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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Remimazolam for procedural sedation

NIHRIO ID	4871	**NICE ID**	10292
Developer/Company	Paion AG	**UKPS ID**	1033

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Remimazolam has completed its main clinical development studies for procedural sedation in adults. Procedural sedation is a technique of administering sedatives or dissociative agents, with or without analgesics, to induce a mental state that allows the patient to tolerate unpleasant diagnostic and therapeutic procedures such as colonoscopy while maintaining cardiorespiratory function. This enables medical procedures to be carried out with the patient benefit of markedly reduced discomfort and no major added risk.

Remimazolam is an ultra-short-acting intravenous benzodiazepine sedative/anaesthetic that in the human body is rapidly transformed (metabolized) to an inactive metabolite. Remimazolam is structurally similar to the commonly used sleep-inducing drug midazolam, but it incorporates the pharmacokinetic properties of remifentanil to make the offset of sedation faster and more predictable. If licensed, remimazolam will offer an additional therapy option for procedural sedation in adults during a diagnostic and/or therapeutic procedures.

PROPOSED INDICATION

Remimazolam is indicated in adults for procedural sedation for diagnostic and therapeutic procedures.[a]

TECHNOLOGY

DESCRIPTION

Remimazolam (CNS-7056) is an ultra-short-acting intravenous benzodiazepine sedative/anesthetic.[1] It was made by applying the design principle of remifentanil to the class of benzodiazepines.[b] Like many drugs used in anaesthesia, introduction of a carboxylic ester linkage makes the drug suitable for metabolism by non-specific tissue esterases in the liver.[2] In the human body, remimazolam is rapidly metabolized to an inactive metabolite by tissue esterases and is not metabolized by cytochrome-dependent hepatic pathways.[1] Like other benzodiazepines, remimazolam acts on GABA receptor, specifically GABA-A, and like other benzodiazepines, remimazolam can be reversed with flumazenil to rapidly terminate sedation or anaesthesia if necessary.[1,2]

Remimazolam has completed clinical development for procedural sedation in adults. In the US phase III clinical trials (NCT02290873, NCT02532647 and NCT02296892), participants received either remimazolam 2.5 – 5.0 mg, intravenous (IV) for sedation induction, followed by 1.25 – 2.5 mg top-up doses as required to maintain sedation or midazolam 1.0 – 1.75 mg IV initially, followed by 0.5 – 1.0 mg for sedation maintenance or placebo IV for sedation induction and maintenance.[3-5] Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table section of this briefing.

INNOVATION AND/OR ADVANTAGES

Remimazolam is an innovative medicinal product designed for procedural sedation/anaesthesia. It combines the properties of two currently licensed medicines already established in anaesthesia – midazolam and remifentanil. Remimazolam acts on GABA receptors like midazolam and has a CYP-independent metabolism like remifentanil. Thus, no dose adjustment is required for remimazolam in patients with renal impairment, including those with end-stage renal impairment. Careful titration to effect is recommended in severe hepatic impairment (Child-Pugh scores 10-15), but not in mild or moderate hepatic impairment. Since remimazolam is not metabolised by cytochrome P450 enzymes, any potential for drug-drug interactions is very low.[b] Unlike most rapidly acting intravenous sedatives available presently, the propensity to cause apnoea is low. Availability of a specific antagonist (flumazenil) adds to its safety even in cases of overdose.[2]

Due to its high clearance, short half-life and inactive primary metabolite, remimazolam's sedative effect is very predictable and allows great level of control over the depth of sedation. Based upon exploratory comparisons to IV midazolam (see respective study designs) patients treated with remimazolam (and IV fentanyl in both treatment groups) had a faster recovery of neuropsychatric function after colonoscopies and bronchoscopies. They also had shorter times to ready for discharge and feeling "back to normal" than those treated with midazolam. Furthermore, the incidences of cardio-respiratory adverse reactions were lower for remimazolam than for midazolam. Considering the above mentioned the product may improve Quality of Life of patients and carers. The reduced time for the patient to feel "normal" again

[a] Information provided by Paion AG in UK PharmaScan
[b] Information provided by Paion AG

after procedural sedation compared to midazolam may lead to a reduced need for supervision after procedure and discharge.[c]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

A marketing authorization application for procedural sedation in adult patients has been filed to EU authorities in Nov 2019.[1] A paediatric program has been agreed with EU authorities.

License partners of the developer have submitted dossiers for procedural sedation in the US and China and for general anaesthesia in South Korea and Japan. [c]

Remimazolam has completed phase II and III of development for the sedation use in patients undergoing different clinical procedures such as bronchoscopy, colonoscopy, and endoscopy.[6]

Remimazolam is currently in phase III of development for general anaesthesia in adults for a marketing authorisation application in the EU.[c]

PATIENT GROUP

DISEASE BACKGROUND

Procedural sedation is a treatment strategy for the administration of sedative or analgesic medications to intentionally suppress a patient's level of consciousness. The intended sedation depth vary in accordance with the specific needs of the patient and procedure. Sedation depths level may be "mild", "moderate", and "deep". These descriptors are visualized as depressed levels of consciousness along a continuum of sedation that eventually leads to general anaesthesia.[7]

Minimal sedation describes a patient with a near-baseline level of alertness, a pharmacologically induced state during which patients respond normally to verbal commands. Although cognitive function and coordination might be impaired, ventilatory and cardiovascular functions are unaffected. In the emergency department, minimal sedation is commonly administered to facilitate minor procedures.[7]

Moderate sedation is a pharmacologically induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patient's airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Moderate sedation patients often exhibit eyelid ptosis, slurred speech, and delayed or altered responses to verbal stimuli. Event amnesia will frequently occur under moderate sedation levels.[7]

Dissociative sedation is a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability. Dissociative state can facilitate moderate to severely painful procedures, as well as procedures requiring immobilization in uncooperative patients.[7]

Deep sedation is a pharmacologically induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.[7]

[c] Information provided by Paion AG

CLINICAL NEED AND BURDEN OF DISEASE

A survey of National Health Service activity on the state of anaesthesia in the UK performed in 2013 showed that the annual numbers (% of total) of general anaesthesia, sedation, and awake case were 2.766.600 (76.9%), 308.800 (8.6%), and 523.100 (14.5%), respectively.[8]

In the EU, colonoscopies and bronchoscopies are listed among the top 10 surgical operations and procedures. European guidelines recommend the initiation of colorectal cancer screening colonoscopies and 23 EU member states have already implemented or are planning to introduce population based screening programmes for a population of 110 million men and women (72% of the total target population).[9]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The appropriate choice of pharmacological agents for procedural sedation and analgesia depends on:[10]

- The nature of the procedure
- The planned level of sedation
- The estimated duration of the procedure
- Training and familiarity of the sedating practitioner with potential pharmacological agents
- Patient factors
- The local environment

There are many variations in the combinations of pharmacological agents described in the literature and many different ways of delivering the pharmacological agents.[10]

Having selected the appropriate drugs for the needs of the patient, doses and routes of administration of the pharmacological agents need to be tailored to the individual patient to deliver the required effects. Great care should be used when administering sedatives because of:[10]

- Slow and variable onset time
- Inter-patient variability in dose requirement
- Synergistic action between drugs

CURRENT TREATMENT OPTIONS

The selection of the pharmacological agents used for procedural sedation and analgesia in adults depend on, amongst others (see above), patient factors and sedation depths level needed.[10]

Moderate sedation is commonly achieved with a benzodiazepine, often in conjunction with an opioid such as fentanyl.[7]

Deep sedation is commonly achieved with short-acting sedative agents such as propofol, etomidate, or a benzodiazepine. For painful procedures, an opioid such as fentanyl or morphine sulfate may be used in concert with the sedative. Many recent studies have described the use of ketamine administered with propofol to evoke deep sedation levels during painful emergency department procedures.[7]

PLACE OF TECHNOLOGY

If licensed, remimazolam will offer an additional option for intravenous procedural sedation in adults for diagnostic and therapeutic procedures.

CLINICAL TRIAL INFORMATION

Trial	NCT02290873, CNS7056-006; A Prospective, Double-blind, Randomized, Placebo and Active Controlled, Multi-center, Parallel Group Study Comparing Remimazolam to Placebo, With an Additional Open-label Arm For Midazolam, in Patients Undergoing a Colonoscopy for Diagnostic or Therapeutic Reasons **Phase III** **Location:** USA
Trial design	Randomised, placebo and active-controlled, double-blind for remimazolam and placebo, open-label for midazolam
Population	N=461; aged 18 years and older, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures could include haemostasis, resection, ablation decompression, foreign body extraction, for example); American Society of Anaesthesiologists Score 1 through 3; body mass index ≤40 kg/m^2.
Intervention	Remimazolam 5 mg, IV for sedation induction, and 2.5 mg top-ups for sedation maintenance Fentanyl pre-treatment (25-50 µg or less for elderly/disabled subjects) and 25 µg top-up doses were used for analgesia. In case of inadequate sedation, rescue midazolam was used, dosed according to the clinical judgement of the investigator.[d]
Comparator(s)	- Placebo iv for sedation induction and maintenance - Midazolam iv 1.75 mg* for sedation induction and 1.0 mg* for sedation maintenance. *1.0 mg for induction and 0.5 mg for maintenance in adults over 60, debilitated or chronically ill.
Outcome(s)	Success of the procedure, as measured by: o Completion of the colonoscopy procedure, AND no requirement for a rescue sedative medication, AND no requirement for more than 5 doses of study medication within any 15-minute window in the blinded arms (remimazolam/placebo) or no requirement for more than 3 doses within any 12-minute window in the midazolam arm.[d] See trial record for full list of other outcomes.
Results (efficacy)	The primary endpoint was met for remimazolam, placebo, and midazolam in 91.3%, 1.7%, and 25.2% of patients, respectively (P < .0001 for remimazolam vs placebo). Patients administered remimazolam received less fentanyl, had faster recovery of neuropsychiatric function, were ready for discharge earlier, and felt back to normal sooner than patients with both placebo and midazolam.

[d] Information provided by Paion AG

Results (safety)	Hypotension was less frequent with remimazolam, and hypoxia occurred in 1% of patients with remimazolam or midazolam. There were no treatment-emergent serious adverse events.

Trial	NCT02296892, CNS7056-008; A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy **Phase III** **Location:** USA
Trial design	Randomised, placebo and active-controlled, double-blind for remimazolam and placebo, open-label for midazolam
Population	N=446, aged ≥ 18 years older, scheduled to undergo a diagnostic or therapeutic flexible bronchoscopy in the bronchoscopy suite (therapeutic bronchoscopies could include e.g., lavage, biopsies, brushings, and foreign body extraction); American Society of Anaesthesiologists Physical Status Score (ASA PS) 1 through 3; body mass index (BMI) ≤ 45; peripheral blood oxygen saturation (measured by pulse oximetry: SpO2) ≥ 90% in ambient air or with no more than 2 L/min of oxygen support.
Intervention	Double-blind Remimazolam arm: 5 mg IV for sedation induction, and 2.5 mg IV top-ups for sedation maintenance. For all of them, was provided Fentanyl pre-treatment: 25-50 µg (or less for elderly/disabled subjects), and 25 µg top-up doses. In case of inadequate sedation, rescue midazolam was used, dosed according to the clinical judgement of the investigator.
Comparator(s)	- Double-blind placebo arm as inactive control. - Open-label Midazolam arm: 1.75 mg* IV for sedation induction and 1.0 mg* IV for sedation maintenance. *1.0 mg for induction and 0.5 mg for maintenance in adults over 60, debilitated or chronically ill.
Outcome(s)	Success of the procedure, as measured by: o Completion of the colonoscopy procedure, AND no requirement for a rescue sedative medication, AND no requirement for more than 5 doses of study medication within any 15-minute window in the blinded arms (remimazolam/placebo) or no requirement for more than 3 doses within any 12-minute window in the midazolam arm.[d] See trial record for full list of other outcomes.
Results (efficacy)	The success rates were 80.6% in the remimazolam arm, 4.8% in the placebo arm (P < .0001), and 32.9% in the midazolam arm. Bronchoscopy was started sooner in the remimazolam arm (median 4.1 min, 95% CI, 4.0-4.8) compared with placebo (17.0, 95% CI, 16.0-17.5 P < .0001) and midazolam (15.5, 95% CI 13.8 to 16.7). Time to full alertness after the end of bronchoscopy was significantly shorter in patients treated with remimazolam (median, 6.0 min; 95% CI, 5.2-7.1) compared with those treated with placebo (13.6 min; 95% CI, 8.1-24.0; P = .0001) and midazolam (12.0 min; 95% CI, 5.0-15.0). Remimazolam registered superior restoration of neuropsychiatric function, shorter time to discharge and time for the patient to feel back to normal compared with placebo and midazolam.

Results (safety)	Safety was comparable among all three arms, and 5.6% of the patients in the remimazolam group had serious treatment-emergent adverse events as compared with 6.8% in the placebo group.

Trial	NCT02532647, CNS7056-015; A Study Evaluating the Safety and Efficacy of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in ASA III and IV Patients Undergoing Colonoscopy **Phase III** **Location:** USA
Trial design	Randomised, placebo and active-controlled, double-blind for remimazolam and placebo, open-label for midazolam
Population	N=79, aged ≥ 18 years older, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures may include haemostasis, resection, ablation decompression, and foreign body extraction, for example); American Society of Anaesthesiologists grade III/IV.
Intervention	Remimazolam 2.5 - 5.0 mg initially, followed by 1.25 - 2.5 mg top-up doses as required to maintain sedation. For all of them, was provided Fentanyl pre-treatment: 25-50 µg (or less for elderly/disabled subjects), and 25 µg top-up doses. In case of inadequate sedation, rescue midazolam was used, dosed according to the clinical judgement of the investigator.
Comparator(s)	- Midazolam 1.0 mg initially, followed by 0.5 mg top-up doses as required to maintain sedation. - Placebo administered in double-blind manner.
Outcome(s)	Assess the safety of multiple doses (initial dose and additional supplemental doses) of remimazolam compared to placebo and midazolam, following administration of a standard dose of fentanyl, in ASA-PS III/IV subjects undergoing colonoscopy.[e]
Results (efficacy)	One outcome was a composite endpoint, composed of success of the procedure, no need for rescue medication, and completion of the procedure with no more than 5 doses given within any 15-minute interval. This endpoint was achieved in 84.4% of the patients in the remimazolam arm and 0% in the placebo arm. Further relevant endpoints for remimazolam showed a median time from start of medication to start of procedure of 5.0 minutes (placebo 18.3 minutes) and a median time from end of procedure to return to full alertness of 3.0 minutes (placebo 5.3 minutes). This study also included an open label arm in which midazolam was dosed according to U.S. label. Success of the procedure was achieved in 12.9% of the midazolam patients. Midazolam patients showed a median time from start of medication to start of procedure of 19.0 minutes and a median time from end of procedure to return to full alertness of 7.0 minutes.
Results (safety)	Safety was comparable among all three arms, and 3.33% of the patients in the midazolam group had serious adverse events as compared with 0% in the remimazolam and placebo group

[e] Information provided by Paion AG

ESTIMATED COST

The cost of remimazolam is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- American Society of Anaesthesiologists. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. 2018.[11]
- The Royal College of Emergency Medicine. Pharmacological Agents for Procedural Sedation and Analgesia in the Emergency Department. 2017.[10]

ADDITIONAL INFORMATION

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