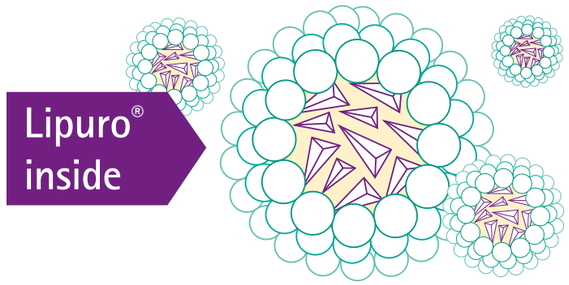
B BRAUN
SHARING EXPERTISE

Lipuro®-Technology

Good tolerability through MCT/LCT combination

Lipuro®-Technology

The B. Braun Lipuro®-Technology uses mid- and long-chain triglycerides (MCT/LCT) as a carrier solution, to improve the receptibility of lipophilic drugs that are hard to dissolve in water. Thereby, it can improve the product characteristics of such drugs.



The MCT/LCT fat emulsion shows clinically relevant advantages while no negative effect on the pharmacological properties of the dissolved drug substance appears.[1,2,3,4]

Drugs with Lipuro®-Technology
Propofol-Lipuro®/Etomidate-Lipuro®/Diazepam-Lipuro®

Reduced pain on injection

The Lipuro®-Technology evidently reduces the pain on injection, which may result from injection of Propofol[5,6,7] and Etomidate[8].

Better vein tolerability

Through use of the Lipuro®-Technology, the osmolarity of e.g., Etomidate can be reduced, which leads to a reduction in hemolysis.[9] Etomidate Lipuro® is also shown to reduced irritation of the veins and thereby can reduce the risk of consequential damages such as thrombophlebitis compared to the original formulation with propylene glycol.[4,8]

The Lipuro®-Technology – for the good of the patient

- MCT/LCT fat emulsion as carrier solution – the original Lipuro®-Technology.
- Through Lipuro®-Technology, there is less free, lipophilic and low-water soluble drug substance that can cause pain on injection compared to products dissolved in water, e.g., for Propofol.[10]
- Better vein tolerability for Etomidate.[4]
- Less pain on injection for Propofol[5,6,7] and Etomidate.[8]

REFERENCES

1. Doenicke AW, Roizen MF, Rau J, et al. Pharmacokinetics and pharmacodynamics of propofol in a new solvent. Anesth Analg 1997;85:1399–403.
2. Shafer SL. Advances in propofol pharmacokinetics and pharmacodynamics. J Clin Anesth 1993;5(Suppl 1):14S-21S.
3. Suttmann H, Doenicke A, Kugler J, Laub M. Eine neue Zubereitung von Etomidat in Lipidemulsion--Bioverfügbarkeit und Venenreizung [A new formulation of etomidate in lipid emulsion--bioavailability and venous provocation]. Anaesthesist. 1989 Aug;38(8):421-3.
4. Doenicke A, Kugler A, Vollmann N, Suttmann H, Taeger K. Etomidat mit einem neuen Lösungsvermittler. Klinisch-experimentelle Untersuchungen zur Venenverträglichkeit und Bioverfügbarkeit [Etomidate using a new solubilizer. Experimental clinical studies on venous tolerance and bioavailability]. Anaesthesist. 1990 Oct;39(10):475-80.
5. Larsen B. et al. Less pain on injection by a new formulation of propofol? A comparison with propofol LCT. Anaesthetist 2001; 50(11):842-5.
6. Rau J et al. Propofol in an emulsion of long- and medium chain triglycerides: The Effect on pain. Anesth Analg 2001; 93:382-4.
7. Soltesz S et al.: Effect of a 0.5 % Dilution of Propofol on Pain on Injection during Induction of Anesthesia in Children. Anesthesiology 2007; 106:80-4.
8. Altmayer P, Grundmann U, Ziehmer M, Larsen R. Vergleichende Wirksamkeits- und Verträglichkeitsuntersuchung einer neuen galenischen Zubereitung von Etomidat. Anasthesiol Intensivmed Notfallmed Schmerzther 1993; 28(7):415–9.
9. Doenicke A, Roizen MF, Hoernecke R, Mayer M, Ostwald P, Foss J. Haemolysis after etomidate: Comparison of propylene glycol and lipid formulations. Br J Anaesth 1997; 79(3):386–8.
10. Yamakage M, Iwasaki S, Satoh JI, Namiki A. Changes in concentrations of free propofol by modification of the solution. Anesth Analg. 2005 Aug;101(2):385-388.

Product Information

Propofol-®Lipuro 5 mg/ml emulsion for injection or infusion
Propofol-®Lipuro 10 mg/ml emulsion for injection or infusion
Propofol-®Lipuro 20 mg/ml emulsion for injection or infusion

COMPOSITION
The emulsion for injection or infusion contains:

1 ml	Propofol 5 mg/ml	Propofol 10 mg/ml	Propofol 20 mg/ml
in 1 ampoule of 10 ml	-	100 mg propofol	-
in 1 ampoule or vial of 20 ml	100 mg propofol	200 mg propofol	-
in 1 vial of 50 ml	-	500 mg propofol	1,000 mg propofol
in 1 vial or of 100 ml	-	1,000 mg propofol	-

Excipients with known effect:
1 ml of emulsion for injection or infusion contains Soya-bean oil (refined) 50 mg

Excipients:
Soya-bean oil (refined), medium-chain triglycerides, glycerol, egg phospholipids for injection, sodium oleate, water for injections.

THERAPEUTIC INDICATIONS
Propofol-®Lipuro is a short-acting intravenous general anaesthetic indicated for

Indication
Induction of general anaesthesia
Propofol 5 mg/ml: adults and children > 1 month
Propofol 10 mg/ml: adults and children > 1 month
Propofol 20 mg/ml: adults and children > 3 years

Maintenance of general anaesthesia
Propofol 5 mg/ml: -
Propofol 10 mg/ml: adults and children > 1 month
Propofol 20 mg/ml: adults and children > 3 years

Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia
Propofol 5 mg/ml: in adults only[1]
Propofol 10 mg/ml: adults and children > 1 month
Propofol 20 mg/ml: adults and children > 3 years

Induction of sedation for diagnostic and surgical procedures
Propofol 5 mg/ml: adults and children > 1 month
Propofol 10 mg/ml: -
Propofol 20 mg/ml: -

Sedation of ventilated patients in the intensive care unit
Propofol 5 mg/ml: -
Propofol 10 mg/ml: > 16 years of age
Propofol 20 mg/ml: > 16 years of age

[1] only short term sedation

CONTRAINDICATIONS
Hypersensitivity to the active substance, soya, peanut or to any of the excipients listed.
Propofol-®Lipuro 5 mg/ml is contraindicated for maintenance of general anaesthesia; for maintenance of sedation for diagnostic and surgical procedures in children; for sedation for intensive care. Safety and efficacy for these indications have not been demonstrated.
Propofol-®Lipuro 10 mg/ml and 20 mg/ml must not be used in patients of 16 years of age or younger for sedation for intensive care. Safety and efficacy for these age groups have not been demonstrated.

UNDESIRABLE EFFECTS
Induction and maintenance of anaesthesia or sedation with propofol is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic/sedative agent, such as hypotension. The nature, severity and incidence of adverse events observed in patients receiving propofol may be related to the condition of the recipients and the operative or therapeutic procedures being undertaken.

Undesirable effects are listed according to their frequencies as follows:

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)

System organ class

Immune system disorders
Very rare: Anaphylaxis up to anaphylactic shock – may include angioedema, bronchospasm, erythema and hypotension

Metabolism and Nutritional disorder
Not known (9): Metabolic acidosis (5), hyperkalaemia (5), hyperlipidaemia (5)

Psychiatric disorders
Very rare: Sexual disinhibition
Not known (9): Euphoric mood, drug abuse and drug dependence (8)

Nervous system disorders
Common: Headache during recovery phase
Rare: Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
Very rare: Postoperative unconsciousness
Not known (9): Involuntary movements

Cardiac disorders
Common: Bradycardia (1)
Very rare: Pulmonary oedema
Not known (9): Cardiac arrhythmia (5), cardiac failure (5), (7)

Vascular disorders
Common: Hypotension (2)

Respiratory, thoracic and mediastinal disorders
Common: Transient apnoea during induction
Not known (9): Respiratory depression (dose-dependent)

Gastrointestinal disorders
Common: Nausea and vomiting during recovery phase
Very rare: Pancreatitis

Hepatobiliary disorders
Not known (9): Hepatomegaly (5)

Musculoskeletal and connective tissue disorders
Not known (9): Rhabdomyolysis (3), (5)

Reproductive system and breast disorders
Not known (9): Priapism

Renal and urinary disorders
Very rare: Discolouration of urine following prolonged administration
Not known (9): Renal failure (5)

General disorders and administration site conditions
Very common: Local pain on induction (4)
Uncommon: Injection site thrombosis and injection site phlebitis
Very rare: Tissue necrosis (10) following accidental extravascular administration (11)
Not known (9): Local pain, swelling, and inflammation following accidental extravascular administration (11)

Investigations
Not known (9): Brugada type ECG (5), (6)

Injury, poisoning and procedural complications
Very rare: Postoperative fever

(1) Serious bradycardias are rare. There have been isolated reports of progression to asystole.
(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of propofol.
(3) Very rare reports of rhabdomyolysis have been received where propofol has been given at doses greater than 4 mg/kg/hr for ICU sedation.
(4) May be minimised by using the larger veins of the forearm and antecubital fossa.
With Propofol-®Lipuro local pain can also be minimised by the co-administration of lidocaine.
(5) Combinations of these events, reported as "Propofol infusion syndrome", may be seen in seriously ill patients who often have multiple risk factors for the development of the events.
(6) Brugada-type ECG - elevated ST-segment and coved T-wave in ECG.
(7) Rapidly progressive cardiac failure (in some cases with fatal outcome) in adults. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.
(8) Abuse of and drug dependence on propofol, predominantly by health care professionals.
(9) Not known as it cannot be estimated from the available clinical trial data.
(10) Necrosis has been reported where tissue viability has been impaired.
(11) Treatment is symptomatic and may include immobilisation and, if possible, elevation of affected limb, cooling, close observation, consultation of surgeon if necessary.

WARNINGS
Keep out of the sight and reach of children.

MARKETING AUTHORIZATION HOLDER
B. Braun Melsungen AG, 34212 Melsungen, Germany

Last revision: 03/2022

Prescription only

Not all products are registered and approved for sale in all countries or regions. Indications of use may also vary by country and region.

Please contact your country representative for product availability and information.

Etomidate-®Lipuro 2 mg/ml Emulsion for injection

COMPOSITION
The emulsion for injection contains:

1 ml	2 mg etomidate
in 1 ampoule of 10 ml	20 mg etomidate

Excipients with known effect:
Each 10 ml ampoule (10 ml) contains 1.0 g Soya-bean oil, refined and 0.23 mg Sodium (as sodium oleate).

Excipients:
Soya-bean oil, refined, medium-chain triglycerides, glycerol, egg lecithin, sodium oleate, water for injection.

THERAPEUTIC INDICATIONS
Etomidate-Lipuro 2 mg/ml is indicated for the induction of general anaesthesia in adults, infants and toddlers older than 6 months, children and adolescents.

CONTRAINDICATIONS
Hypersensitivity to etomidate, soya, peanut or to any of the excipients listed.

Neonates and infants up to the age of 6 months should be excluded from treatment with Etomidate-Lipuro 2 mg/ml except for imperative indications during in-patient treatment.

UNDESIRABLE EFFECTS
Like most general anaesthetics, etomidate may affect respiratory and vascular functions.

Like some other general anaesthetics, etomidate may cause involuntary muscle movements.

Besides this, etomidate frequently affects adrenocortical functions.

Undesirable effects are listed according to their frequencies as follows:

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)

System organ class

Immune system disorders
Not known: Hypersensitivity* (such as anaphylactic shock, anaphylactic reaction, anaphylactoid reaction)

Endocrine Disorders
Very common: Cortisol decreased
Not known: Adrenal insufficiency

Nervous system disorders
Very common: Dyskinesia
Common: Myoclonus
Uncommon: Hypertonia, muscle contractions involuntary, nystagmus, shivering
Not known: Convulsion (including grand mal convulsion)

Cardiac disorders
Uncommon: Bradycardia, extrasystoles, ventricular extrasystoles
Not known: Cardiac arrest, atrioventricular block complete

Vascular disorders
Common: Hypotension
Uncommon: Hypertension
Not known: Shock

Respiratory, thoracic and mediastinal disorders
Common: Apnoea**, hyperventilation, stridor
Uncommon: Hypoventilation, hiccups, cough
Rare: Laryngo-spasm
Not known: Respiratory depression**, bronchospasm (including fatal outcome)

Gastrointestinal disorders
Common: Vomiting, nausea
Uncommon: Salivary hypersecretion

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Erythema
Not known: Stevens-Johnson syndrome, Urticaria

Musculoskeletal and Connective Tissue Disorders
Uncommon: Muscle rigidity
Not known: Trismus

General Disorders and Administration Site Conditions
Uncommon: Injection site pain

Injury, Poisoning and Procedural Complications
Uncommon: Anaesthetic complication, delayed recovery from anaesthesia, inadequate analgesia, procedural nausea

* After administration of etomidate, release of histamine has been noted. Etomidate-®Lipuro 2 mg/ml contains soya-bean oil, which may very rarely cause severe allergic reactions.

** Respiratory depression and apnoea may occur especially after administration of higher doses of etomidate in combination with central depressant drugs. In patients of 55 years of age or older, respiratory depression and apnoea may occur especially after doses exceeding the recommended maximum dose of 0.2 mg of etomidate per kg body weight.

WARNINGS
Keep out of the sight and reach of children.
Contains no antimicrobial preservatives.
For single use only. Discard unused contents.

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Prescription only

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Product Information

Diazepam-®Lipuro 5 mg/ml emulsion for injection

COMPOSITION
The emulsion for injection contains:

1 ml	5 mg diazepam
in 1 ampoule of 2 ml	10 mg diazepam

Excipients with known effect:
Each 2 ml ampoule contains 200 mg Soya-bean oil, refined and 0.06 mg Sodium.

Excipients:
Soya-bean oil, refined, medium-chain triglycerides, glycerol, egg lecithin, sodium oleate, water for injections.

THERAPEUTIC INDICATIONS
Preparation (premedication) for operations and diagnostic procedures, (e.g. endoscopy) and postoperative medication, immediate treatment of acute tension, excitement, anxiety, restlessness, status epilepticus, tetanus, states of increased muscle tension.

CONTRAINDICATIONS
Hypersensitivity to the active substance, other benzodiazepines, soya, peanut or to any of the excipients, drug dependence, *myasthenia gravis*, severe respiratory insufficiency, sleep apnoea syndrome, severe liver insufficiency, acute alcohol, sedative, analgesic and psychotropic drug intoxication (neuroleptic drugs, antidepressants, lithium).

UNDESIRABLE EFFECTS
The most frequently observed undesirable effects of diazepam are related to its pharmacological effects. Intensity and frequency are dependent on the individual sensitivity of the patient as well as dose-dependent and occur especially at the beginning of therapy. Side effects can mostly be avoided or reduced by careful and individual adaptation of the daily dose and respectively decrease in the course of therapy.

Most common side effect is drowsiness.

Undesirable effects are listed according to their frequencies as follows:

Common:	(≥ 1/100 to < 1/10)
Rare:	(≥ 1/10,000 to < 1/1,000)
Not known:	(cannot be estimated from the available data)

System organ class

Metabolism and nutritional disorders
Rare: Increased appetite

Psychiatric disorders
Common: Stronger sedation than desired over the day, confusion, and anterograde amnesia
Rare: Depressed mood, depression, aggravation of pre-existing depressive disease. If this occurs, the diazepam dose must be reduced for subsequent administrations. Decrease of libido.
Not known: Drug dependence see "Information on particular undesirable effects" below.

Nervous system disorders
Common: Fatigue, (including somnolence, sedation, hypoaesthesia, lengthened reaction times), vertigo, ataxia headache. A "hangover" effect after evening administration of diazepam, i.e., residual sedation, can affect reactivity on the following day
Not known: After high doses dysarthria, more frequent after prolonged administration

Eye disorders
Not known: Vision blurred, (diplopia, nystagmus), more frequent after prolonged administration and/or high doses

Cardiac disorders
Rare: Bradycardia, arrhythmia, cardiac failure*, cardiac arrest*

Vascular disorders
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Rare: Laryngospasm; depression of respiration*. The respiratory depressant effect can be more pronounced in the presence of airway obstruction or preexisting cerebral damage. It can generally be avoided by a careful adjustment of the dose for each individual, especially if other medicaments acting on the central nervous system are taken concomitantly.

Gastrointestinal disorders
Rare: Nausea, vomiting, epigastric discomfort, constipation, diarrhoea, dry mouth
Not known: Increased salivation

Hepatobiliary disorders
Rare: Jaundice

Skin and subcutaneous tissue disorders
Rare: Allergic skin reactions (pruritus, urticaria, flush)

Musculoskeletal and connective tissue disorders
Common: Muscle weakness

Renal and urinary disorders
Rare: Urinary retention
Not known: Incontinence

Reproductive system and breast disorders
Rare: In women: Dysmenorrhoea

General disorders and administration site conditions
Rare: I.m. injections: Irritation and pain at the injection site
Not known: Risk of falling, paradoxical drug reaction, drug tolerance, drug withdrawal syndrome see "Information on particular undesirable effects" below.

Investigations
Not known: Increased transaminases and alkalic phosphatase

**During rapid i.v. administration the cardiovascular and respiratory functions may be affected which could lead to a drop in blood pressure, cardiac arrest and respiratory arrest. In particular for children, cardiovascular instable and elderly patients, supportive measures for cardiovascular and respiratory functions should be available. Injection into a vein that is too small could cause irritation of the vein wall (also thrombophlebitis).*

Information on particular undesirable effects

PARADOXICAL REACTIONS
Patients may experience "paradoxical" reactions such as acute excitement instead of sedation, anxiety, insomnia, outbursts of temper, increased incidence of muscle cramps, or suicidal tendencies. If such reactions occur, treatment with diazepam should be stopped.

WITHDRAWAL SYMPTOMS
Especially following continued daily treatment it is possible that stopping diazepam may produce sleep disturbances and increased dreaming after 2 – 4 days. Anxiety, tension, excitement or internal restlessness may reappear at a higher degree. Symptoms of withdrawal may include trembling and sweating, and proceed to dangerous somatic and psychic reactions such as convulsions and symptomatic psychoses (e.g. withdrawal delirium).

DEPENDENCE, TOLERANCE
Tolerance towards Diazepam-®Lipuro may develop during longer lasting or repeated use of this drug.
Diazepam-®Lipuro contains soya-bean oil, which rarely may cause allergic reactions.

WARNINGS
Keep out of the sight and reach of children.
Contains soya-bean oil.

MARKETING AUTHORIZATION HOLDER
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Germany

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