ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Byfavo 20 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains remimazolam besylate equivalent to 20 mg remimazolam.
After reconstitution each mL contains 2.5 mg remimazolam.

Excipient with known effect

Each vial contains 79.13 mg of dextran 40 for injection.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remimazolam is indicated in adults for procedural sedation.

4.2 Posology and method of administration

Remimazolam must only be administered by healthcare professionals experienced in sedation. The patient should be monitored throughout by a separate healthcare professional, who is not involved in the conduct of the procedure, and whose sole task is to monitor the patient. This personnel must be trained in the detection and management of airway obstruction, hypoventilation and apnoea, including the maintenance of a patent airway, supportive ventilation and cardiovascular resuscitation. The patient´s respiratory and cardiac function must be continuously monitored. Resuscitative medicinal products and age- and size-appropriate equipment for restoring airway patency and bag/valve/mask ventilation must be immediately available. A benzodiazepine reversal medicinal product (flumazenil) must be immediately available for use.

Posology

Remimazolam dosing should be individually titrated to an effective dose which provides the desired level of sedation and minimises adverse reactions (see Table 1). Additional doses can be administered as needed to induce or maintain the desired level of sedation. At least 2 minutes should elapse prior to administration of any supplemental dose in order to fully assess the sedative effect. If 5 doses of remimazolam within 15 minutes do not result in the desired level of sedation then an additional or another sedative should be considered. Remimazolam is associated with fast onset and offset of sedation. In clinical trials, peak sedation occurred 3-3.5 minutes after the initial bolus and patients became fully alert 12-14 minutes from last dose of remimazolam.

Opioid co-administered medicinal products are known to increase the sedative effect of remimazolam and to depress the ventilatory response to carbon dioxide stimulation (see sections 4.4 and 4.5).

Table 1: Dosing guidelines for adults*

	Adults < 65 years of age	**Elderly ≥ 65 years of age and/or with ASA-PS# III-IV and/or body weight < 50 kg**
Procedural sedation with opioid**	Induction Administer opioid* Wait 1-2 min Initial dose: Injection: 5 mg (2 mL) over 1 min Wait 2 min Maintenance / titration Injection: 2.5 mg (1 mL) over 15 sec Maximal total dose administrated in the clinical trials was 33 mg.	Induction Administer opioid* Wait 1-2 min Initial dose: Injection: 2.5-5 mg (1-2 mL) over 1 min Wait 2 min Maintenance / titration Injection: 1.25-2.5 mg (0.5-1 mL) over 15 sec Maximal total dose administrated in the clinical trials was 17.5 mg.
Procedural sedation without opioid	Induction Injection: 7 mg (2.8 mL) over 1 min Wait 2 min Maintenance / titration Injection: 2.5 mg (1 mL) over 15 sec Maximal total dose administrated in the clinical trials was 33 mg.	Induction Injection: 2.5-5 mg (1-2 mL) over 1 min Wait 2 min Maintenance / titration Injection: 1.25-2.5 mg (0.5-1 mL) over 15 sec Maximal total dose administrated in the clinical trials was 17.5 mg.

* For administration to patients concomitantly taking opioids, CNS depressants, alcohol or benzodiazepines see section 4.4.

** e.g. 50 micrograms fentanyl or a suitably reduced dose for elderly or debilitated patients. For fentanyl doses administered in clinical trials see section 5.1.

American Society of Anesthesiologists Physical Status

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 sedatives. Before administration of remimazolam a careful assessment of the overall condition of patients ≥65 years of age and/or with ASA-PS III-IV, especially with low body weight (< 50 kg), is therefore of particular relevance when deciding upon individualised dosage adjustments for these patients (see sections 4.4).

Renal impairment

No dosage 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.

Method of administration

Remimazolam is for intravenous use. Remimazolam must be reconstituted before use with sodium chloride (0.9%) solution for injection.

For instructions on reconstitution 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 benzodiazepines or 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 (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

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.

Excipients

Dextran
This medicinal product contains 79.13 mg of dextran 40 for injection in each 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 (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 (for details see section 5.3). A risk to newborns/infants cannot be excluded; therefore, administration of remimazolam to breastfeeding mothers should be avoided. If there is a need to administer remimazolam, then discontinuation of breastfeeding for 24 hours after administration is advised.

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, using the recovery data from the pivotal clinical trials as a basis for their decision (see section 5.1). 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 are hypotension (37.2%), respiratory depression (13.1%), and bradycardia (6.8%). Safety precautions must be taken to manage the occurrence of these adverse reactions in clinical practice (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions associated with intravenous remimazolam observed in controlled clinical trials in procedural sedation and the postmarketing setting are tabulated below in Table 2 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 2: Tabulated list of adverse reactions

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

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

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 2); the incidence of those reported in at least 1% of patients who received remimazolam are presented in Table 3 below by severity level:

Table 3: Selected adverse reactions

Adverse reaction Reported event term	Mild	Moderate	Severe
Bradycardia			
Bradycardia	6.0%	0.1%	0.4%
Hypotension			
Hypotension	30.1%	1.1%	0.1%
Diastolic hypotension	8.7%	0	0
Respiratory depression			
Hypoxia	8.0%	0.9%	0.3%
Respiratory rate decreased	1.5%	0.4%	0

Other special populations

Elderly and/or patients with ASA-PS III-IV
In controlled trials in procedural sedation, patients ≥65 years old had a higher frequency of events grouped under the terms hypotension (47.0% vs 33.3%) and respiratory depression (22.8% vs 9.0%)

than patients below 65 years old. Patients with ASA-PS III-IV also showed higher frequencies for hypotension (43.6% vs 35.6%) and respiratory depression (17.6% vs 11.8%) than patients with ASA-PS I-II. Older age and higher ASA-PS were not associated with a higher frequency of bradycardia. See also sections 4.2 and 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 trial assessing remimazolam in hepatic impairment. See also 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 listed in Appendix V.

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 and symptoms: dizziness, confusion, drowsiness, blurred vision or nystagmus, agitation, weakness, hypotension, bradycardia, respiratory depression and coma.

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. 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.
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. Depth, duration and recovery from sedation is dose-dependent. Time to fully alert was 10 min for 0.075 mg/kg of remimazolam.

Remimazolam can cause anterograde amnesia after administration, which prevents patients from remembering events occurring during the procedure. Brice questionnaire data from 743 remimazolam-treated patients, assessed 10 minutes after the patient became fully alert and one day after the procedure, show that 76% of patients had no recollection of the procedure.

Clinical efficacy and safety

The efficacy of remimazolam was based on two pivotal studies CNS7056-006 and CNS7056-008 in adult patients (aged 18 to 95 years) with ASA-PS I-III who were scheduled for colonoscopy or bronchoscopy, respectively. The safety database for remimazolam additionally comprised a dedicated safety and efficacy trial in ASA-PS III/IV patients, CNS7056-015.

CNS7056-006 and CNS7056-008 are two Phase 3 double-blind, randomised, active- and placebo-controlled clinical trials in adult patients undergoing colonoscopy and bronchoscopy, respectively. All patients received fentanyl for analgesia before and during the procedure (50 or 75 µg or a reduced dose for elderly/debilitated patients and supplemental doses of 25 µg at least 5 min apart, as needed, but not to exceed 200 µg). Patients were randomised to remimazolam, midazolam dosed according to the U.S. local approved posology, or placebo with rescue midazolam dosed at the investigator's discretion.
The remimazolam and placebo groups were double-blinded, while the midazolam arm was open-label due to the different dosing regimen for midazolam. After pre-treatment with fentanyl to ensure analgesia, patients received an initial dose of 5.0 mg (2 mL) remimazolam or matching placebo over 1 minute or 1.75 mg midazolam over 2 minutes (or 1.0 mg midazolam for patients ≥ 60 years of age or debilitated or chronically ill). For the remimazolam and placebo arms, supplemental doses of 2.5 mg (1 mL) at least 2 min apart were allowed until adequate sedation was achieved, and as necessary to maintain sedation. For midazolam, supplemental doses of 1.0 mg over 2 minutes with 2 minutes between doses (or 0.5 mg for patients aged ≥ 60 years or debilitated or chronically ill) were allowed to achieve and maintain adequate sedation.

The number of top-up doses and total doses of remimazolam, rescue midazolam and fentanyl administered are presented in Table 4.

Table 4: Number of top-up doses and total doses of remimazolam, rescue midazolam and fentanyl in Phase 3 clinical trials with intravenous remimazolam (Safety set)

	CNS7056-006			CNS7056-008		
Parameter (mean ± standard deviation)	Remimazolam (N=296)	Midazolam (N=102)	Placebo (rescue midazolam) (N=60)	Remimazolam (N=303)	Midazolam (N=69)	Placebo (rescue midazolam) (N=59)
Number of top-up doses of study drug	2.2 ± 1.6	3.0 ± 1.1	5.1 ± 0.5	2.6 ± 2.0	2.8 ± 1.6	4.1 ± 0.8
Total doses of study drug [mg]	10.5 ± 4.0	3.9 ± 1.4	0	11.5 ± 5.1	3.2 ± 1.5	0
Total doses of rescue midazolam [mg]	0.3 ± 2.1	3.2 ± 4.0	6.8 ± 4.2	1.3 ± 3.5	2.6 ± 3.0	5.9 ± 3.7
Total doses of fentanyl [µg]	88.9 ± 21.7	106.9 ± 32.7	121.3 ± 34.4	81.9 ± 54.3	107.0 ± 60.6	119.9 ± 80

The safety set consists of all randomised patients who receive any amount of study drug.

The primary endpoint, success of procedure was defined as meeting all of the following:

- Completion of the colonoscopy/bronchoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement of more than 5 doses of study medication within any 15 min window (for midazolam: no requirement of more than 3 doses within any 12 min window).

Statistically significant higher success rates were observed for the difference between remimazolam and placebo ($p< 0.0001$; Table 5 and Table 6). Comparisons between remimazolam and midazolam are descriptive and significance testing was not performed. In the dedicated safety and efficacy trial in ASA-PS III/IV patients, CNS7056-015, similar results were observed, the procedure success rate was 27/32 (84.4%) for remimazolam, and 0% for placebo.

Table 5: Procedure success rates in Phase 3 clinical trials with intravenous remimazolam for procedure duration < 30 minutes (intent-to-treat set)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remimazolam (N=297)	Midazolam (N=100)	Placebo (rescue midazolam) (N=58)	Remimazolam (N=280)	Midazolam (N=69)	Placebo (rescue midazolam) (N=58)
Procedure success [N (%)]	272 (91.6%)	26 (26.0%)	1 (1.7%)	232 (82.9%)	22 (31.9%)	2 (3.5%)
Procedure failure [N (%)]	25 (8.4%)	74 (74.0%)	57 (98.3%)	48 (17.1%)	47 (68.1%)	56 (96.6%)
Rescue sedative medication taken [N]	9	63	55	38	37	53
Too many doses within time [N]	17	55	42	10	10	10
Procedure not completed [N]	7	2	1	9	5	3

The intent-to-treat analysis set includes all patients who were randomised.

Table 6: Procedure success rates in Phase 3 clinical trials with intravenous remimazolam for procedure duration ≥ 30 minutes (intent-to-treat set)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remimazolam (N=1)	Midazolam (N=3)	Placebo (rescue midazolam) (N=2)	Remimazolam (N=30)	Midazolam (N=4)	Placebo (rescue midazolam) (N=5)
Procedure success [N (%)]	0	0	0	18 (60.0%)	2 (50.0%)	1 (20.0%)
Procedure failure [N (%)]	1 (100%)	3 (100.0%)	2 (100%)	12 (40.0%)	2 (50.0%)	4 (80.0%)
Rescue sedative medication taken [N]	1	3	2	11	2	4
Too many doses within time [N]	1	1	2	4	0	0
Procedure not completed [N]	0	0	0	0	0	0

The intent-to-treat analysis set includes all patients who were randomised.

The onset and recovery profile of remimazolam was characterised by time-to-event secondary endpoints assessed in the two Phase 3 trials, CNS7056-006 and CNS7056-008. Time to start of procedure was shorter ($p < 0.01$) in remimazolam group compared to placebo (rescue midazolam) group (Table 7). Time to recovery is presented according to procedure duration (Tables 8 and 9).

Table 7: Time to start of procedure in Phase 3 clinical trials with intravenous remimazolam (intent-to-treat set)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remimazolam	Midazolam	Placebo (rescue midazolam)	Remimazolam	Midazolam	Placebo (rescue midazolam)
Number of patients in analysis	296	102	60	300	68	60
Median (95% CI)	4.0 (-, -)	19.0 (17.0, 20.0)	19.5 (18.0, 21.0)	4.1 (4.0, 4.8)	15.5 (13.8, 16.7)	17.0 (16.0, 17.5)
Min, max	0, 26	3, 32	11, 36	1, 41	3, 53	4, 29

The Intent-to-treat analysis set includes all patients who were randomised.

Table 8: Time to recovery in Phase 3 clinical trials with intravenous remimazolam for procedure duration < 30 minutes (Intent-to-treat set)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remimazolam	Midazolam	Placebo (rescue midazolam)	Remimazolam	Midazolam	Placebo (rescue midazolam)
Time to Fully Alert[1] from Last Dose (minutes)						
Number of patients in analysis	284	97	57	268	63	54
Median (95% CI)	13.0 (13.0, 14.0)	23.0 (21.0, 26.0)	29.0 (24.0, 33.0)	10.3 (9.8, 12.0)	18.0 (11.0, 20.0)	17.5 (13.0, 23.0)
Min, max	3, 51	5, 68	9, 81	1, 92	2, 78	5, 119
Time to Ready for Discharge[2] from Last Dose (minutes)						
Number of patients in analysis	294	98	58	260	62	53
Median (95% CI)	51.0 (49.0, 54.0)	56.5 (52.0, 61.0)	60.5 (56.0, 67.0)	62.5 (60.0, 65.0)	70.0 (68.0, 87.0)	85.0 (71.0, 107.0)
Min, max	19, 92	17, 98	33, 122	15, 285	27, 761	40, 178
Time to Back to Normal[3] from Last Dose (hours)						
Number of patients in analysis	292	95	54	230	56	46
Median (95% CI)	3.2 (3.0, 3.5)	5.7 (4.5, 6.9)	5.3 (3.3, 7.2)	5.4 (4.6, 6.2)	7.3 (5.2, 16.4)	8.8 (6.7, 17.0)
Min, max	0, 77	1, 34	1, 23	0, 46	1, 35	2, 30

Note[1]: Fully alert is defined as the first of three consecutive MOAA/S measurements of 5 after start time of the last dose of study or rescue drug.

Note[2]: Ready for discharge time was determined by a walking test.

Note[3]: Date and time of ´back to normal´ in the patient´s subjective view were recorded via telephone contact by the study nurse on Day 4 (+3/-1 days) after the procedure.

The Intent-to-treat analysis set includes all patients who were randomised.

Table 9: Time to recovery in Phase 3 clinical trials with intravenous remimazolam for procedure duration ≥30 minutes (Intent-to-treat set)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remimazolam	Midazolam	Placebo (rescue midazolam)	Remimazolam	Midazolam	Placebo (rescue midazolam)
Time to Fully Alert[1] from Last Dose (minutes)						
Number of patients in analysis	1	3	2	30	4	5
Median (95% CI)	6.0 (N/A)	27.0 (25.0, 28.0)	22.5 (21.0, 24.0)	34.8 (16.2, 47.4)	26.1 (16.0, 42.0)	48.0 (22.0, 123.0)
Min, max	6, 6	25, 28	21, 24	4, 114	16, 42	22, 123
Time to Ready for Discharge[2] from Last Dose (minutes)						
Number of patients in analysis	1	3	2	29	4	5
Median (95% CI)	58.0 (N/A)	66.0 (58.0, 74.0)	60.0 (52.0, 68.0)	83.0 (72.0, 103.0)	63.5 (38.0, 98.0)	95.0 (73.0, 157.0)
Min, max	58, 58	58, 74	52, 68	26, 165	38, 98	73, 157
Time to Back to Normal[3] from Last Dose (hours)						
Number of patients in analysis	1	3	2	19	4	3
Median (95% CI)	3.3 (N/A)	8.1 (7.0, 14.4)	5.2 (4.6, 5.8)	16.7 (4.7, 21.0)	2.7 (0.9, 5.1)	9.1 (3.6, 37.0)
Min, max	3, 3	7, 14	5, 6	3, 38	1, 5	4, 37

Note[1]: Fully alert is defined as the first of three consecutive MOAA/S measurements of 5 after start time of the last dose of study or rescue drug.
Note[2]: Ready for discharge time was determined by a walking test.
Note[3]: Date and time of ´back to normal´ in the patient´s subjective view were recorded via telephone contact by the study nurse on Day 4 (+3/-1 days) after the procedure.
The Intent-to-treat analysis set includes all patients who were randomised.
N/A: not applicable

Clinical Safety

In procedures less than 30 minutes, the incidence of treatment-emergent adverse events was 80.9%, 90.8%, and 82.3% in the remimazolam, midazolam, and placebo group, respectively. In procedures 30 minutes or longer, the incidence of treatment-emergent adverse events was 87.1% in the remimazolam group, and 100% in both the midazolam and the placebo groups.

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 sedation (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 (Vz) 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 the 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 ($t_{1/2ß}$) of 7 to 11 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 given for procedural sedation (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 the one 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 and rabbits. The inactive main metabolite CNS7054 was detected in the plasma of suckling rabbit kits, however it is not known if remimazolam is transferred via milk to suckling offspring.

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

4 years

In-use stability after reconstitution

Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C.

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

This medicinal product does not require any special temperature storage conditions.

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 blue polypropylene flip-off cap.

Pack size: 10 vial pack

6.6 Special precautions for disposal and other handling

Instructions for use

Byfavo must be reconstituted under aseptic conditions before administration.
Byfavo should be reconstituted by adding 8.2 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. The reconstituted solution is clear, colourless to pale yellow and practically free from visible particulate matter and contains 2.5 mg/mL of remimazolam. The solution is to be discarded if visible particulate matter or discolouration is observed. Byfavo is for single use only. Once opened the content of the vial should normally be used immediately (section 6.3). For instructions on administration see section 4.2.

Administration with other fluids

When Byfavo is reconstituted in sodium chloride (0.9%), 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)

Disposal

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

7. MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany
Tel: +800 4453 4453
e-mail: info@paion.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1505/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: March 26, 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Byfavo 50 mg powder for concentrate for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 198 mg of dextran 40 for injection

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

The rate of infusion of remimazolam should be set to 6 mg/min and measured against the response of the patient until clinical signs show the onset of anaesthesia and, in cases where needed, could be up-titrated to a maximum of 12 mg/min.
Most adult patients are likely to require 10-40 mg Byfavo.

Maintenance of anaesthesia

Anaesthesia is maintained by administering remimazolam by continuous infusion.

Recommended starting dose for maintenance of anaesthesia is 1 mg/min remimazolam with a range of 0.1-2.5 mg/min based on clinical judgement in order to maintain satisfactory anaesthesia.

For maintenance of anaesthesia, during the ongoing infusion, additional boluses of 6 mg over one minute can be given according to clinical requirements. A maximum of three (3) boluses not less than 5 min apart can be administered within 60 min.

Towards the end of surgery (e.g. 15 min before the end) the dose of remimazolam may be titrated down to facilitate more rapid recovery from the anaesthetic effects.

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 listed in Appendix V

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 Patients (n) 95% CI Q1; Q3 Min; Max	12 min 263 11 – 13 min 8; 18 min NA	11 min 95 10 – 12 min 8; 15 min NA	15.5 min 150 NA NA 3; 104 min	18 min 150 NA NA 2; 58 min	12 min 75 NA NA 3; 42 min
- Awakening[#] Patients (n) 95% CI Q1; Q3 Min; Max	15 min 257 13 – 17 min 9; 26 min NA	12 min 95 10 – 13 min 8; 16 min NA	12 min 150 NA NA 1; 87 min	12 min 150 NA NA 0; 50 min	10 min 75 NA NA 0; 24 min
- Orientation[##] Patients (n) 95% CI Q1; Q3 Min; Max	54 min 262 47 – 61 min 31; 88 min NA	30 min 95 27 – 33 min 22; 48 min NA	21 min 149 NA NA 3; 106 min	21 min 149 NA NA 2; 125 min	14 min 75 NA NA 4; 86 min
- Modified Aldrete score ⩾9 Patients (n) 95% CI Q1; Q3 …Min; Max	53 min 260 44 – 58 min 30; 98 min NA	37 min 94 28 – 45 min 21; 88 min NA	NA	NA	NA
- Discharge from operation room Patients (n) 95% CI Q1; Q3 Min; Max	NA	NA	25 min 150 NA NA 4; 144 min	25 min 150 NA NA 5; 125 min	16 min 75 NA NA 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 ($t_{1/2ß}$) 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

4 years

In-use stability after reconstitution

Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C.

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

This medicinal product does not require any special temperature storage conditions.

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 green polypropylene flip-off cap.

Pack size: 10 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. MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany
Tel: +800 4453 4453
e-mail: info@paion.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1505/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 March 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicine's web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation, aligned to International Birth Date.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Byfavo 20 mg powder for solution for injection
remimazolam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains remimazolam besylate equivalent to 20 mg remimazolam.
Concentration after reconstitution: 2.5 mg/mL

3. LIST OF EXCIPIENTS

Excipients: Dextran 40 for injection, lactose monohydrate, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1505/001 10 vial pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

12mL Glass vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Byfavo 20 mg powder for solution for injection
remimazolam
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

After reconstitution: 2.5 mg/mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Byfavo 50 mg powder for concentrate for solution for injection/infusion
remimazolam

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains remimazolam besylate equivalent to 50 mg remimazolam.
Concentration after reconstitution (5 mg/mL)
Concentration after dilution: 1 or 2 mg/mL

3. LIST OF EXCIPIENTS

Excipients: Dextran 40 for injection, lactose monohydrate, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for concentrate for solution for injection/infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1505/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

12mL Glass Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Byfavo 50 mg powder for concentrate
remimazolam
IV after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Byfavo 20 mg powder for solution for injection
remimazolam

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effect you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Byfavo is and what it is used for

Byfavo is a medicine that contains the active substance remimazolam.
Remimazolam is one of a group of substances known as benzodiazepines.

Byfavo is a sedative given before a medical test or procedure to make you feel relaxed and sleepy (sedated).

2. What you need to know before you are given Byfavo

You must not be given Byfavo if:
- you are allergic to remimazolam or other benzodiazepines (such as midazolam) or any of the other ingredients of this medicine (listed in section 6).
- you have an unstable form of a condition called myasthenia gravis (weakness of muscles) in which your chest muscles that help you breathe get weak

Warnings and precautions
Talk to your doctor or nurse before using Byfavo if you have any severe illness or condition and in particular if:
- you have very low or very high blood pressure or tend to faint
- you have heart problems especially a very slow and/or irregular (arrhythmic) heart rate
- you have any breathing problems including shortness of breath
- you have severe liver problems.
- you have a condition called myasthenia gravis in which your muscles are weak
- you regularly take recreational drugs or you have had problems with drug use in the past.

Byfavo can cause temporary loss of memory. Your doctor will assess you before you leave the hospital or clinic and give you necessary advice.

Children and adolescents
Byfavo should not be given to patients under the age of 18 years because it has not been tested in children and adolescents.

Other medicines and Byfavo
Tell your doctor if you are taking, have recently taken or might take any other medicines, in particular about:
- opioids (including painkillers such as morphine, fentanyl and codeine or certain cough medicines or medicines for use in drug substitution therapy)
- antipsychotics (medicines to treat certain psychiatric illnesses)
- anxiolytics (tranquilizers or medicines that reduce anxiety)
- medicines that cause sedation (for example temazepam or diazepam)
- antidepressants (medicines to treat depression)
- certain antihistamines (medicines to treat allergies)
- certain antihypertensives (medicines to treat high blood pressure)

It is important to tell your doctor or nurse if you are taking other medicines, as using more than one at the same time can change the effect of the medicines involved.

Byfavo with alcohol
Alcohol can change the effect of Byfavo. Tell your doctor or nurse:
- how much alcohol you drink regularly or if you have had problems with alcohol use;

Do not drink alcohol for 24 hours before you are given Byfavo.

Pregnancy and breast-feeding
You should not use Byfavo if you are pregnant or think you may be pregnant. Tell your doctor or nurse if you are pregnant or think you may be pregnant.
If you are a breastfeeding mother, do not breastfeed for 24 hours after you are given this medicine.

Driving and using machines
Byfavo makes you sleepy, forgetful and affects your ability to concentrate. Even though these effects wear off rapidly, you must not drive and operate machinery until these effects are completely gone. Ask your doctor about when you can drive or operate machinery again.

Byfavo contains dextran 40 for injection
This medicine contains 79.13 mg of dextran 40 for injection in each vial. Rarely, dextrans can cause severe allergic reactions. If you have breathing difficulty or swelling or you feel faint, get medical help at once.

3. How Byfavo is given

Your doctor will decide on the right dose for you.

Your breathing, heart rate and blood pressure will be monitored during the procedure and the doctor will adjust the dose if needed.

A doctor or nurse will give you Byfavo by injection into your vein (blood stream) before and during your medical test or procedure. Byfavo is mixed with sterile saline to make a solution before it is used.

After the procedure
Your doctor or nurse will check on you for a while after sedation to make sure that you feel well and are fit to go home.

If you are given too much Byfavo
If you are given too much Byfavo, you may have the following symptoms:

- you may feel dizzy
- you may get confused
- you may feel sleepy
- your eyesight may get blurry or you may have involuntary eye movements (dancing eyes)
- you may get agitated
- you may feel weak
- your blood pressure may drop
- your heartbeat may slow down
- your breathing may become slow and shallow
- you may lose consciousness

Your doctor will know how to treat you.

Ask your doctor or nurse if you have any questions about the use of this medicine.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common *(may affect more than 1 in 10 users)*
- Low blood pressure
- Unusually slow or shallow breathing (and low oxygen level in blood)

Common *(may affect up to 1 in 10 users)*
- Headache
- Feeling dizzy
- Slow heart rate
- Feeling sick (nausea)
- Being sick (vomiting)

Uncommon *(may affect up to 1 in 100 users)*
- Sleepiness
- Feeling cold
- Chills
- Hiccups

Not known *(frequency cannot be estimated from the available data)*
- sudden, severe allergic reaction

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How Byfavo is stored

Professionals in the hospital or clinic are responsible for storing this medicine.

Keep this medicine out of the sigth and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label. The expiry date refers to the last day of that month.

Chemical and physical in-use stability has been demonstrated for 24 h at 20 - 25°C.

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 (see SmPC section 6.3).

Do not use this medicine if you notice visible particulate matter or discolouration.

6. Contents of the pack and other information

What Byfavo contains
- The active substance is remimazolam. Each vial contains remimazolam besylate equivalent to 20 mg of remimazolam. After reconstitution each mL contains 2.5 mg of remimazolam.
- The other ingredients are:
    - Dextran 40 for injection
    - Lactose monohydrate
    - Hydrochloric acid
    - Sodium hydroxide

See section 2, “Byfavo contains dextran 40 for injection”.

What Byfavo looks like and contents of the pack
Byfavo is a white to off-white powder for solution for injection.

Pack sizes
10 vial pack

Marketing Authorisation Holder
PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

Manufacturer
PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien Viatris Tél/Tel: + 32 (0)2 658 61 00	**Lietuva** PAION Pharma GmbH Tel: + 49 800 4453 4453
България PAION Pharma GmbH Тел.: + 49 800 4453 4453	**Luxembourg/Luxemburg** PAION Pharma GmbH Tél/Tel: + 49 800 4453 4453
Česká republika PAION Pharma GmbH Tel: + 49 800 4453 4453	**Magyarország** PAION Pharma GmbH Tel.: + 49 800 4453 4453

Danmark PAION Pharma GmbH Tlf: + 49 800 4453 4453	**Malta** PAION Pharma GmbH Tel: + 49 800 4453 4453
Deutschland PAION Pharma GmbH Tel: + 49 800 4453 4453	**Nederland** PAION Pharma GmbH Tel: + 49 800 4453 4453
Eesti PAION Pharma GmbH Tel: + 49 800 4453 4453	**Norge** PAION Pharma GmbH Tlf: + 49 800 4453 4453
Ελλάδα Viatris Hellas Ltd Τηλ: +30 210 0100002	**Österreich** PAION Pharma GmbH Tel: + 49 800 4453 4453
España Viatris Pharmaceuticals, S.L. Tel: + 34 900 102 712	**Polska** Viatris Healthcare Sp. z o.o. Tel.: + 48 22 546 64 00
France Viatris Santé Tél: +33 4 37 25 75 00	**Portugal** PAION Pharma GmbH Tel: + 49 800 4453 4453
Hrvatska PAION Pharma GmbH Tel: + 49 800 4453 4453	**România** BGP Products SRL Tel: +40 372 579 000
Ireland PAION Pharma GmbH Tel: + 49 800 4453 4453	**Slovenija** PAION Pharma GmbH Tel: + 49 800 4453 4453
Ísland PAION Pharma GmbH Sími: + 49 800 4453 4453	**Slovenská republika** PAION Pharma GmbH Tel: + 49 800 4453 4453
Italia Viatris Italia S.r.l. Tel: + 39 02 612 46921	**Suomi/Finland** PAION Pharma GmbH Puh/Tel: + 49 800 4453 4453
Κύπρος PAION Pharma GmbH Τηλ: + 49 800 4453 4453	**Sverige** PAION Pharma GmbH Tel: + 49 800 4453 4453
Latvija PAION Pharma GmbH Tel: + 49 800 4453 4453	**United Kingdom (Northern Ireland)** PAION Pharma GmbH Tel: + 49 800 4453 4453

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Byfavo 20 mg powder for solution for injection

FOR INTRAVENOUS USE ONLY

Must be reconstituted before use with Sodium Chloride 9 mg/mL (0.9%) solution for injection

Read the Summary of Product Characteristics (SmPC) carefully before use.

Remimazolam must only be administered by health care professionals experienced in sedation. The patient should be monitored throughout by a separate healthcare professional, who is not involved in the conduct of the procedure, and whose sole task is to monitor the patient. All personnel must be trained in the detection and management of airway obstruction, hypoventilation and apnoea, including the maintenance of a patent airway, supportive ventilation and cardiovascular resuscitation. The patient´s respiratory and cardiac function must be continuously monitored. Resuscitative medicinal products and age- and size-appropriate equipment for restoring airway patency and bag/valve/mask ventilation must be immediately available. A benzodiazepine antagonist (flumazenil, a medicine for counteracting the effects of remimazolam) must be immediately available for use.

Reconstitution instructions

Note: Strict aseptic techniques must be mainted during handling, preparation and use of Byfavo.

To reconstitute, use a sterile needle and a 10 mL sterile syringe, remove the vial cap, puncture the vial stopper at an angle of 90° and add 8.2 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, directing the stream of saline toward the wall of the vial. Gently swirl the vial until the contents are fully dissolved. The reconstituted solution should be clear and colourless to light yellow. The vial delivers a final concentration of 2.5 mg/mL of remimazolam.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If particles or discolouration are present then the solution should be discarded.

The reconsituted solution is for single use only, any unused portion must be disposed of in accordance with local requirements.

Incompatibilities

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.

After reconstitution, this medicinal product must not be mixed with other medicinal products except those mentioned below.

Compatibilities

Reconstituted Byfavo has been shown to be compatible with the following i.v. fluids when administered through the same i.v. line:
- Glucose (5%) solution for injection
- Glucose (20%) solution for injection
- Glucose (5%) - sodium chloride (0.45%) solution for injection
- Ringers Solution
- Sodium chloride (0.9%) solution for injection

Compatibility with other i.v. fluids has not been evaluated.

Shelf life

Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C.

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.

Special precautions for storage

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

Package leaflet: Information for the patient

Byfavo 50 mg powder for concentrate for solution for injection/infusion
remimazolam

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effect you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Byfavo is and what it is used for

Byfavo is a medicine that contains the active substance remimazolam. This is one of a group of medicines known as benzodiazepines. Byfavo is given to make you lose consciousness (sleep) when you have surgery.

2. What you need to know before you are given Byfavo

You must not be given Byfavo if:
- you are allergic to remimazolam or other benzodiazepines (such as midazolam) or any of the other ingredients of this medicine (listed in section 6).
- you have an unstable form of a condition called myasthenia gravis (weakness of muscles) in which your chest muscles that help you breathe get weak

Warnings and precautions
Talk to your doctor or nurse before using Byfavo if you have any severe illness or condition and in particular if:
- you have very low or very high blood pressure or tend to faint
- you have heart problems especially a very slow and/or irregular (arrhythmic) heart rate
- you have any breathing problems including shortness of breath
- you have severe liver problems
- you have a condition called myasthenia gravis in which your muscles are weak
- you regularly take recreational drugs or you have had problems with drug use in the past.

Byfavo can cause temporary loss of memory. Your doctor will assess you before you leave the hospital or clinic and give you necessary advice.

Some patients undergoing surgical operations may experience sudden mental confusion (delirium) after the operation. This is more common in patients who have major surgeries, are older, have memory problems, are exposed to anaesthesia/sedation which is deep and/or for a long period, or have infections.

Patients with delirium may find it difficult to follow a conversation, be confused at some times more than others, become agitated and restless or sleepy and very slow, and have vivid dreams or hear noises or voices which do not exist. Your doctor will assess your condition and organise the necessary treatment to manage it.

Benzodiazepines sometimes cause effects which are the opposite of the medication is meant to do. You may hear these referred to as 'paradoxical' effects. They include e.g. aggressive behaviour, agitation, anxiety. These are more common in older people when receiving high doses of the drug or when the drug is given rapidly.

Children and adolescents
Byfavo should not be given to patients under the age of 18 years because it has not been tested in children and adolescents.

Other medicines and Byfavo
Tell your doctor if you are taking, have recently taken or might take any other medicines, in particular about:
- opioids (including painkillers such as morphine, fentanyl and codeine or certain cough medicines or medicines for use in drug substitution therapy)
- antipsychotics (medicines to treat certain psychiatric illnesses)
- anxiolytics (tranquilizers or medicines that reduce anxiety)
- medicines that cause sedation (for example temazepam or diazepam)
- antidepressants (medicines to treat depression)
- certain antihistamines (medicines to treat allergies)
- certain antihypertensives (medicines to treat high blood pressure)

It is important to tell your doctor or nurse if you are taking other medicines, as using more than one at the same time can change the effect of the medicines involved.

Byfavo with alcohol
Alcohol can change the effect of Byfavo. Tell your doctor or nurse how much alcohol you drink regularly or if you have had problems with alcohol use.

Do not drink alcohol for 24 hours before you are given Byfavo.

Pregnancy and breast-feeding
You should not use Byfavo if you are pregnant or think you may be pregnant. Tell your doctor or nurse if you are pregnant or think you may be pregnant.
If you are a breastfeeding mother, do not breastfeed for 24 hours after you are given this medicine.

Driving and using machines
Byfavo makes you sleepy, forgetful and affects your ability to concentrate. Even though these effects wear off rapidly, you must not drive and operate machinery until these effects are completely gone. Ask your doctor about when you can drive or operate machinery again.

Byfavo contains dextran 40 for injection
This medicine contains 198 mg of dextran 40 for injection in each vial. Rarely, dextrans can cause severe allergic reactions. If you have breathing difficulty or swelling or you feel faint, get medical help at once.

3. How Byfavo is given

Your doctor will decide on the right dose for you.

Your breathing, heart rate and blood pressure will be monitored during the procedure and the doctor will adjust the dose if needed.

A doctor or nurse will give you Byfavo by injection into your vein (blood stream) before and during surgery. Byfavo is mixed with sterile sodium chloride solution to make a solution before it is used. You may need several medicines to keep you asleep, free from pain, breathing well with a steady blood pressure. The doctor will decide which medicines you need.

Time to recovery after end of administration is expected to be 12-15 min.

If you are given too much Byfavo
If you are given too much Byfavo, you may have the following symptoms:
- your blood pressure may drop
- your heartbeat may slow down
- your breathing may become slow and shallow

Your doctor will know how to treat you.

Ask your doctor or nurse if you have any questions about the use of this medicine.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common *(may affect more than 1 in 10 users)*
- Slow heart rate
- Low blood pressure
- Feeling sick (nausea)
- Being sick (vomiting)

Common *(may affect up to 1 in 10 users)*
- Feeling agitated
- Headache
- Feeling dizzy
- Unusually slow or shallow breathing (and low oxygen level in blood)
- Prolonged sleepiness or being unconscious after the operation
- Chills

Uncommon *(may affect up to 1 in 100 users)*
- Hiccups
- Abnormal positioning of the tongue in the mouth (higher, toward the roof, and further back in the mouth than usual)
- Feeling cold

Not known *(frequency cannot be estimated from the available data)*
- Sudden, severe allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Byfavo

Professionals in the hospital or clinic are responsible for storing this medicine.

Keep this medicine out of the sigth and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label. The expiry date refers to the last day of that month.

Chemical and physical in-use stability has been demonstrated for 24 h at 20 - 25°C.

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 (see SmPC section 6.3).

Do not use this medicine if you notice visible particulate matter or discolouration.

6. Contents of the pack and other information

What Byfavo contains

- The active substance is remimazolam. Each vial contains remimazolam besylate equivalent to 50 mg of remimazolam. After reconstitution each mL contains 5 mg of remimazolam which is further diluted before use. Your doctor will decide the exact amount that is right for you.
- The other ingredients are:
  - Dextran 40 for injection
  - Lactose monohydrate
  - Hydrochloric acid
  - Sodium hydroxide

See section 2, “Byfavo contains dextran 40 for injection”.

What Byfavo looks like and contents of the pack
Byfavo is a white to off-white powder for concentrate for solution for injection/infusion (powder for concentrate).

Pack sizes
10 vial pack

Marketing Authorisation Holder
PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

Manufacturer
PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien Viatris Tél/Tel: + 32 (0)2 658 61 00	**Lietuva** PAION Pharma GmbH Tel: + 49 800 4453 4453
България PAION Pharma GmbH Тел.: + 49 800 4453 4453	**Luxembourg/Luxemburg** PAION Pharma GmbH Tél/Tel: + 49 800 4453 4453
Česká republika PAION Pharma GmbH Tel: + 49 800 4453 4453	**Magyarország** PAION Pharma GmbH Tel.: + 49 800 4453 4453
Danmark PAION Pharma GmbH Tlf: + 49 800 4453 4453	**Malta** PAION Pharma GmbH Tel: + 49 800 4453 4453
Deutschland PAION Pharma GmbH Tel: + 49 800 4453 4453	**Nederland** PAION Pharma GmbH Tel: + 49 800 4453 4453
Eesti PAION Pharma GmbH Tel: + 49 800 4453 4453	**Norge** PAION Pharma GmbH Tlf: + 49 800 4453 4453
Ελλάδα Viatris Hellas Ltd Τηλ: +30 210 0100002	**Österreich** PAION Pharma GmbH Tel: + 49 800 4453 4453
España Viatris Pharmaceuticals, S.L. Tel: + 34 900 102 712	**Polska** Viatris Healthcare Sp. z o.o. Tel.: + 48 22 546 64 00
France Viatris Santé Tél: +33 4 37 25 75 00	**Portugal** PAION Pharma GmbH Tel: + 49 800 4453 4453
Hrvatska PAION Pharma GmbH Tel: + 49 800 4453 4453	**România** BGP Products SRL Tel: +40 372 579 000
Ireland PAION Pharma GmbH Tel: + 49 800 4453 4453	**Slovenija** PAION Pharma GmbH Tel: + 49 800 4453 4453
Ísland PAION Pharma GmbH Sími: + 49 800 4453 4453	**Slovenská republika** PAION Pharma GmbH Tel: + 49 800 4453 4453
Italia Viatris Italia S.r.l. Tel: + 39 02 612 46921	**Suomi/Finland** PAION Pharma GmbH Puh/Tel: + 49 800 4453 4453
Κύπρος PAION Pharma GmbH Τηλ: + 49 800 4453 4453	**Sverige** PAION Pharma GmbH Tel: + 49 800 4453 4453
Latvija PAION Pharma GmbH Tel: + 49 800 4453 4453	**United Kingdom (Northern Ireland)** PAION Pharma GmbH Tel: + 49 800 4453 4453

This leaflet was last revised in <{MM/YYYY}>

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

<--->

The following information is intended for healthcare professionals only:

Byfavo 50 mg powder for concentrate for solution for injection/infusion

FOR INTRAVENOUS USE ONLY

Must be reconstituted and further diluted before use with Sodium chloride 9 mg/mL (0.9%) solution for injection

Read the summary of product characteristics (SmPC) carefully before use.

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. ECG, pulse oximetry) and facilities for maintenance of patent airways, artificial ventilation, and other resuscitation facilities should be immediately available at all times.

Instructions for use

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 (SmPC section 6.3). To prevent coring, the needle should be inserted at a 45–60° angle with the opening of the needle tip facing up (i.e., away from the stopper), sometimes referred to as "bevel up". A small amount of pressure is applied, and the angle is gradually increased as the needle enters the vial. The needle should be at a 90° angle just as the needle bevel passes through the stopper.

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 2).

Table 2 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

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% 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% 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

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 "Administration with other fluids".

In-use stability after reconstitution

Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C.

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.

Special precautions for storage

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