Psychotropic | Prescription Drug | IV

1. NAME OF THE MEDICINAL PRODUCT

Byfavo 50 mg powder for solution for injection/infusion (Lyophilised Powder)
(remimazolam besylate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[COMPOSITION]
Each vial contains:
■ Active ingredient: remimazolam besylate ---------- 69.37mg
(equivalent to 50mg remimazolam)
■ Excipient (stabilizer): Dextran 40 ---------- 201.8 mg
■ Excipient (stabilizer): Lactose monohydrate ---------- 134.53mg
■ Animal origin: Lactose monohydrate (milk from cow)
■ Other excipients: Sodium hydroxide, Hydrochloric acid.

Each vial contains remimazolam besylate equivalent to 50 mg remimazolam.

After reconstitution each mL of concentrate contains 5 mg remimazolam.
Dilution is required to reach final concentration of 1-2 mg/mL.

Excipient with known effect

Each vial contains 201.8 mg of dextran 40 for injection

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each clear glass vial of BYFAVO (remimazolam) for injection contains powder for concentrate for solution for injection/infusion (powder for concentrate). White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remimazolam 50 mg is indicated in adults for intravenous induction and maintenance of general anaesthesia.

4.2 Posology and method of administration

Remimazolam must only be given in hospitals or adequately equipped day therapy units by physicians trained in anaesthesia.

Circulatory and respiratory functions should be constantly monitored (e.g. electrocardiogram (ECG), pulse oximetry) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times (see section 4.4).

Posology

The dose of Byfavo should be individualised based on the response of the patient and premedications used.
Supplementary opioid analgesic agents are usually given in combination with Byfavo.

Induction of anaesthesia

Normally, for adults, remimazolam is continuously infused intravenously at a rate of 12 mg/kg/hour while observing the patient's general condition until loss of consciousness is achieved. The administration rate should be reduced appropriately depending on the patient's age and condition.

Maintenance of anaesthesia

Normally, for adults, remimazolam is continuously infused intravenously at a rate of 1 mg/kg/hour, and the administration rate should be adjusted appropriately while observing the patient's general condition so that an appropriate depth of anesthesia can be maintained, with an upper limit of 2 mg/kg/hour. The administration rate should be reduced appropriately depending on the patient's age and condition. If signs of awakening are observed, a maximum of 0.2 mg/kg may be administered intravenously.

Special populations

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

Renal impairment
No dose adjustment is required in any grade of renal impairment (including patients with glomerular filtration rate [GFR] < 15 mL/min).

Hepatic impairment
The metabolising 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 (see section 4.4).

Paediatric population
The safety and efficacy of remimazolam in children and adolescents aged 0 to <18 years have not yet been established. No data are available.

Other populations
The safety and efficacy of remimazolam in patients undergoing intracranial surgery and patients with pre-existing cognitive disorders have not yet been established. No data are available.

Method of administration

Remimazolam is for intravenous use. Remimazolam must be reconstituted and diluted before use with sodium chloride 9 mg/mL (0.9%) solution for injection.

For instructions on reconstitution and dilution of the medicinal product before administration, and on administration with other fluids see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, other benzodiazpines or to any of the excipients listed in section 6.1.
Unstable myasthenia gravis.

4.4 Special warnings and precautions for use

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. 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 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 / Central Nervous System (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 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/hypnotic effects of remimazolam. Hence, a larger cumulative dose of remimazolam may be required to achieve the desired level of anaesthesia. A similar effect may also be observed with other CNS depressants. It is recommended to follow the titration regimen in section 4.2 and titrate up based on the patient's response, until the desired depth of anaesthesia is achieved (see section 4.5).

Monitoring

Remimazolam should be administered only by health care professionals trained in anaesthesia 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). 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). 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

Remimazolam has an abuse and dependence-inducing potential. This should be considered when prescribing or administering remimazolam where there is concern about an increased risk of misuse or abuse.

Delirium

Post-operative delirium and related neuropsychiatric events occur with reported incidence rate ranging from 4 to 53.3% in various published studies with sedatives or anaesthetic agents used for surgery or deep sedation in the intensive care. Risk factors include, but are not limited to, old age, pre-existent cognitive disorders, length and depth of anaesthesia or sedation, higher doses of longer acting benzodiazepines, metabolic disorders such as diabetes, electrolyte disorders, hypoxia, hypercapnia, hypotension, and infections. Although it is unclear whether remimazolam can itself cause or contribute to the risk of post-operative delirium, the lowest effective dose should be used. If post-operative delirium occurs, besides appropriate treatment of the delirium itself, any addressable risk factors should be appropriately treated. Patients should not be discharged prior to full recovery of cognition due to the potential risk of e.g. accidents.

Paradoxical reactions

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with benzodiazepines. These reactions are more likely to occur in elderly patients, with high doses and/or when the injection is given rapidly.

Prolonged effect of medicinal product

Prolonged effect of remimazolam (sedation, time to orientation) was observed postoperatively in some patients after the end of remimazolam administration. This occurred more frequently in elderly ($\geq$ 65 years old) patients, those with ASA III-IV and those receiving higher dose rates of remimazolam during the last hour of anaesthesia (see section 4.8.).

Excipients

This medicinal product contains 198 mg of dextran 40 for injection in each 50 mg vial.
Dextrans can cause anaphylactic/anaphylactoid reactions in some patients.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic drug interactions

Remimazolam is metabolised by CES, type 1A. No *in vivo* drug interaction study was conducted. *In vitro* data is summarised in section 5.2.

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/anaesthesia (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 Fertility, pregnancy and lactation

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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Byfavo during pregnancy.

Breastfeeding

It is unknown whether remimazolam and its main metabolite (CNS7054) are excreted in human breast milk. Available toxicological data in animals have shown excretion of remimazolam and CNS7054 in milk (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 stop of administration is advised.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Remimazolam has a major influence on the ability to drive and use machines. Prior to receiving remimazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. A physician should decide when the patient can be allowed to go home or resume normal activities. It is recommended that the patient is given appropriate advice and support when returning home after discharge (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions in patients with intravenous remimazolam for general anaesthesia are hypotension (51%), nausea (22.1%), vomiting (15.2%), and bradycardia (12.8%). Safety precautions must be taken to manage the occurrence of hypotension and bradycardia in clinical practice (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions associated with intravenous remimazolam observed in controlled clinical trials in general anaesthesia are tabulated below in Table 1 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
Psychiatric disorders Common	 Agitation
Nervous system disorders Common	 Headache Dizziness
Cardiac disorders Very common	 Bradycardia[1*]
Vascular disorders Very common	 Hypotension[2*]
Respiratory, thoracic and mediastinal disorders Common Uncommon	 Respiratory depression[3*] Hiccups
Gastrointestinal disorders Very common Very common Uncommon	 Nausea Vomiting Glossoptosis
General disorders and administration site conditions Common Common Uncommon	 Chills Drug effect prolonged[4*] Hypothermia

[1] Bradycardia covers the following identified events: bradycardia, sinus bradycardia, and heart rate decreased.

[2] Hypotension covers the following identified events: hypotension, procedural hypotension, post procedural hypotension, blood pressure decreased, mean arterial pressure decreased, orthostatic hypotension and orthostatic intolerance.

[3] Respiratory depression covers the following identified events: hypoxia, respiratory rate decreased, dyspnoea, oxygen saturation decreased, hypopnoea, respiratory depression, and respiratory disorder.

[4] Drug effect prolonged covers the following identified events: delayed recovery from anaesthesia, somnolence, and therapeutic product effect prolonged.

* See description of selected adverse reactions

Description of selected adverse reactions

The reported adverse reactions hypotension, respiratory depression and bradycardia represent medical concepts which encompass a group of events (refer to footnotes 1 - 3 under table 1); the incidence of

those reported in at least 1% of patients who received remimazolam are presented in table 2 below by severity level:

Table 2: Selected adverse reactions

Adverse reaction Reported event term	Mild	Moderate	Severe
Bradycardia			
Bradycardia	6.1%	3.7%	0.3%
Heart rate decreased	1.2%	0.6%	0%
Hypotension			
Blood pressure decreased	18%	2.1%	0%
Hypotension	14.8%	9.7%	0.6%
Mean arterial pressure decreased	3%	0.1%	0%
Procedural hypotension	2.5%	0.6%	0%
Respiratory depression			
Oxygen saturation decreased	3.7%	0.7%	0.3%
Hypoxia	3%	0.3%	0%

Other special populations

Elderly and/or patients with ASA-PS III-IV

Cardio-respiratory events
In controlled trials in general anaesthesia, patients ≥65 years old had a higher frequency of events grouped under the terms hypotension (64.2% vs 35.4%), respiratory depression (11.6% vs 5.8%) and bradycardia (19% vs 4.5%) than patients below 65 years old. Patients with ASA-PS III-IV also showed higher frequencies for hypotension (70.2% vs 32.6%), respiratory depression (15.7% vs 2.4%) and bradycardia (18.1% vs. 6.9%) than patients with ASA-PS I-II (see sections 4.2 and 4.4).

Prolonged sedation
In controlled trials in general anaesthesia, patients ≥65 years old had a higher frequency of events grouped under the term drug effect prolonged (11% vs 2.3%) than patients below 65 years old. Patients with ASA-PS III-IV also showed higher frequencies for drug effect prolonged (12.7% vs 1.2%) than patients with ASA-PS I-II (see section 4.4).

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 clinical trial assessing remimazolam in hepatic impairment (see section 4.2).

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 the national reporting system.

4.9 Overdose

Symptoms

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: hypotension, bradycardia, and respiratory depression.

Management of overdose

The patient's vital signs should be monitored and supportive measures should be started as indicated by the patient's clinical state including securing airway passages, assuring adequate ventilation and establishing adequate intravenous access. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with remimazolam is known or suspected.
Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Flumazenil will only reverse benzodiazepine-induced effects but will not reverse the effects of other concomitant medicinal products, e.g. that of opioids.
Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. However, since the elimination half-life of flumazenil is approximately the same as remimazolam the risk of re-sedation after flumazenil administration is low.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, hypnotics and sedatives, ATC code: N05CD14.

Mechanism of action

Remimazolam is an ultra-short acting benzodiazepine sedative/hypnotic. The effects of remimazolam on the CNS are dependent on the dose administered intravenously and presence or absence of other medicinal products. Remimazolam binds to benzodiazepine sites of gamma amino butyric acid type A [$GABA_A$] receptors with high affinity, while its carboxylic acid metabolite (CNS7054) has approximately 300 times lower affinity for these receptors. Remimazolam does not show clear selectivity between subtypes of the $GABA_A$ receptor.

Pharmacodynamic effects

The primary pharmacodynamic effect of remimazolam is sedation and hypnosis.
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 of mild 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. During maintenance of anaesthesia plasma concentrations of remimazolam are normally in the range of 1 µg/mL when remifentanil was co-administered. 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.

Clinical efficacy and safety

The efficacy of remimazolam was based on two pivotal studies CNS7056-022 and ONO-2745-05 in adult patients (aged 20 to 91 years) with ASA-PS I-IV who were undergoing mixed elective surgeries. The database for remimazolam additionally comprised additional propofol-controlled clinical trials in cardiac surgeries (CNS7056-010 and CNS7056-011).

ONO-2745-05: This was a phase IIb/III multicenter, randomized, parallel-group trial of remimazolam compared with propofol in surgical patients rated as ASA class I or II undergoing general anaesthesia conducted in Japan. Remimazolam was administered at a dose of 6 (n=158) or 12 mg/kg/h (n=156) by continuous intravenous infusion until loss of consciousness. After loss of consciousness, continuous intravenous infusion at a dose of 1 mg/kg/h was started, after which the infusion rate was adjusted as appropriate (maximum allowed dose, 2 mg/kg/h) based on monitoring of the general condition of individual subjects until the end of the surgery.

CNS7056-022: This was a European, confirmatory trial to establish non-inferior efficacy and superior haemodynamic stability of remimazolam compared with propofol for induction and maintenance of general anaesthesia during elective surgery in patients rated as ASA class III or IV. Patients were randomly assigned to the remimazolam (n=270) or the propofol arm (n=95). Remimazolam was administered at a dose of 6 mg/min for 3 min, followed by 2.5 mg/min for 7 min and 1.5 mg/min for an additional 10 min. Thereafter general anaesthesia was maintained with an infusion rate of 1 mg/min with adjustments between 0.7-2.5 mg/min based on monitoring of the general condition of individual subjects until the end of surgery.

The primary endpoints in the pivotal clinical trials, were defined as :

- Percentage of general anaesthesia maintenance time with Narcotrend index (NCI) ≤60 (CNS7056-022)
- Functional capability as a general anaesthetic as assessed by a composite of 3 variables: “intraoperative awakening or recall”, “requirement of rescue sedation with other sedatives” and “body movement.” (ONO-2745-05).

The primary endpoint was reached in both clinical trials (see table 3). All doses of remimazolam were non-inferior to propofol.

Table 3: Primary endpoints from pivotal clinical trials

	CNS7056-022		**ONO-2745-05**		
	RMZ6[1]	PROP	RMZ6[2]	RMZ12[3]	PROP
Capability as a general anaesthetic	-	-	100%	100%	100%
Mean time Narcotrend index ≤ 60	95%	99%	-	-	-

Induction dose 6 mg/min (1), 6 mg/kg/h (2) or 12 mg/kg/h (3); RMZ; remimazolam, PROP: propofol

In CNS7056-022, haemodynamic stability, assessed as absolute or relative hypotension and vasopressor use, was a key secondary endpoint. This was assessed during the period before start of surgery and is summarised in table 4. Remimazolam treated patients had fewer events of mean arterial pressure (MAP) of 1 min below 65 mmHg and fewer vasopressor dosing events.

Table 4: Secondary endpoints in phase 3 clinical trial CNS7056-022

Endpoint	Remimazolam N = 270	Propofol N = 95
MAP < 65 mmHg		
MAP <65 mmHg within start of IMP to 15 minutes after first skin incision over 1 minute, number of events		
Mean ± Standard deviation	6.62 ± 6.604	8.55 ± 8.944
CI 95%	(5.83 to 7.41)	(6.75 to 10.4)
Median (minimum, maximum)	5 (2, 10)	6 (3, 11)
Difference of least square means between treatments (95% CI)	1.9292 (0.2209 – 3.6375)	
Norepinephrine Use		
Norepinephrine boluses or infusion or continuous infusion over 2 minutes, number of events		
Mean ± Standard deviation	14.06 ± 13.540	19.86 ± 14.560
CI 95%	(12.4 to 15.7)	(16.9 to 22.8)
Median (minimum, maximum)	12 (0, 63)	21 (0, 66)
Difference of least square means between treatments (95% CI)	5.8009 (2.5610 – 9.0409)	
MAP < 65 mmHg AND/OR Norepinephrine use		
Number of events		
Mean ± Standard deviation	20.68 ± 16.444	28.41 ± 17.468
CI 95%	(18.7 to 22.6)	(24.9 to 31.9)
Median (minimum, maximum)	21 (0, 68)	30 (0, 75)
Difference of least square means between treatments (95% CI)	7.7301 (3.8090 – 11.651)	

IMP = investigational medicinal product; MAP = mean arterial pressure

The onset and recovery profile of remimazolam was characterised by time-to-event secondary endpoints assessed in the pivotal clinical trials. In each trial, time to recovery endpoints were slightly longer in the remimazolam groups than in the propofol group (table 5).

Table 5: Induction and recovery endpoints in phase 3 clinical trials

Median time	CNS 7056-022		ONO-2745-05		
	RMZ[1]	PROP[4]	RMZ6[2]	RMZ12[3]	PROP
Induction endpoints					
- Time to loss of consciousness	2.5 min	3 min	100.5 s	87.5 s	80 s
Patients (n)	268	95	150	150	75
95% CI	2.5 – 2.8 min	3.0 – 3.2 min	NA	NA	NA
Q1; Q3	2.0; 3.3 min	2.5; 3.7 min	NA	NA	NA
Min; Max	NA	NA	24; 165 s	30; 170 s	17; 280 s

Median time	**CNS 7056-022**		**ONO-2745-05**		
	RMZ[1]	PROP[4]	RMZ6[2]	RMZ12[3]	PROP
Recovery endpoints Time from stop of IMP[§] administration to					
- Extubation	12 min	11 min	15.5 min	18 min	12 min
Patients (n)	263	95	150	150	75
95% CI	11 – 13 min	10 – 12 min	NA	NA	NA
Q1; Q3	8; 18 min	8; 15 min	NA	NA	NA
Min; Max	NA	NA	3; 104 min	2; 58 min	3; 42 min
- Awakening[#]	15 min	12 min	12 min	12 min	10 min
Patients (n)	257	95	150	150	75
95% CI	13 – 17 min	10 – 13 min	NA	NA	NA
Q1; Q3	9; 26 min	8; 16 min	NA	NA	NA
Min; Max	NA	NA	1; 87 min	0; 50 min	0; 24 min
- Orientation[##]	54 min	30 min	21 min	21 min	14 min
Patients (n)	262	95	149	149	75
95% CI	47 – 61 min	27 – 33 min	NA	NA	NA
Q1; Q3	31; 88 min	22; 48 min	NA	NA	NA
Min; Max	NA	NA	3; 106 min	2; 125 min	4; 86 min
- Modified Aldrete score ⩾9	53 min	37 min			
Patients (n)	260	94			
95% CI	44 – 58 min	28 – 45 min	NA	NA	NA
Q1; Q3	30; 98 min	21; 88 min			
…Min; Max	NA	NA			
- Discharge from operation room			25 min	25 min	16 min
Patients (n)			150	150	75
95% CI	NA	NA	NA	NA	NA
Q1; Q3			NA	NA	NA
Min; Max			4; 144 min	5; 125 min	5; 87 min

Induction doses remimazolam (1) 6 mg/min, (2) 6 mg/kg/h or (3) 12 mg/kg/h, (4) propofol dose equipotent to remimazolam

\# ONO-2745-05: eye opening; CNS7056-022: response to verbal command ((MOAA/S≥4)

ONO-2745-05: stating date of birth; CNS7056-022: orientation to place, time, situation and person

§ Investigational medicinal product

Clinical Safety

The incidence of treatment-emergent adverse events in the propofol-controlled trials was 90.7% in the low induction dose remimazolam groups, 83.7% in the high induction dose remimazolam groups and 92.5% in the propofol groups. Particularly the incidence of haemodynamic adverse events was lower for the remimazolam dose groups as compared to the propofol groups (table 6).

Table 6: Number of patients with haemodynamic instability adverse events in propofol-controlled clinical trials

Total number of patients	remimazolam N=671	propofol N=226
Number of patients with events		
Hypotension n (n/N%) [95%CI]	344 (51.3%) [47.5-55.0]	150 (66.4%) [59.0-72.2]
Bradycardia n (n/N%) [95%CI]	96 (14.3%) [11.9-17.2]	50 (22.1%) [17.2-28.0]

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Byfavo in one or more subsets of the paediatric population in the condition of general anaesthesia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Remimazolam is administered intravenously.

Distribution

Remimazolam has a mean distribution half-life ($t_{1/2\alpha}$) of 0.5 to 2 min. Its volume of distribution (V_d) is 0.9 L/kg. Remimazolam and its main metabolite (CNS7054) show moderate (~90%) binding to plasma proteins, predominantly albumin.

Biotransformation

Remimazolam is an ester drug that is rapidly converted into a pharmacologically inactive carboxylic acid metabolite (CNS7054) by CES-1, mainly located in the liver.
The main route of metabolism of remimazolam is via conversion to CNS7054, which is then to a small extent further metabolized by hydroxylation and glucuronidation. Conversion to CNS7054 is mediated by liver carboxylesterases (primarily type 1A), with no meaningful contribution by cytochrome P450 enzymes.
In vitro studies have shown no evidence that remimazolam or CNS7054 inhibit cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2B6 and CYP2C8. There is no induction of the main inducible P450 isoenzymes 1A2, 2B6, and 3A4 in man. *In vitro* studies showed no clinically relevant influence of CES inhibitors and substrates on the metabolism of remimazolam. Remimazolam was not a relevant substrate of a panel of human drug transporters (OATP1B1, OATP1B3, BCRP, and MDR1 (=P-glycoprotein)). The same is true of CNS7054, tested for MRP2-4. By contrast, CNS7054 was found to be a substrate of MDR1 and BCRP. No or no relevant inhibition of the human drug transporters, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, BCRP, BSEP, or MDR1, was seen with remimazolam or CNS7054.

Elimination

Remimazolam has a mean elimination half-life ($t_{1/2\beta}$) of 7 to 11 minutes. The simulated context sensitive half-time after an infusion of 4 h is 6.6 ± 2.4 minutes. Clearance is high (68 ± 12 L/h) and not related to body weight. In healthy subjects at least 80% of the remimazolam dose is excreted in urine as CNS7054 within 24 hours. Only traces (<0.1%) of unchanged remimazolam are detected in urine.

Linearity

Remimazolam dose versus remimazolam maximal plasma concentration (C_{max}) and total exposure ($AUC_{0-\infty}$) suggested a dose-proportional relationship in human volunteers in the dose range 0.01-0.5 mg/kg.

Special population

Elderly
There is no significant effect of age on the pharmacokinetics of remimazolam (see section 4.2).

Renal impairment
The pharmacokinetics of remimazolam were not altered in patients with mild to end stage renal disease not requiring dialysis (including patients with a GFR < 15 mL/min) (see section 4.2).

Hepatic impairment
Severe impairment of hepatic function resulted in a reduced clearance and, as a consequence, a prolonged recovery from sedation (see sections 4.2 and 4.8).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.
The following adverse reaction was not observed in clinical studies, but was seen in animals infused with the dosing solution of concentrations similar to those used in clinical practice: primary lesions due to a mechanical irritation of the vessel wall during the puncture procedure can be aggravated by concentrations of remimazolam above 1 to 2 mg/mL (infusion) or above 5 mg/mL during bolus administration.

Reproduction and development

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,rabbits and sheeps. The inactive main metabolite CNS7054 was detected in the plasma of suckling rabbit kits. In suckling lambs, oral administration of remimazolam spiked milk resulted in negligable bioavalibility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

Unopened vials

3 years

In-use stability after reconstitution

BYFAVO must be immediately used after opening and discarded after use. Stability of the reconstituted BYFAVO has not been established.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store BYFAVO under 30 °C in a sealed package

Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass vial with a stopper (bromobutyl rubber) and seal (aluminium) with polypropylene flip-off cap.

Pack size: 5 Vial pack

6.6 Special precautions for disposal and other handling

General precautions

Each vial is for single use only.

Reconstitution and dilution of the product should be conducted using aseptic techniques. Once opened the contents of the vial should be used immediately (section 6.3).

Instructions for reconstitution

Byfavo should be reconstituted by adding 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection and swirled gently until the powder has entirely dissolved. Reconstituted Byfavo will be clear and colourless to light yellow. The solution is to be discarded if visible particulate matter or discolouration is observed.

Instructions for dilution

For administration, the reconstituted solution must be further diluted. The appropriate volume of reconstituted remimazolam solution must be withdrawn from the vial(s) and added to a syringe or infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection in order to achieve a final concentration of 1-2 mg/ml remimazolam (table 7).

Table 7 Dilution instructions

Reconstituted solution	Final concentration 2 mg/mL	Final concentration 1 mg/mL
5 mg/mL (50 mg reconstituted with 10 mL)	Dilute 10 mL of reconstituted solution with 15 mL of sodium chloride (0.9%) solution for injection	Dilute 10 mL of reconstituted solution with 40 mL of sodium chloride (0.9%) solution for injection

For instructions on administration see section 4.2.

Administration with other fluids

When Byfavo is reconstituted and diluted for use in sodium chloride (0.9%) as described above, compatibility has been shown with:
Glucose 5% w/v intravenous infusion,
Glucose 20% w/v solution for infusion,
Sodium chloride 0.45% w/v and glucose 5% w/v solution for infusion,
Sodium chloride 0.9% w/v intravenous infusion,
Ringers solution (sodium chloride 8.6 g/L, potassium chloride 0.3 g/L, calcium chloride dihydrate 0.33 g/L)

This medicinal product must not be mixed or co-administered through the same infusion line with medicinal products other than those fluids described in this section.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Product Registration Holder

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9 DATE OF REVISION

APR 2026