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HEALTH TECHNOLOGY BRIEFING MARCH 2020

Remimazolam for general anaesthesia – first line

NIHRIO ID	26953	**NICE ID**	10270
Developer/Company	Paion AG	**UKPS ID**	654913

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Remimazolam is in clinical development as an anaesthetic for induction and maintenance of general anaesthesia in adults. General anaesthesia is a technique of administering anaesthetic drugs into a vein (intravenous) or breathing anaesthetic gases into the lungs to put the patient into a reversible state of unconsciousness so that the patient is unaware of surgery and do not move or feel pain while it's carried out. This enables the physician to perform surgery which would be extremely painful if the patient was awake and able to feel. Some serious complications associated with general anaesthesia include anaphylaxis, waking up during operation and, rarely death.

Remimazolam is an intravenous anaesthetic which is similar to the commonly used sleep-inducing drug midazolam, but it incorporates properties to make the offset of sedation faster and more predictable. If licensed, remimazolam will offer an additional first-line intravenous general anaesthetic treatment for induction and maintenance of general anaesthesia in adults.

PROPOSED INDICATION

First-line therapy for induction and maintenance of general anaesthesia in adults.[1]

TECHNOLOGY

DESCRIPTION

Remimazolam (Aptimyda, CNS7056, ONO-2745) is an ultra-short-acting intravenous benzodiazepine sedative/anaesthetic.[2] Like many drugs used in anaesthesia, the introduction of a carboxylic ester linkage makes the drug suitable for metabolism by non-specific tissue esterases in the liver.[3] In the human body, remimazolam is rapidly metabolized to an inactive metabolite by tissue esterases and is not metabolized by cytochrome-dependent hepatic pathways.[2] Like other benzodiazepines, remimazolam acts on GABA receptor, specifically GABA-A, and it can be reversed with flumazenil to rapidly terminate sedation or anaesthesia if necessary.[2,3]

Remimazolam is currently in clinical development for general anaesthesia. In the phase III clinical trial (NCT03661489), patients received separate dosing for induction and maintenance.[1] Details of the dosing regimen and administration schedule assessed in each study are detailed in the clinical trial table of this briefing.

INNOVATION AND/OR ADVANTAGES

Remimazolam combines the properties of two unique drugs already established in anaesthesia- midazolam and remifentanil. It acts on GABA receptors like midazolam and has organ-independent metabolism like remifentanil. Due to organ-independent elimination, it can be safely used in patients with hepatic or renal impairment.[4] No dosage adjustment is required in any grade of renal impairment including end-stage disease. However, careful titration to effect is recommended in patients with severe hepatic impairment.[a]

Remimazolam has been developed after the incorporation of metabolically liable ester moiety into the benzodiazepine core. This modification makes remimazolam highly susceptible to hydrolysis by plasma esterases. Because of its organ-independent metabolism rapid and predictable onset and recovery, remimazolam has potential as a useful general anaesthetic that combines the advantages of propofol (short-acting effects) and the benzodiazepine midazolam (less undesired haemodynamic effects). Unlike propofol, remimazolam does not cause pain on injection.[3]

Furthermore, a phase IIb/III study presented at Anaesthesiology Annual Meeting 2015, anaesthesia with remimazolam could be reversed with flumazenil in patients (9.7%)[a] that had longer than expected (30 min) wake up times and hypotensive adverse drug reactions, including needs for vasopressor treatment was significantly reduced in remimazolam versus propofol patients.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Remimazolam does not currently have EU/UK Marketing Authorisation for any indication.

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

[a] Information provided by Paion AG

PATIENT GROUP

DISEASE BACKGROUND

General anaesthesia is a reversible state of controlled unconsciousness that is achieved with drugs which prevent awareness, pain, recall, distress and movement in patients during surgery.[7] General anaesthesia is frequently used during surgery to essentially put patients into a medically induced coma.[8] General anaesthesia is the strongest type of anaesthesia among other types including local, regional and epidural anaesthesia, spinal anaesthetic and sedation which do not make patients unconscious.[9] General anaesthesia is essential for some surgical procedures where it may be safer or more comfortable for the patient to be unconscious. It is usually used for long operations or those that would otherwise be very painful.[10] So general anaesthesia not only allows a patient to undergo surgery without pain but also allows the patient to be unconscious for the surgery.[8]

The risks associated with general anaesthesia vary widely from surgery to surgery, and from patient to patient. Older adults, or those with serious medical problems, particularly those undergoing more extensive procedures, may be at increased risk of complications.[11] The most common complications include anaesthesia awareness, aspiration, pneumonia or other breathing problems, malignant hyperthermia, cardiovascular problems and, rarely, death.[8]

The most common side effects of general anaesthesia occur immediately after surgery may include feeling sick and vomiting, shivering and feeling cold, confusion and memory loss, bladder problems, dizziness, bruising and soreness, sore throat and damage to the mouth or teeth.[10]

CLINICAL NEED AND BURDEN OF DISEASE

A survey of National Health Service activity on the state of anaesthesia in the UK in 2013 reported that the annual number (% of total) of general anaesthetics cases was 2,766,600 (76.9).[12] In England, between 2009 and 2014, there were 22,053,498 routine procedures undertaken in an operating theatre using general or regional anaesthesia.[13] Furthermore, the company estimates the population to receive this therapy is between 3,000 per 100, 000 in the UK.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Anaesthetics are administered by anaesthetists (doctors/perioperative physicians) who look after patients before, during and after surgery and ensure patients are fit to have surgery. Overall, anaesthesia is a process rather than an action and is about maintaining safety, physiological stability and comfort during surgery and into the recovery period.[14] The process of general anaesthesia often starts with sedation, to make it possible to insert a breathing tube. The type of sedation can vary widely depending upon the patient and the type of surgery.[8] The anaesthetist will insert a tube into a vein, usually in the back of the patient's hand. All anaesthetic drugs can then be given through this without the need for more needles or patients

[b] Information provided by Paion AG on UK PharmaScan

may be anaesthetised using gaseous anaesthetics through a face mask. A patient may feel light-headed, dizzy or sleepy and this process usually takes place in the operating theatre.[14]

Once the patient is on the operating table and safe, the process of anaesthesia will start. Patients are normally asked to breathe some oxygen from a facemask. The anaesthetist's assistant will put monitors (to measure oxygen levels, heart rate and blood pressure) on the patients. The patient may feel light-headed and may have an odd taste in their mouth. Hands or arm may feel cold, or occasionally sore. These feelings will last only a few seconds as the anaesthetic starts to work. Once anaesthetised, the patient will not be aware of anything until after their surgery has finished.[14]

CURRENT TREATMENT OPTIONS

Several different types of drugs are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug; anaesthesia is maintained with an intravenous or inhalational anaesthetic. Smaller doses are indicated in ill, shocked, or debilitated patients and in patients with significant hepatic impairment, while robust individuals may require larger doses.[15]

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout the surgery. Drugs that are most widely used for intravenous anaesthesia include:[15]

- Propofol
- Thiopental sodium
- Etomidate
- Ketamine

Inhalational anaesthetics include gases and volatile liquids such as isoflurane, desflurane, sevoflurane and nitrous oxide.[15]

PLACE OF TECHNOLOGY

If licensed, remimazolam will offer an additional first-line treatment option for induction and maintenance of general anaesthesia in adults.

CLINICAL TRIAL INFORMATION

Trial	NCT03661489; **Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anesthesia during elective surgery in ASA class III/IV patients** **Phase III- Ongoing** **Location(s): EU (Including the UK)**
Trial design	Randomised, parallel assignment, single-blinded
Population	N=500 (planned); aged 18 and older; male or female ASA III/IV; scheduled for elective surgery of a minimum duration of approximately 90 minutes
Intervention(s)	Remimazolam: For induction of anaesthesia: from t = 00:00 to 03:00: 6.0 mg/minute, from t = 03:00 to 10:00: 2.5 mg/minute, from t = 10:00 to 20:00: 1.5 mg/minute.

	During maintenance, remimazolam is to be titrated between ≥0.7 mg/min and ≤2.5 mg/min. It is allowed to administer boluses of remimazolam with 6 mg/min for 1 min. A maximum of 3 boluses within 60 min are allowed and there need to be at least 5 min between 2 boluses.[c]
Comparator(s)	Intravenous propofol 2%; propofol is co-administered with remifentanil for analgesia and with a muscle relaxant as necessary.
Outcome(s)	Percentage (%) of time of Narcotrend Index (NCI) values ≤ 60 during maintenance phase of general anaesthesia (defined as time between the first skin incision and the completion of the last skin suture) [Time frame: maintenance phase of general anaesthesia (time between the first skin incision and the completion of the last skin suture)]
Results (efficacy)	-
Results (safety)	-

Trial	NCT01937767, **CNS7056-010, EudraCT-**2013-001113-32 **- A randomized, single-blind phase II study evaluating the efficacy, safety and pharmacokinetics of remimazolam in general anesthesia in adult patients undergoing cardiac surgery, including follow-up sedation in the PACU/ICU** **Phase II- Completed** **Location(s): Germany**
Trial design	Randomised, parallel assignment, single-blinded
Population	N=90; aged 18 and older; scheduled for major elective cardiac surgery; scheduled for mechanical ventilation via tracheal intubation
Intervention(s)	Remimazolam 6 mg/kg/hr • Induction: Remimazolam 6 mg/kg/hr, fentanyl, rocuronium • Maintenance: Remimazolam up to 2mg/kg/hr titrated to effect remifentanil Remimazolam 12mg/kg/hr • Induction: Remimazolam 12mg/kg/hr fentanyl, rocuronium • Maintenance: Remim vnazolam up to 2mg/kg/hr titrated to effect remifentanil
Comparator(s)	Propofol; • Induction: propofol, fentanyl, rocuronium • Maintenance: sevoflurane, remifentanil
Outcome(s)	Proportion of patients with successful anaesthesia [Time frame: Between the start of study medication and the end of the surgical procedure (up to approx. 12 hours)]
Results (efficacy)	-
Results (safety)	-

[c] Information provided by Paion AG

ESTIMATED COST

The cost of remimazolam is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- Royal College of Anaesthetists. Guidelines for the Provision of Anaesthetic Services (GPAS). January 2019.[16]

ADDITIONAL INFORMATION

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