SUMMARY OF PRODUCT CHARACTERISTICS

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, 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 monitoring section below.

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 monitoring section below.

Chronic benzodiazepine 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 monitoring section below.

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.

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. Frequency groupings are as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), 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 Yellow Card Scheme, website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 [GABAA] 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)	Remima-zolam (N=296)	Midazolam (N=102)	Placebo (rescue midazolam) (N=60)	Remima-zolam (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	Remima-zolam (N=297)	Mida zolam (N=100)	Placebo (rescue midazolam) (N=58)	Remima-zolam (N=280)	Mida zolam (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%)

Trial	CNS7056-006			CNS7056-008		
Treatment arm	Remima-zolam (N=297)	Mida zolam (N=100)	Placebo (rescue midazolam) (N=58)	Remima-zolam (N=280)	Mida zolam (N=69)	Placebo (rescue midazolam) (N=58)
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	Remima zolam (N=1)	Mida zolam (N=3)	Placebo (rescue midazolam) (N=2)	Remima zolam (N=30)	Mida zolam (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

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. For information on pharmacokinetic/pharmacodynamic relationships see section 5.1.

Absorption

Remimazolam is administered intravenously.

Distribution

Remimazolam's 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

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 distribution half-life ($t_{1/2\alpha}$) of 0.5 to 2 min and 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

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

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% 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)

Disposal

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

7 MARKETING AUTHORISATION HOLDER

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52078 Aachen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 59768/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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