Gadovist®

(gadobutrol)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gadovist 1.0 mmol/ml solution for injection in prefilled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 604.72 mg gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

1 prefilled syringe with 7.5 ml contains 4535.4 mg gadobutrol.

Excipient with known effect:

1 ml contains 0.00056 mmol (equivalent to 0.013 mg) of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in prefilled syringe

Clear, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. Gadovist is indicated in adults and children of all ages (including term neonates) for:

- Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).
- Contrast-enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.
- Contrast enhancement in magnetic resonance angiography (CE-MRA).

Gadovist can also be used for MR imaging of pathologies of the whole body. It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.

Gadovist should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

4.2 Posology and method of administration

Gadovist should only be administered by healthcare professionals experienced in the field of clinical MRI practice.

Method of administration

This medicinal product is for intravenous administration only.

The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination).

Optimal signal enhancement is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of Gadovist for CNS indications (time depending on type of lesion/tissue).

T_1 - weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time (see section 4.4).

Instructions for use:

This product is intended for single use only.

This medicinal product should be visually inspected before use.

Gadovist should not be used in case of severe discolouration, the occurrence of particulate matter or a defective container.

Prefilled syringes

The prefilled syringe must be taken from the pack and prepared for the injection immediately before the administration.

The tip cap should be removed from the prefilled syringe immediately before use.

Cartridges

Administration of contrast media should be performed by qualified personnel with the appropriate procedures and equipment. Sterile technique must be used in all injections involving contrast media.

The contrast medium must be administered by means of a MEDRAD Spectris® type injector.

Instructions of the device manufacturer must be followed.

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Adults

CNS indications

The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.

If a strong clinical suspicion of a lesion persists despite an unremarkable MRI or when more accurate information might influence therapy of the patient, a further injection of up to 0.2 ml/kg BW within 30 minutes of the first injection may be performed.

A dose of 0.075 mmol gadobutrol per kg body weight (equivalent to 0.075 ml Gadovist per kg body weight) may be administered at minimum for imaging of the CNS (see section 5.1).

Whole-body MRI (except MRA)

In general, the administration of 0.1 ml Gadovist per kg body weight is sufficient to answer the clinical question.

CE-MRA

Imaging of 1 field of view (FOV): 7.5 ml for body weight below 75 kg; 10 ml for body weight of 75 kg and higher (corresponding to 0.1-0.15 mmol/kg BW).

Imaging of >1 field of view (FOV): 15 ml for body weight below 75 kg; 20 ml for body weight of 75 kg and higher (corresponding to 0.2-0.3 mmol/kg BW).

Special populations

Renal impairment

Gadovist should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast-enhanced MRI (see section 4.4). If it is necessary to use Gadovist, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadovist injections should not be repeated unless the interval between injections is at least 7 days.

Paediatric population

For children of all ages (including term neonates) the recommended dose is 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) for all indications (see section 4.1).

Neonates up to 4 weeks of age and infants up to 1 year of age

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadovist should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadovist injections should not be repeated unless the interval between injections is at least 7 days.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

While injecting Gadovist into veins with a small lumen there is the possibility of adverse effects such as reddening and swelling.

The usual safety requirements for magnetic resonance imaging, especially the exclusion of ferromagnetic materials, also apply when using Gadovist.

Hypersensitivity reactions

As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock. In general, patients with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions.

The risk of hypersensitivity reactions may be 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 Gadovist 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 (see section 4.2).

Delayed reactions (after hours up to several days) have been rarely observed (see section 4.8).

Impaired renal function

Prior to administration of Gadovist, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73 m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group.

As there is a possibility that NSF may occur with Gadovist, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast-enhanced magnetic resonance imaging (MRI).

Haemodialysis shortly after Gadovist administration may be useful at removing Gadovist from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadovist should only be used in these patients after careful consideration.

Elderly

As the renal clearance of gadobutrol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Seizure disorders

Like with other gadolinium-containing contrast agents special precaution is necessary in patients with a low threshold for seizures.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount given to a 70 kg person), i.e. essentially 'sodium-free'. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of gadobutrol in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3).

Gadovist should not be used during pregnancy unless the clinical condition of the woman requires use of gadobutrol.

Breast-feeding

Gadolinium-containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing of breast-feeding for a period of 24 hours after administration of Gadovist should be at the discretion of the doctor and lactating mother.

Fertility

Animal studies do not indicate impairment of fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The overall safety profile of Gadovist is based on data from more than 6,300 patients in clinical trials and from post-marketing surveillance.

The most frequently observed adverse drug reactions (≥0.5%) in patients receiving Gadovist are headache, nausea and dizziness.

The most serious adverse drug reactions in patients receiving Gadovist are cardiac arrest and severe anaphylactoid reactions (including respiratory arrest and anaphylactic shock).

Delayed anaphylactoid reactions (hours later up to several days) have been rarely observed (see section 4.4).

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

The adverse drug reactions observed with Gadovist are represented in the table below. They are classified according to system organ class (MedDRA). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies.

Frequency groupings are defined according to the following convention: common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000. 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 Gadovist

	Frequency			
System organ class	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders		Hypersensitivity/ anaphylactoid reaction*# (e.g. anaphylactoid shock§*, circulatory collapse§*, respiratory arrest§*, pulmonary oedema§*, bronchospasm§, cyanosis§, oropharyngeal swelling§*, laryngeal oedema§, hypotension*, blood pressure increased§, chest pain§, urticaria, face oedema, angioedema§, conjunctivitis§, eyelid oedema, flushing, hyperhidrosis§, cough§, sneezing§, burning sensation§, pallor§)		
Nervous system disorders	Headache	Dizziness, dysgeusia, paresthesia	Loss of consciousness*, convulsion, parosmia	
Cardiac disorders			Tachycardia, palpitations	Cardiac arrest*
Respiratory, thoracic and mediastinal disorders		Dyspnoea*		
Gastrointestinal disorders	Nausea	Vomiting	Dry mouth	
Skin and subcutaneous tissue disorders		Erythema, pruritus (including generalised pruritus), rash (including generalised, macular, papular, pruritic rash)		Nephrogenic systemic fibrosis (NSF)
General disorders and administration site conditions		Injection site reaction⁰, feeling hot	Malaise, feeling cold	

* There have been reports of life-threatening and/or fatal outcomes from this ADR.

\# None of the individual symptoms ADRs listed under hypersensitivity/ anaphylactoid reactions identified in clinical trials reached a frequency greater than 'rare' (except for urticarial).

§ Hypersensitivity/anaphylactoid reactions identified only during post-marketing surveillance (frequency not known)

⁰ Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, injection site haematoma

Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with Gadovist (see section 4.4).

Fluctuations of renal function parameters including increases of serum creatinine have been observed after administration of Gadovist.

Paediatric population

Based on two single-dose phase I/III studies in 138 subjects aged 2-17 years and 44 subjects aged 0-<2 years (see section 5.1), the frequency, type and severity of adverse reactions in children of all ages (including term neonates) are consistent with the adverse drug reaction profile known in adults.

This has been confirmed in a phase IV study including more than 1,100 paediatric patients and post-marketing surveillance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

To report any side effect(s):

Egypt:

Egyptian Pharmaceutical Vigilance Centre
Hotline: 15301
Email: pv.followup@edaegypt.gov.eg
Website: www.edaegypt.gov.eg

United Arab Emirates (UAE):

Pharmacovigilance & Medical Device section
Tel: 80011111 / +971 42301000
Email: pv@mohap.gov.ae
Website: www.mohap.gov.ae
P.O.Box 1853 Dubai

Kuwait:

Drug &Food Control, Ministry of Health
Tel.: +965-24811532
Fax: +965-24811507
Email : Adr_reporting@moh.gov.kw
Website: http://eservices.moh.gov.kw/SPCMS/DrugCmp.aspx

Other Countries:

Please contact the relevant competent authority

4.9 Overdose

The maximum daily single dose tested in humans is 1.5 mmol gadobutrol/kg body weight.

No signs of intoxication from an overdose have so far been reported during clinical use.

In case of inadvertent overdosage, cardiovascular monitoring (including ECG) and control of renal function is recommended as a measure of precaution.

In case of overdose in patients with renal insufficiency, Gadovist can be removed by haemodialysis. After 3 haemodialysis sessions approx. 98% of the agent are removed from the body. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paramagnetic contrast media,
ATC code: V08C A09

Mechanism of action

The contrast-enhancing effect is mediated by gadobutrol, the non-ionic complex consisting of gadolinium (III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

Pharmacodynamic effects

The relaxivity of gadobutrol, measured in vitro in human blood/plasma at physiological conditions and at clinical relevant field strengths (1.5 and 3.0 T), is in the range of 3.47 – 4.97 L/mmol/sec.

In clinical doses, the pronounced relaxivity of gadobutrol leads to a shortening of the relaxation times of protons in tissue water.

The stability of the gadobutrol complex has been studied in vitro at physiological conditions (in native human serum, at pH 7.4 and 37°C) over the time period of 15 days. The amounts of released gadolinium ions from gadobutrol were below the limit of quantification of 0.1mol% of total gadolinium demonstrating the high complex stability of gadobutrol under the tested conditions.

Clinical efficacy

In a pivotal phase III liver study average sensitivity in combined pre- and post-contrast MRI for Gadovist-treated patients was 79% and specificity was 81% for lesion detection and classification of suspected malignant liver lesions (patient-based analysis).

In a pivotal phase III kidney study average sensitivity was 91% (patient-based analysis) and 85% (lesion-based analysis) for classification of malignant and benign renal lesions. Average specificity in a patient-based analysis was 52% and in a lesion-based analysis 82%.

The increase of sensitivity from pre-contrast to combined pre- and post-contrast MRI for Gadovist-treated patients was 33% in the liver study (patient-based analysis) and 18% in the kidney study (patient-based analysis as well as lesion-based analysis). The increase in specificity from pre-contrast to combined pre- and post-contrast MRI was 9% in the liver study (patient-based analysis) while there was no increase in specificity in the kidney study (patient-based analysis as well as lesion-based analysis).

All results are average results obtained in blinded reader studies.

In a study designed as an intra-individual, crossover comparison, Gadovist was compared to gadoterate meglumine (both at 0.1 mmol/kg) in the visualization of cerebral neoplastic enhancing lesions in 132 patients.

The primary efficacy endpoint was the overall preference for either Gadovist or gadoterate meglumine by the median blinded reader. Superiority of Gadovist was demonstrated by a p-value of 0.0004. In detail, a preference of Gadovist was given for 42 patients (32%) compared to an overall preference for gadoterate meglumine for 16 patients (12%). For 74 patients (56%) no preference for one or the other contrast agent was given. For the secondary variables lesion-to-brain ratio was found to be statistically significantly higher for Gadovist ($p < 0.0003$). Percent of enhancement was higher with Gadovist compared to gadoterate meglumine, with a statistical significant difference for the blinded reader ($p < 0.0003$).

Contrast-to-noise ratio, showed a higher mean value following Gadovist (129) compared to gadoterate meglumine (98). The difference was not statistically significant.

In a study designed as an intra-individual, crossover comparison, gadobutrol at a reduced dose of 0.075 mmol/kg was compared to gadoterate meglumine at its standard dose of 0.1 mmol/kg for contrast enhanced MRI of the CNS in 141 patients with enhancing CNS lesions on gadoterate meglumine enhanced MRI. The primary variables included lesion contrast enhancement, lesion morphology, and lesion border delineation. Images were analysed by three independent blinded readers. Noninferiority to gadoterate meglumine for the degree of improvement over unenhanced imaging was demonstrated for all three primary variables (at least 80% of effect retained) based on the average reader. The mean number of lesions detected by gadobutrol (2.14) and gadoterate (2.06) were similar.

Paediatric population

Two single-dose phase I/III studies in 138 paediatric subjects scheduled for CE-MRI of CNS, liver and kidneys or CE-MRA and in 44 subjects aged 0-<2 years (including term neonates) scheduled to undergo routine CE-MRI of any body region have been performed. Diagnostic efficacy and an increase in diagnostic confidence was demonstrated for all parameters evaluated in the studies and there was no difference among the paediatric age groups and when compared to adults. Gadovist was well tolerated in these studies with the same safety profile of gadobutrol as in adults.

Clinical safety

The type and frequency of adverse reactions following the administration of Gadovist in various indications was evaluated in a large international prospective non-interventional trial (GARDIAN). The safety population encompassed 23,708 patients of all age groups including children (n = 1,142; 4.8%) and elderly (n = 4,330; 18.3% between the ages of 65 and < 80 and n = 526; 2.2% of ≥ 80 years of age). Median age was 51.9 years.

Two hundred and two patients (0.9 %) reported overall 251 adverse events (AEs), and 170 (0.7%) reported 215 events categorized as adverse drug reactions (ADRs), majority (97.7%) of which were mild or moderate in intensity.

Most commonly documented ADRs were nausea (0.3 %), vomiting (0.1 %) and dizziness (0.1 %). ADR rates were 0.9 % in females and 0.6 % in males. There were no differences in ADR rates according to the dose of gadobutrol. Four of the 170 patients with ADRs (0.02 %) experienced a serious adverse event, with one event (Anaphylactic shock) leading to fatal outcome.

In the pediatric population AEs were reported in 8 of the 1,142 (0.7%) children. In six children these AEs were classified as ADRs (0.5%).

Renal impairment

In a prospective pharmacoepidemiologic study (GRIP) to assess the magnitude of potential risk for development of NS in renally impaired patients, 908 patients with varying degrees of renal impairment received Gadovist at the standard approved dose for CE-MRI.

All patients, including 234 with severe renal impairment (eGFR <30 mL/min/1.73 m^2) who had not received other GBCAs were followed over the course of two years for signs and symptoms of NSF. No patient enrolled in the study developed NSF.

5.2 Pharmacokinetic properties

Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extra cellular space. Plasma protein binding is negligible. The pharmacokinetics of gadobutrol in humans are dose-proportional. After doses up to 0.4 mmol gadobutrol/kg body weight, the plasma level declines in a biphasic manner. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 0.59 mmol gadobutrol/l plasma was measured 2 minutes after the injection and 0.3 mmol gadobutrol/l plasma 60 minutes post-injection.

Biotransformation

No metabolites are detected in plasma or urine.

Elimination

Within two hours more than 50% and within 12 hours more than 90% of the given dose is eliminated via urine with a mean terminal half-life of 1.8 hours (1.3 - 2.1 hours), corresponding to the renal elimination rate. At a dose of 0.1 mmol gadobutrol/kg BW, an average of 100.3 ± 2.6% of the dose was excreted within 72 h after administration. In healthy persons renal clearance of gadobutrol is 1.1 to 1.7 ml min^{-1} kg^{-1} and thus comparable to the renal clearance of inulin, pointing to the fact that gadobutrol is eliminated primarily by glomerular filtration. Less than 0.1% of the dose is eliminated via faeces.

Characteristics in special patient populations

Paediatric population

Pharmacokinetics of gadobutrol in paediatric population aged < 18 years and in adults are similar (see section 4.2).

Two single-dose phase I/III studies in paediatric patients < 18 years have been performed.

The pharmacokinetics were evaluated in 130 paediatric patients aged 2 - < 18 years and in 43 paediatric patients <2 years of age (including term neonates).

It was shown that the pharmacokinetic (PK) profile of gadobutrol in children of all ages is similar to that in adults resulting in similar values for area under the curve (AUC), body weight normalised plasma clearance (CL_{tot}) and volume of distribution (V_{ss}), as well as elimination half-life and excretion rate.

Approximately 99% (median value) of the dose was recovered in urine within 6 hours (this information was derived from the 2 to < 18 year old age group).

Elderly (aged 65 years and above)

Due to physiological changes in renal function with age, in elderly healthy volunteers (aged 65 years and above) systemic exposure was increased by approximately 33% (men) and 54% (women) and terminal half-life by approximately 33% (men) and 58% (women). The plasma clearance is reduced by approximately 25% (men) and 35% (women) respectively. The recovery of the administered dose in urine was complete after 24 h in all volunteers and there was no difference between elderly and non-elderly healthy volunteers.

Renal impairment

In patients with impaired renal function, the serum half-life of gadobutrol is prolonged due to the reduced glomerular filtration. The mean terminal half-life was prolonged to 5.8 hours in moderately impaired patients (80 >CL_{CR} > 30 ml/min) and further prolonged to 17.6 hours in severely impaired patients not on dialysis (CL_{CR}<30 ml/min). The mean serum clearance was reduced to 0.49 ml/min/kg in mild to moderately impaired patients (80>CL_{CR} >30 ml/min) and to 0.16 ml/min/kg in severely impaired patients not on dialysis (CL_{CR}<30 ml/min). Complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function about 80% of the administered dose was recovered in the urine within 5 days (see also sections 4.2 and 4.4).

In patients requiring dialysis, gadobutrol was almost completely removed from serum after the third dialysis.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

Repeated intravenous treatment in reproductive toxicology studies caused a retardation of embryonal development in rats and rabbits and an increase in embryolethality in rats, rabbits and monkeys at dose levels being 8 to 16 times (based on body surface area) or 25 to 50 times (based on body weight) above the diagnostic dose in humans. It is not known whether these effects can also be induced by a single administration. Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in children of all ages including term neonates and infants.

Radioactively labelled gadobutrol administered intravenously to lactating rats was transferred to the neonates via milk at less than 0.1% of the administered dose.

In rats, absorption after oral administration was found to be very small and amounted to about 5% based on the fraction of the dose excreted in urine.

In preclinical cardiovascular safety pharmacology studies, depending on the dose administered, transient increases in blood pressure and myocardial contractility were observed. These effects have not been observed in humans.

Environmental studies have shown that persistence and mobility of GBCAs indicate a potential for distribution in the water column and possibly into groundwater.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcobutrol sodium
Trometamol
Hydrochloric acid 1N (pH-adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

Shelf life after first opening of the container:

Any solution for injection not used in one examination must be discarded. Chemical, physical and microbiological in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass syringes:

One 10-ml prefilled syringe (type I glass) with a plunger stopper (chlorobutyl elastomer) and a tip cap (chlorobutyl elastomer) contains 7.5 ml solution for injection.

Pack sizes of:

1 and 5 prefilled syringes
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any contrast medium solution not used in one examination must be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The peel-off tracking label on the pre-filled syringes/cartridges should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
Kaiser-Wilhelm-Allee 1
51368 Leverkusen, Germany.

MANUFACTURER

Bayer AG
Mullerstrasse 178
13353 Berlin, Germany.

8. DATE OF REVISION OF THE TEXT

July 2022

9. PRESCRIPTION/PHARMACY STATUS

Available on prescription only

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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