COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atropinesulfaat Accord 0.1 mg/ml solution for injection in pre-filled syringe

(atropine sulphate monohydrate)

NL/H/4788/001/DC

Date: 22 February 2023

This module reflects the scientific discussion for the approval of Atropinesulfaat Accord 0.1 mg/ml. The procedure was finalised on 17 September 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AMI	Acute Myocardial Infarction
ASA PS	American Society of Anesthesiologist Physical Status
AV	Atrioventricular
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
CPR	Cardiopulmonary resuscitation
DBP	Diastolic blood pressure
ED	Emergency Department
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
IV	Intravenous
MAH	Marketing Authorisation Holder
MBP	Mean blood pressure
OHCA	Out-of-hospital Cardiac Arrest
OP	Organophosphate Poisoning
OPP	Organo-phospheros Poisoning
OR	Odds Ratio
PAM	Pralidoxime
PDA	Patent Ductus Arteriosus
PEA	Pulseless Electrical Activity
PH	Prehospital
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PVC	Premature Ventricular Contractions
RH	Relative Humidity
RMP	Risk Management Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atropinesulfaat Accord 0.1 mg/ml solution for injection in pre-filled syringe from Accord Healthcare B.V.

The product is indicated in adults and in paediatric population from birth, but with a body weight superior to 3 kg (see section 4.2 of the SmPC):

- As a pre-anaesthetic medication to prevent vagal reactions associated with tracheal intubation and surgical manipulation,
- To limit the muscarinic effects of neostigmine, when given post-surgically to counteract non depolarising muscle relaxants
- Treatment of hemodynamically compromising bradycardia and/ or atrioventricular block due to excessive vagal tone in emergency situations
- Cardiopulmonary resuscitation: to treat symptomatic bradycardia and AV block
- As antidote following overdosage or poisoning with acetylcholinesterase-inhibitors e.g. anticholinesterases, organophosphorus, carbamates and muscarinic mushrooms

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of atropine sulphate. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Atropine sulphate as solution for injection was first introduced into the European market at least ten years ago as a preoperative medication for the reduction of salivary and bronchial secretions and vagal reactions, to treat sinus bradycardia and as antidote following overdosage or poisoning with acetylcholinesterase-inhibitors.

The MAH submitted a justification for bridging between their product and the product used in the literature, Atropine sulfate 0.1 mg/ml and 0.2 mg/ml by Laboratoire Aguettant France (FR/H/0583/001/MR and FR/H/0429/001/MR; licenced in 2015), based on comparable composition of the two formulations.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Malta, Norway, Poland, Portugal, Romania, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Atropinesulfaat Accord 0.1 mg/ml is a clear and colourless solution, free from visible particles with pH 3.0 - 4.0. Each ml of solution for injection contains 0.1 mg atropine sulphate monohydrate, equivalent to 0.083 mg atropine.

The solution is packed in 5 mL or 10 mL clear glass (type I) pre-filled syringe with tip cap, plunger stopper (bromobutyl rubber) and plunger rod (polypropylene).

The excipients are: sodium chloride, sulfuric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injection.

II.2 Drug Substance

The active substance is atropine sulphate monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder or colourless crystals. The active substance is very soluble in water and freely soluble in ethanol (96%).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The specification comprises the characters and tests of the Ph. Eur. monograph with additional tests for residual solvents, bacterial endotoxins and microbial examination. The specification covers also the additional tests from the CEP. As the active substance is dissolved during the finished product manufacturing process, tests for polymorphism and particle size are not required.

Stability of drug substance

Stability data on the active substance have been provided for 6 batches, stored at 25°C/60% RH (3 x 36 months, 3 x 24 months) and 40°C/75% RH (6 months). Based on the provided data, a shelf life of 36 months was accepted for the drug substance.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients justified and their functions explained. The development of the product is simple and straightforward. The pH and osmolality are suitable. The concentration and pH are comparable with currently approved products and products from the indication-supporting literature. The drug product is terminally sterilised by autoclavation. The accuracy and precision (ISO 7886-1) and the suitability and adequacy (EMA QWP Q&A Part 2) of the graduations on the prefilled syringes have been demonstrated. Delamination of the glass walls of the prefilled syringe has not been observed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been adequately described and validated according to relevant European/ICH guidelines. The process consists of dissolution, filling and terminal sterilisation. Operating parameters and in-process controls are specified. The provided validation data of three full-scale batches from both syringe volumes, 5 mL and 10 mL, are acceptable.

Control of excipients

The excipients are controlled for compliance with the Ph. Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, acidity, clarity and colour of solution, extractable volume, related substances, assay, particulate contamination, bacterial endotoxins, sterility, break loose force, glide force and dose accuracy. The proposed tests are acceptable in view of the tests and requirements of the British Pharmacopoeia (BP) monograph 'Atropine Injection', the Ph. Eur. monograph 'Parenteral preparations' and ICH Q6A.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data provided of three full scale batches of both packaging volumes (5 mL and 10 mL) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three production-scale batches for both packaging volumes, stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear glass pre-filled syringes with plunger. Upward trends are seen for the specified impurities and total impurities; the increase is slow and all batches stay within specification. Furthermore, extrapolation of the data indicates that all batches will stay within specification at the proposed shelf-life of 24 months. In addition, a downward trend is observed for assay, and also this parameter is expected to stay within specification

up to 24 months. All batches stay within specification for 6 months under accelerated conditions. In view of the photostability studies a specific storage condition on light protection is not required. Based on the provided data, the shelf-life of 24 months has been granted without any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atropinesulfaat Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Atropine is used for the treatment of intoxication with organophosphorus compounds, which are acetylcholinesterase inhibitors, and it is expected to be effective against poisoning with carbamate compounds (also cholinesterase inhibitors) (Brittain et al, 2016).

The pharmacology of atropine is well-known. No literature was provided regarding the safety pharmacology of atropine. Considering the clinical experience with atropine, no additional non-clinical data are necessary.

III.2 Pharmacokinetics

The information on non-clinical pharmacokinetics provided by the MAH was limited. Considering the clinical experience with atropine, additional non-clinical data are not expected to add relevant new information and are therefore not required.

III.3 Toxicology

The information provided on toxicology was limited. Nevertheless, considering the amount of clinical experience with atropine, the limited amount of relevant non-clinical literature is accepted. The impurity apotropine is limited at NMT 0.4%. This is acceptable as it is below the qualification threshold of 0.5% for a maximum daily dose of 10 – 100 mg.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Atropinesulfaat Accord is intended for substitution of comparable products currently on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance atropine sulphate are well known. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

For this bibliographic application according to article 10a, no pharmacokinetic studies have been performed. The MAH demonstrated instead that the composition of the product applied for, Atropinesulfaat Accord, is essentially similar to the reference product used in the literature, Atropine sulfate by Laboratoire Aguettant France (FR/H/0583/001/MR and FR/H/0429/ 001/MR). The use of sodium hydroxide, as an additional pH adjusting agent, is not expected to have any influence on the disposition of the active substance. In addition, the MAH sufficiently substantiated pharmacokinetic data in the SmPC with literature.

IV.2 Pharmacodynamics

Atropine is an antimuscarinic agent which competitively antagonises acetylcholine at postganglionic nerve endings, thus affecting muscarinic acetylcholine receptors (M1, M2, M3, M4 , and M5) in the exocrine glands, smooth muscle, cardiac muscle and the central nervous system. Peripheral effects include decreased production of saliva, sweat, nasal, lachrymal and gastric secretions, decreased intestinal motility and inhibition of micturition. Atropine increases sinus rate and sinoatrial and atrioventricular (AV) conduction. Usually heart rate is increased, but there may be an initial bradycardia. Atropine inhibits secretions throughout the respiratory tract and relaxes bronchial smooth muscle producing bronchodilation.

IV.3 Clinical efficacy

The data to justify the use of atropine in the various proposed indications as submitted by the MAH are presented in the tables below.

Table 1. Summary of studies in support of the indication "as a pre-anaesthetic medication to prevent vagal reactions associated with tracheal intubation and surgical manipulation"

Author, Year	Trial Design, No. of Subjects	Patient Population	Intervention (and Control)	Results
Durrmeyer X, 2014	Monocentric, prospective observational study N=24	Premature infants before 32 weeks of gestational age (median weight: 850g [740-1000g])	Atropine (**15µg/kg IV**)-sufentanil-atracurium anaesthesia for endotracheal intubation	Quality of sedation: Excellent: 80% Good: 14% Acceptable: 6% Poor: 0% No significant change in heart rate and blood pressure
Nielsen MB, 2000	Randomised double-blind study N =20	Healthy intubated adults	Atropine (**1.0 mg IV**) or saline	Respiratory dynamic compliance increased significantly after IV administration of atropine. To conclude, atropine protects against an intubation-induced decline in respiratory dynamic compliance.
Shaw CA, 2000	Randomised double-blind study N=120	Infants < 1 years of age undergoing standardized anaesthetic	Atropine (**40 µg/kg**) or saline	Mean heart rate at induction and in the perioperative period was significantly higher in the group receiving atropine. There was an increased incidence of bradycardia (decrease in heart rate of 320%) at induction in the non-premedicated group (23% in the no premedication group compared with 10% in the atropine group), but this was not statistically significant.
Mirakhur RK, 1980	Double-blind study N= not provided	Subjects undergoing elective operations	Glycopyrrolate (5, 10, 15 µg/kg IV) or Atropine (**10, 20 and 30 µg/kg IV**)	Both drugs produced a dose-related increase in heart rate. Glycopyrrolate was approximately twice as potent as atropine in increasing heart rate. Bradycardia was not observed, even following the lowest doses of both drugs in the present study.
Jones P, 2013b	A 2-year prospective, observational study N= 327	Children < 8 years of age	Intubation with or without atropine (**20 µg/kg**)	The unadjusted ICU mortality was 7.2% (9/124) for those who received atropine compared to 15.7% (22/140) for those who did not (OR 0.42)
Lim HH, 2000	Study design not provided N= 75	Elderly undergoing transurethral prostate or bladder surgery	Placebo (n=25) Atropine **5 µg/kg IV** (n=25) Atropine **10 µg/kg IV** (n=25) after the induction of	The systolic blood pressure decreased in all three groups after spinal anaesthesia. There was a significant increase in the mean heart rate in both atropine groups as compared to the placebo group. There was a significant decrease in

			spinal anaesthesia	the incidence of hypotension in patients who received atropine. IV atropine may be a useful supplement to the existing methods in preventing hypotension induced by spinal anaesthesia.
Barois J, 2013	Prospective observational study N= 57	Preterm newborns (birth weight: 1361± 347)	N=15 no analgesia N= 39 ketamine analgesia plus atropine (**20 µg/kg IV**) for tracheal intubation	Short venous catheter insertion with immediate ketamine analgesia plus atropine for tracheal intubation of preterm newborns in the delivery room was effective in decreasing pain and preventing vagal bradycardia.
Barrington KJ, 1989	Randomised controlled study N=20	Preterm newborns	Atropine alone (**20 µg/kg)** or atropine plus succinylcholine (2 mg/kg) before nasotracheal intubation	No infants developed bradycardia or hypoxia. Blood pressure increased during intubation in both groups, and the overall peak blood pressure was not significantly different between the groups. Premedication with succinylcholine and atropine will facilitate intubation of neonates, and ameliorate the adverse physiologic consequences of this procedure.
Kwak HJ, 2013	Study design not provided N=56	Patients aged 18-50 undergoing general anaesthesia	atropine (**10 µg/kg IV**) or saline	Atropine maintained bispectral index increases in response to endotracheal intubation during anaesthetic induction with propofol and remifentanil target-controlled infusion.
Gilani SM, 2005	Study design not provided N=60	Patients (age 2-30 years) operated for squint surgery under general anaesthesia	Atropine IV (n=30) or no atropine (n=30) Dose of atropine not presented by MAH	Occurrence of 70% oculocardiac reflex in the control group as compared to only 10% in the atropine group. Severe bradycardia in 40% cases of the control group needed intervention by IV injection of atropine.
Green DW, 1984	Double-blind study N= 26	Children who required suxamethonium	Glycopyrrolate (5 and 10 µg/kg IV) or Atropine (**10 and 20 µg/kg IV**)	Bradycardia (defined as a decrease in heart rate to less than 50 beat/ min) was prevented when the larger dose of either active drug was used. It is recommended that either glycopyrrolate 10 µg/kg or atropine 20 µg/kg IV should immediately precede induction of anaesthesia, in children, if the repeated administration of suxamethonium is

				anticipated.
Ahn EJ, 2016	Randomised, double-blind, placebo-controlled study N= 114	Patients ranged 2-65 years willing to be sedated and to undergo spinal anaesthesia by dexmedetomidine	Atropine (**IV bolus of 0.5 mg**) vs placebo	The incidence of bradycardia requiring atropine treatment was significantly higher in the placebo than in the atropine group (P = 0.035). However, the incidence of hypotension needing ephedrine treatment showed no significant difference between the 2 groups (P = 0.7). Systolic blood pressure and heart rate showed no significant differences between the 2 groups (P = 0.138 and 0.464, respectively). However, the atropine group showed significant increases in DBP and MBP, where the placebo group did not (P = 0.014 and 0.008, respectively).
Luo XJ, 2016	Double-blind randomised controlled study N= 160	Women under spinal anaesthesia for elective caesarean delivery	Methoxamine 2 mg alone (M; n = 40), or Methoxamine with addition of atropine **0.1 mg IV** (MA1; n = 40), atropine **0.2 mg IV** (MA2; n = 40) or atropine **0.3 mg IV** (MA3; n = 40) upon a maternal systolic pressure ≤ 80% of baseline.	Changes in systolic blood pressure were similar among the four groups. The incidences of bradycardia in groups M and MA1 were significantly higher than those in group MA2 and MA3. In conclusion, methoxamine-atropine combination has a similar efficacy to methoxamine alone but has an increased hemodynamic stability and a less adverse effect occurrence.

Table 2. Summary of studies in support of the indication "to limit the muscarinic effects of neostigmine, when given post surgically to counteract non-depolarising muscle relaxants"

Author, Year	Trial Design, No. of Subjects	Patient Population	Intervention (and Control)	Results
Oduro KA, 1975	Randomised study N=98	Patients undergoing elective intra-abdominal operations under general anaesthesia	Glycopyrrolate 0.2 mg (n=49) or Atropine **0.4 mg** (n=49)	By intramuscular administration, both drugs produced the same degree of tachycardia, although atropine tended to cause no change in the pulse rate or even to produce bradycardia in a greater number of patients. Administered

				intravenously, atropine produced a more significant tachycardia in a large number of patients prior to neostigmine administration.
Black GW, 1980	Double-blind study N=64	Children 1-12 years of age, who weighted between 9 and 40 kg and were undergoing various types of elective surgery	Atropine (**0.8 mg**) with neostigmine (2.0 mg) or Glycopyrrolate (0.4 mg) with neostigmine (2.0 mg)	Both atropine and glycopyrrolate can be used as effectively in children as it can be in adults for reversal of non-depolarising neuromuscular block.
Rosner V, 1971	Details study design not provided N= 50	Patients undergoing intra-abdominal or intra-thoracic surgery	Group A+B: atropine **6 µg/kg** with neostigmine 20 µg/kg Group C+D: atropine **12 µg/kg** and neostigmine 40 µg/kg Group E: atropine **8 µg/kg** and neostigmine 20 µg/kg	Of the different dosages and sequences of administration investigated, the combined injection of atropine 6 µg/kg and neostigmine 20 µg/kg over 60 seconds appears to be most suitable for the reversal of residual neuromuscular block.
Hakimoglu S, 2016	Details study design not provided N=60	Patients ages 18-65 years with ASA I-II who underwent arthroscopic surgery under general anaesthesia	Atropine (**15 µg/kg**) with neostigmine (50 µg/kg) or Sugammadex (4 mg/kg)	Elevation in intraocular pressure of patients reversed using sugammadex was similar to that recorded in patients reversed using neostigmine-atropine. When heart rate was compared, there was a significant difference between basal values and those obtained at 30 seconds and 10 minutes after extubation in the neostigmine-atropine group.
Ittichaikulthol W, 2014	Randomised controlled study N= 51	Patients with ASA I-II undergoing elective gynaecological surgery under general anaesthesia	Control group: Atropine (**1.2 mg**) with neostigmine (2.5 mg) Intervention group: Atropine (**0.6 mg**) and glycopyrrolate (0.2 mg) with neostigmine	There was no different increase in heart rate after administration of reversal agent between control group and intervention group at any time. There was no incidence of significant arrhythmia in both groups. Therefore, atropine 0.6 mg and glycopyrrolate 0.2 mg is an alternative to antagonize the muscarinic effects of neostigmine.

			(2.5 mg)	
Sen A, 2016	Randomised double-blind controlled study N= 72	Patients with ASA I-II and scheduled for total thyroid surgery	Neostigmine 0.04 mg/kg with atropine **0.015 mg/kg** (n=36) vs Sugammadex 2 mg/kg (n=36)	Median time of first flatus was 24 hours (18-32 [10-36]) in the neostigmine-atropine group, and 24 (18-28 [12-48]) in the sugammadex group. Median (IQR) time of first faeces was 24 hours (18-36 [10-48]) in the neostigmine-atropine group, 32 hours (28-36 [12-72]) in the sugammadex group. There were no occurrences of nausea, vomiting, diarrhea, or constipation.

Table 3. Summary of studies in support of the indication "Treatment of hemodynamically compromising bradycardia and/or atrioventricular block due to excessive vagal tone in emergency situations"

Author, Year	Trial Design, No. of Subjects	Patient Population	Intervention (and Control)	Results
Brady WJ, 1999	Retrospective descriptive study N= 172	Prehospital patients with hemodynamically compromising bradycardia or atrioventricular block with evidence of spontaneous circulation	Atropine as delivered by emergency medical services personnel	Atropine: range 0.5 to 3 mg (mean 0.97 ± 0.55 mg)
Swart G, 1999	Retrospective and descriptive study N= 131	Patients experiencing hemodynamically compromising bradyarrhythmia related to acute myocardial infarction (AMI) in the prehospital (PH) setting and the therapeutic impact of the PH response to atropine on further Emergency Department (ED) care.	PH: Atropine (**0.97 mg ± 0.55**) ED interval: Atropine (**1.2 mg ± 0.96**)	The mean time from first dose of atropine to ED arrival and the total dose of atropine received in the PH setting did not differ between AMI and non-AMI groups (15.2 ± 7.7 v 16.2 ± 8.7 minutes). The likelihood of achieving normal sinus rhythm in the PH setting did not differ between AMI and non-AMI groups (40% v 18.6%). No differences were found between AMI and non-AMI groups in the amount of additional atropine given (1.2 ± 0.58 v 1.3 ± 1.1 mg) or the use of other resuscitative therapies after ED arrival.
Chadda KD, 1975	Details study design not provided N= 68	Patients with acute myocardial infarction	Atropine Dose atropine not presented	In 61 of the 68 patients, the administration of atropine significantly increased the heart rate (from 46 plus or minus 14 to

			by the MAH	79 plus or minus 12/min) (p less than 0.01) and systolic blood pressure (from 70 plus or minus 15 to 105 plus or minus 13 mm Hg) (p less than 0.001).
Sodeck GH, 2007	Retrospective study N= 277	Patients presenting with compromising bradycardia	Atropine (**up to 3 mg; mean 1 mg**)	Intravenous drugs to increase ventricular rate were given to 170 (61%) patients, 54 (20%) required additional temporary transvenous/ transcutaneous pacing. In the majority of patients though, initial stabilisation was achieved by simple interventions including bed rest and the administration of intravenous atropine and/or catecholamines. Atropine up to 3 mg (mean 1 mg) was administered in 141 patients.
Aghamohammadi H, 2009	Details of study design not provided N= 64	Patients undergoing urological laparoscopic surgery	Atropine vs placebo. Dose of atropine not presented by the MAH	A significant decreasing trend was seen in the heart rates during the operation in patients without atropine sulphate. Nine of 32 patients (28.1%) in this group developed bradycardia, while none of the patients with atropine sulfate prophylaxis had bradycardia perioperatively (P < .001).
<u>Additional scientific documentation provided by the MAH to support the posology</u>				
Clinical studies				
Chadda KD, 1977	Details of study design not provided (N=100)	Patients with a heart rate < 60/min following acute myocardial infarction	Atropine **0.4 to 1.5 mg** IV	A relatively lower dose of atropine (**<0.8 mg**) had a beneficial antiarrhythmic effect. Higher dosage caused an inappropriate tachycardia, angina and ventricular premature beats, and should be avoided.
Smith I, 1994	Details of study design not provided (N= 64)	Unpremedicated patients receiving a standardized sufentanil/N_2O/ vecuronium anaesthetic	Atropine **5 µg/kg** or Glycopyrrolate 2.5 µg/kg or Transophageal atrial pacing	The average total dose required for atropine was **0.63 mg**. There were no significant differences in postoperative side effects between the three groups, or when compared with patients who did not receive treatment for bradycardia.
Sigdel S, 2015	Randomised, double-blind, controlled trial (N=40)	American Society of Anesthesiologist physical status Physical Status (ASA PS) I–II patients undergoing	Atropine **0.6 mg** IV or saline	Intravenous administration of atropine 0.6 mg, one minute after the induction of spinal anaesthesia in an elderly patient, is a safe and effective method in the prevention of spinal anaesthesia induced hypotension and bradycardia.

		urological surgeries		
Shahriari A, 2017	Retrospective cohort study (N=194)	Patients with symptomatic bradycardia during skin tumour resection	Atropine **0.5 mg** (N=86) or Ephedrine 10 mg (N=108)	35 patients in the atropine group required the second drug for bradycardia management; therefore, 51 patients were treated with only atropine (efficacy: 51/86, 59.30%). Moreover, 21 patients in the ephedrine group required the second dose of ephedrine for the management of bradycardia; consequently, 87 patients were treated with only ephedrine (efficacy: 87/108, 80.55%). There was a statistically significant difference between the 2 groups (P = 0.001).
Guidelines				
Neumar RW, 2010	Atropine remains the first-line drug for acute symptomatic bradycardia (Class IIa, LOE B). The recommended atropine dose for bradycardia is **0.5 mg IV every 3 to 5 minutes** to a maximum total dose of 3 mg. Doses of atropine sulphate of <0.5 mg may paradoxically result in further slowing of the heart rate.			
Reviews				
Gunaydin B, 2005	The recommended dose in pulseless electrical activity (PEA) associated with bradycardia (<60 beat/min) and asystole is 3 mg iv and 6 mg endotracheally. For the treatment of sinus bradycardia, **0.5 mg** (approximately 10 µg/kg) iv should be given and repeated if required up to a total dose of 40 µg/kg. Atropine is the drug of choice in PEA associated with bradycardia and asystole.			
Papastyliano A, 2012	Atropine is administered in doses of **0.6–3.0 mg IV** to counteract bradycardia in the presence of hypotension and to prevent the bradycardia associated with vagal stimulation. A study noted the possible role of the parasympathetic nervous system in cardiac arrest and reported that atropine is beneficial during cardiac arrest.			

Table 4. Summary of studies in support of the indication "Cardiopulmonary resuscitation: to treat symptomatic bradycardia and AV block"

Author, Year	Trial Design, No. of Subjects	Patient Population	Intervention (and Control)	Results
Yano T, 2019	Retrospective observational study N= 367	Out-of-hospital cardiac arrest (OHCA) patients	Epinephrine (IV 1 mg dose every 3-5 minutes) with atropine (**IV 1 mg which could be repeated every 3-5 minutes, max of 3 mg**) or Epinephrine only	At the outcome, the epinephrine with atropine and epinephrine-only groups had a similar survival rate to that at hospital admission (28.7% vs. 26.7%: p=0.723). The odds ratio (OR) for the survival to hospital admission after the administration of atropine with epinephrine was 1.33 (95% CI 1.09-1.62; p<0.01), while that after the administration of epinephrine was 0.64 (95% CI: 0.55-0.74, p<0.01). The addition of atropine (within 2 mg) following

				epinephrine was a comprehensive independent predictor of the survival to hospital admission for non-shockable (especially asystole) OHCA adults.
Ohshige K, 2005	Prospective comparative study N= 434	Cardiac arrest patients	Phase I: administration of epinephrine Phase II: started with the use of lidocaine or atropine Phase III: started with administration of another drug	For non-traumatic cardiac arrest, outcomes through phase II in the experimental areas were significantly better than those in the reference areas. Phase I—only outcomes in the experimental areas (doctor-manned ambulances) were better, but not significantly better, than those in the reference areas (basic life support ambulances). Use of resuscitative drugs for non-traumatic prehospital cardiopulmonary resuscitation (CPR) appears to be effective in terms of resuscitation rates and 1-month survival rates.
Scheinman MM, 1975	Details of study design not provided N= 56	Patients with acute myocardial infarction and sinus bradycardia	Initial dose of atropine (**i.e. 1.0 mg as compared with the usual 0.5 or 0.6 mg**) or Total cumulative dose exceeding **2.5 mg over 21/2 hours**	Atropine decreased or completely abolished premature ventricular contractions (PVCs) and/or bouts of accelerated idioventricular rhythm in 27 of 31 patients (87%) and brought systemic blood pressure up to normal in 15 of 17 patients (88%) with hypotension. In addition, atropine administration was associated with improved atrioventricular conduction in 11 of 13 patients (85%) with acute inferior myocardial infarction associated with 2 degrees or 3 degrees atrioventricular block.
Tortolani AJ, 1989	Retrospective study N= 123	Patients in whom the initial rhythm was asystole	Details of intervention not presented by the MAH	Twenty-eight (22.8 percent) of these patients were alive 24h after CPR initiation. Patients who received norepinephrine drip (N = 43) were more likely to survive than those who did not (39.5 percent vs 14.1 percent; p less than 0.01), and those who received lidocaine drip were more likely to survive than those who did not (47.6 percent vs 18.2 percent; p less than 0.01). The best survival rate (57.1 percent) occurred among those who received both norepinephrine and lidocaine (N = 14). Survivors did not

				differ significantly from non-survivors in terms of age, gender, primary diagnosis, location of arrest, or duration of CPR efforts. The results suggest that aggressive resuscitation efforts which include the addition of norepinephrine and lidocaine drips to the AHA-recommended regimen of epinephrine and atropine may substantially increase the number of 24-h survivors.
Graf JL, 2000	Case report N=1	A 23-week gestation foetus with bradycardia after in utero resection of a sacrococcygeal teratoma coupled with a transfusion of packed red blood cells.	Chest compressions were begun and epinephrine, atropine (**0.01 mg/kg**), and sodium bicarbonate were given, while the foetus remained bathed in warm saline.	After 3 rounds of drugs, and just before withdrawing support, the foetal heart resumed beating and normal cardiac function.
Gibbs MW, 2003	Case report N=1	Patient who developed a type 1 anaphylactic reaction to intravenous cefazolin	Resuscitation included endotracheal intubation, external cardiac compression, electrical defibrillation and multiple large doses of epinephrine, atropine (**1 mg IV**), and sodium bicarbonate over the course of 2.5 h and three cardiac arrests.	Patient fully recovered
Additional scientific documentation provided by the MAH to support the posology				
Clinical studies				
Stueven HA, 1984	Retrospective review (N= 170)	Patients presented in cardiorespiratory arrest with an initial rhythm of asystole	Atropine Control group (Dose not provided)	The successful resuscitation rate in the atropine group was 14% (6/43), while in the control group it was 0% (0/41)

Suljaga-pechtel K, 1984	Prospective study (N=226)	Hospitalized patients	**0.5 mg** IV and repeat every 5 min up to a total dose of 2 mg	No correlation of immediate outcome was found with the following variables: location of arrest; time of day; pre-existence of shock; coma; stroke; malignancy. Uraemia and/or chronic obstructive pulmonary disease was not significantly associated with failed resuscitation. Most notable in our results of specific treatments was the evidence for the need to improve the initial pH, particularly when it was less than 7.2.
Guidelines				
Diamond LM, 2007	If the patient is suffering from poor perfusion, the recommendation is to apply transcutaneous pacing (class I recommendation for symptomatic bradycardias). It is to be started immediately for patients who are unstable with Mobitz Type II second-degree block or third- degree block. The downside of transcutaneous pacing is that it may not be effective and can be very painful to the patient. While preparing for transcutaneous pacing, atropine at a dose of **0.5 mg every 3 to 5 minutes**, to a maximum of 3 mg should be given. Transcutaneous pacing is also indicated for bradycardia if the patient fails to respond to atropine.			
O'Conner RE, 2017	Atropine sulphate is a vagolytic drug that increases heart rate and conduction through the atrioventricular node. It is given for symptomatic bradyarrhythmia and high-degree atrioventricular nodal block. The adult dose of atropine during cardiopulmonary resuscitation is **0.5 to 1 mg;** and the paediatric dose is **0.02 mg/kg.**			
Teo WS, 2007	In Pulseless electrical activity (PEA) algorithm, atropine **0.6 mg IV** (if PEA rate is slow), repeat every 3 to 5 minutes as needed, to a total dose of 0.04 mg/kg. It has been suggested that atropine should be used with caution in AV block at the His-Purkinje level (type II AV block and new third-degree block with wide ORS complexes (Class IIb)). The intervention sequence for serious bradycardia is atropine 0.6 to 1.2 mg. Atropine should be given in repeat doses every 3-5 minutes up to total of 0.03-0.04 kg			

Table 5. Summary of studies in support of the indication "as antidote following overdosage or poisoning with acetylcholinesterase-inhibitors e.g. anticholinesterases, organo-phosphorus, carbamates and muscarinic mushrooms"

Study, Author, Year	Trial Design, No. of Subjects	Patient Population	Intervention (and Control)	Results
Bhandarkar AA, 2014	Retrospective study N= 199	Patients with organophosphate poisoning (OP)	Atropine or Atropine with glycopyrrolate Dose of atropine not presented by the MAH	A total of 159 patients received only atropine as treatment with an average hospital stay of 12.66 (SD= 11.88) days and a mean of 8.71 (SD= 10.03) days duration in ICU. Whereas the other 40 patients received both atropine and glycopyrrolate as treatment with an average stay of 15.68

				(SD= 12.76) days and a mean of 12.12 (SD= 10.40) days duration in ICU. Amongst the 159 patients who received only atropine 40.9% received ventilation and for the other 40 who received atropine and glycopyrrolate 60% received ventilation. In conclusion, atropine was found to be more effective when given alone when compared with atropine and glycopyrrolate combination in OP poisoning.
Abedin MJ, 2012	Open-label randomised study N= 156	Patients with organophosphate poisoning (OP)	Bolus injections of atropine (**2 to 5 mg, could be repeated every 10 -15 min**) (group A; n=81) or Incremental boluses plus infusion of atropine (**first dose of 1.8 – 3.0 mg, this was repeated every 5 min**) (group B; n=75)	The mortality in group A was 22.5% (18/80) and in group B 8% (6/75). The mean duration of atropinisation in group A was 151.74 min compared to 23.90 min for group B ($p < 0.001$). More patients in group A experienced atropine toxicity than in group B (28.4% versus 12.0%). Rapid incremental dose atropinisation followed by atropine infusion reduces mortality and morbidity from OP poisoning and shortens the length of hospital stay and recovery. Incremental atropine and infusion should become the treatment of choice for OP poisoning.
Liu HX, 2015	Details of the study design are not provided N= 60	Patients with organophosphate poisoning (OP)	Constant micropump infusion of atropine and pralidoxime chloride (experimental group) Vs Repeated bolus doses of atropine and pralidoxime (control group) Dose atropine not presented by the MAH	Compared to patients in the control group, the time to atropinisation, AchE recovery time, dose of atropine when atropinisation occurred, and APACHE II score in the experimental group showed a statistically significant therapeutic effect. In conclusion, continuous micropump of atropine and pralidoxime chloride combined is more effective than the use of repeated-bolus injection in the treatment of severe acute organophosphorus insecticide poisoning.

Additional scientific documentation provided by the MAH to support the posology				
Clinical studies				
Chugh SN, 2005	Non-randomised clinicotherapeutic trial (N=30)	Patients of moderate-to-severe organophosphorus poisoning	Atropine **2 mg** IV and then 2 mg after **every 5-10 min** Or Atropine + pralidoxime (PAM) (Atropine was used in intermittent dosage and PAM was given in a fixed dosage of 1 g intravenous after every 6 hours)	PAM neither improved the atropine profile in group II patients (atropine + PAM treated) as compared to group I (atropine alone treated) nor ventilatory profile changed significantly in the two groups. Mortality was negligible in both the groups. Data does not support the widely accepted use of pralidoxime in the treatment of moderate to severe OP poisoning as it does not have any added advantage over atropine.
MMWR CDC, 1999	Case report	20 company lunch employees	Dose atropine not provided	In cases of aldicarb poisoning, atropine sulphate is the antidote of choice and can be supplemented by treatment of symptoms and rapid removal of the toxin (e.g., by induced vomiting)
Sofer S, 1989	Details of the study design are not provided (N=25)	Infants and young children intoxicated by carbamate and organophosphorus compounds	Atropine **0.05 mg/kg** every 5 to 10 minutes	Atropine sulphate was found to have a clear beneficial CNS effect in addition to its known peripheral antimuscarinic effect
Bardin PG, 1990	Randomised, double-blind (N=44)	Consecutive patients with acute organo-phosphorus poisoning (OPP)	Atropine vs Glycopyrrolate Dose Atropine not provided	Glycopyrrolate offers no clinical advantage to atropine in acute OPP.
Ozturk MA, 1990	Retrospective study (N=269)	Patients with anticholinesterase poisoning **207 patients were 17 days - 10 years of age**.	Atropine **0.05 mg/kg** Some patients were given pralidoxime 25 mg/kg and some obidoxime 4-8 mg/kg	Atropine treatment must be continued at least for 48 h. If atropine is stopped earlier, respiratory depression and pulmonary oedema may occur. No difference was found between the use of atropine alone or in combination with oximes.
Singh S, 2007	Prospective study (N= 79)	Patients with anticholinesterase poisoning by	OPP: Atropine + 2-pralidoxime	The mean (±SD) dose of atropine required on day one was 163.2 ± 100.2 mg (range 6–

		organophosphate or carbamates	(2-PAM) Carbamates: Atropine alone Atropine was administered **5 mg** bolus intravenously followed by 2 mg every 5 min till atropinised	480 mg) with mean ±SD total dose being 247.3 ± 199.4 mg (range 12–1682 mg). 2-PAM was administered to 31 patients with mean ± SD dose being 40.9 ± 31.7 mg (range 8–120 mg)
Konickx LA, 2014	Prospective cohort study (N= 1957)	Patients poisoned by anticholinesterase pesticides	Dose Atropine not provided	The study found no evidence of a high number of early deaths in an observational study of 1957 patients routinely given atropine before oxygen that might support guidance that oxygen must be given before atropine. Moreover, adequate atropinisation is key for the management of OP and carbamate poisoning and should be done early, with appropriate titration and monitoring of developing adverse events.
Guidelines/ reviews				
Tafuri J, 1987 (review)	In moderately severe poisoning, adults should receive **2 mg** atropine IV every 15 minutes until adequate atropinisation is established. The **paediatric dosage** is **0.05 mg/kg**, repeated every 15 minutes as necessary. Some authors have advocated the use of a continuous infusion of atropine in a dosage of **0.02 to 0.08 mg/kg/hr**. A severely poisoned individual will exhibit marked atropine refractoriness and may require up to two to three times the standard doses. Although the average patient will require only 40 mg of atropine per day, doses of more than 1,000 mg per day have been needed.			
Davies DR, 1959 (review)	In conjunction with atropine PAM was effective against almost all the more common organophosphate anticholinesterases, although when given alone its activity was generally small.			
Eddleston M, 2008 (review)	Treatment of organophosphorus pesticide poisoning includes resuscitation of patients and giving oxygen, a muscarinic antagonist usually atropine at a dose of **1-3 mg** as a bolus, depending on severity, fluids, and an acetylcholinesterase reactivator (an oxime that reactivates acetylcholinesterase by removal of the phosphate group). If no improvement has taken place, give double the original dose of atropine. Continue to review every 5 minutes; give doubling doses of atropine if response is still absent.			
Grob D, 1955	If liquid nerve gas should get into the eye, instant action is necessary to prevent absorption of a lethal dose. The pupil of the contaminated eye should be watched during the next minute. If it rapidly gets smaller, **2 mg** of atropine should be injected intramuscularly at once.			
Grob D, 1963	If appreciable absorption of nerve gas is known to have occurred, **2 mg** of atropine may be injected intramuscularly before the effects of poisoning appear. The administration of atropine alleviates the muscarine-like and central neural manifestations of nerve-gas poisoning, even though, in severe poisoning, such relief may be transient and repeated			

	administration of atropine may be required. The amount of atropine required to alleviate these manifestations varies with the severity of the poisoning, and the duration of the relief afforded by the atropine varies inversely with the severity of the poisoning. The administration of a single dose of **2 mg** of atropine by any route to a subject who has absorbed little or no nerve gas produces mild symptoms of atropinisation in most subjects, and repetition of this dose within one or two hours produces more moderate symptoms of atropinisation. Atropine should be limited to a total of 6 mg.
Haywood PT, 2000	One of the measures of treatment of organophosphorus compound poisoning is atropine IV **2 mg** (0.05 mg/kg) every 5-10 min, **children 0.02 mg/kg**. Continue, if no adverse effects, until signs of atropinisation, e.g. the abolition of bronchospasm, bronchorrhea and dry mouth. Atropine effectively antagonizes the muscarinic actions of excessive acetylcholine (increased tracheobronchial secretions, bradycardia, salivation, bronchoconstriction). In children, doses of **0.015-0.05 mg/kg** should be given every 10-30 min. After atropinisation is achieved, this status should be maintained until there is complete clinical recovery. The usual maintenance dose of atropine is 0.5 mg/h.
Mortensen ML, 1986	Anticholinergic therapy must be initiated immediately if a severe organophosphate poisoning is suspected. Children older than 12 years may be given the adult dosage of **1.0** to **2.0 mg** of atropine, intravenously, every 10 to 30 minutes until cholinergic signs are completely reversed. For a child younger than 12 years, an initial intravenous atropine dose of **0.05 mg/kg** is followed by a maintenance dose of **0.02**-**0.05 mg/kg**, repeated every 10 to 30 minutes until cholinergic signs are reversed. Atropine should be given intravenously, and the frequency of dosing should be titrated to the patient's signs.
Karalliedde L, 1999	The atropine initial dose should be **2 mg** intravenously, **repeated** at **5–10 min** intervals until signs of atropinisation occur: a pulse rate >80 beat/min and dilatation of the initially constricted pupils. Atropine therapy should be maintained until there is complete recovery. Paediatric treatment comprises doses of **0.02–0.05 mg/kg every 10–30 min**. Infusions of atropine (0.02–0.08 ml/kg/h) have produced significant reductions in mortality in some centres when compared with conventional intermittent therapy.
Weinbroum AA, 2004	Atropine must be given in large amounts that may reach up to 50 mg/70 kg in a 24 h period before signs of full atropinisation appear. The initial dose (**2 mg** for adults and **0.02 mg/kg for children**) should be administered intravenously; the full atropinisation effect (flushed dry skin, pupillary dilatation, increased heart rate and attenuation of bronchorrhea) is achieved only with large doses.

Intramuscular route for administration

Sixty patients in the age group of 18-60 years of ASA Grade I/II risk, scheduled for elective orthopaedic surgeries under general anaesthesia were studied for pre-medication with either oral clonidine or with combination of effects of diazepam and atropine. Patients in Group A (clonidine group) received clonidine tablet 100 mcg (1 tablet) if less than 50 kg in weight and 200 mcg if weighing more than 50 kg two hours before surgery. Patients in Group B (diazepam-atropine group) received one tablet of diazepam (10 mg) orally two hours before surgery and injection atropine-sulphate 0.01 mg/kg half an hour preoperatively by intramuscular route. The sedative and anti-sialagogue effects of clonidine were comparable to those of diazepam-atropine combination, which are commonly used premedicine. The anti-anxiety effect of clonidine was found to be better than that of diazepam-atropine combination (Chaurasia SK et al. 1999).

A study evaluated the comparison of pethidine, pethidine + atropine and pethidine + hyoscine (percentages) 60-90 minutes after intramuscular injection. Pethidine 100 mg has been studied alone and in combination with atropine (0.6 mg) or hyoscine (0.4 mg). Pre-

operatively there was a very high incidence of nausea or vomiting after pethidine which was diminished when atropine was given in conjunction and even more when hyoscine was added. Dizziness was also a common toxic effect in all three groups. As judged by lack of excitatory phenomena and hypotension during anaesthesia, pethidine with atropine was the combination of choice. Atropine and hyoscine were equally effective in reducing the pre-operative emetic effects of pethidine, but vomiting was reduced more than nausea. Atropine, and to a much lesser degree hyoscine, increased the tachycardia following the injection of pethidine (Dundee JW et al. 1964).

A review evaluated the blinded studies. The preponderance of the data was obtained from the patient population (953 patients) of a large municipal hospital. The pre-anaesthetic medication schedule is shown in the below table (Lear E et al. 1960).

Table 6. Pre-anaesthetic medication schedule (Lear E et al. 1960)

Age groups (years)	2 hours pre-op. antihistamine (I.M.) (mg)	1 hour pre-op. narcotic (I.M.) (mg)	1 hour pre-op. atropine (I.M.) (mg)
12–40	50	50	0.4–0.3
41–55	50–35	50–35	0.3
56–70	35–25	35–25	0.3–0.2
71 and over	25–12.5	25–12.5	0.2

In a study, 80 children were divided into four groups of 20 each, they were of physical status ASA I between the ages of 1 and 13 years, undergoing elective surgery. None were receiving any medication. Premedication consisted of 1.0 mg/kg pethidine and either 5 or 10 µg/kg of glycopyrrolate or 15 µg/kg of atropine. The fourth group did not receive any anticholinergic premedication. All premedication drugs were administered intramuscularly approximately 60 to 90 minutes prior to anaesthesia, the anticholinergic component being given in a double-blind fashion from specially prepared coded ampoules. Both atropine and the higher dose of glycopyrrolate produced significant increases in heart rate prior to introduction of anaesthesia. The subsequent increase during the process of induction was less than in those who had not received an anticholinergic drug or glycopyrrolate 5 µg/kg. Dysrhythmias during induction of anaesthesia occurred slightly less frequently in the patients given atropine or the higher dose of glycopyrrolate. Although the incidence was similar in these two groups, ventricular ectopic beats occurred less frequently following the use of glycopyrrolate. The control of secretions was also superior with this anticholinergic premedication (Mirakhur RK, 1982).

If liquid nerve gas should get into the eye, instant action is necessary to prevent absorption of a lethal dose. The pupil of the contaminated eye should be watched during the next minute. If it rapidly gets smaller, 2 mg of atropine should be injected intramuscularly at once (Grob D, 1955).

In treatment of severe anti-ChE intoxication, particularly by organophosphorus compounds, 2 to 4 mg should be administered intravenously, followed by 2 mg every 3 to 10 minutes

until muscarinic symptoms and signs disappear, and whenever they reappear; a total of 24 to 48 mg may be required during the first day; in less severe intoxication, 2 mg intravenously or intramuscularly, repeated at ten to thirty-minute intervals until muscarinic symptoms are relieved; maintenance of a mild degree of atropinisation for twenty-four to forty-eight hours (Grob D, 1963).

A double-blind study was designed to compare the clinical usefulness of glycopyrrolate with atropine as a pre-anaesthetic medication in adults; and to compare the relative effectiveness of glycopyrrolate and atropine in antagonizing the muscarinic effects of neostigmine methylsulfate given to reverse neuromuscular blockade. The study evaluated 98 patients undergoing elective intra-abdominal operations under general anaesthesia. There were 49 patients in each of the glycopyrrolate and the atropine groups. All the patients for cholecystectomy were given a premedication intramuscularly consisting of meperidine 50 to 100 mg (the majority receiving the lower dosage) and either atropine 0.4 mg or glycopyrrolate 0.9 mg, from the coded supply, 45 minutes to 1 hour before operation.
Intramuscular administration of atropine 0.4 mg or glycopyrrolate 0.2 mg produced the same degree of dryness of the pharynx. By intramuscular administration, both drugs produced the same degree of tachycardia, although atropine tended to cause no change in the pulse rate or even to produce bradycardia in a greater number of patients. Administered intravenously, atropine produced a more significant tachycardia in a large number of patients prior to neostigmine administration (Oduro KA, 1975).

Vagal arrhythmias during induction of anaesthesia in children are extremely common. They can occur at any time during induction but are more prone to occur at the time of intubation, particularly of succinylcholine has been administered intravenously. The intravenous administration of atropine 0.01 mg/kg prior to the administration of succinylcholine-and/or intubation is very effective in abolishing and preventing these cardiac arrhythmias. The administration of atropine 0.03 mg/kg, intramuscularly one hour prior to induction is very effective in preventing cardiac arrhythmias provided succinylcholine is not employed (Sagailminag J et al. 1963).

IV.4 Clinical safety

The safety profile of Atropinesulfaat Accord provided by the MAH is based on data from various published clinical studies and reference to the SmPC of Atropine Aguettant (licenced in 2015).

Safety in published clinical studies as presented by the MAH
A study examined the association of the use of atropine as a premedication in Patent Ductus Arteriosus (PDA) ligation and the risk of post-operative respiratory complications. This retrospective cohort study included 150 newborns who had failed medical treatment for PDA and received PDA ligation in a single tertiary medical centre. Ninety-two of them (61.3%) received atropine as premedication for general anaesthesia while 58 (38.7%) did not. Patients with atropine use were associated with increased odds of respiratory acidosis in both univariate analysis (22.9% vs 7.3%; OR=3.785) and multivariate analysis (OR = 4.030), with an even higher odds of respiratory acidosis in patients receiving both atropine and ketamine. In conclusion, the use of atropine as premedication in general anaesthesia for

neonatal PDA ligation is associated with higher risk of respiratory acidosis, which worsens with the combined use of ketamine (Chang SL et al. 2017).

In a case report, a 58-year-old male was scheduled to undergo radical gastrectomy for cancer under general anaesthesia. The patient developed agitation and irregular breathing after receiving a single dose of atropine (0.5 mg) to treat bradycardia immediately prior to induction of anaesthesia. Within 5 minutes after the atropine injection, the patient became unresponsive with facial flushing and diaphoresis. When a drop in oxygen saturation was observed, a laryngeal mask airway was inserted after administering a small bolus dose of propofol (80 mg) and the patient was ventilated with 100% oxygen. Physostigmine was not administered because of the relatively low dose of atropine and the fact that his symptoms were not totally consistent with central anticholinergic syndrome. The differential diagnosis at the time also included an acute cardiovascular event and an idiosyncratic reaction to atropine. The patient fully recovered within 80 minutes from this highly unusual reaction to a single 0.5 mg IV dose of atropine (Cao X et al. 2016).

A 25-year-old male presented with severe hypotension and erythema after intravenous atropine administration during general anaesthesia. Postoperative laboratory findings demonstrated elevated serum tryptase and total immunoglobulin E. An intradermal test showed atropine sensitivity. Although atropine is used widely as a perioperative anticholinergic agent, it is a potential risk factor for a severe anaphylactic reaction. Therefore, prompt recognition and adequate therapeutic measures are necessary to avoid fatal consequences (Choi J et al. 2015).

The safety of atropine and glycopyrrolate were compared when given in a mixture with neostigmine for the reversal of non-depolarising neuromuscular block in children. Five patients in the atropine group, but none in the glycopyrrolate group, showed bradycardia (a rate of < 70/min) at 4 minutes after the reversal mixture, this difference between the groups was significant. The ECG's showed no important dysrhythmias. One patient in the glycopyrrolate group exhibited two ventricular ectopic beats just before extubation and one in the atropine group showed a single atrial ectopic beat. The changes in blood pressure were minimal and not significant. In was concluded that both atropine and glycopyrrolate can be used as safely in children as it can be in adults for reversal of non-depolarising neuromuscular block (Black GW et al. 1980).

The safety of intravenous atropine in 56 patients with acute myocardial infarction complicated by sinus bradycardia were evaluated. Seven patients developed ten significant adverse effects: ventricular tachycardia or fibrillation in three, sustained sinus tachycardia in three, increased PVCs in three, and toxic psychosis in one. These major adverse effects correlated with either a higher initial dose of atropine (i.e. 1.0 mg as compared with the usual 0.5 or 0.6 mg) or a total cumulative dose exceeding 2.5 mg over 21/2 hours. In conclusion, serious adverse effects, however, preclude use of atropine without careful medical supervision (Scheinman MM et al. 1975).

Atropine sulphate, a mydriatic and cycloplegic agent, is frequently used in patients undergoing glaucoma surgery. Trabeculectomy with peripheral iridectomy is the most common glaucoma surgery performed to decrease intraocular pressure and preserve vision.

Systemic absorption of ophthalmic atropine does occur and may result in toxic and adverse side effects. Cardiac dysrhythmias are one of the major adverse reactions. A case study reviews three patients who had a trabeculectomy for glaucoma and received ophthalmic atropine. One patient received both systemic and ocular atropine. Two patients developed atrial fibrillation and one a supraventricular tachycardia. Two patients required admission to a cardiac intensive care unit for management of the dysrhythmia and a third reverted to normal sinus rhythm spontaneously. The cardiac effects of ophthalmic atropine should be considered in the preoperative and postoperative assessment of patients with dysrhythmias (Merli GJ et al. 1986).

A study evaluated the tolerance of intubation following anaesthesia with atropine, sufentanil and atracurium in very premature infants. Infants received intravenously 15 µg/kg of atropine as a bolus followed by 0.2 µg/kg of sufentanil over 60 seconds and 0.3 mg/kg of atracurium over 30 seconds. A desaturation ≤ 80% lasting > 60 seconds was observed in 18 intubations (51%). During the 35 analysed intubations, we observed 2 bradycardias < 100 bpm lasting longer than 60 seconds, 3 traumatic injuries of upper airways and 8 chest-wall rigidities. In all cases of reported chest-wall rigidity but one, a prolonged desaturation was observed. No other adverse event was reported (Durrmeyer X et al. 2014).

Literature describes an incident where 3 children received 1000 times the prescribed dose of atropine sulphate and recovered from the main effects of excitatory behaviour and hallucinations in 48 hours. The atropine sulphate is dispensed as 0.3 mg/5 ml but the atropine solution given to these children was later discovered to contain 290 mg/5 ml. Diazepam was effective in the control of this behaviour. It was suggested that physostigmine should be available where atropine and hyoscine are used or where overdoses are managed (Arthurs GJ et al. 1980).

A study evaluated the safety of sugammadex and neostigmine-atropine in 60 patients who underwent arthroscopic surgery under general anaesthesia. When complications were assessed, it was found that nausea, vomiting, breath holding, and tremors were more common in the neostigmine-atropine group than in the sugammadex group, while laryngospasm and cough were equally common in both groups (Hakimoglu S et al. 2016).

A 38-year-old woman developed symptoms of anaphylactic shock after intravenous 0.01 mg/kg atropine and required adrenaline to maintain perfusion pressure. A strongly positive response was obtained on intradermal testing. The Pruusnitz-Kuestner test was also positive, which indicated the presence of drug specific IgE untibodies. No response was obtained after hyoscine (Aguilera L et al. 1988).

A 35-year-old woman was scheduled for elective excision of fibroadenoma of the right breast, was administered intravenous 0.01 mg/kg atropine as a part of anesthetic management. She developed anaphylactic shock and required adrenaline to maintain perfusion pressure. She became anxious and drowsy shortly afterwards, she developed generalized urticaria over the face, neck, upper chest and upper limbs. Her systolic blood pressure dropped from 120 to 60 mmHg. The heart rate increased to 120 beats/minute. ST-T segment depression (–2 mV) was seen. The patient developed bronchospasm and stopped breathing. She was intubated and ventilated with 100% O_2. Peripheral pulses were

impalpable; pupils were dilated but reactive to light. She was placed in the head down position and IV infusion rate of ringer lactate was increased. IV hydrocortisone 200 mg and adrenaline 0.5 mg subcutaneously was given. The blood pressure increased to 100/70 mmHg 15 minutes later and heart rate came down to 100 beats/minute. Antihistamines were also given IV, steroids and antihistamines were continued to 48 hours. The clinical picture dissolved completely in approximately 30 minutes (Hiremath DA, 2013).

A study evaluated the side effects of atropine and glycopyrrolate in acute organophosphate poisoning. A statistically insignificant trend toward increased respiratory infections was detected in the atropine group. No differences in level of consciousness or central nervous system side effects were found (Bardin PG et al. 1990).

A study evaluated 0.4 to 1.5 mg intravenously administered atropine in 100 patients with a heart rate <60/min following acute myocardial infarction. Data from recent clinical studies suggest a possible relationship between the doses of atropine, maximum induced heart rates and the adverse effects of such therapy. Adverse arrhythmogenic effects of atropinisation in patients with acute myocardial infarction do occur, although infrequently. In only 3 of the 100 patients given atropine did new ventricular arrhythmia or worsening of pre-existing arrhythmia occur. Ventricular tachycardia reported elsewhere did not occur in any of the patients. Ventricular premature beats became more frequent or appeared suddenly in patients with an inappropriate response. A worsening or induction of ventricular arrhythmia with rather low dosage of atropine and small increments in rate, although not seen in this study but rarely reported, may even be a result of sudden abolition of vagal tone. Both tachycardia and bradycardia are adverse in the setting of acute myocardial infarction (Chadda KD et al. 1977).

A study compared the side effects of atropine, glycopyrrolate, and a trans-oesophageal atrial pacing stethoscope used for treating intraoperative bradycardia in 64 unpremedicated patients receiving a standardized sufentanil/N_2O/vecuronium anaesthetic. Patients were allocated randomly to receive either atropine, 5 µg/kg (Group 1), glycopyrrolate, 2.5 µg/kg (Group 2) or trans-oesophageal atrial pacing (Group 3) after the onset of bradycardia, defined as a heart rate of ≤50 beats/min (or ≤60 beats/min with concurrent hypotension). When compared to the untreated control patients, none of the three treatments seemed to produce any clinically significant postoperative side effects. The high incidence of dry mouth in all four groups probably was related to the routine use of glycopyrrolate, a potent anti-sialagogue, for reversal of residual neuromuscular block. (Smith I et al. 1994).

The main adverse-effect of atropine is anticholinergic delirium in patients who receive too high a dose (Eddleston M et al. 2008).

A meta-analysis of 19 studies that included 3137 children evaluated the adverse effects of various doses of atropine in the therapy for myopia in children. In total, 308 adverse effect events were reported in 2425 patients in the atropine groups from all included studies, with an incidence of 12.7%. Of those, the most common were photophobia (205 of 816 [25.1%]), followed by poor near visual acuity (48 of 636 [7.5%]), and allergy (20 of 679 [2.9%]). Other adverse effects included headache, chalazion, systemic effects, and those that occurred in fewer than 1% of the patients. Only two events of photophobia among 721 patients were

reported in the control groups. Therefore, the incidence of any adverse event was significantly greater in the atropine compared with the control groups. The incidence of allergy for moderate-dose atropine was 2.9%; for high-dose atropine, 3.9%. High-dose atropine were associated with more adverse effects, such as the 43.1% incidence of photophobia compared with 6.3% for low-dose atropine and 17.8% for moderate-dose atropine. In addition, differences in the incidence of adverse effects between Asian and white patients were not identified (Gong Q et al. 2017).

A study reported a case of organophosphate poisoning in a 52-year-old man where atropine therapy was given and led to drug associated toxic megacolon. Soon after atropine was administered, there were clinical and imaging signs of megacolon, but the Electromyogram/Nerve Conduction Velocity findings were normal. Accordingly, the risk of developing megacolon should be considered when prescribing atropine (Mostafazadeh B et al. 2017).

Adverse events as stated in the SmPC of Atropine Aguettant

The evaluation of adverse reactions is based on the following definition of frequency (SmPC 2015):
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;
Not known: cannot be estimated from the available data

Table 7. Adverse events as stated in the SmPC of Atropine Aguettant

Frequency System Organ Class	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)	Not known (cannot be estimated from the available data)
Immune system disorders				Allergic reactions	Anaphylaxis	
Nervous system disorders		Excitement, incoordination, mental confusion, and/or hallucinations (especially with higher dosages), hyperthermia	Psychotic reactions	Seizure, drowsiness		Headache, restlessness, ataxia, insomnia
Eye disorders	Visual disturbances (mydriasis, inhibition of accommodation, blurred vision, photophobia)					
Cardiac disorders		Tachycardia (arrhythmias, transient exacerbation of bradycardia)			Atrial arrhythmias, ventricular fibrillation, angina, hypertensive crisis	
Vascular disorders		Flushing				

Respiratory, thoracic and mediastinal disorders	Reduced bronchial secretion					
Gastrointestinal disorders	Dryness of the mouth (difficulty in swallowing and talking, thirst), parasympathetic inhibition of gastrointestinal tract (constipation and reflux), inhibition of gastric secretion, loss of taste, nausea, vomiting, bloated feeling					
Skin and subcutaneous tissue disorders	Anhidrosis, urticaria, rash					
Renal and urinary disorders		Inhibition of the parasympathetic control of the urinary bladder, urinary retention				

Paediatric population
Infants, children and children with spastic paralysis or brain damage may be more susceptible to antimuscarinic effects.

Special populations
Atropine may cause excitement, incoordination, confusion and/or hallucinations, especially in the elderly. An epidemiological study similarly reported lower cognitive performance in elderly patients receiving antimuscarinics. Patients with Down syndrome may be more susceptible to antimuscarinic effects.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atropinesulfaat Accord 0.1 mg/ml.

Table 8. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Pharmacokinetics

The MAH has adequately substantiated bridging between their product and the product used in the literature, Atropine sulfate by Laboratoire Aguettant France, based on comparable composition of the two formulations.

Pharmacodynamics

Atropine is an antimuscarinic agent which competitively antagonizes acetylcholine at postganglionic nerve endings, thus affecting receptors of the exocrine glands, smooth muscle, cardiac muscle and the central nervous system. The pharmacodynamics of atropine is well established by literature. No new data have been submitted, which is acceptable for this bibliographic application.

Efficacy/safety

Data on extensive use of atropine has not been provided by the MAH. However, several other atropine products are currently registered in the Netherlands for more than 10 years for the same indications, indicating that the use of atropine in the various proposed indications can be considered well-established.

The efficacy of atropine for each proposed indication and associated posology has been sufficiently substantiated with an updated list of published literature. Furthermore, the proposed indications and posologies are in line with the SmPCs of other atropine products currently registered in the EU.

The provided literature describing the safe use of atropine in the proposed indications and proposed posologies is limited. However, it is in line with the SmPCs of other atropine products. The safety profile of atropine is well known and adverse events occurring with atropine are mostly related to its pharmacological actions at muscarinic receptors. The adverse events are dose-related and usually reversible when therapy is discontinued. The most common effects occurring with relatively small doses are visual disturbances, reduced bronchial secretion, dry mouth, constipation, reflux, flushing, difficulty in micturition and dryness of the skin. Transient bradycardia may develop, followed by tachycardia with palpitations and arrhythmias. No new safety signals have been identified in the provided literature. Overall, the safety profile is considered acceptable. Risk management is adequately addressed.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. For content, the proposed PL was compared to the PL of a comparable product (Atropine sulfate Aguettant 0.1 mg/ml solution for injection in prefilled syringe). This product is nationally approved in France. It can be concluded that the content of both leaflets is comparable. For design/layout, the proposed PL uses the design/layout of another product of the same MAH (Zoledronic Acid Accord 4 mg/5ml concentrate for solution for infusion), approved in procedure EMEA/H/C/002667. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atropinesulfaat Accord 0.1 mg/ml solution for injection in pre-filled syringe has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indications are in line with current atropine recommendations. The active substance has been registered in Europe for over 10 years. Based upon clinical data and the longstanding clinical experience, the use of atropine in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for this medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 September 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4788/001/IB/001/G	To introduce additional primary and secondary packaging site To introduce additional manufacturing site A minor change in manufacturing process To include additional batch sizes for both packaging volumes	No	28-12-2020	Approved	N/A
NL/H/4788/001/IB/002	Change to in-process tests or limits applied during the manufacture of the finished product	No	12-9-2022	Approved	N/A
NL/H/4788/001/P/001	Repeat use – CMSs: AT, BE, CZ, DE, DK, ES, FI, FR, IT, MT, NO, PL, PT, RO and SE	No	9-9-2022	Approved	N/A

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