Dr. F. Köhler Chemie GmbH
Werner-von-Siemens-Str. 22
D-64625 Bensheim

Anticholium®
Injection Solution

1. Name of the medicinal product
Anticholium®

2. Composition of the medicinal product
2a Active substance
5 ml injection solution contains:
2.0 mg physostigmine salicylate (Ph. Eur.)

3. Pharmaceutical form
Injection solution

4. Clinical particulars
4.a Therapeutic indications

For the treatment of postoperative disorders:
- Central anticholinergic syndrome (CAS)
- Delayed postoperative awakening
- Shivering

As antidote and/or antagonist in case of intoxication with and/or overdose of:
- Alcohol
- Tropane alkaloids (hyoscyamine, atropine, scopolamine, e.g. in brugmansia, datura, atropa belladonna)
- Amanita pantherina/amanita muscaria
- Tricyclic antidepressants (amitriptyline, imipramine, trimipramine, clomipramine, doxepin)
- Antiemetics/antihistamines (phenothiazine, thioridazine, chlorpromazine, promethazine, diphenhydramine, dimenhydrinate)
- Neuroleptic drugs (especially butyrophenones)
- Benzodiazepines
- Antispasmodics (tolterodine, oxybutynine)
- Parkinson disease medication (amantadine, diphenhydramine)
- Baclofen, 4-hydroxybutyric acid (GHB)
- Inhalation anaesthetics
- Ketamine
- 3-quinuclidinyl benzilate

4.b Posology (single and daily doses) and method of administration

In case of intoxication:
- *Paediatric population: Infants:* Start with a low dose of 0.5 mg of physostigmine salicylate administered intravenously or intramuscularly, repeat this dose every 5 minutes up to the overall dose of 2 mg, as long as the toxic, anticholinergic symptoms continue to persist and no cholinergic symptoms occur.

- *Adults:* Slowly inject 0.04 mg/kg bodyweight (2 mg) of physostigmine salicylate either intravenously or intramuscularly and subsequently inject 1-4 mg every 20 minutes. Repeat the effective dose if the intoxication symptoms occur again, possibly also in the form of a continuous infusion.

For the treatment of postoperative awakening disorders:
Slowly inject physostigmine intravenously at a dose of 0.04 mg/kg bodyweight (approx. 1 mg/min), the max. individual dose is 2 mg. In case of insufficient effect, make subsequent injections after 5 to 20 minutes at the earliest, after a positive evaluation of the effect of the first injection.

Intravenously, intramuscularly or as brief infusion in 50 ml physiological isotonic saline solution over 10-15 minutes. A general criterion for adequate physostigmine dosing is the recognizable recovery of mental abilities and responsiveness (e.g. specifying name, address, date).

4.c Contraindications
Anticholium® must not be used in case of hypersensitivity to physostigmine salicylate (Ph. Eur.), sodium metabisulfite (Ph. Eur.) or to any of the excipients. Bronchial asthma, gangrene, coronary heart disease, mechanical constipation and mechanical ischuria (urinary retention).

Absolute contraindications:
Myotonic dystrophy, depolarization block after depolarizing muscle relaxants, intoxications due to "irreversibly acting" cholinesterase inhibitors, closed traumatic brain injuries, obstruction of the gastrointestinal tract and of the lower urinary system.

Relative contraindications:
Bronchial asthma, diabetes mellitus, bradycardia, disturbances of the atrioventricular conduction system, pregnancy, Parkinson's disease, ulcerative colitis.

4.d Special warnings and precautions for use:
Due to the content of sodium metabisulfite, hypersensitivity reactions may occur in individual cases, particularly in asthmatics, which are manifested in nausea, diarrhoea, wheezing, acute asthma attack, disturbed consciousness or shock. These reactions may vary individually and may also cause life-threatening conditions. Under these circumstances, a risk/benefit analysis should be performed for Anticholium® as an intoxication antidote, and a cortisone product should be made available. Acute cardiac arrest may be possible during tricyclic antidepressant treatment, therefore Anticholium® should only be considered as an antidote for this indication if the patient has continuous ECG monitoring.

4.e Interaction with other medicinal products
Caution should be exercised in case of simultaneous administration of other cholinesterase inhibitors because of the potentiating effect.

Anticholium® is contraindicated in intoxication with depolarizing muscle relaxants of the suxamethonium-type.

4.f Pregnancy and lactation
There is no experience of the use of Anticholium® in pregnant women. Physostigmine, the active substance contained in Anticholium®, passes to the placenta. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, birth and postnatal development. The potential risk for humans is unknown. Anticholium® should only be used during pregnancy if considered to be strictly necessary by the treating doctor.

There is no experience of the use of Anticholium® during breastfeeding. It is unknown whether physostigmine, the active substance contained in Anticholium®, is excreted in human breast milk. Anticholium® should only be used during breastfeeding if considered to be strictly necessary by the treating doctor.

4.g Effects on ability to drive and use machines
None known.

4.h Undesirable effects
Nausea, vomiting, change of heart rate (both bradycardia and tachycardia), sinoatrial block, hypotension, hypersalivation, sweating.
In rare cases, sodium metabisulfite (Ph. Eur.) may cause hypersensitivity reactions and bronchospasm.

4.i. Overdose: symptoms, emergency measures, antidotes
Overdose of Anticholium® can cause bradycardia, hypersalivation, vomiting and generalized tonic-clonic seizures. Patients should be closely monitored by ECG.
Intravenous administration of atropine up to normalization of the symptoms. Normally, half the amount of the administered physostigmine salicylate is sufficient. In case of intoxication, measures are to be started immediately to prevent absorption (such as gastric lavage, administration of activated charcoal and laxatives).

5. Pharmacological properties
5.a Pharmacodynamic properties
Pharmacotherapeutic group:
Indirect parasympathomimetic
ATC code: S01EB05
Like all medically used cholinesterase inhibitors, physostigmine is a carbamate, as far as its chemical structure is concerned. Its structure is similar to that of the substances neostigmine and pyridostigmine, however, unlike the latter, it has a tertiary nitrogen atom instead of a quaternary nitrogen atom. Physostigmine is a reversible inhibitor of acetylcholinesterase. As an inhibitor of acetyl-

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cholinesterase, physostigmine slows down the degradation of acetylcholine and acts like an indirect parasympathomimetic drug due to an increase of the acetylcholine concentration at the receptor. Unlike the quarternary amines, physostigmine is able to pass the blood-brain barrier and to act in the CNS.
The main effect of physostigmine salicylate (also utilized therapeutically) is the inhibition of cholinesterase, limited in time, which causes increased formation of acetylcholine.

In vitro, physostigmine inhibits the cholinesterase in the brain of rats up to a dilution of 1.2 x 10^{-7} g (50 %).

5.a Pharmacodynamics
Physostigmine is well and quickly absorbed, both after intestinal and after subcutaneous and intramuscular administration. Absorption via the nasal mucosa after local use in the eye may also be clinically and systemically effective. The degradation of physostigmine is caused partly by hydrolysis, partly by enzymes. Hydrolysis produces metabolites, excretion is either in glucuronic or sulfactic form, predominantly via the urine (approx. 80 %), to a lesser extent via the faeces (approx. 5 %). Excretion of physostigmine is completed after 24 hours. Doses administered in intervals of 60 to 90 minutes do not cause accumulation.

Due to its structure as a tertiary amine, distribution is according to lipophilicity, i.e. with good passability of the blood-brain barrier. This is an important feature for the indications of physostigmine which is, therefore, used mainly in circumstances that require the inhibition of acetylcholinesterase in the CNS. Due to the lipophilicity and the increased affinity of physostigmine for the central nervous enzyme, doses are sufficient to obtain this effect which almost completely put the peripheral effects of physostigmine into the background.

Eseroline, the physostigmine metabolite, has analgesic effects which cannot be eliminated by naloxone or atropine. Eseroline causes cardiovascular stimulation due to a central effect on the peripheral release of adrenaline from the adrenal gland, which predominates over the peripheral vagal effect, so that a pulse increase is observed instead of bradycardia. After intravenous administration, the effect of physostigmine can be observed after only a few minutes. The antagonizing of anticholinergic effects requires a physostigmine-plasma concentration of 3 to 5 ng /l.

The pronounced effect lasts for approx. 20 minutes and wears off almost completely up to the 30th - 40th minute.

5.b Pharmacokinetics
In animals, the elimination half-life of physostigmine is between 20 and 30 minutes after intravenous administration, in human subjects it is between 18 and 30 minutes. This is in conformity with clinical experience in human subjects, with a pronounced effect for approx. 20 minutes and a wearing-off of the effect starting after the 30th to the 40th minute. In human subjects, clearance is between 1.5 and 5.7 l / min.

5.c Toxicology
Toxicity studies with single administration have shown that the average lethal dose in rats is 1.28 mg/kg bodyweight after intramuscular administration, in rabbits it is 1.57 mg/kg bodyweight. An average lethal dose of 310 µg/kg bodyweight in mice and of 910 µg/kg bodyweight in rabbits has been determined after intravenous administration. Death occurred after unconsciousness and respiratory arrest.

Transient tremor, loss of body weight and decrease of body temperature and the death of 50 % of the test animals have been observed after infusion of 0.24 mg/kg bodyweight/hour over 7 days in guinea pigs. Bacterial tests showed no evidence of mutagenic properties. Further studies with regard to mutagenic potential have not been done. No carcinogenicity studies have been performed.

No reproduction toxicology studies have been performed.

6. Pharmaceutical particulars
6.a List of excipients
2.5 mg sodium metabisulfite (Ph. Eur., equivalent max. 1.7 mg SO_2), sodium edetate (Ph. Eur.), water for injections, nitrogen

6. b Incompatibilities
None known.

6.c Shelf life
Shelf life in undamaged ampoules: 3 years
The infusion solution should be used immediately after preparation.
Do not use the medicinal product after the expiry date stated on the pack.

6.d Special precautions for storage
Do not store above 25°C, store in the outer packaging, protected from light.

6.e Nature and contents of container
5 ml ampoules in packs containing 1 to 5 ampoules.

7. Marketing authorisation holder
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8. Marketing authorisation number
6073341.00.00

9. Date of first authorisation /renewal of the authorisation
28.11.2005

10. Date of revision of the text
January 2011

General classification for supply
Medicinal product subject to medical prescription