1.3.1.1 Package insert

The under-mentioned information with regard to this medicine shall appear on the package insert. The information shall be presented in the format stipulated, provided that the Council may authorize any deviation from such information or such format (Refer to Regulation 9 of the Act).

1. Scheduling status
2. Proprietary name and dosage form
3. Composition
4. Pharmacological classification
5. Pharmacological action (pharmacokinetics, pharmacodynamics and summary of clinical studies, where applicable)
6. Indications
7. Contra-indications
8. Warnings
9. Interactions
10. Pregnancy and lactation
11. Dosage and directions for use
12. Side effects and special precautions
13. Known symptoms of over dosage and particulars of its treatment
14. Identification
15. Presentation
16. Storage instructions
17. Registration number (or reference number)
18. Name and business address of the applicant
19. Date of publication of this package insert

PACKAGE INSERT

SCHEDULING STATUS: S5

PROPRIETARY NAME **ADCO PROPOFOL 2 % (20 ml)**

ADCO PROPOFOL 2 % (50 ml)

ADCO PROPOFOL 2 % (100 ml)

(AND DOSAGE FORM): **Emulsion for infusion**

COMPOSITION:

Every ml contains 20 mg Propofol.

PHARMACOLOGICAL CLASSIFICATION:

A 2.1 Anaesthetics

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Propofol (2,6-diisopropylphenol) is a short acting intravenous anaesthetic agent with a rapid onset of action of approximately 30 seconds. The mechanism of action of Propofol is not clear yet.
Propofol decreases systemic arterial pressure by approximately 30 %, but this effect is due more to peripheral vasodilation than to decreased cardiac output. Following induction of anaesthesia with Propofol, respiration is so depressed that apnoea may occur for 30 seconds; tidal volume, minute volume, and functional residual capacity are all subsequently reduced, as is the respiratory response to carbon dioxide or hypoxia. Cerebral blood flow, cerebral metabolic rate, and intracranial pressure appear to be reduced.

Propofol has an anti-emetic effect.

Pharmacokinetics:

Following a bolus dose or following the termination of an infusion, the kinetics of propofol can be described by a three compartment model: A rapid distribution phase (half-life 2 – 4 minutes), followed by a rapid elimination phase (half-life 30 – 60 minutes) and a slower final phase. The decrease in

blood levels during the final phase is slow because of the slow redistribution of propofol from poorly perfused tissue.

Propofol is extensively distributed in the body. It is mainly metabolised by conjugation in the liver, to form inactive conjugates of propofol and its corresponding quinol (total body clearance 1,5 – 2 litres/minute). The inactive metabolites are excreted mainly by the kidney.

The pharmacokinetics of propofol over the recommended range of infusion rates, are linear.

Significant accumulation of propofol has not been seen under the usual maintenance regimen.

INDICATIONS:

- Induction and maintenance of general anaesthesia as part of a balanced anaesthetic technique.
- Sedation of ventilated adult patients under intensive care for a period of up to 3 days.

CONTRA-INDICATIONS:

Known hypersensitivity to Propofol.

Adco Propofol 2 % should not be used in conjunction with electroconvulsive therapy.

Sedation of children of all ages with serious viral respiratory tract infections, croup or epiglottitis receiving intensive care.

Propofol is not recommended in children younger than 3 years.

Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed to fat embolism and in other conditions where lipid emulsions must be used continuously. Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolism disorders, severe trauma including long-bone and multiple fractures, and sepsis.

WARNINGS:

Respiration will be depressed and must be monitored. Apnoea may be frequent and apnoea lasting longer than 60 seconds has been reported. Special care should be exercised when used together with other respiratory depressants.

Anaphylactic-like reactions may occur following Adco Propofol 2 % administration.

There may be a risk of convulsions when Adco Propofol 2 % is administered to an epileptic patient.

Pregnancy and Lactation: Safety in pregnancy and lactation has not been established. Propofol crosses the placental barrier and is distributed into breast milk. Therefore it should not be used in pregnancy and lactation.
Propofol is not recommended for use in obstetrics, including caesarian section.

In the elderly, debilitated or ASA Grade 3 or 4 patients, rapid single or repeated bolus administration should not be used in order to minimise undesirable cardiorespiratory side-effects.

DOSAGE AND DIRECTIONS FOR USE:

Adco Propofol 2 % may be given by infusion only.
Where analgesia is required, Adco Propofol 2 % should be used in conjunction with supplementary analgesic agents.
Propofol has been used in association with spinal and epidural anaesthesia. It has also been used commonly with premedication, neuromuscular blocking agents, inhalation or analgesic agents; no pharmacological incompatibility has been encountered. Dosage adjustment may be necessary when used together with the above agents, particularly the narcotics (e.g. morphine, meperidine and fentanyl), combinations of opioids and sedatives (e.g. benzodiazepines, droperidol etc.), supplementary analgesic agents (e.g. nitrous oxide or opioids) and the potent inhalation agents (e.g. isoflurane, enflurane and halothane).

When Adco Propofol 2 % is used simultaneously with a regional anaesthetic technique for general anaesthesia, lower doses of Adco Propofol 2 % may be required.

Administration of Adco Propofol 2 % by bolus injection is not recommended.
Equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.
Adco Propofol 2 % must be used undiluted.
It can be used for infusion undiluted from glass infusion bottles or plastic syringes.

Co-administration of Adco Propofol 2 % with either a sodium chloride 0,9 % solution or a glucose 5 % solution, is permitted via a Y-piece connector close to the injection site.

Should Adco Propofol 2 % be administered to patients thought to be at particular risk of fat overload, it is recommended that blood lipid levels be monitored routinely. If the monitoring indicates that fat is being inadequately cleared from the body, administration of Adco Propofol % should be adjusted appropriately. Should the patient be receiving other IV lipid concurrently, a reduction in quantity should be made in order to take into account the amount of lipid infused as part of the Adco Propofol 2 % formulation (1,0 ml of Adco Propofol 2 % contains 0,1 g of fat).

Fluid-volume deficits should be corrected in patients with hypovolaemia, prior to administration of Adco Propofol 2 %.
It is recommended that Adco Propofol 2 % should be titrated against the response of the patient until clinical signs show the onset of anaesthesia.

Induction of General Anaesthesia:
Adults (including Elderly):
Adco Propofol 2 % should be used to induce anaesthesia by infusion and only in those patients who will receive Adco Propofol 2 % for maintenance of anaesthesia.
The dose for most adult patients aged less than 55 years is 1,5 – 2,5 mg/kg body weight (0,075 – 0,125 ml/kg) of Adco Propofol 2 %. Healthy adults require an administration rate of approximately 40 mg per 10 seconds. The total dose required can be reduced by lower rates of administration (20 – 50 mg/minute [1 – 2,5 ml/minute]).
Over the age of 55 years the requirement is 1,0 – 1,5 mg/kg body weight. For patients at increased risk, including elderly patients, an administration rate of 20 mg every 10 seconds may be used.
In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg (1 ml) per 10 seconds).
The dose and rate of administration should be titrated against the response of the patient until clinical signs show the onset of anaesthesia.

Children over 3 years of age:

Most patients over the age of 8 years, require approximately 2,5 mg/kg body weight (0,125 ml/kg) of Adco Propofol 2 % for the induction of general anaesthesia. Children under this age may require a higher dose. Lower dosage is recommended for children of ASA Grades 3 and 4. The dose should also be adjusted according to the child's age and/or mass. Adco Propofol 2 % must be administered slowly until the clinical signs show the onset of anaesthesia.

Maintenance of General Anaesthesia:

Adco Propofol 2 % must be administered by continuous infusion to prevent the clinical signs of light anaesthesia and to maintain the depth of anaesthesia required.

Adults (including Elderly):

Infusion: Administration rates in the region of 4 – 12 mg/kg/hour (0,2 – 0,6 ml/kg/hour) usually maintain satisfactory anaesthesia. The average rate of administration varies between patients. After induction of anaesthesia, slightly higher rates of administration may be required for 10 – 20 minutes.

Children over 3 years of age:

A dose of 9 – 15 mg/kg/hour (0,45 – 0,75 ml/kg/hour) of Adco Propofol 2 % usually achieves satisfactory anaesthesia. The required rate of administration varies considerably between patients.

Sedation during Intensive Care:

Adults (including Elderly):

Ventilated adult patients undergoing intensive care – To provide sedation, it is recommended that Adco Propofol 2 % be given by continuous infusion, for up to 72 hours.

The rate of infusion may be adjusted according to the depth of sedation required.

Generally, satisfactory sedation will be achieved with a dose of 0,3 – 4,0 mg/kg/hour.

Rates above 4,0 mg/kg/hours are not recommended.

Children:

Adco Propofol 2 % is not recommended for sedation in children.

Incompatibilities:

Adco Propofol 2 % should not be mixed prior to administration with injections or infusion fluids. Atracurium and mivacurium (neuromuscular blocking agents) should not be administered through the same intravenous line as Adco Propofol 2 % without prior flushing.

Instructions for use/handling:

General:

Containers should be shaken before use. When 2 layers can be seen after shaking, then the product should not be used. It should also be inspected for particulate matter and discolouration.

Strict aseptic techniques must be maintained when handling Adco Propofol 2 %, as it contains no antimicrobial preservatives and the vehicle can support rapid growth of micro-organisms.

Adco Propofol 2 % must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Adco Propofol 2 % must be administered immediately.

Throughout the infusion period, aseptic technique must be maintained for both Adco Propofol 2 % and infusion equipment.

Addition of infusion fluids to the Adco Propofol 2 %, must be made close to the cannula site, i.e. via a Y-piece connector close to the injection site.

Adco Propofol 2% must not be administered via a microbiological filter.

Any container or syringe containing Adco Propofol 2 % is for single use in a single patient only. Any portion of the contents remaining after first use should be discarded.

General Anaesthesia:

Following established guidelines for other lipid emulsions, a single infusion of Adco Propofol 2 % must not exceed 6 hours.

At the end of the surgical procedure, or at 6 hours, whichever is the sooner, the syringe or giving set and any unused portion of Adco Propofol 2 % or solution containing Adco Propofol 2 % must be discarded, and replaced as appropriate.

Intensive Care Sedation:

Adco Propofol 2 % must be administered immediately and administration must be completed within 12 hours once the vial has been spiked. The administration set and any unused portion of Adco Propofol 2 % must be discarded after 12 hours.

The handling procedure described above for General Anaesthesia should be followed if Adco Propofol 2 % is transferred to a syringe or other container prior to administration. The product should be discarded and administration lines changed after 6 hours.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

Local: During the induction phase of Adco Propofol 2 % anaesthesia, the local pain experienced, can be minimised by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis may occur less frequently.

The general side-effects include excitation, involuntary movement, hiccup, flushing and hypertension. Apnoea and hypotension may occur during induction and maintenance of anaesthesia.

Hypotension may require use of IV fluids and a reduction of the rate of administration of Adco Propofol 2 % during the period of anaesthetic maintenance.

Side-effects noted less frequently, are tachycardia, premature ventricular contractions, premature atrial contractions, syncope, abnormal ECG, and ST segment depression.

At induction of anaesthesia, during maintenance of anaesthesia and during recovery, epileptiform movements, including convulsions and opisthotonos have been reported.

Nausea, vomiting and headache may occur during the recovery phase. Sexual disinhibition has also been reported.

Rhabdomyolysis has been reported when doses greater than 4 mg/kg/hour have been administered for ICU sedation.

There have also been reports of post-operative fever and pulmonary oedema. Following prolonged administration of propofol, discolouration of urine has been reported.

Special Precautions:

Adco Propofol 2 % should be administered only by a doctor trained in the field of anaesthesia and/or intensive care.

Facilities for maintenance of an open and unobstructed airway, artificial ventilation and oxygen enrichment and other resuscitative facilities should be readily available at all times. Patients should be constantly monitored.

Adco Propofol 2 % should not be administered by the person conducting the diagnostic or surgical procedure.

Full recovery from general anaesthesia should be confirmed prior to discharge. The use of propofol may very rarely be associated with the development of a period of post-operative unconsciousness. This may be accompanied by an increase in muscle tone and may or may not be preceded by a period of wakefulness. Appropriate care should be provided to an unconscious patient, even though recovery is spontaneous.

Patients should be advised that skills such as driving and operating machinery may be impaired for some time after general anaesthesia.

Adco Propofol 2 % should be administered with caution to patients with cardiac, respiratory, renal or hepatic impairment, or in hypovolaemic or debilitated patients. The pharmacokinetic effects of propofol may be prolonged in patients with chronic hepatic cirrhosis or chronic renal impairment and as a result, recovery time may double. The effects on the pharmacokinetics of propofol in patients with acute hepatic or renal failure have not been studied.

Adco Propofol 2 % should be administered with caution to patients with hypovolaemia, epilepsy, lipid metabolism disorders and the elderly.

When Adco Propofol 2 % is used to provide continuous sedation for ventilated adult patients under intensive care, account should be taken of increasing the patients’ lipid load. If the duration of sedation is longer than 3 days, lipid concentrations should be monitored.

When used in patients with raised intracranial pressure, it should be administered slowly to avoid a substantial decrease in mean arterial pressure, and a resultant decrease in cerebral perfusion pressure.

Propofol lacks vagolytic activity and has been associated with reports of bradycardia, occasionally profound, and asystole. Premedication intravenously with an anticholinergic before induction or during maintenance of anaesthesia may be advisable, especially where vagal tone is likely to predominate or when Adco Propofol 2 % is used in conjunction with other agents likely to cause bradycardia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See “Side-Effects and Special Precautions”. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patients head, and, if severe, use of plasma expanders and pressor agents.

IDENTIFICATION:

White, homogeneous emulsion.

PRESENTATION:

Packs of 1, 5 or 10 clear glass ampoules containing 20 ml emulsion.

Packs of 1, 5 or 10 clear glass vials containing 50 ml emulsion.

Packs of 1, 5 or 10 clear glass vials containing 100 ml emulsion.

STORAGE INSTRUCTIONS:

Store between 4 ºC and 25 ºC; protected from light.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

Adco Propofol 2 % (20 ml): 37/2.1/0247

Adco Propofol 2 % (50 ml): 37/2.1/0248

Adco Propofol 2 % (100 ml): 37/2.1/0249

NAME AND BUSINESS ADDRESS OF APPLICANT:

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