**Brand Name:** Byfavo

**Generic Name:** Remimazolam

**Manufacturer**[1]: Acacia Pharma, Inc

**Drug Class**[1,2,3,4,5]: Benzodiazepine

**Labeled Uses**[1,2,3,4,5]:Sedation for Procedures lasting 30 minutes or less

**Mechanism of Action[1,2,3,4,5]:**
Remimazolam is a benzodiazepine that binds to GABA-A receptors in the brain. The formation of the benzodiazepine-GABA complex increases the effects of GABA which increases the inhibition of the ascending reticular activating system. It appears that Remimazolam does not have selectivity between different GABA receptors.

**Pharmacokinetics[1,2,3,4,5]:**
**Absorption:**

| | |
|---|---|
| **Tmax** | 20-30 minutes |
| **Vd** | 0.76-0.98 L/kg |
| **T1/2** | 37-53 minutes |
| **Clearance** | 54-75 L/hr |
| **Protein Binding** | >91% |
| **Bioavailability** | Unknown |

**Metabolism:** Remimazolam is metabolized by tissue carboxylesterases to an inactive metabolite CNS7054. There does not appear to be any major CYP450 metabolism.

**Elimination:** Remimazolam is mainly excreted in the urine as its metabolite CNS7054 (50-60%). A very small amount of remimazolam is also excreted unchanged in the urine (0.003%)

**Efficacy[6,7,8]:**

**Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg*. 2015;120(4):771-780.**

**Study Design:** Randomized, double blind, active control, parallel study
**Description of Study:** Methods: 100 patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: one dose of remimazolam 0.1, 0.15, or 0.2 mg/kg; or one dose of midazolam 0.075 mg/kg. The patients were given their medication as an IV injection over one-minute by an anesthesiologist. Patients were eligible for the studies if they were 18-65 years old, were receiving an upper GI endoscopy had a ASA physical status score of 1 or 2, weight range of 60 to 120 kg, and a BMI of 18-29 kg/$m^2$. The study assessed the efficacy of the treatments using 4 criteria; did the patient have a modified observer's assessment of alertness/sedation scale (MOAA/S) $\leq 4$ for 3 consecutive measures? Did the patient complete the endoscopy? Did the

patients require rescue sedative medications? And did the patient require mechanical ventilation? The patient's sedation level was also assessed throughout the process using the MOAA/S score, measured every 30 seconds for the first 3 minutes then every 2 minutes for the next 12 minutes and then every 5 minutes until the patient was fully alert. The patients also were assessed using the Brice Questionnaire through the Hopkins Verbal Learning Test (HLVT-R). The study also monitored pain on injection of each medication using a visual analog scale of 0-100. Safety measures included adverse events and changes in vitals. **Outcome Results:** The success rate of remimazolam was found to be 32% in the 0.1 mg/kg group, 56% in the 0.15 mg/kg group, and 64% in the 0.2 mg/kg group. The success rate of midazolam was found to be 44%. The onset of sedation was found to be 1.5 to 2.5 minutes in the remimazolam doses and 5 minutes in the midazolam treatment groups. 20 patients in the midazolam group could not recall the procedure while 19, 21, and 20 patients in each of the remimazolam groups could not recall the procedure (0.1 ,0.15, 0.2 respectively). Adverse effects appeared to occur in similar amounts between all of the treatment groups.

**Limitations:** Multiple researchers that took part in this study worked for PAION which is a pharmaceutical company that produces Remimazolam in the UK. Power of the study was not reported. The study also did not report the P values for many of its measures.

**Conclusion:** Remimazolam 0.15m/kg and 0.2mg/kg, showed higher efficacy when compared to midazolam 0.075mg. The study also shows that both treatment options had similar adverse effect profiles.

**Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437**

**Study Design:** Prospective, double blind, randomized, placebo and active controlled, parallel study.

**Description of Study:** Methods: 461 patients were randomized between remimazolam (n = 298), placebo (n = 60), and open label midazolam (n = 103). The primary outcome of this study was the completion of colonoscopy with no requirement for alternative sedation and no more than 5 uses of the study medication within any 15-minute period. For midazolam this was no more than 3 doses in a 12-minute period. The secondary objectives of the study were time to start procedure after administration, time to peak sedation, time to readiness for discharge, time to full alert, recall of procedure by Brice questionnaire, change in patients cognitive function by the Hopkins Verbal Learning Test Revised, safety of multiple doses of remimazolam, ready to discharge 30, 60, and 90 minutes after injection, assessment of re-sedation using a visual analogue scale for drowsiness, requirement for flumazenil during procedure, patients self-evaluation of back-to-normal after procedure, pain on injection, and population pharmacokinetics in patients less then 65 years and patients 65-74 years. All patients received fentanyl before their assigned study medication. The first 80% of participants received 75 mcg of fentanyl but this was changed to 50 mcg of fentanyl since multiple patients had achieved MOAA/S scores of 0 on the higher fentanyl dose. Patients then received oxygen until fully alert after which they received their assigned

medication. Patients would either receive 5 mg of remimazolam or equal volume of placebo over 1 minute. They received colonoscopy when a MOAA/S score of 3 or less was achieved. The patients then received top up doses of 2.5 mg of remimazolam or equal volume placebo as needed for sedation. If any patients were determined as treatment failure, they were then switched to midazolam to finish the colonoscopy. Midazolam was dosed at the endoscopist's discretion. Inclusion criteria included, male and female patients over the age of 18 who were undergoing a colonoscopy, ASA Physical Status Risk Class 1-3, BMI less than 40 $kg/m^2$, and a negative pregnant status.
**Outcome Results:** The difference in success rate were 91.3 % in the remimazolam group and 1.7% in the placebo group. The difference in success rate was 0.896 (95% CI: 0.851-0.942, $p < .0001$). The difference between remimazolam and midazolam was 0.6606 (95% CI: 0.5705-0.7501, no p-value reported). The mean total fentanyl was 88.6 mcg in the remimazolam group, 121.3 mcg in the placebo, and 106.9 mcg in the midazolam ($p = 0.0000$). The mean number of fentanyl top ups was 0.76 mcg in the remimazolam group, 1.93 mcg in the placebo group, and 1.34 mcg in the midazolam ($p = 0.0000$). Pain at injection site was reported at 4.9 for remimazolam and 5.7 for placebo ($p = 0.5902$). The pain score for midazolam was 5.8. The mean sedative dose for remimazolam was 10.53 mg (±3.98). Time from start of medication to sedation was 5.1 (±3.82) minutes with remimazolam, 20.3 (± 4.34) minutes with placebo, and 16.9 (± 6.31) minutes with midazolam. The recovery with remimazolam were consistently shorter than when compared to placebo ($p < 0.001$). The study also reported the safety of the medications. Hypotension was reported in 61.8% of midazolam patients, 41.7% of placebo patients, and 38.9% of remimazolam patients. The rate of adverse events was 73.6% in the remimazolam group, 78.3% in the placebo group, and 91.2% in the midazolam group with $p < 0.0001$ between remimazolam and midazolam.
**Limitations:** The midazolam arm of the study was given as an open label medication which could have potentially caused bias in the patients or the researchers. PAION UK participated in the design, provided funding, performed statistical tests, and reviewed the manuscript for this study. Also, some of the researchers in the study reported potential conflicts of interest. The dose of fentanyl was changed part of the way through the study which could have affected some of the results of the study. Midazolam was also given at a lower dose and rate then what is normally used in clinical practice which could have led to a delay in sedation in the midazolam group.
**Conclusion:** This study demonstrated the efficacy of remimazolam as a sedative. When compared to placebo remimazolam was significantly more effective (pvalue <0.0001). Remimazolam also was shown to have statistically significantly less adverse effects then midazolam ($p < 0.0001$).

**Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest.* 2019;155(1):137-146.**

**Study Design:** Prospective, double-blind, randomized, placebo and active control, multicenter, parallel study
**Description of Study:**
**Methods:** 446 patients were randomized between the three different groups of the study, remimazolam group (n = 310), placebo (n = 63), and midazolam group (n = 73). The study durations was ≤ 28 days. Patients were screened within 21 days of their bronchoscopy with a

follow up 4-7 days after the procedure. Inclusion criteria included male and female patient > 18 years of age with a scheduled bronchoscopy, ASA Physical Status Score 1-3, BMI ≤ 45, $SP0_2$ ≥ 90%, and female patients with a negative pregnancy test. The primary outcomes of the study were the success of bronchoscopy, completion of bronchoscopy, no requirement of rescue sedative, no more than 5 top offs required. Secondary objectives included time to start of procedure after administration, time to peak sedation, time till ready for discharge, time till fully alert, MOAA/S score, recall of procedure by Brice Questionnaire, changes in patients cognitive function by the HVLT-R, safety of multiple doses, ready to discharge score at 30, 60, and 90 minutes, drowsiness visual analogue scale, requirement of flumazenil, patient's self-evaluation, pain on injection, and population PK.

**Outcome Results:** Success rates were 80.6% in the remimazolam group, 32.9% in the midazolam group, and 4.8% in the placebo group. There was a statistically significant difference ($p < 0.0001$) in results between the remimazolam and placebo groups. The amount of fentanyl given in the remimazolam group was 82 mcg, 120 mcg in the placebo group, and 107 mcg in the midazolam group. Patients started their bronchoscopy sooner in the remimazolam group (6.4 ± 5.82 min), compared to the placebo and midazolam groups. The time in the placebo group was 17.2 min (±4.15) and 16.3 min (±8.6) in the midazolam group. The remimazolam group also showed a faster time to alertness then the other two treatments ($p < 0.0001$ for placebo).

**Limitations:** The main limitation of this study is that the manufacturer of remimazolam, PAION UK, was highly involved throughout this study. Another limitation of this study is that remimazolam was compared to placebo and not the other active treatment, so it is hard to determine which of the actual treatments is more efficacious.

**Conclusion:** This study proves that remimazolam is more efficacious then placebo as a sedative for bronchoscopy ($p < 0.0001$). This study also shows that remimazolam has a faster recovery time when compared to placebo ($p < 0.0001$).

**Contraindications[1,2,3,4,5]:**

**Dextran Hypersensitivity:** Remimazolam is contraindicated in patients who have a hypersensitivity reaction to dextran 40 or products containing dextran 40.

**Precautions[1,2,3,4,5]:**

**Personnel and equipment for monitoring and resuscitation**: Only individuals who are trained to administer procedural sedation should administer remimazolam. They also must be trained to detect and manage airway obstruction, hypoventilation, and apnea. They must also be trained in the maintenance of patent airway, supportive ventilation and cardiovascular resuscitation. Also, since remimazolam has been associated with hypoxia, bradycardia, and hypotension patients should receive continuous vital monitoring both during sedation and the recovery period.

**Concomitant Opioid Use**: Use of opioid and benzodiazepines could result in increased sedation, respiratory depression, coma, and death. These respiratory effects are more common in patients with obstructive sleep apnea, the elderly, and ASA status 3 and 4 patients. Patients respiratory and sedation levels should be continuously monitored while receiving remimazolam.

**Hepatic Impairment:** Use caution in patient with hepatic impairment, carefully titrate to effect, it may be required to lower the frequency of supplemental doses of remimazolam.

**Pediatric:** It is possible that neurotoxicity may occur in pediatric patients, especially after repeat or prolonged exposure to anesthetic agents early in life. This might result in cognitive or behavioral effect.

**Elderly:** Potentially faster onset and duration onset of action. Sedation may cause confusion especially in the elderly.
**Pregnancy:** Benzodiazepines can cross the placenta. Teratogenic results have been seen with some benzodiazepines, but the data is inconsistent and additional studies are needed. In animal studies medications that potentiate GABA activity may affect brain development.
**Lactation:** Lactating mothers should discard milk for 5 hours after administration of remimazolam to decrease the potential of exposure to infant. Monitor the infant while breastfeeding for signs of sedation, respiratory depression, and feeding problems.
**Adverse Effects [1,2,3,4,5]:**
*Cardiovascular:*
Bradyarrhythmia (3-11%) | Hypertension (20-42%) | Hypotension (33-58%) | Tachycardia (8%)
*Respiratory:*
Increased respiratory rate (14%) | Hypoxia (22%) | Respiratory Acidosis (19%) | Upper respiratory infection (3%)
**Drug Interactions[1,2,3,4,5]**:
**Opioid Analgesics** (hydrocodone, codeine, fentanyl, etc.)- Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Benzodiazepines** (diazepam, alprazolam, clonazepam, etc.)- Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Propofol-** Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Barbiturates (phenobarbital, pentobarbital, butobarbital)-** Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Zolpidem-** Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Eszoplicone-** Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Other CNS Depressants-** Increased risk of sedation, respiratory depression, coma, and death. Monitor patient if using medications concomitantly.

**Dosing and Administration[1,2,3,4,5]:**
Usual Dose:
Induction of procedural sedation
Healthy Adults: 5 mg IV over 1 minute
ASA Physical Status 3 or 4: 2.5 to 5mg over 1 minute
Maintenance
Healthy Adults: 2.5 mg IV over 15 seconds as needed; at least 2 minutes must elapse prior to administration of supplemental dose

ASA Physical Status 3 or 4: 1.25 to 2.5mg IV over 15 seconds as needed; at least 2 minutes must elapse prior to supplemental dose.

**Conclusion:** Remimazolam appears to be effective and relatively well tolerated. Additional studies comparing remimazolam to other sedatives used for procedural sedation should be conducted to assess remimazolam's place in therapy. Other agents may be less costly and provide similar efficacy for procedural sedation. Because of this, use of remimazolam should be limited until further studies can be performed that prove that remimazolam is more effective than other agents used for procedural sedation.

**References**


1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma; 2020
2. Remimazolam. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed September 17, 2020.
3. Remimazolam Monograph. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: September, 17, 202
4. Remimazolam. Facts & Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed September 17, 2020.
5. Remimazolam. Lexi-Drugs [database online]. Lexi-Comp, Inc; September 17, 2020.
6. Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg*. 2015;120(4):771-780.
7. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437
8. Pastis NJ, Yarmus LB, Schippers F, et al. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest*. 2019;155(1):137-146.


Prepared by: Jordan Eckman, Doctor of Pharmacy Candidate.