Summary of Product Characteristics (SmPC)

1. Name of the Medicinal Product

BYFAVO™ 20 mg (remimazolam besylate) Lyophilized Powder for Injection

2. Quality and Quantitative Composition

Each vial contains remimazolam besylate equivalent to 20 mg remimazolam.
For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

White to off-white lyophilised powder for injection contained in a clear colorless vial

4. Clinical Particulars

4.1 Therapeutic Indications

BYFAVO is indicated for :
1. The induction and maintenance of general anesthesia in adults
2. The induction and maintenance of procedural sedation in adults

4.2 Posology and Method of Administration

Conditions for use

- BYFAVO should be administered only by a medical doctor trained in anesthesia. Equipment for the maintenance of a patient airway, an oxygenator, and cardiovascular resuscitation should be immediately available during administration of BYFAVO
- Individualize BYFAVO dosing depending on the patient's age, drug sensitivity, general condition, and concomitant use of other medications due to the difference in drug response between individuals.
- 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.
- 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.
- 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.
- During administration of BYFAVO, it is appropriate that flumazenil (a benzodiazepine reversal agent) is immediately available as needed.

Posology

1. General Anesthesia

BYFAVO should be administered in combination with other analgesics and muscle relaxants as appropriate. [See Condition for use]

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

1) Induction

For adult patients: Administer 5 mg intravenously over a 1-minute time period. For ASA-PS (American Society of Anesthesiologists Physical Status) III and IV patients, administer 2.5 mg to 5 mg intravenously over 1 minute based on general condition of the patient.

2) Maintenance (if needed)

For adult patients, administer 2.5 mg intravenously over 15 seconds. For ASA-PS III and IV patients, administer 1.25 mg to 2.5 mg intravenously over 15 seconds. At least 2 minutes must elapse prior to administration of any supplemental dose.

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 anesthetics. 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 individualized dose adjustments for these patients (see section 4.4). The starting dose should be considered at the lower range.

4. Patients with Hepatic Impairment

The metabolizing enzyme (carboxylesterase-1 [CES-1]) for remimazolam is predominantly located in the liver, and the clearance of remimazolam is affected by increasing stages of hepatic impairment (see section 5.2). No dose adjustment is recommended for patients with mild (Child-Pugh scores 5 and 6) or moderate (Child-Pugh scores 7 to 9) hepatic impairment. In patients with severe hepatic impairment (Child-Pugh scores 10 to 15; data from only 3 subjects in clinical trials), the clinical effects may be more pronounced and last longer than in healthy subjects. No dose adjustments are required, but careful attention should be paid to the timing of titration doses, and remimazolam should be carefully titrated to effect in these patients.

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 3.13. 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]

   BYFAVO must be immediately used after opening and discarded after use.

   This drug should be inspected visually for particulate matter and discoloration prior to administration. Upon reconstitution, the solution should be a clear, colorless to pale yellow solution. Discard if particulate matter or discoloration is observed.

4.3 Contraindication

Patients with

- Severe hypersensitivity events to BYFAVO, other benzodiazepine drugs, or the composition of BYFAVO
- Acute narrow-angle glaucoma
- In shock or coma
- Acute alcoholism with suppressed vital signs
- Sleep apnea syndrome
- Alcohol or drug dependence
- Severe or acute respiratory failure
- Genetic disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption (BYFAVO contains lactose)
- History of severe hypersensitivity to dextran 40
- Unstable myasthenia gravis.

4.4 Special Warning and Precautions for Use Special warnings

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 (see section 4.2).

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 (see section 4.5).

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. (see section 4.5)

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. (see section 4.5)

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 resuscitation (see section 4.2). 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 (see section 5.1), 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.

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.

Hepatic impairment

The clinical effects may be more pronounced and last longer in patients with severe hepatic impairment due to reduced clearance (see section 5.2). Special attention is required for the timing of titration doses (see section 4.2). These patients may be more susceptible to respiratory depression (see section 4.8).

Myasthenia gravis

Particular care should be taken when administering remimazolam to a patient with myasthenia gravis (see section 4.3).

Drug abuse and physical dependence

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.

Excipients

Dextran

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.

Precautions for use

- Patients with myasthenia gravis
- 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.
- Patients with a heart disorder (e.g., congestive heart failure)
- Debilitated patients

Patients with:

- Organic cerebral dysfunction
- Chronic renal failure
- Acute decompensated disease (e.g., severe body fluids or electrolyte disorders)
- Acute drug poisonings caused by sedative-hypnotics, analgesics, antipsychotics, antidepressants, or lithium
- Severe hepatic impairment (Child-Pugh class C)
- ASA-PS III and above (Administer BYFAVO LYOPHILIZED POWDER FOR INJECTION 20MG/VIAL carefully at a reduced infusion rate and monitor patients for apnea, hypotension, or cardiorespiratory complications)

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

The sedative effect of intravenous BYFAVO can be accentuated by co-administered CNS depressants, other benzodiazepines, including anesthetics and sedative hypnotics, or opioid analgesics, including fentanyl and remifentanil.

The dose and infusion rate of BYFAVO should be adjusted carefully when administered in concomitant use of those medications. Continuously monitor patients for respiratory depression, sedative signs and symptoms, and vital signs.

Pharmacodynamic drug interactions

Increased sedation with CNS depressants and opioids

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 medicinal products.

Concomitant use of remimazolam and opioids may result in profound sedation and respiratory depression. Patients should be monitored for respiratory depression and depth of sedation (see sections 4.2 and 4.4).

Alcohol intake should be avoided for 24 hours before remimazolam administration since it may markedly enhance the sedative effect of remimazolam (see section 4.4).

4.6 Pregnancy and lactation

Pregnant or Fertile Women
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.

Lactation
In a non-clinical study, it was reported that remimazolam is present in animal milk.
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.

4.7 Effects on Ability to Drive and Use Machine

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.

4.8 Undesirable Effects

BYFAVO was administered to 623 patients undergoing general or heart surgeries with general anesthesia in the Phase 2 and Phase 3 studies.

The most common adverse events 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 events 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
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 severe adverse reactions were observed in two patients (0.6%, 2 out of 362).
The most common adverse events 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 events 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 events of more than 2% in any group by System Organ Class (SOC) and the frequency of event.

Table 1: Adverse Events Reported by More Than 2% in BYFAVO 6mg/kg/hr (n=181)

Psychiatric disorders	
Common	Delirium
Common	Insomnia
Nervous system disorders	
Common	Headache
Cardiac Disorders	
Common	Bradycardia
Skin and subcutaneous tissue disorders	
Common	Erythema
Very common	Vomiting
Musculoskeletal and connective tissue disorders	
Common	Back pain
Common	Musculoskeletal pain
General disorders and administration site conditions	
Very common	Fever
Common	Chills
Very rare	Pain on injection site
Investigations	
Very common	Blood pressure decrease
Very common	Blood pressure increased
Very common	Hematuria
Common	Serum albumin decreased
Common	Total protein decreased
Common	Blood creatine phosphokinase (CPK) increased

Common	White cell count increased
Common	Hemoglobin decreased
Common	Protein presence in urine
Common	Red cell count decreased
Common	Hematocrit decreased
Common	Ketone bodies presence in urine (ketonuria)
Common	Blood bilirubin increased
Common	Aspartate aminotransferase increased
Common	Heart rate decreased
Common	Heart rate increased
Common	Lymphocyte percentage decreased
Common	Oxygen saturation decreased
Common	Neutrophil percentage increased
Injury, poisoning and procedural complications	
Very common	Wound complications
Common	Procedural pain

Table 2: Adverse Events Reported by More Than 2% in BYFAVO 12mg/kg/hr (n=181)

Psychiatric disorders	
Common	Delirium
Common	Insomnia
Nervous system disorders	
Common	Headache
Cardiac Disorders	
Common	Bradycardia
Skin and subcutaneous tissue disorders	
Common	Erythema
Very common	Vomiting
Musculoskeletal and connective tissue disorders	
Common	Back pain

Common	Musculoskeletal pain
General disorders and administration site conditions	
Common	Fever
Common	Chills
Very rare	Pain on injection site
Investigations	
Very common	Blood pressure decrease
Common	Blood pressure increased
Very common	Hematuria
Common	Serum albumin decreased
Common	Total protein decreased
Very common	Blood creatine phosphokinase (CPK) increased
Common	White cell count increased
Common	Hemoglobin decreased
Common	Protein presence in urine
Common	Red cell count decreased
Common	Hematocrit decreased
Common	Ketone bodies presence in urine (ketonuria)
Common	Blood bilirubin increased
Uncommon	Aspartate aminotransferase increased
Common	Heart rate decreased
Common	Heart rate increased
Common	Lymphocyte percentage decreased
Common	Oxygen saturation decreased
Common	Neutrophil percentage increased
Injury, poisoning and procedural complications	
Very common	Wound complications
Common	Procedural pain

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

Clinical Trial in South Korea

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 events were mild to moderate and temporary. No cases of study discontinuation of a patient for reasons related to the adverse events were reported in both groups.

Table 3. The most common adverse events (≥10%)

Nervous system disorders	
Very common	Headache
Very common	Dizziness
Investigations	
Very common	Blood pressure decrease
Very common	Blood pressure increased
Injury, poisoning and procedural complications	
Very common	Procedural pain

In BYFAVO group, the most common adverse events (≥10%) include 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 events 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).

Table 4. The most common adverse drug reactions

Nervous system disorders	
Somnolence	Common
Headache	Common
Skin and subcutaneous tissue disorders	
Vomiting	Common
Investigations	
Blood pressure decrease	Common

Clinical Trial in Germany

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.

Table 5. The most common adverse events

Repiratory, thoracic and mediastinal disorders	
Very common	Pleural effusion
Psychiatric disorders	
Very common	Sleep disorders and agitation
Cardiac Disorders	
Very common	Atrial fibrillation
Very common	Bradycardia
Common	Pericardial effusion
Metabolism and nutrition disorders	
Very common	Fluid retention
Vascular disorders	
Very common	Hypertension
Injury, poisoning and procedural complications	
Very common	Post-operative anemia
Very common	Surgery related nausea

Serious adverse reactions were reported in 20 patients (25.0%, 20 out of 80). The most common adverse events 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 event 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.

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 6 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.

Nervous system disorders	
Common	Headache
Cardiac Disorders	
Common	Bradycardia
Common	Tachycardia
Very common	Hypertension
Very common	Hypotension
Very common	Diastolic hypertension
Very common	Systolic hypertension
Common	Diastolic hypotension
Respiratory disorders	
Common	Hypoxia
Gastrointestinal disorders	
Common	Nausea
Investigations	
Common	Oxygen saturation decreased
Common	Respiration rate increased

Post Marketing Safety Report
The following adverse reaction and incidence frequency had been reported in post-marketing safety report.

- Immune system
  Inciedence rate : Unkown, Anaphylactic reaction.

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

and/or

Corporate Pharmacovigilance Dexa Group
Post: Titan Center. Jalan Boulevard Bintaro, Blok B7/B1, No.5, Bintaro Jaya, Sektor 7, Tangerang Selatan 15424, Indonesia
Email: pv@dexagroup.com
Website: www.dexagroup.com

4.9 Overdose

Management of overdose

- Overdose may lead to dizziness, confusion, drowsiness, blurred vision or nystagmus, agitation, weakness,

hypotension, bradycardia, respiratory depression and coma.

- 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.
- In 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.
- 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.
- 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.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacodynamics

When administered 0.05 to 0.50 mg/kg of BYFAVO to healthy adults, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score (5: Agitated ~ 0: Does not respond to deep stimulus) dropped in a dose-dependent Pharmacodynamics manner. The bispectral index score (BIS) dropped rapidly in 2 to 3 minutes after the administration, but bounced to the prior administration level of the general alertness (90 and above) in 45 to 70 minutes after the administration

In Phase 3 clinical trial for procedural sedation in endoscopy/endoscopic therapy, the median time to peak sedation, defined as the lowest Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score after the initial dose (5mg IV over 1 minute) was 3 to 3.5 minutes and median time to fully alert, defined as time to the first of three consecutive MOAA/S scores of five, following the last dose of BYFAVO was 11 to 14 minutes.

Clinical Pharmacology

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 $GABA_A$ receptor protein as positive allosteric modulator.

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.

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.

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

Information on Clinical Studies

Study 1

In the Phase 2b/3 studies in Japan, randomized, single-blind, 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.

Study 2

In the Phase 3 study in S. Korea, randomized, single-blind, multicenter, parallel group design with active comparator (propofol) in 198 ASA-PS class I to 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 group 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.

Study 3

Phase 3 trial conducted in United States is a randomized, double-blind, 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.

Study 4
Phase 3 trial conducted in United States is a randomized, double-blind, 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.

5.2 Pharmacokinetic Properties

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·hr/mL, which suggested a close to dose-dependent relationship.

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%.

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.

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.

Specific Population
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.

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 T1/2 and Vss 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.

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 m2) and to the healthy adults with normal kidney function (eGFR: above 90 mL/min /1.73 m2), there was no difference found in pharmacokinetic profile.

5.3 Preclinical Safety Data

Information on Toxicity

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.

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.

6. Pharmaceutical Particulars

6.1 List of Excipient

- Dextran 40 for injection
- Lactose monohydrate
- Hydrochloric acid (for pH adjustment)
- Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

- To reconstitute, add sterile 0.9% Sodium Chloride Injection, to the vial. BYFAVO is not compatible with the fluids containing lactic acid and will be precipitated in the solution. Fluids containing lactic acid shall not be used for BYFAVO reconstitution.
- Incompatibilities between Byfavo and co- administered solutions may result in precipitation/turbidity which may cause occlusion of vascular access site. Byfavo is incompatible with lactated Ringer's solution (also known as compound sodium lactate solution or Hartmann's solution), acetated Ringer's solution, and bicarbonated Ringer's solution for infusion and other alkaline solutions since the solubility of the product is low at pH of 4 or higher.
- This medicinal product must not be mixed or co-administered through the same infusion line with other medicinal products except those mentioned in section 6.6

6.3 Shelf Life

24 months from the manufacturing date

6.4 Special Precautions for Storage

Store BYFAVO under 30°C in a sealed package

Protect vials from light once they are removed from packaging.

6.5 Nature and Contents of Container

BYFAVO is filled into clear, 12 mL Type I glass Borosilicate vials fitted with bromobutyl rubber stoppers and

capped with aluminum seals with polypropylene flip-off caps. The finished vials are labeled. 5 Vials are secondarily packaged with PVC(Polyvinylchloride)-Aluminium blister. And then, the blisters are contained in a paper-board carton box with an instruction leaflet.

Pack sizes: Box, 1 blister @ 5 vials @ 20 mg

6.6 Special Precautions for Disposal and Other Handling

- Appropriate infusion instruments (e.g., syringe pump) enabling titration of drug should be used for the continuous infusion of BYFAVO.
- Administer BYFAVO after opening of the drug package and reconstitution immediately. Discard unused portion.

7. MARKETING AUTHORISATION NUMBER(S)

DKIxxxxxxxx

8. Marketing Authorization Holder

PT DEXA MEDICA
Palembang-Indonesia

9. Manufacturer

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

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable

11. DATE OF REVISION OF THE TEXT

Not Applicable

12. DRUG CLASSIFICATION

Prescription Drug

13. SPECIAL PRECAUTION

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCPRIPTION ONLY

BYFAVO

Remimazolam besylate ~ Remimazolam 20 mg

Serbuk injeksi liofilisasi

Baca seluruh isi *leaflet* dengan cermat sebelum Anda menggunakan obat ini karena di dalam *leaflet* ini terdapat informasi penting untuk Anda.

- Simpan *leaflet* ini, mungkin suatu saat Anda perlu membacanya kembali.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Tidak boleh memberikan obat ini pada orang lain karena akan membahayakan, meskipun orang tersebut memiliki gejala yang sama seperti Anda.
- Apabila muncul efek samping, segera hubungi dokter atau apoteker. Termasuk efek samping yang tidak tercantum di dalam *leaflet* ini.

Apa saja yang terdapat pada *leaflet* ini:

1. Apa itu BYFAVO dan apa kegunaannya

BYFAVO adalah obat yang mengandung zat aktif *remimazolam besylate ~ remimazolam* 20 mg.

Remimazolam merupakan suatu senyawa yang termasuk dalam kelompok *benzodiazepine* yang bekerja meningkatkan aktivitas reseptor protein GABA A pada otak.

BYFAVO digunakan pada pasien dewasa untuk membuat Anda kehilangan kesadaran (tertidur) selama menjalani prosedur pembedahan serta sebagai penenang (sedasi) sebelum pemeriksaan atau tindakan medis tertentu agar Anda merasa tenang dan mengantuk.

2. Apa yang perlu Anda ketahui sebelum menggunakan BYFAVO

Bacalah bagian berikut dengan saksama. Informasi yang diberikan harus dipertimbangkan oleh Anda dan dokter sebelum Anda menggunakan BYFAVO.

BYFAVO tidak boleh digunakan pada kondisi berikut:

- jika Anda alergi terhadap *remimazolam*, obat-obat *benzodiazepine* lain, atau bahan lain dari BYFAVO
- jika Anda mengalami kondisi glaukoma sudut sempit akut, syok, koma, kecanduan alkohol akut, dan sindrom apnea tidur (terjadinya henti napas selama lebih dari 10 detik saat tidur)
- jika Anda ketergantungan alkohol atau obat
- jika Anda mengalami gagal napas berat atau akut
- jika Anda memiliki gangguan genetik, seperti tidak toleran terhadap galaktosa, kekurangan enzim laktase, atau gangguan penyerapan glukosa-galaktosa dalam tubuh
- jika Anda memiliki riwayat alergi terhadap *dextran* 40
- jika Anda mengalami kondisi miastenia gravis yang tidak stabil, yaitu kondisi lemah otot.

Perhatian khusus pada penggunaan BYFAVO:

Beritahukan kepada dokter Anda atau tenaga kesehatan profesional sebelum pengobatan BYFAVO apabila Anda mengalami setidaknya salah satu dari kondisi yang disebutkan di bawah ini:

- jika Anda memiliki riwayat hipersensitivitas berat terhadap *dextran* 40 atau produk-produk yang mengandung *dextran* 40. BYFAVO mengandung *dextran* 40 yang dapat menyebabkan reaksi seperti ruam, gatal, dan reaksi anafilaksis pada pasien yang hipersensitif.
- jika Anda mengalami gangguan pernapasan akibat kelainan paru dan jantung, penyakit paru obstruktif kronis, asma bronkial, atau disfungsi serebrovaskular akut (gangguan pada aliran darah

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menuju otak yang mendadak). Pada kondisi tersebut, kemungkinan BYFAVO tidak dapat diberikan atau harus diberikan dengan hati-hati jika diperlukan.
- jika Anda memiliki penyakit kardiovaskular (seperti gagal jantung kongestif), disfungsi serebral organik (gangguan fungsi otak yang disebabkan kondisi fisik tertentu), gagal ginjal kronis, ataksia spinal (gangguan keseimbangan dan koordinasi gerakan karena adanya masalah pada sumsum tulang belakang) atau ataksia serebelar (gangguan keseimbangan dan koordinasi gerakan karena adanya masalah pada bagian otak yang mengontrol gerakan tubuh), gangguan fungsi hati berat, penyakit sistemik berat (status fisik ASA III dan di atasnya), atau penyakit kronis lainnya.
- jika Anda memiliki riwayat gangguan cairan tubuh atau elektrolit berat, keracunan obat yang disebabkan oleh sedatif hipnotik, analgesik (obat antinyeri), antipsikotik (obat untuk gangguan mental), antidepresan (obat antidepresi), atau *lithium.*
- jika Anda mengalami kondisi yang disebut miastenia gravis yaitu kondisi otot Anda lemah.
- jika Anda rutin menggunakan obat-obatan terlarang atau pernah memiliki masalah dengan penggunaan obat-obat tersebut di masa lalu (ketergantungan obat).
- jika Anda berusia lanjut (≥65 tahun) atau dalam kondisi lemah.

BYFAVO dapat menyebabkan hilang ingatan sementara. Dokter akan memeriksa kondisi Anda dan memberikan saran yang diperlukan sebelum Anda meninggalkan rumah sakit.

Obat lain dan BYFAVO
Sampaikan kepada dokter jika Anda sedang menggunakan, baru saja menggunakan atau mungkin akan menggunakan obat-obatan lain baik obat yang diresepkan, vitamin dan suplemen yang digunakan tanpa resep, khususnya:
- obat antipsikotik (obat untuk mengatasi gangguan jiwa tertentu)
- obat penenang atau anticemas/ansiolitik (obat tidur atau obat untuk menenangkan diri)
- obat yang menyebabkan kantuk (misalnya *temazepam* atau *diazepam*)
- obat antidepresan (mengatasi depresi)
- obat antihistamin (obat-obat alergi)
- obat antihipertensi (obat untuk menurunkan tekanan darah tinggi).

BYFAVO dengan alkohol
Alkohol dapat memengaruhi cara kerja BYFAVO. Beritahu dokter atau perawat Anda seberapa sering Anda meminum alkohol, atau jika pernah memiliki masalah dengan alkohol. Jangan meminum alkohol selama 24 jam sebelum mendapatkan BYFAVO.

Kehamilan
Jika Anda sedang hamil atau kemungkinan akan hamil, konsultasikan dengan dokter. Penggunaan obat dihindari selama masa kehamilan.

Menyusui
Jika Anda sedang menyusui, beritahukan kepada dokter. Penggunaan BYFAVO pada ibu menyusui harus dihindari. Jika penggunaan BYFAVO diperlukan, jangan menyusui selama 24 jam setelah Anda diberikan obat ini.

Kemampuan mengemudi dan mengoperasikan mesin
BYFAVO dapat menyebabkan kehilangan kesadaran, mengantuk, penurunan kewaspadaan, dan tertundanya refleks. Anda tidak diperbolehkan untuk mengoperasikan mesin atau mengendarai kendaraan sampai efek obat ini hilang. Konsultasikan kepada dokter kapan Anda dapat mengemudi atau mengoperasikan mesin kembali.

3. Bagaimana cara penggunaan BYFAVO

BYFAVO harus diberikan hanya oleh dokter atau tenaga kesehatan profesional yang terlatih.

Dokter Anda akan menentukan dosis yang tepat untuk Anda. Pernapasan, denyut jantung, dan tekanan darah Anda akan dipantau selama prosedur medis berlangsung dan jika diperlukan dokter akan menyesuaikan dosis BYFAVO yang diberikan.

Dokter atau perawat akan memberikan BYFAVO kepada Anda melalui injeksi ke dalam vena (pembuluh darah) sebelum dan selama prosedur medis.

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Sebelum diberikan kepada pasien, apoteker, perawat, atau dokter akan melarutkan serbuk BYFAVO dengan injeksi *sodium chloride* (0,9%) steril hingga mencapai konsentrasi yang dibutuhkan.

Dokter atau perawat akan memeriksa kondisi Anda sesaat setelah sedasi untuk memastikan bahwa Anda dalam keadaan baik dan dapat pulang ke rumah.

Obat-obatan tambahan
Dokter akan meresepkan obat-obatan lain, seperti analgesik dan relaksan otot bersamaan dengan pemberian BYFAVO. Pemberian BYFAVO bersamaan dengan obat-obatan tersebut dilakukan untuk pemeliharaan efek BYFAVO.

Jika Anda menerima BYFAVO lebih dari yang seharusnya Anda terima
Pusing, kebingungan, mengantuk, penglihatan kabur, gelisah, lemah, tekanan darah rendah, denyut jantung lambat, gangguan pernapasan, hingga koma dapat terjadi pada kelebihan dosis BYFAVO. Jika Anda mengalami gejala-gejala tersebut, segera beritahukan kepada dokter atau apoteker. Dokter dan apoteker Anda akan memberikan terapi untuk gejala-gejala tersebut.

4. Efek samping yang mungkin terjadi

Seperti obat-obat lainnya, BYFAVO dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping BYFAVO dapat berupa:
Sangat umum:
- mual
- muntah
- demam
- penurunan tekanan darah
- peningkatan tekanan darah
- hematuria (darah pada urine)
- peningkatan enzim *creatine phosphokinase*
- komplikasi luka
- depresi pernapasan
- pusing
- nyeri prosedural
- efusi pleura (penumpukan cairan pada paru-paru)
- gangguan tidur
- cemas
- fibrilasi atrium
- retensi cairan
- anemia pascaoperasi

Umum:
- delirium (kondisi kebingungan akut)
- Insomnia
- sakit kepala
- bradikardia (detak jantung lambat)
- eritema (kulit memerah)
- nyeri punggung dan otot
- menggigil
- penurunan kadar albumin dan protein
- penurunan sel darah merah, hemoglobin, hematokrit, dan persentase limfosit
- peningkatan sel darah putih, bilirubin, dan persentase neutrofil
- proteinuria (protein dalam urine)
- ketonuria (keton dalam urine)
- peningkatan enzim hati
- penurunan denyut jantung
- peningkatan denyut jantung
- penurunan saturasi oksigen

- mengantuk
- efusi perikardium (penumpukan cairan pada selaput jantung)
- peningkatan laju pernapasan
- peningkatan *aspartate aminotransferase*

Sangat jarang:
- nyeri pada tempat injeksi

Frekuensi tidak diketahui:
- reaksi anafilaksis (reaksi alergi berat)

Melaporkan efek samping
Apabila Anda mengalami salah satu efek samping tersebut, sampaikan pada dokter Anda atau tenaga kesehatan profesional. Termasuk kemungkinan efek samping yang tidak tercantum dalam *leaflet*. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut terkait keamanan obat ini.

Corporate Pharmacovigilance Dexa Group
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Email: pv@dexagroup.com
Website: www.dexagroup.com

5. Bagaimana cara penyimpanan BYFAVO
Jangan menggunakan obat melewati tanggal kedaluwarsa yang tercantum pada kemasan. Tenaga kesehatan profesional di rumah sakit bertanggung jawab terhadap penyimpanan obat ini.
- Simpan BYFAVO pada suhu di bawah 30^{O}C, dalam kemasan tersegel, dan terlindung dari cahaya.
- Gunakan segera setelah kemasan dibuka dan direkonstitusi. Bagian yang tidak terpakai harus dibuang.

6. Isi kemasan dan informasi lainnya
Apa isi kandungan BYFAVO
Zat aktif:
Zat aktif BYFAVO adalah *remimazolam*.

Setiap vial mengandung *remimazolam besylate* setara dengan *remimazolam* 20 mg.

Bahan tambahan lainnya:
Dextran 40, *lactose monohydrate*, *hydrochloric acid*, *sodium hydroxide.*

Seperti apa BYFAVO dan isi kemasannya
BYFAVO berupa serbuk liofilisasi berwarna putih hingga putih keabu-abuan (*off-white*).

Kemasan dan Nomor Izin Edar:
Kotak, 1 *blister* @ 5 vial @ 20 mg; DKIXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER.

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

Untuk:
PT Dexa Medica
Palembang-Indonesia

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