SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

Bayer (Pty) Ltd	**Date of revision of text: 19 December 2021 (storage conditions)**

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORM:

MAGNEVIST 5 ml
MAGNEVIST 10 ml
MAGNEVIST 15 ml
MAGNEVIST 20 ml
MAGNEVIST 30 ml
MAGNEVIST 100 ml

Solution

COMPOSITION:

Each ml contains 0,5 mmol gadopentetate dimeglumine (equivalent to 469,01 mg gadopentetate dimeglumine).

Excipients: meglumine, pentetic acid, water for injection.

Osmolality at 37 °C (osm/kg H_2O)	1,96
Viscosity (mPa.s or cP)	
at 20 °C	4,9
at 37 °C	2,9
pH	7,0-7,9

PHARMACOLOGICAL CLASSIFICATION:

A 28 Contrast media

PHARMACOLOGICAL ACTION:

Mechanism of action:

MAGNEVIST is a paramagnetic contrast medium for use in magnetic resonance imaging (MRI). When T_1-weighted scanning sequences are used in proton magnetic resonance imaging, the gadopentetate-induced shortening of the spin-lattice relaxation time (T_1) of excited water protons leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

Pharmacodynamic effects:

Gadopentetate is a highly paramagnetic compound which leads to distinct shortening of the relaxation times. The paramagnetic efficacy at a magnetic field strength of 1,5 T and at 37 °C, the relaxivity (r_1) – determined from the influence on the T_1 relaxation time of the water protons in plasma and the relaxivity (r_2) – determined from the influence on the T_2 relaxation time – is about 4,1 ± 0,2 l/(mmol sec) and 4,6 ± 0,8 l/(mmol sec), respectively. The relaxivities display only a slight dependency on the strength of the magnetic field.

Diethylene triamine pentaacetic acid (DTPA) forms a complex with the paramagnetic gadolinium ion with high *in vivo* and *in vitro* stability (thermodynamic stability constant: log K_{GdL} = 22 to 23). Gadopentetate dimeglumine is a highly water-soluble, hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7,6 of about 0,0001. The substance does not display significant inhibitory interaction with enzymes e.g. acetylcholinesterase and lysozyme at clinically relevant concentrations. Gadopentetate does not activate the complement system.

At higher concentrations and on prolonged incubation, gadopentetate dimeglumine has a slight *in vitro* effect on erythrocyte morphology. After intravenous administration of MAGNEVIST in man, the reversible process could lead to weak intravascular haemolysis, which might explain the slight increase in serum bilirubin and iron occasionally observed in the first few hours after injection.

Pharmacokinetic properties:

Gadopentetate behaves in the organism like other highly hydrophilic biologically inert compounds (e.g. mannitol or inulin).

Absorption and distribution:

After intravenous administration of MAGNEVIST, plasma levels decline rapidly bi-exponentially with a terminal half-life of about 90 minutes.

Gadopentetate is rapidly distributed in the extracellular space.

The total distribution volume of gadopentetate is about 0,26 l per kg. Protein binding is negligible.

In studies in rats and dogs, relatively high concentrations of the intact gadolinium complex were found in the kidneys amounting to about 0,15 % of administered dose seven days after intravenous administration of radioactively labelled gadopentetate.

Less than 1 % of the administered dose was found in the remaining parts of the body of both.

Gadopentetate penetrates and passes neither an intact blood-brain nor the blood-testis barrier. The small amount which overcomes the placental barrier is quickly eliminated by the foetus.

Metabolism:

Gadopentetate is not metabolised.

Elimination:

Gadopentetate is eliminated in unchanged form via the kidneys by glomerular filtration. The fraction eliminated extra-renally is less than 1 % of the administered dose. An average of 83 % of the dose was eliminated within 6 hours post injection. About 91 % of the dose was recovered in the urine within the first 24 hours. The renal clearance of gadopentetate was about 120 ml/min/1,73 m^2 and is therefore comparable to substances that are exclusively excreted by glomerular filtration that of inulin or Cr-EDTA.

Characteristics in special populations:

- Elderly population (aged 65 years and above)

In accordance with the physiological changes in renal function with age, the systemic exposure and terminal half-life were increased from 3,3 mmol·h/l to 4,7 mmol·h/l and from 1,8 hours to 2,2 hours, respectively, in elderly healthy subjects (males aged 65 years and above) compared to non-elderly healthy subjects (males age range 18 to 57 years). Total clearance was reduced from 117 ml/min in non-elderly subjects to 89 ml/min in elderly subjects.

- Gender

The pharmacokinetics of gadopentetate in non-elderly healthy male and female subjects (aged 18 to 57 years) were similar.

- Hepatic impairment

In line with the almost exclusive renal elimination pathway, pharmacokinetics of gadopentetate were not altered in patients with hepatic impairment (as studied in patients with Child-Pugh B) as compared to healthy matched subjects. Data on patients with severe hepatic impairment (Child-Pugh C) are not available.

- Renal impairment

In patients with impaired renal function; the serum half-life of gadopentetate is prolonged due to the reduced glomerular filtration rate.

After administration of a single intravenous dose to 10 patients with impaired renal function (4 patients with mild renal impairment [creatinine clearance ≥ 60 to < 90 ml/min] and 6 patients with moderate renal impairment [creatinine clearance ≥ 30 to < 60 ml/min]), mean half-lives were 2,6 ± 1,2 hours and 4,2 ± 2,0 hours for the mildly and moderately impaired patients, respectively, as compared to 1,6 ± 0,13 hours in healthy subjects. In patients with severe renal impairment (creatinine clearance < 30 ml/min) but not on dialysis, mean half-life further increased to 10,8 ± 6,9 hours.

Gadopentetate is completely renally excreted within two days in patients with slightly to moderately impaired renal function (creatinine clearance > 30 ml/min). In patients with severe renal impairment, 73,3 ±16,1 % of the administered dose was recovered in the urine within two days.

In patients with renal impairment gadopentetate could be eliminated by means of hemodialysis. In a clinical study patient with renal impairment received a dose of 0,1 mmol per kg gadopentetate dimeglumine. The patients underwent a 3-hour dialysis session per day on three consecutive days. The plasma concentration of gadopentetate decreased by 70 % with each dialysis session. After the last session, the plasma concentration was less than 5 % of the original value.

Paediatric population:

In a study with pediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalized clearance and distribution volume and terminal half-life) of gadopentetate were similar to adults.

INDICATIONS:

For diagnostic use only.

Cranial and spinal magnetic resonance imaging:

In particular for the demonstration of tumours and for further differential-diagnostic clarification in suspected meningioma (acoustic) neurinoma, invasive tumours (e.g. glioma) and metastases; for the demonstration of small and/or isointense tumours; in suspected recurrence after surgery or radiotherapy; for the differentiated demonstration of rare neoplasms such as haemangioblastomas, ependymomas and small pituitary adenomas; for improved determination of the spread of tumours not of cerebral origin.

Additionally, in spinal MRI: differentiation of intra- and extramedullary tumours; demonstration of solid tumour areas in known syrinx; determination of intramedullary tumour spread.

Whole body MRI:

Including the facial skull, the neck region, the thoracic space including the heart and abdominal space, the female breast, the pelvis and the active and passive musculoskeletal system, and imaging of vessels throughout the body.

In particular, MAGNEVIST permits diagnostic information:
- for the demonstration or exclusion of tumours, inflammation and vascular lesions;
- for determination of the spread and demarcation of these lesions;
- for the differentiation of the internal structure of lesions;
- for assessment of the circulatory situation of normal and pathologically changed tissues;
- for the differentiation of tumour and scar tissue after therapy;
- for the recognition of recurrent prolapse of a disk after surgery;
- for the semi-quantitative evaluation of the renal function combined with anatomical organ diagnosis.

CONTRA-INDICATIONS:

The use of MAGNEVIST is contra-indicated in patients with severe renal impairment (GFR < 30 ml/min/1,73 m^2).

Safety in pregnancy and lactation has not been established (see “Pregnancy and lactation”).

WARNINGS:

Fatal reactions have been associated with the administration of water-soluble contrast media, such as MAGNEVIST. It is therefore of the utmost importance that a course of action be carefully planned in advance for the treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction during and for at least 30 to 60 minutes after administration of MAGNEVIST. Patients with known or suspected hypersensitivity to iodated contrast media should be closely observed.

Hypersensitivity:

Particularly careful risk/benefit judgement (assessment) is required in patients with known hypersensitivity to MAGNEVIST.

Allergy-like hypersensitivity reactions ranging to severe reactions including shock are possible (see “Side effects and special precautions”). Most of these reactions occur within at least half an hour of administration (see “Special precautions”).

In patients with an allergic disposition, premedication with antihistamines and/or glucocorticoids may be considered.

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

There have been reports of nephrogenic systemic fibrosis (NSF) (i.e. increased formation of connective tissue in the skin, which then becomes thickened, coarse and hard, which may lead to contractures) associated with the use of MAGNEVIST in patients with moderate to severe renal impairment or acute renal failure due to hepatorenal syndrome in the peri-operative transplant period.

INTERACTIONS:

No interaction studies with other medicinal products have been conducted.

Interference with diagnostic tests:

Serum iron determination using methods measuring complexes (e.g. bathophenanthroline) may result in falsely low values for up to 24 hours after the administration of MAGNEVIST due to the free DTPA contained in MAGNEVIST.

PREGNANCY AND LACTATION:

Pregnancy:

The safe use of MAGNEVIST during pregnancy has not yet been demonstrated. Consequently, the need for examination merits particularly careful consideration in pregnant women. Reproduction-toxicological studies with MAGNEVIST in animals gave no indication of a teratogenic or other embryotoxic potential following an administration of MAGNEVIST during pregnancy at human diagnostic dose levels.

The potential risk for humans is unknown.

Lactation:

Safety in breastfeeding has not been established.

Minimal amounts of MAGNEVIST (a maximum of 0,04 % of the administered dose) enter the human breast milk.

There is evidence from non-clinical data that the absorption via the gastrointestinal tract is poor with about 4 %.

At clinical doses, no effects on the infant are anticipated.

DOSAGE AND DIRECTIONS FOR USE:

General:

MAGNEVIST is for intravenous administration only.

Post-procedure observation of the patient is recommended.

The usual safety rules customary for MRI (e.g., exclusion of cardiac pacemakers and ferromagnetic implants) must be observed.

The required dose is administered as a single intravenous – if desired, bolus – injection. Optimal opacification is generally observed within a period of about 45 minutes after injection of MAGNEVIST.

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

Between 0,14 Tesla and 1,5 Tesla the recommendations for the use of MAGNEVIST apply, regardless of the field strength of the magnet.

Wherever possible, intravascular administrations of MAGNEVIST are to be given with the patient lying down; after the end of the injection, the patient should be kept under supervision for at least half an hour.

Instructions for use/handling:

- Vials

MAGNEVIST should not be drawn into the syringe until immediately before use. The rubber stopper should never be pierced more than once. Any MAGNEVIST not used in one examination is to be discarded.

- Prefilled syringes

The prefilled syringe must be taken from the pack and prepared for the injection immediately before the examination. The tip cap should be removed from the prefilled syringe immediately before use. Any MAGNEVIST not used in one examination is to be discarded.

- Large volume containers (> 30 ml)

MAGNEVIST must be administered by means of an automatic injector, or by other approved procedures which ensure sterility of the contrast medium. The use of automatic injectors is prohibited in newborns and infants.

The tube from the injector to the patient must be changed after every patient to avoid cross contamination.

The connecting tubes and all disposable parts of the injector system must be discarded when the infusion bottle is empty.

Unused MAGNEVIST in opened containers, the connecting tubes and all disposable parts of the injector system must be discarded at the end of the examination day.

Any additional instructions from the device manufacturer must be followed.

Incompatibilities:

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

Cranial and spinal magnetic resonance imaging:

The following dosage guidelines apply to adults and children (including newborns and infants):

In general, the administration of 0,1 mmol MAGNEVIST per kg body weight (corresponding to 0,2 ml/kg body weight) is sufficient for good opacification and diagnosis.

If a strong clinical suspicion of a lesion persists despite a normal contrast-enhanced MRI, diagnostic yield of the examination may be increased by a further injection of 0,2 ml MAGNEVIST per kg body weight, or in adults of up to 0,4 ml MAGNEVIST per kg body weight, within 30 minutes with MRI being performed immediately thereafter.

For the exclusion of metastases or recurrent tumours in adults, the injection of 0,3 mmol MAGNEVIST per kg body weight (corresponding to 0,6 ml MAGNEVIST per kg body weight) often leads to higher diagnostic confidence.

Maximum dose: 0,6 ml MAGNEVIST per kg body weight.

Whole body magnetic resonance imaging (MRI):

The following dosage guidelines apply to adults and children. Experience in the indication “Whole body MRI” in children under the age of two years is limited.

In general, the administration of 0,1 mmol MAGNEVIST per kg body weight (corresponding to 0,2 ml/kg body weight) is sufficient for good opacification and diagnosis.

In special cases, e.g., in lesions with poor vascularisation and/or a small extracellular space, the administration of 0,4 ml MAGNEVIST per kg body weight may be necessary for an adequate contrast effect especially on use of relatively slightly T_1-weighted scanning sequences.

In cases of exclusion of a lesion or tumour recurrences in adults, the injection of 0,3 mmol MAGNEVIST per kg body weight (corresponding to 0,6 ml MAGNEVIST per kg body weight) may lead to higher diagnostic confidence.

For the visualisation of vessels, depending on the region to be investigated and the examination technique, in adults the injection of up to 0,6 ml/kg body weight may be required.

Maximum dose: 0,6 ml MAGNEVIST per kg body weight for adults.

Additional information on special populations:

Paediatric population:

- All indications

Children: 0,2 ml MAGNEVIST per kg body weight.
Maximum single dose: 0,4 ml MAGNEVIST per kg body weight.
Children below two years of age: limited experience in whole body MRI.
In children below two years of age the required dose should be administered manually and not in combination with an autoinjector to avoid injury.

Patients with renal impairment:

MAGNEVIST should only be used after careful risk/benefit assessment, including consideration of possible alternative imaging methods, and not at doses higher than 0,2 ml/kg body weight in patients with:

- acute or chronic severe renal impairment (GFR < 30 ml/min/1,73 m^2), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period (see "Special precautions").

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The overall safety profile of MAGNEVIST is based on data from post-marketing surveillance and from more than 11 000 patients in clinical trials.

The most frequently observed adverse drug reactions (≥ 0,4 %) in patients receiving MAGNEVIST in clinical trials are:
- various injection site reactions,
- headache,
- nausea.

Most of the adverse drug reactions in the clinical trials were of mild to moderate intensity.

Overall, the most serious adverse drug reactions in patients receiving MAGNEVIST are:
- nephrogenic systemic fibrosis,
- anaphylactoid reactions/anaphylactoid shock.

Delayed hypersensitivity/anaphylactoid reactions (hours later up to several days) have been observed (see "Warnings" and "Special precautions").

Tabulated list of adverse reactions:

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: uncommon: ≥ 1/1000 to < 1/100; rare: ≥ 1/10 000 to < 1/1000.

Adverse drug reactions reported in clinical trials in patients treated with MAGNEVIST:

System organ class (MedDRA)	Uncommon	Rare
Immune system disorders		Hypersensitivity/anaphylactoid reaction (e.g. anaphylactoid shock*, conjunctivitis, throat tightness*, sneezing, urticaria, pruritus, rash, erythema, dyspnea*, wheezing, oedema face*)
Psychiatric disorders		Disorientation
Nervous system disorders	Dizziness Headache Dysgeusia	Convulsion* Paraesthesia Burning sensation Tremor
Cardiac disorders		Tachycardia* Dysrhythmia
Vascular disorders		Thrombophlebitis Flushing Vasodilatation
Respiratory, thoracic and mediastinal disorders		Throat irritation Pharyngolaryngeal pain/pharynx discomfort Cough
Gastrointestinal disorders	Vomiting Nausea	Abdominal pain Stomach discomfort Diarrhoea Toothache Dry mouth

System organ class (MedDRA)	Uncommon	Rare
		Oral soft tissue pain and paraesthesia
Musculoskeletal, connective tissue and bone disorders		Pain in extremity
General disorders and administration site conditions	Pain Feeling hot Feeling cold Injection site reactions (e.g. injection site coldness, paraesthaesia, swelling, warmth, pain, oedema, irritation, haemorrhage, erythema, discomfort)	Chest pain Pyrexia Peripheral oedema Malaise Fatigue Thirst Asthenia

* Life-threatening and/or fatal cases have been reported
** In patients with preexisting renal impairment

Additional adverse reactions from post-marketing surveillance data:

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

System organ class (MedDRA)	Not known
Blood and the lymphatic system disorders	Increased serum iron*
Immune system disorders	Anaphylactoid reaction (e.g., hypersensitivity reactions*, shock*, hypotension*, loss of consciousness, respiratory arrest*, bronchospasm*, laryngospasm*, laryngeal oedema*, pharyngeal oedema*, cyanosis*, rhinitis, angioedema*, reflex tachycardia)
Psychiatric disorders	Agitation Confusion
Nervous system disorders	Coma* Somnolence* Speech disorder Parosmia
Eye disorders	Visual disturbance Eye pain Lacrimation
Ear and labyrinth disorders	Hearing impaired Ear pain
Cardiac disorders	Cardiac arrest* Heart rate decreased/bradycardia*
Vascular disorders	Syncope* Vasovagal reaction Blood pressure increased
Respiratory, thoracic and mediastinal disorders	Respiratory distress Increased respiratory rate or decreased respiratory rate Pulmonary oedema*
Gastrointestinal disorders	Salivation
Hepato-biliary disorders	Blood bilirubin increased Hepatic enzyme increased
Skin and subcutaneous tissue disorders	Nephrogenic systemic fibrosis (NSF)*
Musculoskeletal, connective tissue and bone disorders	Back pain Arthralgia
Renal and urinary disorders	Acute renal failure* ** Increased serum creatinine** Urinary incontinence Urinary urgency

System organ class (MedDRA)	**Not known**
General disorders and administration site conditions	Chills Sweating Increased body temperature or decreased body temperature Injection site reactions (e.g. necrosis, thrombophlebitis, phlebitis, inflammation, extravasation)

* Life-threatening and/or fatal cases have been reported
** In patients with preexisting renal impairment

Description of selected adverse reactions:

In patients with dialysis-dependent renal failure who received MAGNEVIST, delayed and transient inflammatory-like reactions such as fever, chills and C-reactive protein increase have been commonly observed. These patients had the MRI examination with MAGNEVIST on the day before haemodialysis.

Special precautions:

Caution should be exercised in the following cases:

- Hypersensitivity reactions (also see “Warnings”)

MAGNEVIST can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory or cutaneous manifestations and ranging to severe reactions including shock.

Risk of hypersensitivity reactions is higher in case of the following conditions:
- previous reaction to contrast media;
- history of bronchial asthma;
- history of allergic disorders.

In patients with an allergic disposition (especially with a history of the above-mentioned conditions) the decision to use MAGNEVIST must be made after particularly careful evaluation of the risk/benefit ratio.

Therefore, before MAGNEVIST is injected, the patient should be questioned for a history of allergy (e.g., seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma, and premedication with antihistamines and/or glucocorticoids may be considered.

Taking beta blockers:

Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists.

Cardiovascular disease:

Patients with cardiovascular disease are more susceptible to serious, even fatal, outcomes of severe hypersensitivity reactions.

If hypersensitivity reactions occur (see “Side effects”), administration of MAGNEVIST must be discontinued immediately and – if necessary – specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous MAGNEVIST administration. Due to the possibility of severe hypersensitivity reactions after intravenous MAGNEVIST administration, preparedness for institution of emergency measures is necessary, e.g., appropriate medicines, an endotracheal tube and a respirator should be at hand.

- Impaired renal function

The benefits must be weighed very carefully against the risks.
Prior to administration of MAGNEVIST all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

In patients with impaired renal function, acute renal failure requiring dialysis or worsening renal function have occurred. The risk of these events is higher with increasing dose of MAGNEVIST.

Because gadopentetate is renally excreted, a sufficient period of time for elimination of the contrast agent from the body should be ensured prior to any re-administration in patients with renal impairment. Elimination half-life in patients with mild or moderate renal impairment is 3 to 4 hours. Elimination half-life in patients with severe renal impairment is about 11 hours, and about 75 % of the administered dose was recovered in the urine within two days.

MAGNEVIST can be removed from the body by haemodialysis.

After 3 dialysis sessions of 3 hours each, about 97 % of the administered dose is eliminated from the body, by about 70 % with each dialysis session.

For patients already receiving haemodialysis at the time of MAGNEVIST administration, prompt initiation of haemodialysis following the administration of MAGNEVIST should be considered, in order to enhance the contrast agent's elimination.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of MAGNEVIST and some other gadolinium-containing contrast agents in patients with

- acute or chronic severe renal impairment (GFR < 30 ml/min/1,73 m^2) or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period (see “Warnings”).

In these patients, MAGNEVIST should only be used after careful risk/benefit assessment, including consideration of possible alternative imaging methods, and not at doses higher than 0,2 ml/kg body weight (see “Dosage and directions for use” and “Side effects”).

- Newborns and infants

In newborns and infants, the required dose should be administered by hand (see “Known symptoms of overdosage and particulars of its treatment”).

- Seizure disorders

Patients with seizure disorders or intracranial lesions may be at increased risk of seizure activity. For patients predisposed to seizures, precautionary measures should be taken, e.g. close monitoring, all equipment and medicines necessary to manage convulsions, should they occur, must be made ready for use beforehand.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No signs of intoxication secondary to an inadvertent overdose have so far been observed or reported in clinical use. On the basis of the results of the acute toxicity studies, a risk of acute intoxication is highly unlikely on use of MAGNEVIST in adults. This statement is true for newborns and babies only if the dosage of MAGNEVIST specified for this group of patients is injected by hand and no automatic injector is used, based on the limited data available in this age group.

In case of inadvertent overdose, renal function should be monitored in patients with renal impairment.

MAGNEVIST can be removed from the body by haemodialysis (see “Warnings” and “Special precautions”).

IDENTIFICATION:

Clear, sterile, pyrogen-free aqueous solution.

PRESENTATION:

Clear glass vials of 5, 10, 15, 20 or 30 ml packed in a carton containing 10 vials.
Clear glass prefilled syringes of 10, 15 or 20 ml packed in a carton containing 5 prefilled syringes.
Clear glass bottles of 100 ml for use with an automatic injector packed in a carton containing 10 bottles.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light.
Keep the container in the outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

MAGNEVIST 5 ml	28/28/0639
MAGNEVIST 10 ml:	28/28/0640
MAGNEVIST 15 ml:	28/28/0641
MAGNEVIST 20 ml:	W/28/0199
MAGNEVIST 30 ml:	36/28/0026
MAGNEVIST 100 ml:	36/28/0027

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
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27 Wrench Road
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DATE OF PUBLICATION OF THE PACKAGE INSERT:

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