WARNING : NEPHROGENIC SYSTEMIC FIBROSIS AND GADOLINIUM RETENTION

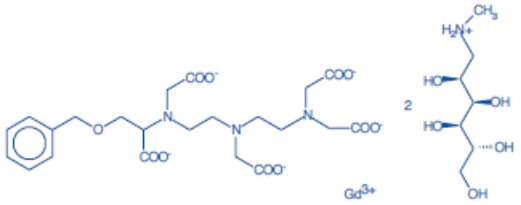
Gadolinium-based contrast agents (GBCAs) increase the risk of NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

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 (e.g. brain, skin, kidney, liver, and spleen).
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.
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.

PRODUCT INFORMATION
NAME OF THE DRUG: gadobenate dimeglumine

DESCRIPTION
MultiHance® is supplied as a sterile, non-pyrogenic, clear colourless to slightly yellow, aqueous solution at neutral pH (6.5-7.3) for intravenous injection. MultiHance® contains no preservatives.
1 mL of solution for injection contains: gadobenic acid 334 mg (0.5M) as the dimeglumine salt.
[gadobenate dimeglumine 529 mg = gadobenic acid 334 mg + meglumine 195 mg].
Chemical name
Gadolinate(2-),(4RS)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato-(5-)-N5,N8,N11,O4,O5,O8,O11,O13]-dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2).
Laboratory name
B19036/7
Gd-BOPTA/dimeg
The structural formula of gadobenate dimeglumine is:



Molecular Formula Molecular Weight
C_{36} H_{62} N_5 O_{21} Gd 1058.17
CAS Number: 127000-20-8

PARAMETER
Osmolality (mOsmol/kg water) @ 37°C: 1970
Viscosity (cP) @ 37°C: 5.3
Density @ 20°C : 1.220g/mL
MultiHance® has an osmolality 6.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

PHARMACOLOGY
Pharmacodynamic properties
Gadobenate dimeglumine is an octadentatate chelate of gadolinium salified with meglumine.
As a paramagnetic contrast agent, it shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons.
The relaxivities of gadobenate dimeglumine in aqueous solution (r_1= 4.39 and r_2= 5.56 $mM^{-1}s^{-1}$ at 20 MHz), are only slightly higher than those of other paramagnetic contrast agents already in clinical use. However, unlike other contrast agents, gadobenate dimeglumine experiences strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins.
Particularly r_1 and r_2 amount to 9.7 and 12.5 (20 MHz) respectively in human plasma.
Gadobenate dimeglumine, is the only gadolinium chelate which combines:

- the mechanism of action of the gadolinium chelates already available on the market, i.e. it produces a significant and marked enhancement of a signal intensity in the extracellular fluid space, with
- that of liver-specific agents, i.e. a specific enhancement of the liver parenchyma secondary to hepatocyte uptake.

Early temporal differences in enhancement between normal and diseased liver can be detected with compact bolus injection of the contrast medium and rapid imaging technique (“dynamic MRI”) to improve liver-lesion characterisation. Different from all the other gadolinium chelates, the liver enhancement produced by gadobenate dimeglumine does not start to decrease in a few minutes, but remains steady for hours. The enhancement of signal intensity in the normal liver parenchyma is much more persistent and long lasting than in lesions, so that the differential contrast between normal parenchyma and lesions results is significantly enhanced on images acquired 40-120 minutes after MultiHance® administration.
The lesion-to-liver contrast enhancement provided by MultiHance® facilitates visualisation and identification of individual lesions in the liver parenchyma.
After rapid intravascular distribution, the gadobenic ion rapidly diffuses into the extracellular-fluid space.

Pharmacokinetic properties

Human pharmacokinetics of gadobenic ion, the MRI contrast effective anion in gadobenate dimeglumine, was described using a biexponential decay model. The apparent distribution and elimination half-lives ranges of means are from 0.084 to 0.36 h and from 1.17 to 1.68 h respectively. The apparent total volume of distribution, ranging from 0.170 to 0.248 L/kg body weight (bw), indicates that the compound is distributed in plasma and in the extracellular space.

Gadobenate ion is rapidly cleared from plasma and is eliminated mainly through urinary route and in less extent through biliary route. Total plasma clearance, ranging from 0.098 to 0.133 L/h kg bw, and renal clearance, ranging from 0.082 to 0.104 L/h kg bw, indicate that the compound is predominantly eliminated by glomerular filtration. Plasma concentration and area under the curve (AUC) values show statistically significant linear dependence on the administered dose.

Gadobenate ion is excreted unchanged in urine in amounts corresponding to 78%-94% of the injected dose within 24 hours. Between 2% and 4% of the dose is recovered in the faeces.

The compound does not bind measurably to plasma proteins, as assessed by equilibrium dialysis.

Disruption of the blood brain barrier or abnormal vascularity allows Gadobenate ion penetration into the lesion.

Gadobenic acid is a linear GdCA. Studies have shown that after exposure to GdCAs, gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs, this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data suggest that gadolinium is released from linear GdCAs.

Renal Impairment

MultiHance® is cleared from the body mainly by glomerular filtration and to a minor degree by hepatobiliary excretion. The pharmacokinetics of an intravenous bolus of 0.2 mmol/kg of gadobenate dimeglumine (0.5M) was evaluated in a double-blind, placebo-controlled, parallel-group study in 20 patients administered MultiHance® and in 12 patients administered placebo. They were patients with moderate (creatinine clearance >30 mL/min and 60 mL/min) and with severe renal impairment (creatinine clearance 10 mL/min and 30 mL/min). The pharmacokinetic terminal half-life of MultiHance® increased as the degree of renal impairment increased (6.1 and 9.5 hr for moderate and severe renal impairment respectively, as compared to 1-2 hours in healthy volunteers).

Clinical trials

Liver

MultiHance® was evaluated in three multicentre, randomized, blinded-read clinical trials in 424 adult patients who underwent hepatic MRI for evaluation of known or suspected focal liver disease.

The first study was an open-label, multicentre, blinded-read trial in a total of 216 adults referred for MRI for diagnosis or follow-up of suspected or known liver lesions. Of the 214 patients who received MultiHance®, 86 patients received a bolus injection of the recommended MultiHance® dose of 0.05 mmol/kg, had MRI scans performed before and within 10 minutes of receiving the injection, and had available histology data. The sets of images were evaluated blindly as predose unenhanced MR images alone and paired predose unenhanced plus postdose contrast-enhanced MRIs. The results of contrast-enhanced MRI scans were compared to non-contrast scans. A total of 107 lesions were histologically characterized in these 86 patients. As shown in Table 1, enhancement of images with MultiHance® significantly improved the accuracy to classify the nature of the lesions (benign or malignant) and to specifically characterize the type of the lesions.

TABLE 1: ACCURACY (MALIGNANT/BENIGN) AND CORRECTLY CLASSIFIED, LESIONS (SPECIFIC) IN A CLINICAL STUDY OF PATIENTS WITH KNOWN OR, SUSPECTED LESIONS OF THE LIVER				
	MultiHance® 0.05 mmol/kg (N = 107 LESIONS)			
Image Set	Accuracy (Nature)	p-value* (Nature)	Correctly Classified (Specific)	p-value* (Specific)
Reviewer 1				
Predose	74.8%	-	48.6%	-
Predose + Dynamic	90.7%	<0.01	75.7%	<0.01
Reviewer 2				
Predose	82.2%	-	61.7%	-
Predose + Dynamic	90.7%	0.02	70.1%	0.06
* p-value based on exact McNemar test comparing accuracy and correctly classified lesions for each of the postdose image sets with predose.				

The other two studies were double-blind, multicentre, parallel-group, blinded-read trials in a total of 210 adults with known or suspected focal liver lesions. Patients had to be referred for either intraoperative ultrasound (IOUS) for surgical resection of a malignancy or computed-tomographic arterial portography (CTAP); in one study, patients could also have been referred for chemoembolization of a liver tumor and required lipiodol computed tomography (L-CT). Of the 210 patients who received MultiHance®, 105 patients received a single intravenous infusion of MultiHance® 0.05 mmol/kg at a rate of 10 mL/min. MRI scans were performed before receiving MultiHance® and at 40 to 120 minutes after receiving MultiHance®. The results of contrast-enhanced MRI scans were compared to non-contrast scans and to the results of the gold-standard procedures (for a subgroup of patients). The combination of predose and postdose image sets detected more lesions (see Table 2) compared to predose image sets alone. Generally, greater concordance in the number of lesions detected with the gold-standard procedures was also seen with the combined predose and postdose image sets than with the predose image sets alone.

TABLE 2: NUMBER OF LESIONS DETECTED (% INCREASE) FOLLOWING DELAYED IMAGING IN TWO CLINICAL STUDIES OF PATIENTS WITH KNOWN OR SUSPECTED FOCAL LIVER LESIONS				
	MultiHance® 0.05 mmol/kg			
	Study A1		Study B2	
	Number of Lesions (% increase from predose)			
Reviewer	Predose	Predose + Postdose	Predose	Predose + Postdose
1	48	58 (21%)	61	87 (43%)
2	56	63 (13%)	69	82 (19%)
3	45	51 (13%)	70	85 (21%)
Predose + Postdose image set includes all available images at all timepoints. 1 Number of patients evaluated ranges from 39 to 41. 2 Number of patients evaluated ranges from 50 to 52.				

INDICATIONS

MultiHance® is a paramagnetic diagnostic contrast medium for use in Magnetic Resonance Imaging (MRI) of the liver in patient with normal renal function.

CONTRAINDICATIONS

MultiHance® is contra-indicated in

- patients with known allergic or hypersensitivity reactions to gadolinium or any other ingredients.
- patients with a history of allergic or adverse reactions to other gadolinium chelates.

PRECAUTIONS

The possibility of a reaction, including serious, life-threatening, or fatal anaphylactic and anaphylactoid reactions should always be considered, especially in patients with a history of asthma or other allergic disorders.

Prior to MultiHance® administration, ensure the availability of trained personnel and medications to treat hypersensitivity reactions.

Patients should be kept under close observation for 15 minutes following the injection as the majority of severe reactions occur at this time. The patient should remain in the hospital environment for one hour after the time of injection.

Appropriate facilities should be available for coping with any complication of the procedure, as well as for the emergency treatment of severe reactions to the contrast itself.

Extravasation of MultiHance® might lead to injection site reactions (see Section Adverse reactions). Exercise caution to avoid local extravasation during intravenous administration of MultiHance®. If extravasation occurs, evaluate and treat as necessary if local reactions develop.

The accepted safety considerations and procedures that are required for Magnetic Resonance Imaging in particular the exclusion of ferromagnetic objects, for example cardiac pace-makers or aneurysm clips, are also applicable when MultiHance® is used for contrast enhancement.

Data on the safety of repeated injections of MultiHance® are not available. If the physician determines sequential or repeat examinations are required, an interval of at least 7 hours between administrations should be observed to allow for clearance of the drug from the body.

Impaired renal function

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

Impaired renal Functions

Prior to administration of Multihance, 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 renal impairment. The GBCA-associated NSF risk appears highest for patients with chronic, severe renal impairment (GFR <30 mL/min/1.73m2) as well as patients with acute renal impairment. The risk appears lower for patients with chronic, moderate renal impairment (GFR 30-59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild renal impairment (GFR 60-89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

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 MultiHance®, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after MultiHance® administration may be useful at removing MultiHance® 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.

Caution is advised in patients with cardiovascular disease.

In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased. Precautions are necessary when examining these patients (e.g. monitoring of the

patient) and the equipment and medicinal products needed for the rapid treatment of possible convulsions should be available.
Insignificant quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Nonetheless MultiHance® should not be used in patients with a history of sensitivity to benzyl alcohol.
Carcinogenicity, mutagenicity and impairment of fertility Long term animal carcinogenicity studies were not conducted with gadobenate dimeglumine.
Gadobenate dimeglumine did not induce gene mutations in Salmonella typhimurium, E. coli or Saccharomyces cerevisiae, nor chromosomal aberrations in Chinese Hamster lung cells, human lymphocytes or human epithelial cells in vitro. Gadobenate dimeglumine did not induce micronuclei in bone marrow cells in rats in vivo.
Intravenous administration of gadobenate dimeglumine did not affect reproduction or fertility in male and female rats at doses up to 1.5 mmol/kg/day (1.4x the maximum clinical dose, adjusted for body surface area). Long term animal carcinogenicity studies were not conducted with gadobenate dimeglumine.
Gadobenate dimeglumine did not induce gene mutation in Salmonella typhimurium, E. coli or mouse lymphoma cells, or chromosomal aberrations in CHO cells in vitro or in bone marrow cells in mice in vivo.

Use in pregnancy
Category B3:
In studies in rats and rabbits, no untoward effects on embryonic or fetal development were exerted by daily intravenous administration of gadobenate dimeglumine in rats up to 2 mmol/kg/day or in rabbits at doses up to 1.5mmol/kg/day. However, an increase in abortions and decreased fetal bodyweights were noted in rabbits at doses of 2 mmol/kg/day (3.3x the maximum clinical dose, adjusted for body surface area). The safety and efficacy of MultiHance® have not been established in pregnant women and, therefore, MultiHance® cannot be recommended for use during pregnancy.
Use in lactation
Gadolinium containing contrast agents are excreted into breast milk in very small amounts. At clinical doses, no effects on the infant are anticipated due to the small amount excreted into milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of MultiHance® should be at the discretion of the doctor and lactating mother.

Use in children
The safety and efficacy of MultiHance® have not been established in patients under 18 years old. Therefore, use of MultiHance® in this patient group cannot be recommended.
Interactions with other drugs Interaction studies with other medicinal products were not carried out during the clinical development of MultiHance®. However no drug interactions were reported during the clinical development program.

Effect on the ability to drive or operate machinery
On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligible influence is expected with the use of MultiHance® on the ability to drive or use machines.

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 (e.g. 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 Warnings and Precautions. 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 [see Adverse Reactions]. 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.

ADVERSE REACTIONS

Clinical trials

The following adverse events were seen during the clinical development of MultiHance®

System organ classes	*Clinical trials*			*Post-marketing surveillance*
	Common (≥1/100, <1/10)	*Uncommon (≥1/1,000, <1/100)*	*Rare (1/10,000, <1/1,000)*	*Frequency unknown***
Immune system disorders			Anaphylactic/ anaphylactoid reaction Hypersensitivity reaction	Anaphylactic shock
Nervous system disorders	Headache	Paraesthesia, Hypoaesthesia, Dizziness, Taste perversion	Convulsion, Syncope, Tremor, Parosmia	Loss of consciousness
Eye disorders			Visual disturbance	Conjunctivitis
Cardiac disorders		First-degree atrioventricular block, Tachycardia	Myocardial ischaemia, Bradycardia	Cardiac arrest, Cyanosis
Vascular disorders		Hypertension, Hypotension, Flushing		
Respiratory, thoracic and mediastinal disorders			Dyspnoea, Laryngospasm, Wheezing, Rhinitis, Cough	Respiratory failure, Laryngeal oedema, Hypoxia, Bronchospasm, Pulmonary oedema
Gastrointestinal disorders	Nausea	Diarrhoea, Vomiting, Abdominal pain	Faecal incontinence, Salivary hypersecretion, Dry mouth	Oedema mouth

Skin & subcutaneous tissue disorders		Urticaria, Rash including erythematous rash, macular, maculo-papular and papular rash, Pruritus, Sweating increased	Face oedema,	Angioedema
Musculoskeletal, connective tissue and bone disorders			Myalgia	
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions	Injection Site Reaction including, injection site pain, inflammation, burning, warmth, coldness, discomfort, erythema, paraesthesia and pruritus	Chest pain, Pyrexia, Feeling hot	Asthenia, Malaise, Chills	Injection site swelling
Investigations		Electrocardiogram abnormalities*, Blood bilirubin increased, Blood iron increased, Increases in serum transaminases, gamma-glutamyl-transferase, lactic dehydrogenase and creatinine	Blood albumin decreased, Alkaline phosphatase increased	

* Electrocardiogram abnormalities include electrocardiogram QT prolonged, electrocardiogram QT shortened, electrocardiogram T wave inversion, electrocardiogram PR prolongation, electrocardiogram QRS complex prolonged.

** Since the reactions were not observed during clinical trials with 4,956 subjects, best estimate is that their relative occurrence is rare (≥ 1/10,000 to <1/1000).
The most appropriate MedDRA (version 16.1) term is used to describe a certain reaction and its symptoms and related conditions.

Laboratory findings were mostly seen in patients with evidence of pre-existing impairment of hepatic function or pre-existing metabolic disease.

The majority of these events were non-serious, transient and spontaneously resolved without residual effects. There was no evidence of any correlation with age, gender or dose administered.

As with other gadolinium-chelates, there were reports of anaphylactic/ anaphylactoid/ hypersensitivity reactions. These reactions manifested with various degrees of severity up to anaphylactic shock and death, and involved one or more body system, mostly respiratory, cardiovascular, and/or mucocutaneous systems. In patients with history of convulsion, brain tumours or metastasis, or other cerebral disorders, convulsions have been reported after MultiHance® administration. (see section PRECAUTIONS)

Injection site reactions due to extravasation of the contrast medium leading to local pain or burning sensations, swelling, blistering and, in rare cases when localised swelling is severe, necrosis have been reported. Localised thrombophlebitis has also been rarely reported.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with MultiHance® in patients co-administered other gadolinium-containing contrast agents (see Section 4.4).

DOSAGE AND ADMINISTRATION

Adults

Imaging of the liver

The recommended dose of MultiHance® in adult patients is 0.05 mmol/kg body weight. This corresponds to 0.1 mL/kg of the 0.5 M solution.

The product should be administered intravenously either as a bolus or as an infusion (10 mL/min.).

Post-contrast imaging can be performed immediately following the bolus (dynamic MRI). Delayed, liver-specific imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

MULTIHANCE IS NOT FOR REPEATED USE

Special Populations

Impaired renal function and impaired liver function: Use of MultiHance® should be avoided in patients with renal impairment (GFR < 60 mL/min) and perioperative liver transplantation.

Administration

MultiHance® should be drawn up into the syringe immediately before use and should not be diluted.

The injection should be followed by a saline flush of at least 5 mL.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

To minimise the potential risks of soft tissue extravasation of MultiHance®, it is important to ensure that the i.v. needle or cannula is correctly inserted into a vein.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

Concurrent medications or Parenteral Nutrition should not be physically mixed with contrast agents and should not be administered in the same intravenous line because of the potential of chemical incompatibility.

Interaction

Interactions studies with other medicinal product were not carried out during the clinical development of MultiHance®. However no drug interaction were reported during the clinical development program.

OVERDOSAGE

There have been no cases of overdose reported to date; consequently neither signs nor symptoms of overdosage have been identified. In the event of overdosage occurring, the patient should be observed and treated symptomatically.

SHELF LIFE

36 months

STORAGE

Store below 25°C. Do not freeze.

PRESENTATION AND REGISTRATION NUMBER

Sterile solution for intravenous injection containing gadobenate dimeglumine 0.529g per mL (0.5M) in vials.

MultiHance® 1 vial @ 10ml, Reg. No.: DKI1010400143A1

HARUS DENGAN RESEP DOKTER

Imported by:
PT. Dipa Pharmalab Intersains
Majalengka - Indonesia
Manufacturer and released by:
Patheon Italia S.p.A, Ferentino - Italy
for Bracco Imaging S.p.A, Milano - Italy

DISETUJUI OLEH BPOM: 31/05/2021 EREG100327VR12100026

LEAFLET INFORMASI PASIEN

MultiHance®

Larutan Injeksi Gadobenate dimeglumine 0,5M

Bacalah leaflet ini dengan seksama sebelum Anda memulai pengobatan dengan obat ini karena mengandung informasi penting untuk Anda.

- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain karena dapat membahayakan mereka, meskipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika terdapat efek samping, konsultasikan kepada dokter, apoteker, atau perawat Anda. Hal ini termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Leaflet ini berisi:

PERINGATAN : *NEPHROGENIC SYSTEMIC FIBROSIS* DAN RETENSI GADOLINIUM

Kontras media berbasis gadolinium (GBCAs) meningkatkan risiko NSF pada pasien dengan kelainan proses eliminasi obat. Hindari penggunaan GBCAs pada pasien ini kecuali jika informasi diagnostic yang dibutuhkan sangat penting dan tidak dapat tersedia dengan proses MRI tanpa agen kontras atau kondisi pengecualian lainnya.

- **Risiko NSF tampak paling tinggi pada pasien dengan:**
  - **penyakit ginjal kronis dan berat**
  - **kerusakan ginjal akut**
- **Periksa pasien untuk mengetahui kerusakan ginjal akut dan kondisi lain yang dapat menurunkan fungsi ginjal. Untuk pasien dengan risiko menurunkan fungsi ginjal secara kronis (misal, usia > 60 tahun, hipertensi atau diabetes), perkirakan tingkat *glomerular filtration rate (GFR)* melalui pemeriksaan laboratorium.**

Gadolinium tersimpan selama beberapa bulan atau tahun pada beberapa organ tubuh. Konsentrasi tertinggi (nanomolekul per gram jaringan) telah teridentifikasi pada tulang, diikuti dengan organ lainnya (misal, otak, kulit, ginjal, hati, dan pankreas).
Akibat dari retensi gadolinium pada otak belum teridentifikasi. Efek patologis dan klinis dari pemberian GBCAs dan retensi pada kulit dan organ lainnya telah diketahui pada pasien dengan kerusakan fungsi ginjal.
Sedangkan efek klinis dari retensi gadolinium pada pasien dengan fungsi ginjal normal belum diketahui, pasien tertentu dapat memiliki risiko yang lebih tinggi. Hal ini termasuk pada pasien yang membutuhkan dosis sumur hidup, hamil, pasien pediatric, dan pasien dengan kondisi inflamasi. Pertimbangkan karakteristik retensi agen kontras saat memilih GBCA untuk pasien tersebut.

DISETUJUI OLEH BPOM: 31/05/2021 EREG100327VR12100026

1. Isi dan indikasi MultiHance®

MultiHance® merupakan media kontras dalam bentuk steril yang mengandung gadolinium yang digunakan selama pemindaian MRI hati pada pasien dengan kondisi ginjal normal. Hal ini membantu dokter Anda untuk mengidentifikasi kelainan hati Anda. Obat ini hanya ditujukan untuk penggunaan diagnostik.

Jika Anda memiliki pertanyaan tentang cara kerja MultiHance® atau tujuan obat ini diresepkan untuk Anda, tanyakanlah kepada dokter Anda.

2. Hal yang perlu Anda ketahui sebelum menggunakan MultiHance®

MultiHance® hanya akan diresepkan kepada Anda di rumah sakit yang memiliki peralatan dan staf yang terlatih secara medis yang dapat menangani reaksi alergi yang mungkin timbul.

Jangan menggunakan MultiHance®:

- Jika Anda alergi atau sensitive terhadap gadobenate dimeglumine atau salah satu bahan lain dari obat ini (tercantum dalam bagian 6)
- Jika sebelumnya Anda pernah mengalami reaksi alergi. Jika ini terjadi pada Anda, beri tahu dokter Anda untuk tidak menggunakan MultiHance® pada pengobatan Anda.

Peringatan dan pencegahan

Konsultasikan kepada dokter Anda sebelum menggunakan MultiHance®:

- Jika Anda memiliki riwayat penyakit ginjal atau ginjal Anda tidak berfungsi dengan baik.
- Jika Anda menderita penyakit jantung atau mengalami peningkatan tekanan darah.
- Jika Anda memiliki riwayat epilepsi atau lesi otak.
- Jika Anda menggunakan alat pacu jantung, atau benda logam lainnya seperti klip, sekrup atau pelat, karena benda tersebut dapat mengganggu magnet pemindai MRI.
- Jika Anda baru saja atau akan menjalani transplantasi hati.

Jika salah satu terjadi pada Anda, **beri tahu dokter Anda sebelum menggunakan MultiHance®.**

Terdapat laporan fibrosis sistemik nefrogenik (yang menyebabkan pengerasan kulit dan dapat mempengaruhi jaringan lunak dan organ dalam) pada pasien yang menerima agen kontras yang mengandung gadolinium.

Dokter Anda mungkin akan melakukan tes laboratorium untuk memeriksa kondisi ginjal Anda sebelum mengambil keputusan untuk menggunakan MultiHance®.

Obat-obatan lain dan MultiHance®

Tidak ada laporan reaksi antara MultiHance® dan obat-obatan lainnya.
Beritahukan kepada dokter Anda jika Anda telah menggunakan, baru-baru ini menggunakan, atau mungkin akan menggunakan obat lain.

Kehamilan dan menyusui

Konsultasikan kepada dokter Anda untuk meminta saran sebelum menggunakan obat ini.

Kehamilan
Jika Anda sedang hamil atau ada kemungkinan Anda sedang hamil atau Anda berencana untuk hamil, konsultasikan kepada dokter Anda untuk meminta saran sebelum menggunakan obat ini karena MultiHance® tidak boleh digunakan selama kehamilan kecuali bila benar-benar diperlukan.

Menyusui
Beritahu dokter Anda jika Anda sedang menyusui atau akan mulai menyusui. Dokter Anda akan mempertimbangkan apakah Anda harus terus menyusui atau menghentikan menyusui selama 24 jam setelah Anda menerima MultiHance®.

Mengemudi dan menggunakan mesin
Tidak ada informasi tentang efek MultiHance® saat mengemudi, atau menggunakan alat atau mesin. Tanyakan kepada dokter Anda apakah Anda dapat mengemudi dan apakah aman bagi Anda untuk menggunakan alat atau mesin apa pun.

Informasi penting tentang MultiHance®
Sejumlah kecil benzil alkohol (turunan alkohol) dapat terlepas dalam larutan MultiHance® selama penyimpanan. Beritahu dokter Anda jika Anda alergi terhadap benzil alkohol.

3. Cara penggunaan MultiHance®
MultiHance disuntikkan ke dalam pembuluh darah, biasanya di lengan Anda tepat sebelum pemindaian MRI. Jumlah yang akan disuntikkan tergantung pada berat badan Anda. Dokter akan menetapkan dosis yang diperlukan untuk Anda, dan perlu diingat bahwa penggunaan Multihance hanya boleh dilakukan oleh staf medis, seperti dokter dan perawat.

Dosis yang dianjurkan :
0,05 mmol/kg berat badan. Jumlah tersebut setara dengan 0,1 mL/kg MultiHance® 0,5 M.

MULTIHANCE TIDAK UNTUK DIGUNAKAN SECARA BERULANG

Dosis untuk kelompok pasien khusus
Gangguan fungsi ginjal dan gangguan fungsi hati: Penggunaan MultiHance® harus dihindari pada pasien dengan gangguan ginjal (GFR <60 mL/menit) dan pasien transplantasi hati perioperatif.

Administrasi
Staf medis yang mengawasi pemindaian Anda akan melakukan penyuntikan MultiHance® untuk Anda. Mereka harus memastikan bahwa jarum sudah diposisikan dengan benar: beri tahu mereka jika Anda merasakan nyeri atau sensasi terbakar di tempat penyuntikan saat sedang diberikan MultiHance®.

Anda harus tetap berada di lingkungan rumah sakit selama satu jam setelah waktu penyuntikan.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter Anda.

4. Efek samping yang mungkin terjadi
Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak setiap orang mengalaminya. Efek samping yang terjadi biasanya ringan sampai sedang.

Sebagian besar efek samping yang dilaporkan dengan bersifat ringan dan tidak berlangsung lama, dan dapat segera teratasi. Namun, reaksi yang parah dan mengancam jiwa dan kadang-kadang menyebabkan kematian pernah dilaporkan terjadi.

- Gangguan sistem imun
  Reaksi alergi termasuk alergi berat yang mengancam jiwa seperti syok anafilaksis.
- Gangguan sistem saraf
  Sakit kepala; rasa kesemutan, tertusuk, atau terbakar pada kulit; rasa kebas; pusing; gangguan indra perasa; kejang; pingsan; menggigil; parosmia (seperti mencium bau busuk secara terus menerus), kehilangan kesadaran
- Gangguan mata
  Gangguan penglihatan, konjungtivitis (mata merah atau peradangan pada mata)
- Gangguan jantung
  Tahap awal penyumbatan katup jantung, takikardia (jantung berdetak lebih lebih cepat), iskemia miokardium, bradikardia (jantung berdetak lebih lambat), gagal jantung, kulit kebiruan
- Gangguan pada pembuluh darah
  Tekanan darah tinggi, tekanan darah rendah, kulit terasa panas dan memerah
- Gangguan pernafasan, bagian belakang kepala, dan rongga jantung
  Sesak nafas, laringospasme (kejang sementara pada pita suara), suara mendenging, rinitis, batuk
- Gangguan pencernaan
  Mual, diare, muntah, sakit perut, buang air besar terus menerus, cairan ludah berlebih, mulut kering, pembengkakan pada mulut
- Gangguan kulit dan jaringan sub kutan
  Gatal-gatal biduran, ruam, keringat berlebih, pembengkakan pada wajah, pembengkakan di bawah kulit
- Gangguan otot, jaringan ikat, dan tulang
  Nyeri otot
- Gangguan ginjal dan saluran kemih
  Proteinuria (terdeteksi protein dalam urin)
- Gangguan umum dan lokasi penyuntikan
  Rekasi pada lokasi penyuntikan termasuk, nyeri pada lokasi penyuntikan, inflamasi, rasa terbakar, rasa hangat, kedinginan, tidak nyaman, eritema, rasa kesemutan, tertusuk, atau terbakar pada kulit, gatal-gatal, nyeri dada, demam, rasa panas, lemas
- Gangguan pada proses diagnosis
  Kelainan bektodiagram, peningkatan bilirubin pada darah, peningkatan besi dalam darah, peningkatan serum transaminase, gamma-glutamil-transferase, dehidrogenase laktat dan kreatinin.

Jika Anda mengalami efek samping setelah pemberian MultiHance®, konsultasikan kepada dokter, apoteker, atau perawat Anda.

Jika Anda memiliki pertanyaan lain yang tidak terjawab dalam leaflet ini, konsultasikan kepada dokter, apoteker, atau perawat Anda.

Pelaporan efek samping
Jika Anda mengalami efek samping, konsultasikan dengan dokter Anda, termasuk kemungkinan efek samping yang tidak tercantum dalam leaflet ini. Anda juga dapat melaporkan efek samping secara langsung:

pharmacovigilance@dipa.co.id
www.dipa.co.id

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan MultiHance®

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada kemasan.
- Simpan di bawah suhu 25°C. Jangan dibekukan.
- MultiHance harus diberikan kepada Anda segera setelah syringe ditarik.
- Jangan gunakan MultiHance jika Anda memperhatikan bahwa wadah dan penutupnya telah rusak atau larutannya telah berubah warna atau terdapat partikulat.
- Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Apoteker rumah sakit akan membuang produk atau bahan limbah yang tidak digunakan. Langkah-langkah ini akan membantu melindungi lingkungan.
- Jangan membuang obat apapun melalui limbah air atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi dalam kemasan dan informasi lainnya

Kandungan MultiHance®

- Zat aktif obat ini adalah asam gadobenic dalam bentuk gadobenate dimeglumine
  1 mL larutan injeksi mengandung: 334 mg (0,5M) asam gadobenic sebagai 529 mg gadobenate dimeglumine.
- Bahan lainnya adalah air untuk injeksi (WFI).

Bentuk MultiHance® dan isi kemasannya

MultiHance® merupakan larutan cairan steril (jernih, tidak berwarna hingga sedikit kuning) untuk injeksi intravena.

HARUS DENGAN RESEP DOKTER

Kemasan dan Nomor Izin Edar

MultiHance® 1 vial @ 10ml, No.Reg.: DKI1010400143A1

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