Summary of Product Characteristics

1. Name of the medicinal product
MAGNILEK
(Gadopentetate Dimeglumine Injection USP)

2. Qualitative and quantitative composition
Each mL contains:
Gadopentetate Dimeglumine……469 mg
Water for Injection USP…….q.s.

3. Pharmaceutical form
Injection

4. Clinical particulars
4.1 Therapeutic indications
Central Nervous System
Gadopentetate Dimeglumine Injection USP is indicated for use with magnetic resonance imaging (MRI) in adults, and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues. Magnilek Injection has been shown no facilitate visualization of intracranial lesions including but not limited to tumors.
Extracranial / Extraspinal Tissues
Magnilek Injection is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the head and neck.
Body
Magnilek Injection is indicated for use in MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the body.

4.2 Posology and method of administration
The recommended dosage of Gadopentetate Dimeglumine Injection USP is 0.2 mL/kg (0.1mmol/kg) administered intravenously, at a rate not to exceed 10 mL per 15 seconds. Dosing for patients in excess of 286 lbs has not been studied systematically.
To ensure complete injection of Gadopentetate Dimeglumine, administer 5 mL normal saline flush after the injection. The imaging procedure should be completed within 1 hour of injection of Gadopentetate Dimeglumine.
Visually inspect for particulate matter and discoloration prior to administration. Do not use the solution if it is discoloured, if particulate matter is present or if the container appears damaged.
Discard any unused portion in accordance with regulations dealing with the disposal of such materials.

Dose and Duration of Gadopentetate Dimeglumine Injection by Body weight		
Body weight		**Total volume, ml***
Lb	**Kg**	
22	10	2
44	20	4
66	30	6

88	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
286	130	26
***Rate of Injection: 10ml/15sec**		

4.3 Contraindications

Gadopentetate Dimeglumine Injection USP is contraindicated in patients with:

- Chronic, severe kidney disease (glomerular filtration rate, GFR<30ml/min/1.73m^2), or
- Acute kidney injury, or
- History of severe hypersensitivity reaction to Gadopentetate Dimeglumine Injection.

4.4 Special warnings and precautions for use

Nephrotic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m2) as well as patients with acute kidney injury. Do not administer Gadopentetate Dimeglumine Injection USP to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30- 59 mL/min/1.73m2) and little, if any, for patients with chronic, mild kidney disease (GFR 60- 89 mL/min/1.73m2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infections, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering Gadopentetate Dimeglumine Injection, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to re-administration.

Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory, and/or cutaneous manifestations rarely resulting in death have occurred. The risk of hypersensitivity reactions

is higher in patients with a history of reaction to contrast media, bronchial asthma, or allergic disorders. Hypersensitivity reactions can occur with or without prior exposure to GBCAs.
Have appropriately trained personnel administer Gadopentetate Dimeglumine Injection in a facility that has immediate availability of resuscitative equipment. If a hypersensitivity reaction occurs, stop Gadopentetate Dimeglumine injection and immediately begin appropriate therapy.
Observe closely patients with a history of drug reactions, allergy, or other hypersensitivity disorders, during and up to several hours after Gadopentetate Dimeglumine Injection.

Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (for example, brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with gadodiamide and gadoversetamide causing greater retention than other linear agents Gadoxetate disodium, Gadopentetate dimeglumine, Gadobenate dimeglumine. Retention is lowest and similar among the macrocyclic GBCAs (gadoterate meglumine, gadobutrol, gadoteridol).
Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies particularly closely spaced studies, when possible.

Renal Failure

In patients with renal impairment, acute renal failure (acute kidney injury) requiring dialysis or worsening renal function has occurred, mostly within 48 hours of Gadopentetate Dimeglumine Injection. The risk of acute renal failure is higher with increasing dose of contrast. Use the lowest possible dose, evaluate renal function in patients with renal impairment, and allow sufficient time for contrast elimination before re-administration. 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. Gadopentetate Dimeglumine Injection is cleared by glomerular filtration and is dialyzable. After 3 dialysis sessions of 3 hours each, about 97% of the administered dose is eliminated from the body; each dialysis session removes about 70% of the circulating drug.

Injection Site Reactions

Skin and soft tissue necrosis, thrombosis, fasciitis, and compartment syndrome requiring surgical intervention (e.g. compartment release or amputation) have occurred very rarely at the site of contrast injection or the dosed limb. Total volume and rate of Gadopentetate Dimeglumine Injection, extravasation of contrast agent, and patient susceptibility might contribute to these reactions. Phlebitis and thrombophlebitis may be observed generally within 24 hours after Gadopentetate Dimeglumine injection and resolve with supportive treatment. Determine the patency and integrity of the intravenous line before administration of Gadopentetate Dimeglumine injection. Assessment of the dosed limb for the development of injection site reactions is recommended.

Interference with Visualization of Lesions Visible with Non-Contrast MRI
As with any paramagnetic contrast agent, Gadopentetate Dimeglumine Injection might impair the visualization of lesions seen on non-contrast MRI. Therefore, caution should be exercised when Gadopentetate Dimeglumine MRI scans are interpreted without a companion non-contrast MRI scan.

4.5 Interaction with other medicinal products and other forms of interaction
Drug Laboratory Test Interactions
There are no known drug interactions. Gadopentetate Dimeglumine Injection does not interfere with serum and plasma calcium measurements determined by colorimetric assays.

4.6 Fertility, pregnancy and breastfeeding
Pregnancy information
Risk Summary
GBCAs cross the placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive.
In animal reproduction studies, repeated intravenous dosing of gadopentetate dimeglumine during organogenesis resulted in delayed fetal development in pregnant rats and rabbits at a dose 2 times and 2.4 times, respectively, the recommended human dose (based on body surface area [BSA]). No teratogenic effects were observed in rats or rabbits at doses or 7.3 times (rats) and 9.7 times (rabbits) the recommended human dose, based on BSA. Because of the potential risks of gadolinium to the fetus, use Gadopentetate Dimeglumine injection only if imaging is essential during pregnancy and cannot be delayed.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and is 15 to 20%, respectively.
Data
Human Data
Contrast enhancement is visualized in the human placenta and fetal tissues after maternal GBCA administration.
Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the maternal indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.
Animal Data
Gadolinium Retention
GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.
Reproductive Toxicology

Gadopentetate dimeglumine was administered intravenous during organogenesis at doses of at 0.25, 0.75, and 1.25 mmol/kg/day for 10 consecutive days in pregnant rats and for 13 consecutive days in pregnant rabbits. Gadopentetate dimeglumine caused retardation of fetal development at a dose of 1.25 mmol per kg (rats) and 0.75 mmol per kg (rabbits); 2 times and 2.4 times, respectively, the recommended human dose (based on BSA).
Gadopentetate dimeglumine was not teratogenic in pregnant rats and rabbits when given repeatedly during organogenesis at a dose of 3 mmol per kg in rabbits and 4.5 mmol per kg in rats; 9.7 and 7.3 times, respectively, the recommended human dose (based on BSA).
Nursing Mothers
Risk Summary
Limited literature reports that breastfeeding after Gadopentetate Dimeglumine administration to the mother would result in the infant receiving an oral dose of 0.001 to 0.04% of the maternal dose. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Additionally, there is limited GBCA gastrointestinal absorption. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gadopentetate Dimeglumine and any potential adverse effects on the breastfed child from Gadopentetate Dimeglumine or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines
Transient increases or decreases in blood pressure may occur after the administration of Gadopentetate Dimeglumine Injection. Caution should be exercised by the patient when driving or operating machinery.

4.8 Undesirable effects
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The mean age of the 1272 patients who received Gadopentetate Dimeglumine Injection in pre-market clinical trials was 46.4 years (range 2 to 93 years). Of these patients, 55% (700) were male and 45% (572) were female. Of the 1271 patients who received Gadopentetate Dimeglumine injection and for whom race was reported, 82.1% (1043) were Caucasian, 9.7% (123) were Black, 5.3% (67) were Hispanic, 2.1% (27) were Oriental/Asian, and 0.9% (11) were other.
The most common adverse reaction was headache (4.8%). The majority of headaches were transient and of mild to moderate severity. Other adverse reactions that occurred in ≥ 1% of patients included: nausea (2.7%), injection site coldness/localized coldness (2.3%) and dizziness (1%).
The following additional adverse reactions occurred in less than 1% of the patients:
General Disorders: Injection site reactions, including phlebitis, pain, localized warmth, localized edema, and burning sensation. Substernal chest pain, back pain, pyrexia, asthenia, feeling cold, generalized warmth, fatigue, and chest tightness, and anaphylactoid reactions characterized by cardiovascular, respiratory and/or cutaneous symptoms, such as dyspnea, bronchospasm, and cough.
Cardiovascular: Hypotension, hypertension, tachycardia, migraine, syncope, vasodilatation, pallor.
Gastrointestinal: Abdominal discomfort, teeth pain, increased salivation, abdominal pain, vomiting, diarrhea.

Nervous System: Agitation, anxiety, thirst, somnolence, diplopia, loss of consciousness, convulsions (including grand mal), paresthesia.
Respiratory System: Throat irritation, rhinitis, sneezing.
Skin: Rash, sweating (hyperhidrosis), pruritus, urticaria (hives), facial edema.
Special Senses: Conjunctivitis, taste abnormality, dry mouth, lacrimation, eye irritation, eye pain, ear pain.

Postmarketing Experience

The following additional adverse reactions have been identified during post-marketing use of Gadopentetate Dimeglumine Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Anaphylactic shock, respiratory distress, and laryngeal edema.
- Cardiac/respiratory arrest, shock
- Nephrogenic systemic fibrosis.
- General Disorders and Administration Site Conditions: Adverse events with variable onset and duration have been reported after GBCA administration. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.
- Skin: Gadolinium associated plaques

The most frequently reported adverse reactions in the post-marketing experience were nausea, vomiting, urticaria, and rash.
General Disorders and Administration Site Conditions: Nephrogenic systemic fibrosis, body temperature decreased, tremor, shivering (chills), injection site reactions including skin and soft tissue necrosis.
Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions that may be fatal and include cardiac or respiratory arrest, respiratory distress, cyanosis, laryngeal edema, laryngospasm, pharyngeal edema, and angioedema.
Delayed hypersensitivity reactions have been reported up to several hours after administration of Gadopentetate Dimeglumine Injection.
Renal and Urinary: Acute renal failure, worsening renal impairment urinary incontinence, urinary urgency.
Vascular: Thrombophlebitis, deep vein thrombophlebitis, compartment syndrome requiring surgical intervention.
Cardiac: Cardiac arrest, heart rate decreased, arrhythmia.
Ear and Labyrinth Disorders: Hearing impairment.
Eye Disorders: Visual disturbance.
Musculoskeletal and Connective Tissue Disorder: Arthralgia.
Nervous System Disorders: Coma, anosmia, speech disorder.
Respiratory System: Respiratory arrest, pulmonary edema.
Skin: Erythema multiforme, pustules

4.9 Overdose

Systemic consequences associate with overdosage of Gadopentetate Dimeglumine have not been reported.

5. Pharmaceutical properties

Gadopentetate Dimeglumine is a paramagnetic agent and, as such, it develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

5.1 Pharmacodynamic properties

In magnetic resonance imaging (MRI), visualization of normal and pathological brain tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) changes in proton density; 2) alteration of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, Gadopentetate Dimeglumine decreases the T1 and T2 relaxation time in tissues where it accumulates. At usual doses, the effect is primarily on the T1 relaxation time.

Disruption of the blood-brain barrier or abnormal vascularity allows accumulation of Gadopentetate Dimeglumine in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of Gadopentetate Dimeglumine in various lesions are not known.

5.2 Pharmacokinetic properties

The pharmacokinetics of intravenously administered Gadopentetate Dimeglumine in normal subjects conforms to a two compartment open-model with mean distribution and elimination half-lives (reported as mean ± SD) of about 0.2 ± 0.13 hours and 1.6 ± 0.13 hours, respectively.

Upon injection, the meglumine salt is completely dissociated from the Gadopentetate Dimeglumine complex. Gadopentetate is exclusively eliminated in the urine with 83 ± 14% (mean ± SD) of the dose excreted within 6 hours and 91 ± 13% (mean ± SD) by 24 hours, post-injection.

The renal and plasma clearance rates (1.76 ± 0.39 mL/min/kg and 1.94 ± 0.28 mL/min/kg, respectively) of Gadopentetate are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys and that the drug is essentially cleared through the kidney. The volume of distribution (266 ± 43 mL/kg) is equal to that of extracellular water and clearance is similar to that of substances, which are subject to glomerular filtration. Following GBCA administration, gadolinium is present for months or years in brain, bone, skin, and other organs.

In vitro laboratory results indicate that Gadopentetate does not bind to human plasma protein. *In vivo* protein binding studies have not been done.

Renal Impairment

Gadopentetate Dimeglulmine is excreted via the kidneys, even in patients with impaired renal function. In patients with impaired renal function, the serum half-life of Gadopentetate Dimeglumine (0.1 mmol/kg) were 2.6 ± 1.2 h, 4.2 ± 2.0 h and 10.8 ± 6.9 h, for mildly (creatinine clearance, CLCR = 60 to < 90 mL/min), moderately (CLCR = 30 to < 60 mL/min) and severely (CLCR = < 30 mL/min) impaired patients, respectively, as compared with 1.6 ± 0.1 h in healthy subjects.

5.3 Preclinical safety data

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

A comprehensive battery of in vitro and in vivo studies in bacterial and mammalian systems suggest that gadopentetate dimeglumine is not mutagenic or clastogenic and does not induce unscheduled DNA repair in rat hepatocytes or cause cellular transformation of mouse embryo fibroblasts. However, the drug did show some evidence of mutagenic potential in vivo in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

When administered intra-peritoneally to male and female rats daily prior to mating, during mating, and during embryonic development for up to 74 days (males) or 35 days (females),

gadopentetate caused a decrease in number of corpora lutea at the 0.1 mmol/kg dose level. After daily dosing with 2.5 mmol/kg suppression of food consumption and body weight gain (males and females) and a decrease in the weights of testes and epididymis were observed.
In a separate experiment in rats, daily injections of gadopentetate dimeglumine over 16 days caused spermatogenic cell atrophy at a dose level of 5 mmol/kg but not at a dose level of 2.5 mmol/kg. This atrophy was not reversed within a 16- day observation period following the discontinuation of the drug.

6. Pharmaceutical particulars

6.1 List of excipients
Pentetic Acid USP
Water for Injection USP

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30ºC. Protect from light.

6.5 Nature and content of container
- 10 ml Clear Transparent Flint Glass vial USP Type-I with 20 mm grey bromobutyl rubber closure sealed with polypropylene plastic covered flip off aluminium seals packed in a carton along with leaflet.
- 15 ml Clear Transparent Flint Glass vial USP Type-I with 20 mm grey bromobutyl rubber closure sealed with polypropylene plastic covered flip off aluminium seals packed in a carton along with leaflet.
- 20 ml Clear Transparent Flint Glass vial USP Type-I with 20 mm grey bromobutyl rubber closure sealed with polypropylene plastic covered flip off aluminium seals packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing authorization holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Div. of J. B. Chemicals and Pharmaceuticals Ltd.)
Neelam Centre, B wing, 4th Floor, Hind Cycle Road,
Worli Mumbai-400 030

8. Marketing Authorization Number
05127/3475/NMR/2017

9. Date of First Authorization/Renewal of the Authorization
20/04/2020

10. Date of revision of the text
27/07/2023