Summary Report of Benefit-Risk Assessment

BYFAVO POWDER FOR SOLUTION FOR INJECTION 20MG

NEW DRUG APPLICATION

Active Ingredient(s)	Remimazolam besylate
Product Registrant	Hyphens Pharma Pte. Ltd.
Product Registration Number	SIN17317P
Application Route	Abridged evaluation
Date of Approval	27 August 2025

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A INTRODUCTION

Byfavo is indicated for the induction and maintenance of general anaesthesia (GA) in adults and for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

The active substance, remimazolam besylate, is a benzodiazepine which enhances γ-aminobutyric acid A (GABAA) receptor activity to induce cell membrane hyperpolarisation, thereby inhibiting neural activity via an increase in chloride influx.

Byfavo is available as powder for solution for injection containing 20 mg of remimazolam. Other ingredients in the vial are lactose monohydrate, dextran 40, sodium hydroxide, and hydrochloric acid.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, remimazolam besylate, is manufactured at Cambrex Karlskoga AB, Karlskoga, Sweden. The drug product, Byfavo powder for solution for injection 20 mg, is manufactured at Hana Pharm. Co., Ltd, Gyeonggi-do, Republic of Korea.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 60 months. The packaging is double low-density polyethylene (LDPE) bags stored in high-density polyethylene (HDPE) drums with a desiccant.

Drug product:

The manufacturing process involves formulation of the drug product, followed by prefiltration, sterile filtration, aseptic filling and lyophilisation. This is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP) standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

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The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is a type I glass vial fitted with bromobutyl rubber stoppers and capped with aluminium cap.

C ASSESSMENT OF CLINICAL EFFICACY

General anaesthesia (GA)

The clinical efficacy of remimazolam for use in GA was based primarily on two pivotal Phase III studies, ONO-2745-05 and HNP-2001-301, as well as two supportive studies, ONO-2745-06 and CNS7056-010.

Study ONO-2745-05 was a Phase III, multicentre, randomised, single-blind, active-controlled, parallel study to evaluate the efficacy and safety of remimazolam versus propofol in surgical patients undergoing GA.

The patients were randomised in a 2:2:1 ratio to receive induction doses of remimazolam 6 mg/kg/h, remimazolam 12 mg/kg/h or propofol 2.0-2.5 mg/kg. In the remimazolam groups, the dose was reduced to 1 mg/kg/h after the loss of consciousness, and the infusion rate was adjusted (maximum 2 mg/kg/h) based on monitoring of the general condition and bispectral index (BIS)[1] values of individual subjects until the end of the surgery. In the propofol group, continuous IV infusion at a dose of 4-10 mg/kg/h was started after the loss of consciousness, and the infusion rate was adjusted as appropriate based on monitoring of the general condition and BIS values of individual subjects until the end of the surgery.

The primary efficacy endpoint was functional capability as a GA assessed by a composite of three variables. The investigational product was assessed as “effective” if all three variables were absent or “ineffective” if at least one of these three variables was present: (1) intraoperative awakening or recall; (2) requirement of rescue sedation with other sedatives; (3) body movement. The secondary efficacy endpoints included time to loss of consciousness from the start of investigational product administration, BIS value (to monitor brain activity via electroencephalogram [EEG] monitoring) at each time point of evaluation, time to awakening from the end of investigational product administration, time to extubation from the end of investigational product administration, time to stating date of birth from the end of investigational product administration, time to decision to exit the operating room from the end of investigational product administration, intraoperative awakening or recall, requirement of rescue sedation with other sedatives, and controllability of anaesthetic depth which was assessed by clinical signs and patient responses such as heart rate, blood pressure, respiration rate, muscle tone and eyelash reflex. The endpoints were considered to be relevant for a GA agent.

[1] The BIS value ranges from 0 to 100 where 0 represented absence of brain activity on the electroencephalogram while 100 represented an awake state. Values <40 represented a deep hypnotic state. Values 40 to 60 are usually required for GA to prevent awareness while under anaesthesia (Mathur S et al., 2023. StatPearls on BIS).

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Non-inferiority in terms of the primary endpoint was concluded (1) between the remimazolam 12 mg/kg/h group and the propofol group, and (2) between the remimazolam 6 mg/kg/h group and the propofol group, if the lower limit of the 95% confidence interval (CI) for the difference between the groups was greater than the pre-defined lower margin of -10%. Noninferiority was also declared if the efficacy rate was 100% for both treatment groups compared and no confidence interval could be calculated. The sample size of 130 patients per remimazolam group and 65 patients in the propofol group provided 90% power at a one-sided significance level of 2.5%, assuming that the anaesthesia success rates was 96% based on the results from earlier studies and allowing for an approximately 10% dropout rate. The statistical plan was considered to be appropriate.

A total of 375 patients were randomised and received study treatment: 150 patients in the remimazolam 6 mg/kg/h group, 150 patients in the remimazolam 12 mg/kg/h group and 75 patients in the propofol group. The median age of the patients was 59 to 61 years (range 20 to 88 years). Approximately half of the patients were ASA[2] physical status I and the other half were ASA physical status II. The mean duration of the surgeries was 123.4 to 155.5 minutes.

Summary of key efficacy results – Study ONO-2745-05

	Remimazolam 6 mg/kg/h (N=150)	**Remimazolam 12 mg/kg/h (N=150)**	**Propofol (N=75)**
Primary endpoint			
No. of patients meeting the primary endpoint (%)	150 (100.0)	150 (100.0)	75 (100.0)
Key secondary endpoints			
Mean time to loss of consciousness, seconds (SD)	102.0 (26.6)	88.7 (22.7)	78.7 (38.4)
P value (vs remimazolam 6 mg/kg/h)	-	<0.0001	-
P value (vs propofol)	<0.0001	0.0149	-
Mean BIS values during maintenance of anaesthesia (range)	40.0-82.0	47.8-84.0	39.0-56.3
Mean time to awakening after end of administration, minutes (SD)	14.9 (11.1)	14.5 (9.8)	10.3 (5.1)
P value (vs remimazolam 6 mg/kg/h)	-	0.7294	-
P value (vs propofol)	0.0007	0.0006	-
Mean time to extubation after end of administration, minutes (SD)	19.2 (14.1)	19.2 (10.8)	13.1 (6.5)
P value (vs remimazolam 6 mg/kg/h)	-	0.9743	-
P value (vs propofol)	0.0004	<0.0001	-
Mean time to stating date of birth after end of administration, minutes (SD)	24.8 (16.2)	24.1 (14.8)	15.6 (11.0)
P value (vs remimazolam 6 mg/kg/h)	-	0.7290	-
P value (vs propofol)	<0.0001	<0.0001	-

[2] American Society of Anesthesiologists

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Mean time to decision to exit the operating room after end of administration, minutes (SD)	28.7 (18.1)	27.9 (15.7)	19.1 (13.1)
P value (vs remimazolam 6 mg/kg/h)	-	0.6730	-
P value (vs propofol)	<0.0001	<0.0001	-

The primary analysis showed that the proportion of subjects in whom the investigational product was assessed as "effective" was 100% in all the groups (remimazolam 6 mg/kg/h, remimazolam 12 mg/kg/h and propofol). Given the 100% effectiveness rates in all the treatment groups, the remimazolam groups were considered to be non-inferior to propofol in terms of functional capability as a GA.

With regard to the secondary endpoints, the mean time to loss of consciousness from the start of investigational product administration was 102.0 and 88.7 seconds in the remimazolam 6 mg/kg/h and remimazolam 12 mg/kg/h groups, respectively, which were statistically significantly longer compared to 78.7 seconds in the propofol group ($p<0.0001$ and $p=0.0149$, respectively). Nonetheless, the anaesthetic depth was determined to be "Very Good" or "Good" in all subjects except for two subjects (1.3%) in the remimazolam 6 mg/kg/h group and 5 subjects (3.3%) in the remimazolam 12 mg/kg/h group. The control of anaesthetic depth was supported by objective measurements using the BIS whereby the values during maintenance of anaesthesia were similar and overlapped between the groups (remimazolam 6 mg/kg/h: 40.0-82.0, remimazolam 12 mg/kg/h: 47.8-84.0, propofol: 39.0-56.3). The mean time to awakening, extubation, stating date of birth, and decision to exit the operating room were statistically significantly longer in the remimazolam 6 mg/kg/h and remimazolam 12 mg/kg/h groups compared to the propofol group (p values ≤0.0007). However, it was reassuring that the absolute differences between remimazolam and propofol were small (≤10 minutes) and none of the subjects had intraoperative awareness and recall from loss of consciousness to the end of surgery or required rescue therapy for sedation.

The results of the two remimazolam doses were similar except that the mean time to loss of consciousness was statistically significantly shorter in the 12 mg/kg/h group compared to the 6 mg/kg/h group (88.7 vs 102.0 seconds, $p<0.0001$).

Study HNP-2001-301 was similar to study ONO-2745-05 except it only investigated remimazolam 6 mg/kg/h. The patients in the study were randomised in a 1:1 ratio to receive remimazolam or propofol.

The primary efficacy endpoint was GA success rate determined by the use of rescue sedatives. 'Success' was defined by the lack of use of other sedatives for anaesthesia from start to finish aside from the investigational product. Otherwise, it was deemed as 'Failure'. The secondary efficacy endpoints included time from investigational product administration to loss of consciousness, number of patients with body movement, BIS value at each evaluation time point, time from investigational product administration completion to eye opening, telling the date of birth, extubation and exit of operating room as well as the controllability of depth of anaesthesia. The endpoints were considered to be relevant for a GA agent.

Non-inferiority between the remimazolam group and propofol group was demonstrated if the lower limit of the 95% CI of the anaesthesia success rate between the two groups was greater than a non-inferiority margin -9.6%. The sample size of 80 patients per group provided a power of 90% at the one-sided significance level of 2.5%, assuming the expected anaesthesia

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success rates to be 96.4% based on the results from earlier studies. The statistical plan was considered to be appropriate.

A total of 182 patients were randomised and received treatment in the per protocol group: 92 patients in the remimazolam group and 90 patients in the propofol group. The median age of the patients was 49 years old (range 20 to 82 years). Approximately half of the patients were ASA class I and the other half were ASA class II. The mean duration of the surgeries was 72.4 to 73.0 minutes.

Summary of key efficacy results – Study HNP-2001-301

	Remimazolam 6 mg/kg/h (N=92)	**Propofol (N=90)**
Primary endpoint		
GA success rate		
Success, n (%)	90 (97.83)	88 (97.78)
Failure, n (%)	2 (2.17)	2 (2.22)
Difference vs propofol, % (95% CI)	0.05 (-4.21, 4.31)	
Secondary endpoints		
Subjects with a body movement from loss of consciousness to surgery completion, n/N (%)	5/90 (5.56)	2/88 (2.27)
P value	0.4439	
Mean BIS immediately before investigational product administration initiation (SD)	93.64 (4.89)	93.28 (5.34)
P value	0.9054	
Mean BIS at loss of consciousness (SD)	68.15 (11.74)	54.32 (15.76)
P value	<0.0001	
Mean BIS at operating room exit	81.22 (5.77)	83.95 (5.89)
P value	0.0021	
Mean time from investigational product administration to loss of consciousness, seconds (SD)	119.02 (32.78)	79.39 (37.59)
P value	<0.0001	
Mean time from investigational product administration completion to first eye opening, minutes (SD)	16.27 (7.13)	10.02 (5.06)
P value	<0.0001	
Mean time from investigational product administration completion to telling the date of birth, minutes (SD)	21.79 (8.18)	12.63 (4.70)
P value	<0.0001	
Mean time from investigational product administration completion to endotracheal tube extubation, minutes (SD)	17.76 (6.61)	11.22 (4.94)
P value	<0.0001	
Mean time from investigational product administration completion to exit operating room, minutes (SD)	23.07 (8.34)	13.83 (4.81)
P value	<0.0001	

The primary analysis showed that the GA success rate was 97.83% in the remimazolam group and 97.78% in the propofol group. Remimazolam was non-inferior to propofol in terms of GA success rate as the lower limit of the corresponding 95% CI for the difference between groups was -4.21%, which met the pre-specified non-inferiority margin.

With regard to the secondary endpoints, the mean time from investigational product administration to loss of consciousness was statistically significantly longer in the

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remimazolam group compared to the propofol group (119.02 vs 79.39 seconds, p<0.0001). The mean times to first eye opening, telling of date of birth, endotracheal tube extubation and exit operating room were also statistically significantly longer in the remimazolam group compared to the propofol group however, the absolute difference between groups was small (≤9.2 minutes). The percentage of subjects with a body movement from loss of consciousness to surgery completion was numerically higher in the remimazolam group than in the propofol group (5.56% vs 2.27%, p=0.4439). Nonetheless, the controllability of depth of anaesthesia was rated as excellent or good in a high proportion of patients in both groups (92.22% in the remimazolam group and 98.87% in the propofol group) and the difference in the proportions was not statistically significant (p=0.0773). The mean BIS at operating room exit was statistically significantly lower in the remimazolam group compared to the placebo group however, the absolute difference between groups was small (Δ=2.73) and not considered to be clinically significant.

The supportive studies, ONO-2745-06 (N=62), a Phase III, uncontrolled, randomised, double-blind, parallel-group study, and CNS7056-010 (N=90), a Phase II, randomised, single-blind, active-controlled, parallel-group study investigated the use of remimazolam as GA in surgical patients. The results of the supportive studies were consistent with that of the pivotal studies as they showed that the functional capability of remimazolam as GA ranged from 96.4% to 100% in the 6 and 12 mg/kg/h groups, with rates comparable to the active comparator sevoflurane plus propofol at 96.4%.

Overall, remimazolam demonstrated a slower onset and recovery compared to propofol. Nevertheless, non-inferiority to propofol was demonstrated in terms of GA success rate for both remimazolam 6 mg/kg/h and 12 mg/kg/h demonstrated with the dose adjusted based on the condition of the patient. Hence, both doses were considered to be acceptable.

Procedural sedation

The clinical efficacy of remimazolam for use in procedural sedation was based primarily on two pivotal Phase III studies, CNS7056-006 and CNS7056-008, as well as one supportive study, CNS7056-015.

Studies CNS7056-006 and CNS7056-008 were similarly designed Phase III, multicentre, double-blind, randomised, active- and placebo-controlled clinical trials in adult patients undergoing colonoscopy and bronchoscopy, respectively. The patients were randomised to remimazolam, midazolam or placebo. The remimazolam and placebo groups were double-blinded, while the midazolam arm was open-label due to the different dosing regimen for the drug and the arm was mainly included to ensure assay sensitivity. After pre-treatment with fentanyl to ensure analgesia, patients received an initial IV dose of 5.0 mg (2 mL) remimazolam or matching placebo over 1 minute or 1.75 mg midazolam over 2 minutes (or 1.0 mg midazolam for patients ≥60 years of age or debilitated or chronically ill). For the remimazolam and placebo arms, supplemental doses of 2.5 mg (1 mL) at least 2 minutes apart were allowed until adequate sedation was achieved, and as necessary to maintain sedation. For midazolam, supplemental doses of 1.0 mg over 2 minutes with 2 minutes between doses (or 0.5 mg for patients aged ≥60 years or debilitated or chronically ill) were allowed to achieve and maintain adequate sedation. Rescue sedation with midazolam in the placebo group or remifentanil in the other treatment groups were dosed at the investigator's discretion to complete the procedure.

The primary endpoint in both the studies was success of the procedure, which was defined as meeting all of the following: (1) completion of the colonoscopy/bronchoscopy procedure; (2)

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no requirement for a rescue sedative medication; and (3) no more than 5 doses of study medication within any 15 minute window (for midazolam: no more than 3 doses within any 12 minute window). The secondary efficacy endpoints included time to start of procedure after administration of the first dose of study medication, time to peak sedation after administration of the first dose of study medication based on the lowest Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score[3] after initial dose, times to ready for discharge (defined as ability to walk unassisted) after the end of colonoscopy (colonoscope out) and after the last injection of study drug, times to fully alert (defined as first of 3 consecutive MOAA/S scores of 5) after the end of colonoscopy (colonoscope out) and after the last injection of study drug. The endpoints were considered to be relevant for a procedural sedative agent.

The primary efficacy analysis of the comparison of the success rates between the remimazolam group and the placebo group in both studies were performed using the Cochran-Mantel-Haenszel test. As the midazolam group was included for assay sensitivity, a 95% CI of the comparison of success rates between midazolam and remimazolam was presented and there was no significance testing.

A sample size of 15 patients per group would provide a power of 90% at the one-sided significance level of 2.5%, assuming the expected success rates to be 90% for remimazolam and 30% for placebo based on results from previous studies. Nonetheless, the sample size was increased to 300 in the remimazolam group in both studies to provide an adequate safety database. The sample size in the placebo group was set to 60 patients to avoid overly unequal sample sizes, and the midazolam group was set to 100 and 60 patients for assay sensitivity in studies CNS7056-006 and CNS7056-008, respectively. The statistical plan was considered to be appropriate.

In study CNS7056-006, a total of 461 patients were randomised in a 30:6:10 ratio: 298 patients in the remimazolam group, 60 in the placebo group and 103 patients in the midazolam group. The median age was 55.5 years (range 19 to 92 years), and the majority of the patients were ASA-PS I (31.2%) or II (62.2%). In study CNS7056-008, a total to 446 patients were randomised in a 30:6:6 ratio: 310 patients in the remimazolam group, 63 in the placebo group and 73 patients in the midazolam group. The median age of the patients was 64.0 years (range 22 to 95 years) and the majority of the patients had ASA-PS II (58.9%) or III (37.6%).

Summary of key efficacy results – Study CNS7056-006

	Remimazolam (N=298)	**Placebo (N=60)**	**Midazolam (N=103)**
Primary endpoint			
Treatment success rate, n (%)	272 (91.3)	1 (1.7)	26 (25.2)
Remimazolam vs placebo (difference in rates) (95%CI)	0.8961 (0.8505, 0.9416)	-	-
P value (vs placebo)	<0.0001	-	-
Remimazolam vs midazolam (difference in rates) (95% CI)	0.6603 (0.5705, 0.7501)	-	-
Secondary endpoints			

[3] The MOAA/S is a widely recognised and validated tool used in clinical settings to objectively measure a patient's level of sedation. The scale ranges from 5 (fully awake) to 0 (unresponsive to painful stimulus) and assesses alertness based on the patient's response to auditory and tactile stimuli, such as speaking their name or squeezing the trapezius muscle (Pastis J N et al., 2022. J Bronchology Interv Pulmonol; 29(1): 54-61).

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Median time to start of procedure from first dose, minutes (95% CI)	4.0 (not evaluable)	19.5 (18.0, 21.0)	19.0 (17.0, 20.0)
P value (vs placebo)	<0.0001		
Median time to peak sedation from first dose, minutes (95% CI)	3.0 (not evaluable)	Not evaluable	Not evaluable
Median time to ready for discharge from end of procedure, minutes (95% CI)	44.0 (42.0, 46.0)	49.0 (44.0, 54.0)	48.0 (41.0, 51.0)
P value (vs placebo)	<0.0001	-	-
Median time to ready for discharge from last dose, minutes (95% CI)	51.0 (49.0, 54.0)	60.5 (55.0, 67.0)	57.0 (53.0, 61.0)
P value (vs placebo)	<0.0001	-	-
Median time to fully alert from end of procedure, minutes (95% CI)	6.0 (5.0, 7.0)	15.0 (13.0, 21.0)	13.0 (11.0, 16.0)
P value (vs placebo)	<0.0001	-	-
Median time to fully alert from last dose, minutes (95% CI)	14.0 (13.0, 14.0)	28.0 (24.0, 32.0)	24.0 (22.0, 26.0)
P value (vs placebo)	<0.0001	-	-

The results of study CNS7056-006 showed a statistically significantly higher colonoscopy success rate in the remimazolam group compared to the placebo group (91.3% vs 1.7%, p<0.0001). The low success rate in the placebo group was expected and procedure completion was achieved by the use of rescue midazolam. The treatment success rate in the remimazolam group was also greater than in the midazolam group (91.3% vs 25.2%). Midazolam is known to exhibit variable pharmacokinetics leading to unpredictable sedation, hence the relatively low success rate and the need for rescue medication were not unexpected.

In terms of the secondary endpoints, the median time to start of procedure was statistically significantly shorter in the remimazolam group compared to the placebo group (4.0 vs 19.5 minutes, p<0.0001) as well as the midazolam group (4.0 vs 19.0 minutes). The median time to peak sedation was 3.0 minutes in remimazolam group, but it could not be estimated in the placebo and midazolam groups as the majority of patients were censored for not reaching MOAA/S score of 3 at the time of assessment. The median time to ready for discharge from the end of procedure was slightly shorter in the remimazolam group compared to the placebo and midazolam group (44.0 vs 49.0 and 48.0 minutes, respectively). The median time to ready for discharge from last dose was statistically significantly shorter in the remimazolam group compared to the placebo group (51.0 vs 60.5 minutes, <0.0001) as well as the midazolam group (51.0 vs 57.0 minutes). The same trend was observed for the times to be alert from the end of colonoscopy (6.0 vs 15.0 vs 13.0 minutes) and from the last dose (14.0 vs 28.0 vs 24.0 minutes) in the remimazolam, placebo and midazolam groups, respectively. In general, the results favoured the remimazolam group while the similar outcomes between the placebo and midazolam groups were expected, as placebo-treated patients received rescue midazolam.

Summary of key efficacy results – Study CNS7056-008

	Remimazolam (N=310)	**Placebo (N=63)**	**Midazolam (N=73)**
Primary endpoint			
Treatment success rate, n (%)	250 (80.6)	3 (4.8)	24 (32.9)

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Remimazolam vs placebo (difference in rates) (95% CI)	0.7588 (0.6903, 0.8274)	-	-
P value (vs placebo)	<0.0001	-	-
Remimazolam vs midazolam (difference in rates) (95% CI)	0.4777 (0.3613, 0.5941)	-	-
Secondary endpoints			
Median time to start of procedure from first dose, minutes (95% CI)	4.1 (4.0, 4.8)	17.0 (16.0, 17.5)	15.5 (13.8, 16.7)
P value (vs placebo)	<0.0001		
Median time to peak sedation from first dose, minutes (95% CI)	3.5 (3.5, 4.0)	Not evaluable	7.0 (7.0, not evaluable)
Median time to ready for discharge from end of procedure, minutes (95% CI)	60.0 (57.0, 63.0)	81.0 (70.0, 100.0)	66.0 (62.0, 72.0)
P value (vs placebo)	0.0004	-	-
Median time to ready for discharge from last dose, minutes (95% CI)	64.8 (62.0, 68.5)	93.0 (75.0, 107.0)	70.0 (67.0, 87.0)
P value (vs placebo)	0.0002	-	-
Median time to fully alert from end of procedure, minutes (95% CI)	6.0 (5.2, 7.1)	13.6 (8.1, 24.0)	12.0 (5.0, 15.0)
P value (vs placebo)	0.0001	-	-
Median time to fully alert from last dose, minutes (95% CI)	11.6 (10.0, 12.8)	20.0 (15.3, 31.0)	18.0 (15.0, 20.1)
P value (vs placebo)	0.0001	-	-

The results of study CNS7056-008 also showed a statistically significantly higher bronchoscopy success rate in the remimazolam group compared to the placebo group (80.6% vs 4.8%, p<0.0001). As anticipated, the placebo group demonstrated a low success rate and rescue midazolam was administered to complete the procedure. The treatment success rate in the remimazolam group was also greater than in the midazolam group (80.6% vs 32.9%). The results in the midazolam group were consistent with what is known for the drug.

In terms of the secondary endpoints, the median time to start of procedure was statistically significantly shorter in the remimazolam group compared to the placebo group (4.1 vs 17.0 minutes, p<0.0001) as well as the midazolam group (4.1 vs 15.5 minutes). The median time to peak sedation was 3.5 minutes in remimazolam group and 7.0 minutes in the midazolam group. It could not be estimated in the placebo group since there was only one patient who achieved peak sedation with MOAA/S ≤3. The median time to ready for discharge from the end of procedure was slightly shorter in the remimazolam group compared to the placebo and midazolam groups (60.0 vs 81.0 and 66.0 minutes, respectively). The median time to ready for discharge from last dose was statistically significantly shorter in the remimazolam group compared to the placebo group (64.8 vs 93.0 minutes, <0.0001) as well as the midazolam group (64.8 vs 70.0 minutes). The same trend was observed for the times to be alert from the end of bronchoscopy (6.0 vs 13.6 vs 12.0 minutes) and from the last dose (11.6 vs 20.0 vs 18.0 minutes) in the remimazolam, placebo and midazolam groups, respectively. Similar to study CNS7056-006, the results generally favoured the remimazolam group, whereas the placebo and midazolam groups yielded comparable outcomes as placebo-treated patients received rescue midazolam.

The supportive study, CNS7056-015, was a Phase III, multicentre, double-blind, randomised, placebo- and active-controlled, parallel group study (N=79) comparing remimazolam to placebo, with an additional open-label arm for midazolam, in ASA grade III/IV patients undergoing a colonoscopy. The results were consistent with that of the pivotal studies whereby the success rates in the remimazolam group were higher compared to the placebo and midazolam groups (84.4% vs 0% vs 12.9%).

Overall, remimazolam was efficacious for the induction and maintenance of procedural sedation, with higher procedure success rates and shorter times to peak sedation, discharge and becoming alert, compared to placebo and midazolam.

D ASSESSMENT OF CLINICAL SAFETY

GA

The clinical safety of remimazolam for use in GA was based primarily on safety data derived from the pivotal studies, ONO-2745-05 and HNP-2001-301, comprising a total of 571 patients who received at least one dose of study treatment.

Overview of safety profile – Study ONO-2745-05

AE	Remimazolam 12 mg/kg/h (N=150)	Remimazolam 6 mg/kg/h (N=150)	Propofol (N=75)
TEAE (no. of patients, %)	127 (84.7%)	121 (80.7%)	63 (84.0%)
Mild (no. of patients, %)	89 (59.3%)	92 (61.3%)	44 (58.7%)
Moderate (no. of patients, %)	36 (24.0%)	29 (19.3%)	18 (24.0%)
Severe (no. of patients, %)	2 (1.3%)	0	1 (1.3%)
SAE (no. of patients, %)	2 (1.3%)	0	0
Discontinuations due to AE (no. of patients, %)	0	0	0
Deaths due to AE (no. of patients, %)	0	0	0

Overview of safety profile – Study HNP-2001-301

AE	Remimazolam 6 mg/kg/h (N=96)	Propofol (N=100)
Injection site AE (no. of patients, %)	2 (2.1%)	0
Total no. of events	2	0
Mild (no. of events)	2 (100.0%)	0
Moderate (no. of events)	0	0
Severe (no. of events)	0	0
Non-injection site AE (no. of patients, %)	75 (78.1%)	72 (72.0%)
Total no. of events	174	161
Mild (no. of events)	165 (94.8%)	158 (98.1%)
Moderate (no. of events)	9 (5.2%)	3 (1.9%)
Severe (no. of events)	0	0
SAE (no. of patients, %)	0	0
Discontinuations due to AE (no. of patients, %)	0	0
Deaths due to AE (no. of patients, %)	0	0

The incidence of treatment-emergent adverse events (TEAEs) was comparable between the remimazolam groups and the propofol group in the pivotal studies (range: 78.1% to 84.7% vs 72.0 to 84.0%). The majority of the TEAEs were mild (range: 58.7% to 100.0%) or moderate (range: 19.3% to 24.0%) in severity.

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In study ONO-2745-05, except for the incidence of blood urine present which was higher (≥10% difference) in the remimazolam groups compared to the propofol group (range: 15.3% to 16.0% vs 5.3%), common TEAEs (incidence ≥10%) occurred at similar rates in the remimazolam groups and propofol group. These included blood pressure decreased (range: 32.7% to 34.0% vs 58.7%), nausea (range: 16.7% to 18.7% vs 14.7%), vomiting (range: 12.7% to 17.3% vs 10.7%), pyrexia (range: 8.0 to 11.3% vs 9.3%) and wound complication (range: 13.3% to 15.3% vs 13.3%).
A similar trend was observed in the other study HNP-2001-301. Aside from a higher incidence (≥5% difference) of blood pressure increased (16.7% vs 8.0%) and headache (14.6% vs 9.0%) in the remimazolam group compared to the propofol group, the incidences of other common TEAEs (incidence ≥10%) were generally similar between the remimazolam group and propofol group. The TEAEs included procedural pain (47.9% vs 48.0%), blood pressure decreased (12.5% vs 17.0%), headache (14.6% vs 9.0%) and dizziness (10.4% vs 10.0%).

A total of 2 serious AEs (SAEs) of post procedural haemorrhage was reported in 2 subjects in the remimazolam 6 mg/kg/h group in study ONO-2745-05. In both subjects, the causal relationship to investigational product was ruled out and the events resolved with treatment. No SAEs were reported in the other study HNP-2001-301. In addition, no discontinuations or deaths due to AEs were reported in both studies.

AEs of special interest related to prolonged sedation during recovery were reported in the supportive study CNS7056-010. Nevertheless, the incidences were comparable between the pooled remimazolam group and the active comparator (sevoflurane plus propofol) (19.4% vs 21.4%). The AE of special interest has been adequately described as warning in the package insert.

Procedural sedation

The clinical safety of remimazolam for use in procedural sedation was based primarily on safety data from the pivotal studies CNS7056-006 and CNS7056-008, comprising a total of 889 patients who received at least one dose of study treatment.

Overview of safety profile – Study CNS7056-006

AE	Remimazolam (N=296)	Placebo (N=60)	Midazolam (N=102)
TEAE (no. of patients, %)	218 (73.6%)	47 (78.3%)	93 (91.2%)
Mild (no. of patients, %)	211 (71.3%)	46 (76.7%)	92 (90.2%)
Moderate (no. of patients, %)	6 (2.0%)	0	1 (1.0%)
Severe (no. of patients, %)	1 (0.3%)	1 (1.7%)	0 (0.0%)
SAE (no. of patients, %)	0	0	0
Discontinuations due to AE (no. of patients, %)	0	0	0
Deaths due to AE (no. of patients, %)	0	0	0

Overview of safety profile – Study CNS7056-008

AE	Remimazolam (N=303)	Placebo (N=59)	Midazolam (N=69)
TEAE (no. of patients, %)	268 (88.4%)	52 (88.1%)	63 (91.3%)
Mild (no. of patients, %)	223 (73.6%)	43 (72.9%)	57 (82.6%)
Moderate (no. of patients, %)	35 (11.6%)	8 (13.6%)	6 (8.7%)
Severe (no. of patients, %)	10 (3.3%)	1 (1.7%)	0
SAE (no. of patients, %)	17 (5.6%)	4 (6.8%)	0
Discontinuations due to AE (no. of patients, %)	1 (0.3%)	0	0
Deaths due to AE (no. of patients, %)	0	0	0

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The incidence of TEAEs in the remimazolam group was similar to that in the placebo group (range: 73.6%-88.4% vs 78.3%-88.1%) but lower than that in the midazolam group (range: 91.2-91.3%) in the studies. In addition, the majority of events (>90%) were mild or moderate in severity.

Across the studies, the most frequently reported TEAEs by system organ class (SOC) were vascular disorders (range: 62.2%-77.6% vs 68.3%-79.7% vs 81.2%-81.4%) in the remimazolam, placebo and midazolam groups, respectively. The most frequently reported vascular disorders TEAEs were hypotension (38.9% vs 41.7% vs 61.8% in study CNS7056-006 and 32.7% vs 47.5% vs 33.3% in study CNS7056-008) and hypertension (19.9% vs 28.3% vs 17.6% in study CNS7056-006 and 28.1% vs 15.3% vs 27.5% in study CNS7056-008). Other frequently reported TEAEs included cardiac disorders (17.9% vs 23.3% vs 25.5%) such as bradycardia (11.1% vs 11.7% vs 15.7%) and tachycardia (7.8% vs 11.7% vs 12.7%) in study CNS7056-006 and respiratory, thoracic, and mediastinal disorders (31.4% vs 33.9% vs 29.0%) such as hypoxia (21.8% vs 20.3% vs 18.8%) and tachypnoea (2.3% vs 10.2% vs 5.8%) in study CNS7056-008.

No SAE was reported in study CNS7056-006. In study CNS7056-008, a total of 17 (5.6%) patients in the remimazolam group and 4 (6.8%) patients in the placebo group reported SAEs, including acute respiratory failure, aspiration, atrial fibrillation / tachycardia, bradycardia, bronchospasm, chronic obstructive pulmonary disease, confusion, dyspnoea, hypoxia, pneumonia, pneumothorax, pneumomediastinum and pleural effusion. All the SAEs were resolved. Only one case of hypoxia and bradycardia in the remimazolam group was assessed as treatment related. One subject discontinued treatment due to AEs and no death was reported.

In study CNS7056-008, the AEs of special interest reported with remimazolam included dyspnoea (1 case), bronchospasm (2 cases), hypoxia, pleural effusion and respiratory failure (1 case), respiratory failure and aspiration (1 case) and confusion (1 case). The causality was assessed as unlikely related in all cases and all the events resolved. No significant AEs were reported in study CNS7056-006.

As remimazolam is a benzodiazepine, the abuse potential of the drug was assessed in a clinical pharmacology study CNS7056-014 (N=40) in comparison with placebo and midazolam in healthy adults who had previously used recreational central nervous system (CNS) depressants. Five different treatments (A: remimazolam 5 mg, B: remimazolam 10 mg, C: midazolam 2.5 mg, D: midazolam 5 mg, E: placebo) were administered as single IV bolus dose on Days 5, 7, 9, 11, and 13 in a crossover fashion. The Drug Liking and Take Drug Again Visual Analogue Scale (VAS) scores at maximum effect (E_{max}) were used in the assessment of abuse potential.

When compared to placebo, the Drug Liking VAS for remimazolam was statistically significantly higher with an LS mean difference (95% CI) of 24.57 (20.34, 28.81) for 5 mg and 26.69 (22.46, 30.92) for 10 mg. The Take Drug Again VAS was also statistically significantly higher with an LS mean difference (95% CI) of 19.81 (8.87, 30.76) for 5 mg and 32.09 (21.14, 43.03) for 10 mg.

When compared to midazolam, the Drug Liking VAS were similar between groups (range: 77.69-81.51). The Take Drug Again VAS for remimazolam 5 mg was statistically significantly lower than for midazolam 2.5 mg with an LS mean difference (95% CI) of -19.35 (-30.30, -8.41), but there was no significant difference between the remimazolam 10 mg and midazolam 5 mg groups with an LS mean difference (95% CI) of -9.01 (-19.95, 1.94).

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The results suggested that remimazolam exhibits abuse potential that is comparable to that of midazolam. Warnings and precautions on the AEs of special interest and abuse potential have been adequately described in the package insert.

No unexpected safety signals were observed for remimazolam in the clinical studies. The safety profile and abuse potential of remimazolam appeared similar to that of other benzodiazepines used for GA and procedural sedation. Overall, no major safety concerns were raised and the safety profile of remimazolam for the induction and maintenance of GA and procedural sedation could be mitigated through product labelling.

E ASSESSMENT OF BENEFIT-RISK PROFILE

GA

GA is usually required for major surgery and can be accomplished through different methods, including inhalation anaesthesia or total intravenous anaesthesia (TIVA). The current available agents for TIVA are limited to propofol and midazolam. Propofol is a lipophilic drug which is short-acting (half-life 2 to 8 minutes) allowing rapid recovery from sedation. However, it is associated with the possible risks of anaphylactic reactions to the soy components in the lipid emulsion, respiratory depression, severe hypotension and bradycardia. Midazolam is a benzodiazepine which is longer acting (half-life 1.5 to 3.5 hours) hence it may result in delayed recovery and a higher risk of post-operative delirium. Remimazolam is a short-acting benzodiazepine (half-life 1 to 2 minutes) which could serve as an alternative option for TIVA.

In study ONO-2745-05 in surgical patients with ASA class I or II undergoing GA, remimazolam was shown to be non-inferior to propofol in terms of functional capability as a GA. The primary efficacy endpoint of functional capability as a GA, characterised by a lack of intraoperative awakening or recall, requirement of rescue sedation with other sedatives, and body movement, was achieved in 100% of patients in all three groups (remimazolam 6 mg/kg/h and 12 mg/kg/h and propofol).

In the other study HNP-2001-301, remimazolam 6 mg/kg/h met the predefined criterion for non-inferiority to propofol with respect to GA success, defined as the absence of rescue sedative use. The lower bound of the 95% confidence interval for the treatment difference (−4.21%) was within the prespecified non-inferiority margin.

With regard to the secondary endpoints, the mean time to loss of consciousness from the start of investigational product administration was longer in the remimazolam groups (range: 88.7 to 119.02 seconds) compared to the propofol group (range: 73.4 to 78.7 seconds) across both studies. However, the difference between groups did not impact the anaesthetic depth which was determined to be “Good” to “Very Good” in more than 96% of the subjects. This was further supported by the overlapping ranges of mean BIS values (39.0 to 84.0) across the groups in study ONO-2745-05 and the small absolute difference (Δ=2.73) between groups in study HNP-2001-301 was not considered to be clinically significant.

The differences in the recovery parameters including mean times to awakening, extubation, stating date of birth, and decision to exit the operating room between the remimazolam groups and the propofol group were also small (<10 minutes) and not considered to be clinically significant. While in study HNP-2001-301 a numerically higher proportion of subjects with a

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body movement from loss of consciousness to surgery completion occurred in the remimazolam group than in the propofol group (5.56% vs 2.27%, p=0.4439), the controllability of depth of anaesthesia was not affected and rated as good to excellent in more than 92% of patients in both groups. In addition, none of the subjects had intraoperative awareness and recall from loss of consciousness to the end of surgery or required rescue therapy for sedation. In all, remimazolam demonstrated functional capability as a GA and was non-inferior to propofol in terms of success rate, albeit with a slower onset and recovery.
Remimazolam 6 mg/kg/h and 12 mg/kg/h showed comparable results aside from a longer mean time to loss of consciousness in the 12 mg/kg/h group compared to the 6 mg/kg/h group (102.0 vs 88.7 seconds). Hence, both doses were considered to be supported, with dose selection to be individualised based on the patient's condition.

With regard to safety, remimazolam was generally well tolerated when used for GA with comparable incidences of AEs between the remimazolam groups and the propofol group across the pivotal studies. The majority of the AEs were mild or moderate in intensity and the incidence of SAEs was low and generally not considered to be related to the study drug. In addition, no discontinuations or deaths due to AEs were reported in the studies. The AEs of special interest included prolonged sedation during recovery and renal insufficiency, renal failure and bleeding disorders, but the incidences were similar with the propofol group, and the risks could be mitigated through warnings and precautions in the package insert.

Overall, the benefit risk profile for the use of remimazolam for the induction and maintenance of GA in adults was considered favourable as efficacy and safety were demonstrated.

Procedural sedation

The drugs which are commonly used for procedural sedation include propofol and midazolam. Due to the known risks associated with propofol, including respiratory and haemodynamic effects, its administration requires close monitoring and is typically performed by a physician trained in the administration of GA or intensive care management. Remimazolam is a short-acting benzodiazepine that may provide an alternative to midazolam, which is longer-acting and associated with a greater potential for prolonged sedation.

In studies CNS7056-006 and CNS7056-008 in patients undergoing colonoscopy and bronchoscopy, respectively, the success of the procedure was observed in a statistically significantly greater proportion of patients treated with remimazolam (range: 80.6% to 91.3%) compared to placebo (range: 1.7% to 4.8%, $p<0.0001$) and was numerically higher compared to midazolam (range: 25.2% to 32.9%). The low success rates in the placebo groups were expected, with the majority of patients requiring rescue midazolam to complete the procedures. For the midazolam groups, the relatively low success rates were consistent with what is known for the drug.

The results of the secondary endpoints supported the primary endpoint, generally favouring the remimazolam group. The placebo and midazolam groups showed comparable results because placebo-treated patients were given rescue midazolam for procedure completion. The findings showed that the median time to peak sedation was reached in 3.0 to 3.5 minutes in patients treated with remimazolam. In study CNS7056-006, the median time to peak sedation could not be estimated for the midazolam and placebo groups as most of the patients in these groups did not achieve MOAA/S score of 3 or less. In study CNS7056-008, the median time to peak sedation was longer in the midazolam group at 7.0 minutes. It was not determined for the placebo group as there was only one patient who achieved MOAA/S score of 3 or less.

The median time to fully alert after the end of the procedure was shorter in patients treated with remimazolam (6.0 minutes in both studies) compared to placebo (range: 13.6 to 15.0 minutes) and midazolam (range: 12.0 to 13.0 minutes). The median time to being fully alert from last dose of study drug was also reached faster in patients treated with remimazolam (range: 11.6 to 14.0 minutes) compared to placebo (range: 20.0 to 28.0 minutes) and midazolam (range: 18.0 to 24.0 minutes).

With regard to safety, remimazolam was generally well tolerated when used for procedural sedation. Most of the AEs were mild or moderate in intensity. The incidence of SAEs was similar between the remimazolam and placebo groups (5.6% vs 6.8%). In addition, only one subject discontinued treatment due to AEs and there were no deaths reported. The AEs of special interest included dyspnoea, bronchospasm, hypoxia, pleural effusion, respiratory failure, aspiration, and confusion. However, the events resolved and were considered unrelated to the study drug. The risks could be mitigated through warnings and precautions in the package insert.

Overall, the benefit-risk profile of remimazolam for the induction and maintenance of procedural sedation in adults undergoing procedures was considered favourable as efficacy and safety were demonstrated.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Byfavo for the induction and maintenance of general anaesthesia in adults as well as the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less was deemed favourable and approval of the product registration was granted on 27 August 2025.

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APPROVED PACKAGE INSERT AT REGISTRATION

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신제품 표시부자재 하니제약(주)

제품명	[싱가포르] 바이파보주 20mg
사이즈(mm)	190 X 540
컬러	BLACK
결재시작/완료	2025. 08. 25.
디자인담당	윤여상 대리 (02-559-5787)
해외사업담당	박현지
업체정보	동아인쇄 land00 / land00

Prescription Drug | IV

Byfavo™ Inj. 20mg
(remimazolam besylate)

Composition : Drug Substances & Excipients
Each vial contains :
- Active ingredient : Remimazolam besylate ····· 27.2mg
  (equivalent to 20mg remimazolam)
- Excipient (Stabilizer) : Dextran 40 ····· 79.13mg
- Excipient (Stabilizer) : Lactose monohydrate ····· 52.75mg
- Animal origin : Lactose monohydrate (milk from cow)
- Other excipients : Sodium hydroxide, Hydrochloric acid

[DESCRIPTION]
Each clear glass vial of BYFAVO (remimazolam) for injection contains white to off-white lyophilized powder ready for reconstitution.
1) Description of the product appearance after reconstitution: A clear colorless to pale yellow solution, practically free from visible particulate matter.
2) Description of the container closure system: Clear 12 mL Type I glass vials fitted with bromobutyl rubber stoppers and capped with aluminium caps.

[INDICATION AND USAGE]
1. The induction and maintenance of general anesthesia in adults
2. The induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less

[DOSAGE AND ADMINISTRATION]
1. General Anesthesia
BYFAVO should be administered in combination with other analgesics and muscle relaxants as appropriate. [See Precautions for Use 5. General Warnings]
1) Induction of General Anesthesia
For adult patients: Administer remimazolam intravenously at the infusion rate of 6 mg/kg/hr (0.1 mg/kg/min) or 12 mg/kg/hr (0.2 mg/kg/min) until the loss of consciousness while observing general condition of the patient.
Infusion rate and dose should be adjusted based on general condition of the patient.
2) Maintenance of General Anesthesia
For adult patients: Administer remimazolam intravenously at the infusion rate of 1 mg/kg/hr once loss of consciousness is achieved, and adjust the infusion rate appropriately while observing general condition of the patient to maintain the adequate depth of anesthesia (up to maximum 2 mg/kg/hr). Infusion rate should be adjusted based on general condition of the patient.

2. Procedural Sedation
Remimazolam dosing should be individually titrated to an effective dose which provides the desired level of sedation and minimizes adverse reactions.
In case of procedural sedation with opioid,
1) Induction: For adult patients, administer opioid and wait 1-2 min. Initial dose should be 5 mg (2 mL) injection over 1 min and wait 2 min. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, administer opioid and wait 1-2 min. Initial dose should be 2.5-5 mg (1-2 mL) injection over 1 min and wait 2 min.
2) Maintenance/titration: For adult patients, administer 2.5 mg (1 mL) injection over 15 sec. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, administer 1.25-2.5 mg (0.5-1 mL) injection over 15 sec.
3) For adult patients, maximal total dose administrated in the clinical trials was 33 mg. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, maximal total dose administrated in the clinical trials was 17.5 mg.
In case of procedural sedation without opioid,
1) Induction: For adult patients, administer 7 mg (2.8 mL) Injection over 1 min and wait 2 min. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, administer 2.5-5 mg (1-2 mL) injection over 1 min and wait 2 min.
2) Maintenance/titration: For adult patients, administer 2.5 mg (1 mL) injection over 15 sec. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, administer, administer 1.25-2.5 mg (0.5-1 mL) injection over 15 sec.
3) For adult patients, maximal total dose administrated in the clinical trials was 33 mg. For elderly≥65 years of age and/or with ASA-PS III-IV and/or body weight<50 kg, maximal total dose administrated in the clinical trials was 17.5 mg.
Additional doses can be administered as needed to induce or maintain the desired level of sedation. At least 2 minutes should elapse prior to administration of any supplemental dose in order to fully assess the sedative effect. If 5 doses of remimazolam within 15 minutes do not result in the desired level of sedation then an additional or another sedative should be considered. Remimazolam is associated with fast onset and offset of sedation. In clinical trials, peak sedation occurred 3-3.5 minutes after the initial bolus and patients became fully alert 12-14 minutes from last dose of remimazolam.
Opioid co-administered medicinal products are known to increase the sedative effect of remimazolam and to depress the ventilatory response to carbon dioxide stimulation.

3. Geriatric Patients
Elderly, American Society of Anesthesiologists Physical Status (ASA-PS) III-IV patients and patients with body weight < 50 kg
Elderly patients and patients with ASA-PS III-IV may be more sensitive to the effects of sedatives. Before administration of remimazolam a careful assessment of the overall condition of patients ≥65 years of age and/or with ASA-PS III-IV, especially with low body weight (< 50 kg), is therefore of particular relevance when deciding upon individualised dosage adjustments for these patients.

4. Patients with Hepatic Impairment
Dose adjustment is not required in patients with mild to severe hepatic impairment based on Child-Pugh classification.
However, infusion rate and dose should be carefully adjusted based on general condition of the patient with severe hepatic impairment. [See Precautions for Use 10. Hepatic Impairment]

5. Patients with Renal Impairment
Dose adjustment is not required in patients with renal impairment.

6. Preparation
1) For General Anesthesia:
(1) In Prior to administration, reconstitute BYFAVO by adding 4.05 mL sterile Sodium Chloride Injection (0.9% w/v) to the vial and dissolve the contents fully. The reconstituted product will deliver a final concentration of 5.0 mg/mL solution of BYFAVO. [See Precautions for Use 13. Precautions for Administration]
(2) If needed, a further dilution to the final concentration of 1.0 mg/mL is allowed.
2) For Procedural Sedation:
In Prior to administration, reconstitute BYFAVO by adding 8.2 mL sterile Sodium Chloride Injection (0.9% w/v) to the vial and dissolve the contents fully. The reconstituted product will deliver a final concentration of 2.5 mg/mL solution of BYFAVO. [See Precautions for Use 13. Precautions for Administration]
3) BYFAVO must be immediately used after opening and discarded after use. Stability of the reconstituted BYFAVO has not been established.

[PRECAUTIONS FOR USE]
1. Warnings
1) Risk of administration error: Due to different reconstitution instructions (concentration of reconstitution) of BYFAVO depending on the intended use, carefully determine the amount of sterilized saline solution required for reconstitution at the necessary concentration. Caution during preparation and administration.
2) Concomitant use of benzodiazepine including remimazolam, opioids or CNS depressant medications may result in profound sedation, respiratory depression, coma, and death. Thus, prescription by BYFAVO for a concomitant use of benzodiazepines and opioids should be limited only to patients without any alternative medications at the lowest effective dose with the shortest period of prescription. Continuously monitor patients with the concomitant use for respiratory depression and depth of sedation.
3) BYFAVO should be administered by a medical doctor trained for either general anesthesia or procedural sedation. Equipment for the maintenance of a patient airway, an oxygenator, and cardiovascular resuscitation should be immediately available during administration of BYFAVO.
4) BYFAVO should not be administered by a person who is involved in the conduct of the diagnostic procedure, or who conducts the operation.
5) Continuously monitor patients for hypotension, apnea, respiratory obstruction, oxygen desaturation during administration of BYFAVO. Such effects on the cardiovascular and respiratory system can occur when BYFAVO is administered rapidly by intravenous injection to the patients, especially geriatric patients, debilitated patients, or patients with ASA-PS Class III or above.
6) Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic/sedative agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drus administration or other factors such as the surgery or underlying illness.
7) Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on bain development in early life and late pregnancy. These studies have demonstrated that anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity during the period of rapid brain growth or synaptogenesis may results in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. The clinical significance of these non-clinical findings is yet to be determined. However, based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend to approximately 3 years of age in humans.
8) Special warnings and precautions for use
A. Cardiorespiratory adverse reactions
Cardiorespiratory adverse reactions have been reported with the use of remimazolam, including respiratory depression, bradycardia and hypotension. Remimazolam administration can be associated with a transient increase in heart rate (10-20 beats per minute) starting as early as 30 seconds after the start of dosing (corresponding to the time of maximum concentration of remimazolam) before resolving within about 30 minutes after the end of administration. This increase in heart rate coincides with a decrease in blood pressure and it may confound QT correction for heart rate translating into a small prolongation in QTcF in the first few minutes following dosing. Special attention is required for elderly patients (≥65 years of age), for patients with impaired respiratory and/or cardiac function or for patients with poorer general health status
B. Concomitant use of opioids
Concomitant use of remimazolam and opioids may result in profound sedation, respiratory depression, coma and death. In patients with longer-term opioid use, caution is advised; it should not be presumed that these effects will be attenuated.
C. Concomitant use of alcohol / CNS depressants
The concomitant use of remimazolam with alcohol or/and CNS depressants should be avoided. Alcohol intake should be avoided for 24 hours before remimazolam administration. Such concomitant use has the potential to increase the clinical effects of remimazolam, possibly including severe sedation or clinically relevant respiratory depression.
D. Chronic CNS depressant use
Patients who receive chronic benzodiazepine therapy (e.g., for insomnia or anxiety disorders) may develop tolerance to the sedative effects of remimazolam. Hence, a larger cumulative dose of remimazolam may be required to achieve the desired level of sedation. It is recommended to follow the titration regimen in section 4.2 and titrate up based on the patient's sedation-response, until the desired depth of sedation is achieved.
E. Monitoring
Remimazolam should be administered only by health care professionals experienced in sedation who are not involved in conducting the procedure, in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function. Administering personnel must be adequately trained in the recognition and management of expected adverse reactions including respiratory and cardiac resuscitationPatients should be monitored closely during and after the procedure for signs and symptoms of respiratory depression and sedation. The physician should also be aware of the typical time taken for patients to recover from the effects of remimazolam and concomitant opioid used in the clinical trials, but that this may vary in individual patients. Patients should be closely monitored until they are judged by the healthcare professional to be sufficiently recovered.
F. Amnesia
Remimazolam can cause anterograde amnesia. Amnesia, if prolonged, can present problems in outpatients, who are scheduled for discharge following intervention. After receiving remimazolam, patients should be assessed and discharged from hospital or consulting room by their physician, only with appropriate advice and support.
G. Hepatic impairment
The clinical effects may be more pronounced and last longer in patients with severe hepatic impairment due to reduced clearance . Special attention is required for the timing of titration doses . These patients may be more susceptible to respiratory depression

2. Contraindications
Patients with
1) Severe hypersensitivity to BYFAVO, other benzodiazepine drugs, or the composition of BYFAVO
2) Acute narrow-angle glaucoma
3) In shock or coma
4) Acute alcoholism with suppressed vital signs
5) Sleep apnea syndrome
6) Alcohol or drug dependence
7) Severe or acute respiratory failure
8) Genetic disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption (BYFAVO contains lactose)
9) History of severe hypersensitivity to dextran 40 [See Precautions for Use 5. General Warning]
10) Unstable myasthenia gravis

3. Administration with Precautions
1) Particular care should be taken when administering remimazolam to a patient with myasthenia gravis [See Precautions for Use 2. Contraindications]
2) Patients with respiratory deterioration due to cor pulmonale, chronic obstructive pulmonary disease, bronchial asthma, or cerebrovascular dysfunction in the acute phase. BYFAVO should not be administered to the patients with those diseases in principle, but may be administered carefully if necessary.
3) Patients with a cardiovascular diseases (e.g., congestive heart failure)
4) Geriatric patients
5) Debilitated patients
Patients with:
1) Organic cerebral dysfunction
2) Chronic renal failure
3) Acute decompensated disease (e.g., severe body fluids or electrolyte disorders)
4) Acute drug poisonings caused by sedative-hypnotics, analgesics, antipsychotics, antidepressants, or lithium
5) Spinal or cerebellar ataxia
6) Organic cerebral dysfunction
7) Chronic renal failure
8) Acute decompensated disease (e.g., severe body fluids or electrolyte disorders)
9) Acute drug poisonings caused by sedative-hypnotics, analgesics, antipsychotics, antidepressants, or lithium
10) Spinal or cerebellar ataxia
11) Chronic diseases
12) Severe hepatic impairment (Child-Pugh class C)
13) ASA-PS III and above (Administer BYFAVO carefully at a reduced infusion rate and monitor patients for apnea, hypotension, or cardiorespiratory complications)

4. Adverse Reactions
1) Adverse reactions associated with intravenous remimazolam are tabulated according to the MedDRA system organ classification and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency groupings are as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from available data).

Table 1: Tabulated list of adverse reactions

Immune system disorders	
Not known	Anaphylactic reaction
Nervous system disorders	
Common Common Uncommon	Headache Dizziness Somnolence
Cardiac disorders	
Common	Bradycardia[1*]
Vascular disorders	
Very common	Hypotension[2*]
Respiratory, thoracic and mediastinal disorders	
Very common Uncommon	Respiratory depression[3*] Hiccups
Gastrointestinal disorders	
Common Common	Nausea Vomiting
General disorders and administration site conditions	
Uncommon Uncommon	Chills Feeling cold

[1] Bradycardia covers the following identified events: bradycardia, sinus bradycardia, and heart rate decreased.
[2] Hypotension covers the following identified events: hypotension, diastolic hypotension, blood pressure decreased, blood pressure decreased systolic, and blood pressure decreased diastolic.
[3] Respiratory depression covers the following identified events: hypoxia, respiratory rate decreased, respiratory acidosis, bradypnoea, dyspnoea, oxygen saturation decreased, breath sounds abnormal, hypopnoea, respiratory depression, and respiratory distress.
* See Description of Selected Adverse Reactions

2) BYFAVO was administered in 623 patients undergoing general or heart surgeries with general anesthesia in Phase 2 and Phase 3 studies.
The most common adverse reactions include blood pressure decrease in 27.3% of the patients (170 out of 623 patients), nausea in 16.5% (103 out of 623), wound complications in 13.5% (84 out of 623), hematuria in 12.8% (80 out of 623), and vomiting in 12.4% (77 out of 623).
Other adverse reactions were hypotension or blood pressure decrease in 29.7% of the patients (185 out of 623), bradycardia in 3.0% (19 out of 623), heart rate decrease in 2.1% (13 out of 623), and respiratory depression (respiratory failure, hypopnea, respiratory depression, respiratory distress syndrome, respiratory rate decrease) in 3.2% (20 out of 623).
The safety of BYFAVO was evaluated in comparative clinical studies in patients undergoing general or cardiac surgeries with general anesthesia.
Comparative Studies
A. Two comparative studies evaluated the safety of BYFAVO, one comparative study on different doses and propofol as active comparator and the other comparative study on different doses in patients undergoing surgeries with general anesthesia in Japan.
A total of 362 patients were administered with BYFAVO and 75 patients were administered with propofol as active comparator. BYFAVO was administered at the infusion rate of 6 mg/kg/hr or 12 mg/kg/hr for induction and at 1 mg/kg/hr for maintenance.
Adverse reactions were mostly mild to moderate and temporary following administration with BYFAVO, and serious adverse reactions were observed in two patients (0.6%, 2 out of 362).
The most common adverse reactions following BYFAVO administration were blood pressure decrease in 38.1% of the patients (138 out of 362 patients), hematuria in 15.5% (56 out of 362), nausea in 18.8% (68 out of 362), vomiting in 15.7% (57 out of 362), wound complications in 13.5% (49 out of 362), and fever in 10.5% (38 out of 362).
In propofol group, the most common adverse reactions were pain on injection site in 18.7% of the patients (14 out of 75 patients), nausea in 14.7% (11 out of 75), wound complications in 13.3% (10 out of 75), a blood creatine phosphokinase increase in 12.0% (9 out of 75), and vomiting in 10.7% (8 out of 75).
The most common adverse reactions following BYFAVO administration were blood pressure decrease in 24.0% of the patients (87 out of 362 patients), nausea in 9.1% (33 out of 362), and vomiting in 8.0% (29 out of 362). In propofol group, the most common adverse drug reactions were blood pressure decrease in 49.3% (37 out of 75) and pain on injection site in 18.7% (14 out of 75). No cases of study discontinuation of a patient for reasons related to the adverse reactions in both groups were reported.
Table 1 shows adverse reactions of more than 2% in any group by System Organ Class (SOC) and the frequency of event.

Table 2: Adverse Reactions Reported by More Than 2% in Both Groups

Adverse Reactions		BYFAVO*		Propofol (N=75) %
System Organ Class (SOC)	Adverse reactions (PT)	6mg/kg/hr (n=181) %	12mg/kg/hr (n=181) %	
Psychiatric	Delirium	2.2	1.7	1.3
	Insomnia	2.8	2.8	1.3
Central nervous system	Headache	1.7	3.9	2.7
Cardiovascular system disorders	Bradycardia	1.7	2.8	1.3
Gastrointestinal system disorders	Nausea	21.0	16.6	14.7
	Vomiting	14.4	17.1	10.7
Skin and subcutaneous tissue disorders	Erythema	2.8	2.2	-
Musculoskeletal system and connective tissue disorders	Back pain	2.8	1.1	1.3
	Musculoskeletal pain	1.1	2.2	-
General disorders and administration site conditions	Fever	11.6	9.4	9.3
	Chills	3.3	7.7	6.7
	Injection site pain	-	-	18.7
Investigations	Decrease in blood pressure	37.6	38.7	58.7
	Blood pressure increased	10.5	7.7	4.0
	Hematuria	15.5	15.5	5.3
	Serum albumin decreased	8.8	9.4	8.0
	Total protein decreased	7.7	9.4	8.0
	Blood creatine phosphokinase (CPK) increased	8.8	10.5	12.0
	White cell count increased	6.1	6.1	5.3
	Hemoglobin decreased	6.6	5.5	4.0
	Protein presence in urine	7.2	6.6	4.0
	Red cell count decreased	5.5	5.5	4.0
	Hematocrit decreased	5.0	6.1	4.0
	Ketone bodies presence in urine (ketonuria)	3.3	2.2	6.7
	Blood bilirubin increased	5.5	3.3	2.7
	Aspartate aminotransferase increased	3.3	0.6	2.7
	Heart rate decreased	3.3	3.3	6.7
	Heart rate increased	2.8	1.1	-
	Lymphocyte percentage decreased	6.6	6.1	4.0
	Oxygen saturation decreased	2.8	1.1	1.3
	Neutrophil percentage increased	5.5	2.8	4.0
Injury, poisoning and procedural complications	Wound complications	13.8	13.3	13.3
	Procedural pain	1.7	2.8	-

* BYFAVO was administered at the infusion rate of 6 or 12 mg/kg/hr for induction and at 1 mg/kg/hr for maintenance.

B. Clinical trial in patients undergoing surgery with general anesthesia in South Korea:
BYFAVO was administered at the infusion rate of 6 mg/kg/h for induction and at 1 mg/kg/hr for maintenance.
The safety of BYFAVO was evaluated in 96 patients administered with BYFAVO and 100 patients administered with propofol as a comparator.
The most common adverse reactions were mild to moderate and temporary. No cases of study discontinuation of a patient for reasons related to the adverse reactions were reported in both groups.
In BYFAVO group, the most common adverse reactions (≥10%) included procedural pain in 47.9% of the patients (46 out of 96), blood pressure increase in 16.7% (16 out of 96), headaches in 14.6% (14 out of 96), blood pressure decrease in 12.5% (12 out of 96), and dizziness in 10.4% (10 out of 96).
In propofol group, the most common adverse reactions were procedural pain in 48% of the patients (48 out of 100 patients), blood pressure decrease in 17% (17 out of 100), nausea in 16% (16 out of 100), and dizziness and somnolence in 10% (10 out of 100).
The most common adverse drug reactions following BYFAVO administration were blood pressure decrease in 7.3% of the patients (7 out of 96 patients), somnolence and headaches in 6.3% (6 out of 96), and vomiting in 6.3% (6 out of 96). In propofol group, the most common adverse drug reactions were blood pressure decrease in 11% of the patients (11 out of 100 patients), somnolence in 8% (8 out of 100), and nausea in 8% (8 out of 100).
C. Clinical trial in patients undergoing cardiac surgeries with general anesthesia in Germany:
The safety of BYFAVO was evaluated in 80 patients who were administered by BYFAVO at the infusion rate of 6 mg/kg/hr or 12 mg/kg/hr for induction.
The most common adverse reactions were mild to moderate and temporary.
Serious adverse reactions were reported in 20 patients (25.0%, 20 out of 80). The most common adverse reactions were pleural effusion in 81.3% of the patients (65 out of 80 patients), sleep disorders and agitation each in 41.3% (33 out of 80), post-operative anemia 41.3% (33 out of 80), surgery related nausea 40.0% (32 out of 80), fluid retention in 27.5% (22 out of 80), atrial fibrillation in 25.0% (20 out of 80), and hypertension in 21.3% (17 out of 80).
Cardiovascular related adverse reactions such as bradycardia in 12.5% of the patients (10 out of 80 patients) and pericardial effusion in 7.5% (6 out of 80) were reported.
There was one case of study discontinuation due to the adverse reaction of a hemothorax in the group administered with BYFAVO at the infusion rate of 12 mg/kg/hr which was however, not related to BYFAVO.

3) Procedural Sedation
BYFAVO was administered to 825 patients undergoing upper gastrointestinal endoscopy, colonoscopy, or bronchoscopy in two Phase 2 and three Phase 3 studies in United States.
The most common adverse reactions were hypotension in 28.4% of the patients (234 out of 825), hypertension in 19.5% (161 out of 825), diastolic hypertension in 13.2% (109 out of 825), systolic hypertension in 10.3% (85 out of 825), hypoxia in 8.4% (69 out of 825), diastolic hypotension in 7.9% (65 out of 825), bradycardia in 5.9% (49 out of 825) and respiratory rate increase in 5.2% (43 out of 825).
Table 2 shows adverse reactions of more than 2% in any group by System Organ Class (SOC) and the frequency of event for clinical studies in patients undergoing upper gastrointestinal endoscopy, colonoscopy, or bronchoscopy.

Table 3: Adverse Reactions Reported by More Than 2% in Both Groups (Sedation for Endoscopy)

Adverse Reactions		BYFAVO*
System Organ Class(SOC)	Adverse reactions(PT)	%
Nervous system	Headache	3.2
Cardiovascular system disorders	Bradycardia	5.9
	Tachycardia	3.3
	Hypertension	19.5
	Hypotension	28.4
	Diastolic hypertension	13.2
	Systolic hypertension	10.3
	Diastolic hypotension	7.9
Respiratory system	Hypoxia	8.4
Gastrointestinal system disorders	Nausea	3.0
Investigations	Oxygen saturation decreased	2.2
	Respiration rate increased	5.2
* 2.5 mg to 8 mg of BYFAVO was administered for induction.		

In the United States, the safety of BYFAVO was evaluated in three clinical trials consists of two
colonoscopy studies and one bronchoscopy study, in which BYFAVO was administered to a total of 630 patients and midazolam as a comparator and placebo were administered to 201 patients and 135 patients, each.
For ASA-PS class I or II patients, BYFAVO 5.0 mg was administered for induction, followed by 2.5 mg for maintenance. For ASA-PS class III or IV patients, BYFAVO 2.5 mg to 5.0 mg was administered for induction, followed by 1.25 mg to 2.5 mg for maintenance.
For ASA-PS class I or II patients, midazolam 1.75 mg was administered for induction and 1.0 mg for maintenance. For >60 years of age, chronic diseases, ASA-PS class III or IV patients, midazolam 1.0 mg was administered for induction and 0.5 mg for maintenance.
One patient each in the BYFAVO arm and midazolam arm discontinued treatment for reasons related to the adverse reactions.
In BYFAVO arm, the most common adverse reactions (≥10%) were hypotension in 36.8%

of the patients (232 out of 630), hypertension in 24.9% (157 out of 630), diastolic hypertension in 17.3% (109 out of 630), blood pressure decreased in 14.3% (90 out of 630), systolic hypertension in 13.5% (85 out of 630) and hypoxia in 10.9% (69 out of 630).
In the midazolam arm, the most common adverse reactions (≥10%) included hypotension in 51.2% of the patients (103 out of 201), hypertension in 24.9% (50 out of 201), diastolic hypertension in 12.4% (25 out of 201), diastolic hypotension in 12.4% (25 out of 201), bradycardia in 11.9% (24 out of 201) and systolic hypertension in 11.4% (23 out of 201).

4) Geriatric patients
In controlled trials in procedural sedation, patients ≥65 years old had a higher frequency of events grouped under the terms hypotension (47.0% vs 33.3%) and respiratory depression (22.8% vs 9.0%) than patients below 65 years old. Patients with ASA-PS III-IV also showed higher frequencies for hypotension (43.6% vs 35.6%) and respiratory depression (17.6% vs 11.8%) than patients with ASA-PS I-II. Older age and higher ASA-PS were not associated with a higher frequency of bradycardia.

5) Patients with hepatic impairment
Respiratory depression (hypoxia/oxygen saturation decreased) was reported in 2 of 8 subjects with moderate hepatic impairment, and 1 of 3 with severe hepatic impairment enrolled in a dedicated trial assessing remimazolam in hepatic impairment.

6) Post-marketing safety report
- The following adverse reactions and incidence frequency had been reported in post-marketing safety report
① Immune system
Incidence rate: Unknown, Anaphylactic reaction

5. General Warinings

1) Individualize BYFAVO dosing depends on the patient's age, drug sensitivity, general condition, and concomitant use of other medications due to the difference in drug response between individuals.

2) Titrate the dose of BYFAVO to the desired clinical effect of an adequate depth of anesthesia while monitoring general condition of the patient including the brain waves, electrocardiogram, and vital signs. The depth of anesthesia should be kept to a minimum level required for surgery.

3) BYFAVO should be always co-administered with other medications such as analgesics and neuromuscular blocking agents for maintenance of anesthesia. Clinical experience with single use of BYFAVO has not been established.

4) BYFAVO has been associated with respiratory depression, blood pressure decrease, and bradycardia and therefore, oxygenator and mechanical ventilator for the maintenance of a patient airway and supportive ventilation must be immediately available during BYFAVO administration. When symptoms such as respiratory depression, blood pressure decrease, or a bradycardia occurred, maintenance of a patient airway and oxygenation should be conducted immediately and also supportive ventilation to the patients through the recovery period.
Remimazolam administration can be associated with a transient increase in heart rate (10-20 beats per minute) starting as early as 30 seconds after the start of dosing (corresponding to the time of maximum concentration of remimazolam) before resolving within about 30 minutes after the end of administration. This increase in heart rate coincides with a decrease in blood pressure and it may confound QT correction for heart rate translating into a small prolongation in QTcF in the first few minutes following dosing. Special attention is required for elderly patients (≥65 years of age), for patients with impaired respiratory and/or cardiac function or for patients with poorer general health status.

5) During administration of BYFAVO, it is appropriate that flumazenil (a benzodiazepine reversal agent) is immediately available as needed.

6) BYFAVO has been associated with somnolence, attention decrease, concentration decrease, or delayed reflex responses and therefore, patient after receiving BYFAVO should not operate any hazardous machinery nor drive a motor vehicle until the full recovery without any residual effects of BYFAVO.

7) Clinical experience in BYFAVO administration for more than 20 hours has not been established. In a study where BYFAVO was evaluated in ICU (Intensive Care Unit) sedation, there was a patient who received BYFAVO for more than 24 hours showing increase of drug plasma concentration and delayed time to fully alert.

8) Drug Abuse: BYFAVO, a benzodiazepine drug, has a known potential for drug abuse, physical and psychological dependence. In a human abuse potential study conducted in recreational sedative abusers, remimazolam showed statistically similar drug abuse potential compared with midazolam and statistically higher drug abuse potential than placebo. This should be considered when prescribing or administering remimazolam where there is concern about an increased risk of misuse or abuse.

9) Hypersensitivity reactions: BYFAVO contains dextran 40, which can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis. BYFAVO is contraindicated in patients with a history of severe hypersensitivity reaction to dextran 40 or products containing dextran 40.

10) In Phase 3 clinical trial for procedural sedation in endoscopy/endoscopic therapy, fentanyl was administered as an analgesic pre-treatment at an initial dose of 25 μg to 75 μg. If necessary, at least 2 minutes must elapse prior to administration of BYFAVO.

11) Patients who receive chronic benzodiazepine therapy (e.g., for insomnia or anxiety disorders) may develop tolerance to the sedative effects of remimazolam. Hence, a larger cumulative dose of remimazolam may be required to achieve the desired level of sedation. It is recommended to follow the titration regimen and titrate up based on the patient's sedation-response, until the desired depth of sedation is achieved.

12) Remimazolam should be administered only by health care professionals experienced in sedation who are not involved in conducting the procedure, in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function. Administering personnel must be adequately trained in the recognition and management of expected adverse reactions including respiratory and cardiac resuscitation. Patients should be monitored closely during and after the procedure for signs and symptoms of respiratory depression and sedation. The physician should also be aware of the typical time taken for patients to recover from the effects of remimazolam and concomitant opioid used in the clinical trials, but that this may vary in individual patients. Patients should be closely monitored until they are judged by the healthcare professional to be sufficiently recovered.

13) Remimazolam can cause anterograde amnesia. Amnesia, if prolonged, can present problems in outpatients, who are scheduled for discharge following intervention. After receiving remimazolam, patients should be assessed and discharged from hospital or consulting room by their physician, only with appropriate advice and support.

14) The clinical effects may be more pronounced and last longer in patients with severe hepatic impairment due to reduced clearance. Special attention is required for the timing of titration doses. These patients may be more susceptible to respiratory depression.

6. Drug Interactions

The co-administration of remimazolam with opioids and CNS depressants including alcohol, is likely to result in enhanced sedation and cardiorespiratory depression. Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines (used as anxiolytics or hypnotics), barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive. The concomitant use of remimazolam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of remimazolam, possibly including severe sedation or clinically relevant respiratory depression.
Concomitant use of remimazolam and opioids may results in profound sedation and respiratory depression. Patients should be monitored for respiratory depression and depth of sedation. In patients with longer-term opioid use, caution is advised; it should not be presumed that these effects will be attenuated.
Alcohol intake should be avoided for 24 hours before remimazolam administration since it may markedly enhance the sedative effect of remimazolam.

7. Pregnancy, fertility and Lactation

1) Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of remimazolam in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of BYFAVO during pregnancy.

2) Fertility
There are no human data on the effects of remimazolam on fertility. In animal studies there was no effect on mating or fertility with remimazolam treatment.

3) Lactation
It is unknown whether remimazolam and its main metaboite (CNS7054) are excreted in human breast milk. Available toxicological data in animals have shown excretion of remimazolam and CNS7054 in milk (for details see section 5.3). A risk to newborns/infants cannot be excluded; therefore, administration of remimazolam to breastfeeding mothers should be avoided. If there is a need to administer remimazolam, then discontinuation of breastfeeding for 24 hours after administration is advised.

8. Pediatric Use

Efficacy and safety of Byfavo in pediatric patients, under the age of 18 have not been established.

9. Geriatric Use

Of the total 527 subjects treated with BYFAVO in Phase 2 and 3 trials for general anesthesia, there were 234 patients (44.4%) who were aged 65 years or older. Of the total 825 subjects treated with BYFAVO in clinical studies for procedural sedation, there were 219 patients (26.5%) who were aged 65 years or older.
No overall differences in safety or effectiveness were observed between these subjects and healthy adults, but other reported clinical experience has identified higher incidence of adverse reaction in cardiovascular system, heart, and respiratory system in the elderly patients.
Some data suggest a faster onset of loss of consciousness and a longer duration of sedation in the elderly patients compared to healthy adults.
It is more likely that the elderly patients will experience adverse reactions, such as accentuation of sedative effect, hypotension and bradycardia with their potential of greater sensitivity than the younger patients.
Therefore, titrate doses of BYFAVO in geriatric patients on the basis of clinical judgment depends on the general condition of a patient. [See Dosage and Administration 3. Geriatric Patients]

10. Hepatic Impairment

Dose adjustment is not required in patients with mild to severe hepatic impairment based on Child-Pugh classification.
However, the dose and infusion rate should be carefully titered to effect while observing the general status of the patients with severe hepatic impairment. [See Precautions for Use 14. Clinical Pharmacology, Patients with Hepatic Impairment]

11. Renal Impairment

Dose adjustment is not required in patients with mild to severe renal impairment. [See Precautions for Use 14. Clinical Pharmacology, Patients with Renal Impairment]

12. Management of Overdosage

1) Overdose may lead to excessive sedation, convulsion, confusion and lethargy.

2) Flumazenil (a benzodiazepine-receptor antagonist) may be used in situations when an overdose with BYFAVO is known or suspected in patients showing delayed time to fully alert, respiratory depression, excessive sedation, and overdosage.

3) Prior to the administration of flumazenil, institute necessary measures and equipment to secure the airway, and ensure adequate ventilation and oxygenation and consult the complete flumazenil package insert, including Precautions for Use (Contraindications etc.) prior to use.
Flumazenil has a short half-life of 1 hour, approximately and therefore, patients administered with flumazenil should be monitored for an appropriate period after treatment without any residual benzodiazepine effects. There is potential for re-sedation by BYFAVO in patients with very high drug plasma concentration after administration of flumazenil.

4) The reversal of benzodiazepine effects may be associated with the onset of seizures in certain seizure patients treated with anticonvulsants of benzodiazepine class. Flumazenil should be administered carefully, particularly in long-term benzodiazepine anticonvulsants users.

5) Patients co-administered with benzodiazepines and tri-(tetra-)cyclic antidepressants may experience accentuation of antidepressant intoxication after reversal of benzodiazepine-induced effects by flumazenil. Supportive ventilation including oxygen supply should be provided to those patients immediately until the full recovery of patients from the intoxication.

6) The symptoms of remimazolam overdose are expected to be an extension of its pharmacological actions and may present with one or more of the following signs and symptoms: dizziness, confusion, drowsiness, blurred vision or nystagmus, agitation, weakness, hypotension, bradycardia, respiratory depression and coma.

13. Precautions for Administration

1) To reconstitute, add sterile 0.9% Sodium Chloride Injection, to the vial. BYFAVO is not compatible with the fluids containing lactic acid and can be precipitated in the solution. Fluids containing lactic acid shall not be used for BYFAVO reconstitution.

2) Reconstitution of BYFAVO with an alkaline fluid should be avoided. BYFAVO is highly water-soluble in a low pH solution and solubility of BYFAVO decreases rapidly in solutions with a pH above 4.0.

3) Appropriate infusion instruments (e.g., syringe pump) enabling titration of drug should be used for the continuous infusion of BYFAVO.

4) Administer BYFAVO after opening of the drug package and reconstitution immediately. Discard unused portion. In-use stability after reconstitution has not been established.

14. Clinical Pharmacology

1) BYFAVO is a benzodiazepine
Like other benzodiazepines, BYFAVO binds to brain benzodiazepine sites (gamma amino butyric acid type A receptors) and increases the activity of GABAA receptor protein as positive allosteric modulator.

a. Assessment of Binding Affinity (In vitro)
The IC50 value of BYFAVO was 30.5nmol/L in binding affinity assay (In vitro) on the benzodiazepine binding site of the GABA A receptor with an inhibitor constant (Ki) of 26.3 nmol/L.

b. Assessment of Sedative Effect (In vivo)
Sedative effect was assessed via three different parameters, Loss of Righting Reflex (LRR), ataxia and decrease of Spontaneous locomotor activity (SLA) in the male mice administered with 15~30 mg/kg i.v. and the rats administered with 0.05~10 mg/kg i.v.
A dose-dependent sedative effect was demonstrated in the animals with increase of the number of animals with LRR, reduction of time to LRR and decrease of SLA.
In the mouse administered with a benzodiazepine reversal agent, flumazenil (20 mg/kg i.p.15 minutes prior to administration of remimazolam) duration of the LRR was reduced and number of animals with LRR was decreased.
BYFAVO demonstrated dose-dependent sedative effect in mouse, rat, minipig and monkey which was reversed when flumazenil was administered.
CNS7054 (metabolite of BYFAVO) and R-isomer did not exert sedative effect.

2) Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

a) Absorption
After single-dose bolus administration over a 1-minute time period (0.05 to 0.50 mg/kg) to healthy adults, BYFAVO overall maximum plasma concentration (C_{max}) was reached within 1 to 2 minutes of administration and the half-life was 1 to 2 minutes.
The C_{max} (average) was 654 to 6,960 ng/mL, and the AUC_{inf} (average) was 49.6 to 452.0 ng·h/mL, which suggested a close to dose-dependent relationship.

b) Distribution
After single-dose bolus administration of BYFAVO (0.05 to 0.50 mg/kg) to healthy adults, the volume of distribution (Vss) was 0.48 to 0.58 L/kg which showed no increase as the dose of BYFAVO was increased.
Plasma protein binding of BYFAVO was 91.6% to 92.1%, and the human blood cell migration rate was 7.5% to 11.7%.

c) Metabolism
The main route of metabolism of BYFAVO is via rapid hydrolysis and conversion to primary inactive metabolite CNS 7054 by tissue carboxylesterases (primarily type 1A), with no meaningful contribution by cytochrome P450 enzymes.

d) Excretion
When administered as single-dose bolus of 0.2 to 0.3 mg/kg to healthy adults, no detectable BYFAVO was excreted in the urine as unchanged until up to 24 hours after administration (below the limit of quantitative analysis), and 80% was excreted in urine as the metabolite CNS 7054.

B. Pharmacodynamics

The primary pharmacodynamic effect of remimazolam is sedation.
Sedation is observed starting at single bolus doses of 0.05 to 0.075 mg/kg in healthy young adults, with an onset of 1 to 2 min following dosing. Induction ofmmild to moderate sedation is associated with plasma levels of around 0.2 μg/mL. Loss of consciousness is seen at doses of 0.1 mg/kg (elderly) or 0.2 mg/kg (healthy young adults) and associated with plasma concentrations of around 0.65 μg/mL. Depth, duration and recovery from sedation is dose-dependent. Time to fully alert was 10 min for 0.075 mg/kg of remimazolam.
Remimazolam can cause anterograde amnesia after administration, which prevents patients from remembering events occurring during the procedure. Brice questionnaire data from 743 remimazolam-treated patients, assessed 10 minutes after the patient became fully alert and one day after the procedure, show that 76% of patients had no recollection of the procedure.

C. Pharmacokinetics for specific populations

a) Geriatric Patients
When approximately 0.1 mg/kg of BYFAVO was administered as single-dose intravenous injection over a 1 minute to the elderly patients group aged over 65 (65 to 73 years old, 66.0 years old on average) and the healthy adults group (20 to 45 years old, 21.0 years old on average), both of the groups showed similar pharmacokinetic profile.
However, dose of BYFAVO should be adjusted and titrated to the desired clinical effect in the elderly patients while observing the general condition of the patients because the elderly patients may have of greater sensitivity (a faster onset of loss of consciousness and a longer duration of sedation in a lower dose) than the healthy adults.

b) Patients with Hepatic Impairment
When approximately 0.1 mg/kg of BYFAVO was administered as single-dose intravenous injection over a 1 minute to the moderate and severe hepatically impaired patients (Child Pugh Classification Grade B and C) group and to the healthy adults group, the $T_{1/2}$ and V_{ss} were prolonged or increased along with the severity of hepatic impairment.
The AUC_{inf} was at a similar level at the moderate hepatically impaired patients group and the healthy adults group.
However, patients with the severe hepatic impairment group showed 1.3 times higher AUC_{inf} than that of the healthy adults group.
Patients with hepatic impairment showed a potential of greater sensitivity (a longer duration of sedation and a prolonged recovery time) than the healthy patients group. Dose of BYFAVO should be adjusted and titrated to the desired clinical effect in the patients with hepatic impairment while observing the general condition of the patients because of a potential of greater sensitivity (a longer duration of sedation in a lower dose) than the healthy adults.

c) Patients with Renal Impairment
When approximately 1.5 mg of single-dose intravenous injection of BYFAVO was administered to the patients with the severe renal diseases (eGFR: below 15 mL/min /1.73 m^2) and to the healthy adults with normal kidney function (eGFR: above 90 mL/min /1.73 m^2), there was no difference found in pharmacokinetic profile.

3) Information on Clinical Studies

(1) Study 1
Phase 2b/3 trials conducted in Japan is a randomized, single-blinded, multicenter, parallel group design with active comparator (propofol) in 375 ASA-PS class I or II adult patients undergoing surgery with general anesthesia. The safety and efficacy of BYFAVO were evaluated to confirm the non-inferiority of BYFAVO compared with propofol in the induction and maintenance of general anesthesia.
In the full analysis set (FAS), BYFAVO was administered as continuous intravenous infusion either at 6 or 12 mg/kg/hr to each 150 patients group and propofol was administered to 75 patients.
BYFAVO was administered as continuous infusion either at 6 or 12 mg/kg/hr for the induction until the loss of consciousness and at 1 mg/kg/hr for maintenance of anesthesia after the loss of consciousness.
Remifentanil and rocuronium were administered concomitantly during induction and maintenance of anesthesia.
The median age of the patients was 59 to 61 in 3 groups, and 51% to 56% of the patients were male.
The median duration of the surgeries was 112 to 131 minutes in 3 groups, and the most common surgical sites were the lower abdomen (17% to 26%), limbs (18% to 24%), and ears and nose (11% to 13%).
The primary efficacy endpoint for BYFAVO versus propofol was success of the anesthesia, defined as a composite of the following:
- no intraoperative awareness/memory, AND
- no requirement for a rescue sedative medication, AND
- no body movement

Success rate of anesthesia was 100% in all groups.
The median duration from the start of the administration to the loss of consciousness was 100.5 seconds in the BYFAVO group with infusion rate of 6 mg/kg/hr, 87.5 seconds in the BYFAVO group with infusion rate of 12 mg/kg/hr, and 80.0 seconds in the propofol group.
The median duration from the completion of administration to the time point of the patient opening their eyes was 12 minutes in the BYFAVO group (6 mg/kg/hr), 12 minutes in the BYFAVO group (12 mg/kg/hr), and 10 minutes in the propofol group.
The time to recovery endpoints were slightly longer in the remimazolam groups than in the propofol group.

(2) Study 2
Phase 3 trial conducted in S. Korea is a randomized, single-blinded, multicenter, parallel group design with active comparator (propofol) in 198 ASA-PS class I or II adult patients undergoing surgery with general anesthesia. The safety and efficacy of BYFAVO were evaluated to confirm the non-inferiority of BYFAVO compared with propofol in the induction and maintenance of general anesthesia.
In the full analysis set (FAS), BYFAVO was administered as continuous intravenous infusion either at 6 or 12 mg/kg/hr to 98 patients and propofol was administered to 100 patients.
BYFAVO was administered as continuous infusion either at 6 mg/kg/hr for the induction until the loss of consciousness and at 1 mg/kg/hr for maintenance of anesthesia after the loss of consciousness.
Remifentanil and rocuronium were administered concomitantly during induction and maintenance of anesthesia.
The median age of the patients was 49 (20 to 82 years old) in both of the groups, and 47% of the patients were male.
The median duration of the surgeries was 63 minutes in both of the groups, and the most common surgical sites were the head and neck (18.4%), liver and gallbladder (16.3%), obstetrics and gynecology areas (14.8%), bones and joints (13.3%), and gastrointestinal tracts (11.7%).
The primary efficacy endpoint for BYFAVO versus propofol was success of the anesthesia with no requirement for a rescue sedative medication.
Success rate of anesthesia were 97.8% (90 out of 92) in the BYFAVO group and 97.8% (88 out of 90) in the propofol group in the Per Protocol Set (PPS).
The difference between the two groups was 0.05% (95% confidence interval -4.21, 4.31), which confirmed the non-inferiority of BYFAVO compared with propofol.
The median duration time from the administration of the first dose of study drug to the loss of consciousness was 121.0 seconds in the BYFAVO group, and 74.0 seconds in the propofol group.
The median duration time from the administration of the last dose of study drug to the time point of the patient opening their eyes was 15 minutes in the BYFAVO group, and 10 minutes in the propofol group.
The time to recovery endpoints were slightly longer in the remimazolam groups than in the propofol group.

(3) Study 3
Phase 3 trial conducted in United States is a randomized, double-blinded, placebo-controlled, parallel group design with active comparator (midazolam) in 461 ASA-PS class I to III adult patients undergoing colonoscopy. The safety and efficacy of BYFAVO were evaluated to confirm the non-inferiority of BYFAVO compared with midazolam in the induction and maintenance of procedural sedation.
In the full analysis set, BYFAVO was administered to 298 patients, placebo was administered to 60 patients and midazolam was administered to 103 patients.
BYFAVO 5 mg was administered as an initial bolus, followed by 2.5mg top-up doses after at least 2 minutes elapsed as needed.
Fentanyl was administered intravenously as an analgesic prior to administration of the study medication.
Demographic analysis was performed to 458 patients who were administered with BYFAVO and fentanyl. The median age of the patients was 54.9, where 47.6% of the patients were male and 52.4% of the patients were female.
There were 143 patients (31.2%) in ASA-PS class I, 285 patients (62.2%) in ASA-PS class II, 30 patients (6.6%) in ASA-PS class III and none who were in ASA-PS class IV.
The primary efficacy endpoint for BYFAVO was success of the colonoscopy procedure, defined as a composite of the following:
- Completion of the colonoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than 5 doses of study medication within any 15-minute window.

Success rate of colonoscopy procedure was evaluated in 461 patients. The colonoscopy sedation success rate was 91.3% (272 out of 298) in the BYFAVO arm, 1.7% (1 out of 60) in the placebo arm and 25.2% (26 out of 103) in the midazolam arm.

(4) Study 4
Phase 3 trial conducted in United States is a randomized, double-blinded, placebo-controlled, parallel group design with active comparator (midazolam) in 446 ASA-PS class I to III adult patients undergoing bronchoscopy. The safety and efficacy of BYFAVO were evaluated to confirm the non-inferiority of BYFAVO compared with midazolam in the induction and maintenance of procedural sedation.
In the full analysis set of the total 431 patients, BYFAVO was administered to 303 patients, placebo was administered to 59 patients and midazolam was administered to 69 patients.
BYFAVO 5 mg was administered as an initial bolus, followed by 2.5mg top-up doses after at least 2 minutes elapsed as needed.
Fentanyl was administered intravenously as an analgesic prior to administration of the study medication.
Patients were 22 to 95 years of age, 45.9% of the patients were male and 54.1% of the patients were female.
There were 15 patients (3.5%) in ASA-PS class I, 254 patients (58.9%) in ASA-PS class II, 162 patients (37.6%) in ASA-PS class III and none who were in ASA-PS class IV.
The primary efficacy endpoint for BYFAVO was success of the bronchoscopy procedure, defined as a composite of the following:
- Completion of the bronchoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than 5 doses of study medication within any 15-minute window.

Success rate of bronchoscopy procedure was evaluated in 446 patients. The bronchoscopy sedation success rate was 80.6% (250 out of 301) in the BYFAVO arm, 4.8% (3 out of 63) in the placebo arm and 32.9% (24 out of 73) in the midazolam arm.

4) Information on Toxicity

A. Local Tolerance Test
Local tolerance tests were conducted in rats, minipigs, rabbits, monkeys and pigs to evaluate the potential of BYFAVO for causing local irritation at the injection sites and the local vascular effects.
Like other benzodiazepines, drug-related thrombus formation was observed after intravenous injection of BYFAVO and the risk of incidence was increased when a high concentration of drug was injected at the same venous site, repeatedly.

B. Genotoxicity and Reproductive/Developmental Toxicology
There was no impact on fertility and early embryonic development confirmed in studies in rats and rabbits and pre-and post-natal study in rats when exposed to the lower doses of BYFAVO than the recommended doses in human.
In embryo-fetal development study in rats and rabbits, increase of the early resorption cases was reported in rats only and no increase of malformation cases in rats and rabbits when exposed to the lower doses of BYFAVO than the recommended doses in human.
There was no impact on genotoxicity confirmed in the bacterial reverse mutation assay, mouse lymphoma assay and rat micronucleus assay.
Reproductive toxicity studies performed at the maximum tolerated dose level revealed no influence on male or female fertility and on reproductive function parameters. In embryotoxicity studies in rats and rabbits, even at the highest dose levels, which displayed maternal toxicity, only marginal embryotoxic effects were observed (reduced foetal weight and slightly increased incidences of early and total resorptions). Remimazolam and its main metabolite are excreted in breast milk of rats and rabbits. The inactive main metabolite CNS7054 was detected in the plasma of suckling rabbit kits, however it is not known if remimazolam is transferred via milk to suckling offspring.

C. Dependence
In a monkey physical dependence study, when BYFAVO administration was abruptly discontinued after administration of 4 weeks, tremors, muscle rigidity, restlessness, impaired motor activity, and a reduction in food consumption were occurred upon drug discontinuation.
One monkey of six in this study exhibited systemic convulsions and dissociation from the environment. These behaviors are consistent with benzodiazepine withdrawal, which suggests that BYFAVO produces physical dependence.

STORAGE AND HANDLING

Store BYFAVO under 30°C in a sealed package
Protect vials from light once they are removed from packaging.

How Supplied: 5 vials/PTP/pack

Manufactured by: Hana Pharm. Co., Ltd.
13-39 Jeyakdanji-ro, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, Republic of Korea

Product Registration Holder: Hyphens Pharma Pte Ltd.
16 Tai Seng Street, #04-01, Singapore 534138

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