion) to propofol for the induction or induction and maintenance of anesthesia were reviewed. Most of the trials included less than 100 patients, were conducted at a single-center outside of the United States, were single-blinded due to difficulty blinding the attending anesthesiologist and enrolled patients with ASA physical status of I-III. In most trials, with post-induction hypotension and use of vasoactive medications as a primary endpoint, investigators reported a statistically significant

lower incidence with remimazolam vs. propofol. However, use of higher induction doses of remimazolam (0.4 mg/kg) increased the incidence of hypotension and was similar to propofol.

- When reported, hemodynamic changes (e.g., HR, MAP, mean BP, SBP, DBP) were not significant between groups during maintenance anesthesia and therefore, replacing propofol with remimazolam for maintenance anesthesia is not supported by the evidence.
- In several studies, the time to LOC, depth of anesthesia and recovery from anesthesia was statistically better with propofol vs. remimazolam. However, it is unclear if the differences are clinically meaningful.
- There are no studies comparing remimazolam to midazolam for anesthesia induction.
- Remimazolam is not FDA approved for induction or induction and maintenance of anesthesia, therefore, optimal dosing has not been established. Dosing varied across studies with use of bolus or infusion for induction. Bolus dosing included: 0.2-0.4 mg/kg; infusion dosing: 6, 9 and 12 mg/kg/h.
- Based upon intermediate outcome measures (reduced post-induction hypotension and/or use of vasopressor drugs), remimazolam may offer an advantage over propofol for induction of anesthesia in patients who may be particularly vulnerable to post-induction hypotension (e.g., elderly, frail, multiple co-morbidities, shock states, at risk for cardiopulmonary collapse, ASA III-IV, etc.), despite a reduction in dose of propofol and potentially to avoid or reduce the need for vasoactive drugs to maintain a safe blood pressure after induction.
- Evidence does not support an advantage of replacing propofol with remimazolam for maintenance of anesthesia and therefore, should not be used for this purpose. Additionally, there are multiple agents available for maintaining sedation in the intensive care unit (ICU) and therefore, remimazolam should generally not be used for this purpose. *Note, evidence for remimazolam in ICU sedation or for procedural sedation was not reviewed as part of this addendum.*
- Risks for delayed emergence, re-sedation after reversal with flumazenil, anaphylaxis and ensuring compatibility with perioperative medications/fluids with remimazolam should be considered.
- Remimazolam is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

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