1. NAME OF THE MEDICINAL PRODUCT

Primovist 0.25 mmol/ml, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.25 mmol gadoxetate disodium (equivalent to 181.43mg gadoxetate disodium) as active ingredient.

Excipient: Each ml contains 0.511 mmol (equivalent to 11.7mg) of sodium (see section "Special warnings and precautions of use").

For full list of excipients, see section "List of excipients".

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to pale yellow solution.

The physico-chemical properties of Primovist listed below are:

Osmolality at 37 °C (mOsm/kg H_2O)	688
Viscosity at 37 °C (mPa·s)	1.19
pH	6.8 – 8.0

4. CLINICAL PARTICULARS

4.1 Indication

Primovist is indicated for use in adults for the enhancement of magnetic resonance imaging (MRI) of focal liver lesions.

4.2 Dosage and method of administration

4.2.1 Method of administration

This medicinal product is for intravenous administration.

The dose is administered undiluted as a bolus injection. After the injection of the contrast medium the intravenous cannula/line should be flushed using physiological saline solution.

After bolus injection of Primovist, dynamic imaging during arterial, portovenous, and equilibrium phases utilizes the different temporal enhancement pattern of different liver lesion types to obtain information about their classification (benign/malignant) and the specific characterization. It further improves visualization of hypervascular liver lesions.

The delayed (hepatocyte) phase starts at about 10 minutes post injection (in confirmatory studies most of the data were obtained at 20 minutes post injection) with an imaging window lasting at least 120 minutes. The imaging window is reduced to 60 minutes in patients requiring hemodialysis and in patients with elevated bilirubin values (> 3 mg/dl) (see also section “Interaction with other medicinal products and other forms of interaction”).

The enhancement of liver parenchyma during the hepatocyte phase assists in the identification of the number, segmental distribution, visualization, and delineation of liver lesions, thus improving lesion detection. The different enhancement/ washout patterns of liver lesions contribute to the information from the dynamic phase.

Hepatic excretion of Primovist results in enhancement of biliary structures.

The usual safety rules for magnetic resonance imaging must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants.

For additional instructions see section “Instructions for use/handling”.

4.2.2 Dosage regimen

Adults:
0.1 ml per kg body weight Primovist (equivalent to 25 µmol per kg body weight)

4.2.3 Additional information on special populations

4.2.3.1 Pediatric population
Primovist is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

4.2.3.2 Elderly population (aged 65 years and above)
No dosage adjustment is necessary. In clinical studies, no overall differences in safety or efficacy were observed between elderly (aged 65 years and above) and younger patients, and other reported clinical experience has not identified differences between the elderly and younger patients (see also section “Pharmacokinetic properties”).

4.2.3.3 Patients with hepatic impairment
No dosage adjustment is necessary. In clinical studies, no overall differences in safety or efficacy were observed between patients with and without hepatic impairment, and other reported clinical experience has not identified differences in patients with hepatic impairment and healthy subjects (see also section “Pharmacokinetic properties”).

4.2.3.4 Patients with renal impairment
In clinical studies, no overall differences in safety and efficacy were observed between patients with renal impairment and patients with normal kidney function. The elimination of gadoxetate disodium is prolonged in renally impaired patients. To ensure diagnostically useful images, no dosage adjustment is recommended (see also section “Special warnings and precautions for use” and section “Pharmacokinetic properties”).

4.3 Contraindications

None

4.4 Special warnings and precautions for use

• Hypersensitivity

Particularly careful risk-benefit assessment is required in patients with known hypersensitivity to Primovist.

As with other intravenous contrast agents, Primovist can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions characterized by cardiovascular, respiratory and cutaneous manifestations, and ranging to severe reactions including shock.

The risk of hypersensitivity reactions is higher in case of:

- Previous reaction to contrast media
- History of bronchial asthma
- History of allergic disorders.

In patients with an allergic disposition the decision to use Primovist must be made after particularly careful evaluation of the risk-benefit ratio.

Most of these reactions occur within half an hour of administration. Therefore, post-procedure observation of the patient is recommended.

Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

If hypersensitivity reactions occur, injection of the contrast medium must be discontinued immediately. It is advisable to use a flexible indwelling cannula for intravenous contrast medium administration in order to give instant specific therapy – if necessary. To permit immediate countermeasures to be taken in emergencies, appropriate drugs, an endotracheal tube and a respirator should be ready at hand.

Delayed reactions after hours up to several days have been rarely observed (see section “Undesirable effects”).

Patients taking beta-blockers who experience such reactions may be resistant to treatment with beta agonists.

- Cardiovascular disease

Caution should be exercised when Primovist is administered to patients with severe cardiovascular problems because only limited data are available so far.

- Severe renal failure

In healthy subjects, gadoxetate disodium is equally eliminated via renal and hepatobiliary routes.

Prior to administration of Primovist, it is recommended, that all patients are screened for renal dysfunction by obtaining a history and/or laboratory tests.

In patients with severely impaired renal function, the benefits must be weighed carefully against the risks, since contrast medium elimination is delayed in such cases. A sufficient period of time for elimination of the contrast agent from the body prior to any re-administration in patients with renal impairment should be ensured.

Gadoxetate disodium can be removed from the body by hemodialysis. About 30% of the administered dose is eliminated from the body by a single dialysis session of 3 hours starting 1 hour post injection. In end-stage renal failure patients, gadoxetate disodium was almost completely eliminated via dialysis and biliary excretion within the observation period of 6 days, the majority within 3 days.

There have been reports of nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy (NFD) associated with the use of some contrast agents containing gadolinium in patients with

- acute or chronic severe renal impairment (GFR<30ml/min/1.73m^2).
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

As there is a possibility that NSF/NFD may occur with Primovist ®, it should only be used in these patients if the benefits outweigh the risks (see section “Undesirable effects”).

There is no robust evidence to suggest that haemodialysis can prevent or treat the development of NSF but haemodialysis shortly after Primovist ® administration in patients currently recently receiving haemodialysis may be useful at removing Primovist ® from the body. There is no evidence to support the initiation of hemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

- Local intolerance

Intramuscular administration must be strictly avoided, because it may cause local intolerance reactions including focal necrosis (see section “Preclinical safety data”).

- QT prolongation

In some *in vitro* and preclinical studies, there was evidence that administration of Primovist at doses significantly higher than recommended can lead to QTc prolongation. ECGs were regularly monitored during clinical studies and transient QT prolongation was observed in some patients without any associated adverse clinical events. 2 of 468 patients (0.4%) in 2 Phase III studies had an increase in QTc of > 60 ms from baseline to time-points up to 20-28 hours after injection; no control group was studied. (QTc was calculated with the Fridericia formula. The baseline value was calculated as the mean QTc from two ECGs recorded before Primovist was given). Given these observations, appropriate caution should be exercised when using Primovist, particularly in patients with known risk factors for arrhythmias associated with QT prolongation (e.g. underlying QT prolongation or use of other drugs that may prolong the QT interval).

- Accumulation of gadolinium in the brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of gadolinium-based contrast agents (GBCAs). Increased signal intensity on non-contrast T1- weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown. In order to minimise potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

4.5 Interaction with other medicinal products and other forms of interaction

- Interference with OATP inhibitors

Animal studies demonstrated that compounds belonging to the class of anionic medicinal products, e.g. rifampicin, block the hepatic uptake of Primovist thus reducing the hepatic contrast effect. In this case, the expected benefit of an injection of Primovist might be limited. No other interactions with other medicinal products are known from animal studies.

An interaction study in healthy subjects demonstrated that the co-administration of the OATP inhibitor erythromycin did not influence efficacy and pharmacokinetics of Primovist. No further clinical interaction studies with other medicinal products have been performed.

• Interference from elevated bilirubin or ferritin levels in patients

Elevated levels of bilirubin (>3mg/dl) or ferritin can reduce the hepatic contrast effect of Primovist. If primovist is used in these patients, complete the magnetic resonance imaging no later than 60 minutes after Primovist administration (see section “Pharmacokinetic properties”).

• Interference with diagnostic tests

Serum iron determination using complexometric methods (e.g. Ferrocine complexation method) may result in falsely high or low values for up to 24 hours after the examination with Primovist because of the free complexing agent caloxetate trisodium contained in the contrast medium solution.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women.

Animal studies at clinically relevant doses have not shown reproductive toxicity afer repeated administration (see section “Preclinical safety data”).

The potential risk for humans is unknown.

Primovist should only be used during pregnancy if the clinical condition of the woman requires the use of gadoxetate disodium.

4.6.2 Lactation

It is unknown whether gadoxetate disodium is excreted in human milk. There is evidence from non-clinical data that gadoxetate is excreted into breast milk in very small amounts (less than 0.5% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (about 0.4% of the dose orally administered were excreted in the urine).

At clinical doses, no effects on the infant are anticipated. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Primovist should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive or use machines

Not known.

4. 8 Undesirable Effects

4.8.1 Summary of the safety profile

The overall safety profile of Primovist is based on data from more than 1,900 patients in clinical trials, and from post-marketing surveillance.

The most frequently observed adverse drug reactions (≥ 0.5 %) in patients receiving Primovist are nausea, headache, feeling hot, blood pressure increased and dizziness.

The most serious adverse drug reaction in patients receiving Primovis is anaphylactoid shock.

Delayed allergoid reactions (hours later up to several days) have been rarely observed.

Most of the undesirable effects were of mild to moderate intensity.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions observed with Primovist are represented in the table below. They are classified according to System Organ Class (MedDRA version 12.1). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under ‘not known’.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Primovist

System Organ Class (MedDRA)	**Common** **≥ 1/100**	**Uncommon** **< 1/100, ≥ 1/1,000**	**Rare** **< 1/1,000**	**Not known**
Immune system disorders				Hypersensitivity /anaphylactoid reaction (e.g. shock*, hypotension, pharyngolaryngeal edema, urticaria, face edema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor)
Nervous system disorders	Headache	Vertigo, Dizziness, Dysgeusia, Paresthesia, Parosmia	Tremor, Akathisia	Restlessness
Cardiac disorders			Bundle branch block, Palpitation	Tachycardia
Vascular disorders		Blood pressure increased, Flushing		
Respiratory, thoracic and mediastinal disorders		Respiratory disorders (Dyspnea*, Respiratory distress)		
Gastrointestinal disorders	Nausea	Vomiting, Dry mouth	Oral discomfort, Salivary hypersecretion	
Skin and subcutaneous tissue disorders		Rash, Pruritus**	Maculopapular rash, Hyperhidrosis	

System Organ Class (MedDRA)	Common ≥ 1/100	Uncommon < 1/100, ≥ 1/1,000	Rare < 1/1,000	Not known
Musculoskeletal, connective tissue and bone disorders		Back pain		
General disorders and administration site conditions		Chest pain, Injection site reaction***, Feeling hot, Chills, Fatigue, Feeling abnormal	Discomfort, Malaise	

* Life-threatening and/or fatal cases have been reported. These reports originated from post-marketing experience.
** Pruritus (Generalized pruritus, Eye pruritus).
*** Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, Injection site burning, Injection site coldness, Injection site irritation, Injection site pain.

4.8.3 Description of selected adverse reactions

Cases of nephrogenic systemic fibrosis (NSF) have been reported with some contrast agents containing gadolinium (see also “Special warnings and precautions for use”).

Slightly elevated serum iron and serum bilirubin values have been observed in less than 1% of patients after administration of Primovist. However, the values did not exceed more than 2-3 times the baseline values and returned to their initial values without any symptoms within 1 to 4 days.

4.9 Overdose

Single doses of gadoxetate disodium as high as 0.4 ml/kg (100 µmol/kg) body weight were tolerated well. In a limited number of patients, a dose of 2.0 ml/kg (500 µmol/kg) body weight was tested in clinical trials, more frequent occurrences of adverse events but no new undesirable effects were found in these patients.

In view of the low volume and the extremely low gastrointestinal absorption rate of Primovist, and based on acute toxicity data, intoxication due to inadvertent oral ingestion of the contrast medium is extremely improbable. There have been no cases of overdose observed or reported in clinical use. Therefore, the signs and symptoms of overdosage have not been characterized.

- Patients with renal and/or hepatic impairment

In case of inadvertent overdosage in patients with severely impaired renal and/or hepatic function, Primovist can be removed from the body by hemodialysis (see section 'Special warnings and precautions for use' and 'Pharmacokinetic properties'). However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

- Mechanism of action

Primovist is a paramagnetic contrast agent for magnetic resonance imaging.

The contrast-enhancing effect is mediated by gadoxetate, an ionic complex consisting of gadolinium (III) and the ligand ethoxybenzyl-diethylenetriamine-pentaacetic acid (EOB-DPTA). When T_1-weighted scanning sequences are used in proton magnetic resonance imaging, the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

The current evidence suggests that gadolinium may accumulate in the brain after repeated administration of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.

- Pharmacodynamic effects

Gadoxetate disodium leads to a distinct shortening of the relaxation times even at low concentrations. At pH 7, a magnetic field strength of 0.47 T and 40°C the relaxivity (r_1) - determined from the influence on the spin-lattice relaxation time (T_1) of protons in plasma - is about 8.18 l/(mmol·sec) and the relaxivity (r_2) - determined from the influence on the spin-spin relaxation time (T_2)- is about 8.56 l/(mmol·sec). At 1.5 T and 37°C the respective relaxivities in plasma are r_1 = 6.9 l/(mmol·sec) and r_2 = 8.7 l/(mmol·sec). The relaxivity displays a slight inverse dependency on the strength of the magnetic field.

Ethoxybenzyl-diethylenetriaminepentaacetate forms a stable complex with the paramagnetic gadolinium ion with extremely high in-vivo and in-vitro stability (thermodynamic stability constant: log K_{Gdl} = 23.46). Gadoxetate disodium is a highly water-soluble, hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.011.

Due to its lipophilic ethoxybenzyl moiety gadoxetate disodium exhibits a biphasic mode of action: first, distribution in the extracellular space after bolus injection and subsequently selective uptake by hepatocytes. The relaxivity r_1 in liver tissue is 16.6 l/(mmol·sec) (at 0.47T) resulting in increased signal intensity of liver tissue. Subsequently gadoxetate disodium is excreted into the bile.

The substance does not display any significant inhibitory interaction with enzymes at clinically relevant concentrations.

5.2 Pharmacokinetic properties

- General Introduction

Gadoxetate disodium behaves in the organism like other highly hydrophilic biologically inert, renally and hepatobiliary excreted compounds.

- Absorption and Distribution

After intravenous administration, the plasma concentration time profile of gadoxetate disodium is characterized by a bi-exponential decline. The total distribution volume of gadoxetate disodium at steady state is about 0.21 l/kg (extracellular space). The plasma protein binding is less than 10%.

The compound diffuses through the placental barrier only to a small extent as demonstrated in rats.

In lactating rats, less than 0.5% of the intravenously administered dose (0.1 mmol/kg) of radioactively labeled gadoxetate was excreted into the breast milk. Absorption after oral administration was very small in rats with 0.4%.

- Metabolism

Gadoxetate disodium is not metabolised.

- Elimination

Gadoxetate disodium is completely excreted in equal amounts via the renal and hepatobiliary routes.

Seven days after intravenous injection of gadoxetate, less than 1% of the dose administered was found in the bodies of rats and monkeys. Of this, the highest concentration was found in kidney and liver.

The mean terminal elimination half–life of gadoxetate disodium (dose 0.01 to 0.1 mmol/kg) observed in healthy subjects was about 1 hour.

The total serum clearance (CL) was 250 ml/min. The renal clearance (CL_R) corresponds to about 120 ml/min, a value similar to the glomerular filtration rate in healthy subjects.

- Linearity/ non-linearity

Gadoxetate disodium shows linear pharmacokinetics i.e. pharmacokinetic parameters change dose proportionally (e.g. C_{max}, AUC) or are dose independent (e.g. V_{ss}, $t_{1/2}$), up to a dose of 100 µmol/kg body weight (0.4 ml/kg).

- Characteristics in special patient populations

A phase III study with 25 µmol per kg body weight Primovist compared subjects with various levels of impaired hepatic function, impaired renal function, coexistent hepatic and renal impairment, and healthy subjects of different age groups, including elderly.

- Gender

Total clearance was about 20% lower in female (185 ml/min) than in male subjects (236 ml/min).

- Elderly population (aged 65 years and above)

In accordance with the physiological changes in renal function with age, the plasma clearance of gadoxetate disodium was reduced from 210 ml/min in non-elderly subjects to 163 ml/min in elderly subjects aged 65 years and above. Terminal half-life and systemic exposure were higher in the elderly (2.3 h and 197 µmol*h/l, respectively) compared to the control group (1.8 h and 160 µmol*h/l, respectively). The renal excretion was complete after 24 h in all subjects with no difference between elderly and non-elderly healthy subjects.

- Renal and/or hepatic impairment

In patients with moderate renal impairment, an increase in AUC to 237 µmol*h/l and of terminal half-life to 2.2 h was observed. In patients with end-stage renal failure, the AUC was increased to about 903 µmol*h/l and the terminal half-life prolonged to about 20 h in patients. About 55% of the administered dose was recovered in feces within the observation period of 6 days, the majority within 3 days.

In patients with mild or moderate hepatic impairment, a slight to moderate increase in plasma AUC, half-life and urinary excretion, as well as a decrease in hepatobiliary excretion were observed in comparison to healthy subjects.

In patients with severe hepatic impairment, especially in patients with abnormally high serum bilirubin levels (> 3 mg/dl), the AUC was increased to 259 µmol*h/l compared to 160 µmol*h/l in the control group. The elimination half-life was increased to 2.6 h compared to 1.8 h in the control group. The hepatobiliary excretion substantially decreased to 5.7% of the administered dose in these patients.

Gadoxetate disodium can be removed from the body by hemodialysis. About 30 % of the administered dose were recovered in the dialysate in a 3 hour dialysis starting 1 hour post injection. In the study with end-stage renal failure patients, gadoxetate disodium was almost completely eliminated via dialysis and biliary excretion within 6 days. Plasma concentrations of gadoxetate disodium were measurable up to 72 hours post-dose in these patients (see section “Special warnings and precautions for use”).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of systemic toxicity, genotoxicity, contact-sensitizing potential.

- Genotoxic potential, tumorigenicity

Studies into genotoxic effects (gene-, chromosomal- and genome mutation tests) with Primovist in vivo and in vitro indicated no mutagenic potential.

Studies for the evaluation of the tumorigenic potential of Primovist were not performed. This was not considered necessary since Primovist showed no genotoxic properties and no toxic effect on fast growing tissues. In addition, Primovist will usually be administered only once to an individual patient for diagnostic purposes.

- Reproduction toxicology

Repeated intravenous dosing of Primovist in studies on embryofetal development caused embryotoxicity (increased post implantational loss) in rabbits at 25.9 times (based on body surface area) or 80 times (based on body weight) the human single dose.

- Local tolerance

Experimental local tolerance studies with Primovist indicated good local tolerability after intravascular (intravenous and intraarterial) and paravenous administration.

However, intramuscular administration caused local intolerance reactions, and must therefore be strictly avoided in humans (see section “Special warnings and precautions for use”).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caloxetate trisodium
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Trometamol
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life and Storage Conditions

Please refer to labels

- Shelf life after first opening of the container

Primovist should be used immediately after opening.

6.4 Special precautions for storage

Primovist should be stored below 30ºC.

6.5 Instructions for use/handling

Visual Inspection
The medicinal product should be visually inspected before use.
Primovist should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

Vials
This medicinal product is a ready-to-use solution for single use only. Vials containing contrast media are not intended for the withdrawal of multiple doses.
Primovist should only be drawn into the syringe immediately before use.
The rubber stopper should never be pierced more than once.
Any contrast medium solution not used in one examination must be discarded.

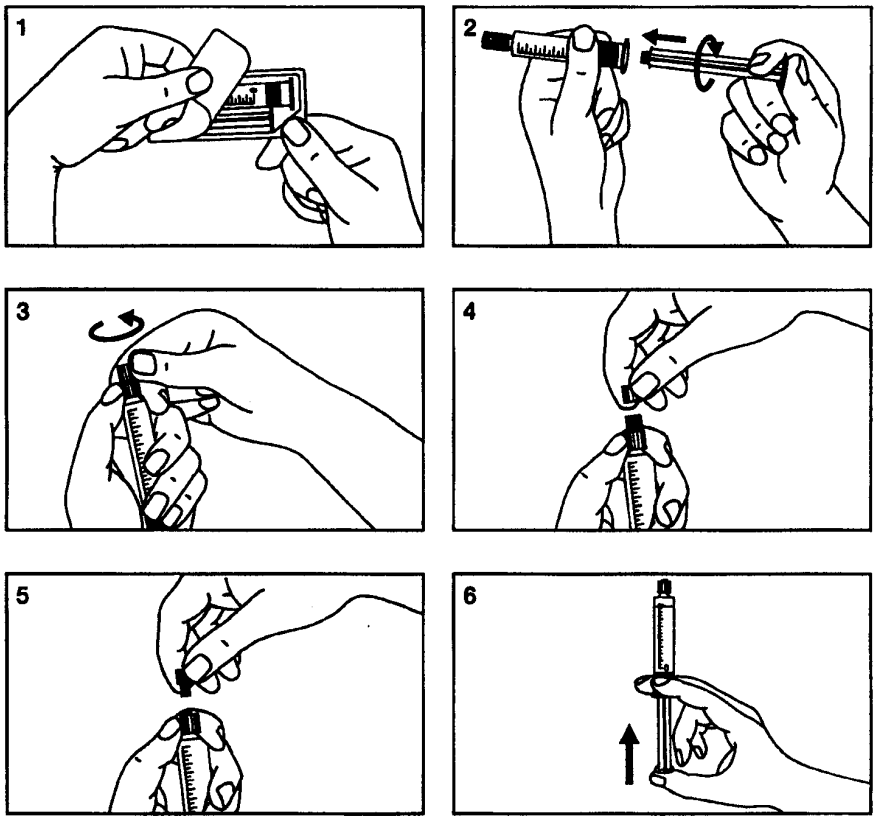
Prefilled syringes
The prefilled syringe must be taken from the pack and prepared for the injection immediately before the examination.
Any contrast medium not used in one examination is to be discarded.

PRESENTATION

1 x 10 ml (in 10 ml glass prefilled syringe)
1 x 10ml (in 10ml plastic prefilled syringe)
Injection vials of 1 x 10 ml

Not all presentations may be marketed.

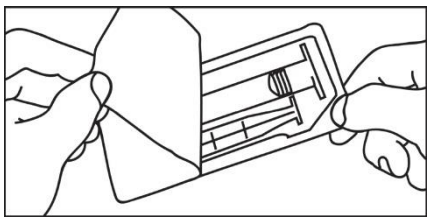
Glass syringe only:



1. Open the package
2. Screw the plunger on the syringe
3. Break the protective cover
4. Remove the protective cover
5. Remove the rubber stopper
6. Remove the air in the syringe

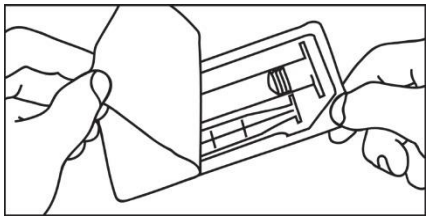
Plastic syringe only:

HAND INJECTION

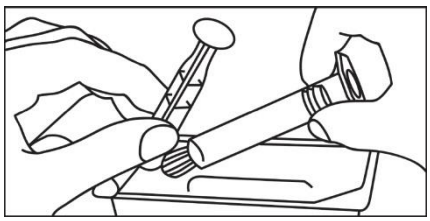


1. Open the package

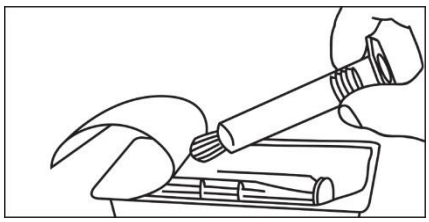
INJECTION WITH A POWER INJECTOR



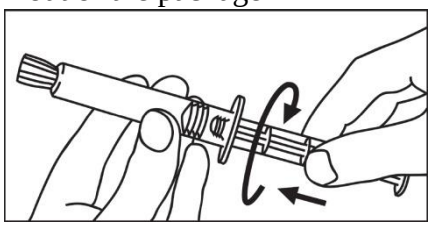
1. Open the package



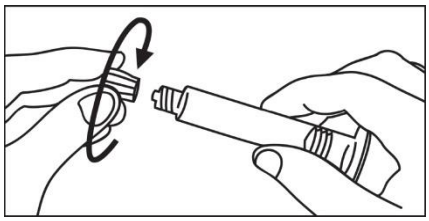
2. Take syringe and plunger rod out of the package



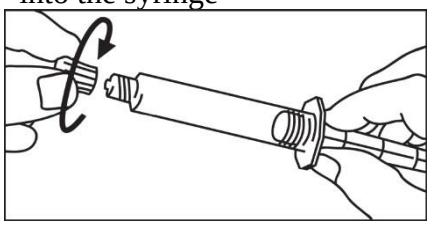
2. Take syringe out of the package



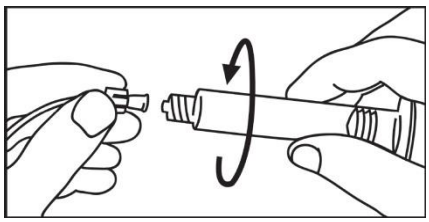
3. Turn clock-wise the plunger rod into the syringe



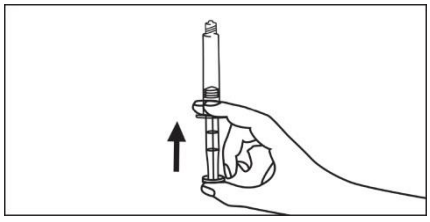
3. Open the cap with a twist



4.Open the cap with a twist



4. Connect the tip of the syringe to the tubing system clock-wise and go on according to the instructions of the device manufacturer



5. Remove the air in the syringe

Manufactured by
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

Date of Revision of Package Insert
03 Nov 2020