16 DIC 2024
CROMinFOTO s.n.c.
GRAFICA - FOTOCOMPOSIZIONE
Via G. Tartini, 2 - 20158 - MILANO
AZIENDA CERTIFICATA UNI EN ISO 9001:2015

FCI00K9-10 PIL MULTI VIAL
Versione interna: 01

Impianto di proprietà della:	BRACCO	Bracco s.p.a. via E. Folli, 50 - 20134 Milano - Italy			
patheon by Thermo Fisher Scientific	Patheon Italia S.p.A. viale G.B. Stucchi, 110 - 20900 Monza (MB)- Italy		Cliente: BRACCO s.p.a.		
Prodotto: MULTIHANCE VIAL (MALAYSIA)					
SPECIFICA RIFERIMENTO: SF 0003 IS + P	Materiale: Istruzione	Codice Patheon: 000000	Codice Patheon superato: 256808	Codice Bracco: CI00K9-10	Codice Bracco superato: CI00K909
Dimensioni: 150x560 mm	Stesa ☒ Piegata ☒ Bobina ☐ Pre taglio ☐ Passo di taglio a mm			CODICE LAETUS	Apri nota digitale se presente
Colori n°: 01	Pantone Reflex Blu				
Modifica rispetto la versione precedente:	UPDATE OF PACKAGE INSERT IN LINE WITH EU SPC/PIL				

Packaging Development	Data Emissione	Data Obsolescenza	Status

I colori su questa prova sono approssimativi, questa è una stampa a 600 dpi ottenuta con colori a base acqua CMYK. Definizione e colori non riflettono il risultato finale della produzione stampata.

FRONTE - Font size heading c.19.5 - Font size subheading c.10 - Font size main text c.8 - Font size line-spacing 9.1

BRACCO

MultiHance®

Gadobenate dimeglumine

NAME OF THE MEDICINAL PRODUCT
MultiHance, 0.5 M solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
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].
Osmolality at 37°C: 1.97 osmol/kg
Viscosity at 37°C: 5.3 mPa.s
For excipients, see List of excipients.

PHARMACEUTICAL FORM
Solution for injection
Clear aqueous solution filled into colourless glass vials.

CLINICAL PARTICULARS

Therapeutic indications
This medicinal product is for diagnostic use only.
MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (e.g. hepatocellular carcinoma) or metastatic disease. MultiHance should be used only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required.

Posology and method of administration
The recommended dose of gadobenic acid in adult patients is 0.05 mmol/kg body weight (0.1 mL/kg of the 0.5 M solution). 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.
MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations.
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.
The product should be administered intravenously either as a bolus or slow injection (10 mL/min.).
The injection should be followed by a saline flush.

Post-contrast imaging acquisition:

Liver	Dynamic imaging:	Immediately following bolus injection.
	Delayed imaging:	between 40 and 120 minutes following the injection, depending on the individual imaging needs.

Special Populations
Impaired renal function
Use of MultiHance should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see ***Special Warning and special precaution for use***).
If use of MultiHance cannot be avoided, the dose should not exceed 0.05 mmol/kg body weight. Because of the lack of information on repeated administration, MultiHance 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 ***Special Warning and special precaution for use***).
Paediatric population
No dosage adjustment is considered necessary.
Use of MultiHance is not recommended in children less than 2 years of age.

Contra-indications
MultiHance is contra-indicated in:
- patients with hypersensitivity to any of the ingredients.
- In patients with a history of allergic or adverse reactions to other gadolinium chelates.

Special warnings and precautions for use

Exposure to Gadolinium - based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:
- acute or chronic severe renal insufficiency (glomerular filtration rate <30mL/min/1.73m2),
or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the preoperative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering GBCAs, do not exceed the dose recommended in product labeling.
Allow sufficient time for elimination of the GBCA prior to any readministration.

Patients should be kept under close supervision 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.
The accepted general safety procedures 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.
Caution is advised in patients with cardiovascular disease.
The use of diagnostic contrast media, such as MultiHance, should be restricted to hospitals or clinics staffed for intensive care emergencies and where cardiopulmonary resuscitation equipment is readily available.
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.
Gadobenic acid must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use.
After administration of gadobenic acid, gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. The possible diagnostic advantages of using MultiHance in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.
Hypersensitivity reactions
As with other gadolinium chelates, the possibility of a reaction, including serious, life-threatening, or fatal anaphylactic and anaphylactoid reactions involving one or more body systems, mostly respiratory, cardiovascular and/or mucocutaneous systems, 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.
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.
As with other gadolinium-chelates, a contrast-enhanced MRI should not be performed within 7 hours of a MultiHance-enhanced MRI examination to allow for clearance of MultiHance from the body.
Extravasation of MultiHance might lead to injection site reactions (see ***Undesirable Effects***). Exercise caution to avoid local extravasation during intravenous administration of MultiHance. If extravasation occurs, evaluate and treat as necessary if local reactions develop.
Impaired renal function
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 severe renal impairment (GFR<30ml/min/1.73m²).
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.
Elderly
As the renal clearance of gadobenate dimeglumine may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Interaction with other medicinal products and other forms of interaction
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 programme.

Pregnancy and lactation
Pregnancy
Data on the use of gadolinium-based contrast agents including gadobenic acid in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the foetus. Animal studies have shown reproductive toxicity at repeated high doses (see ***Preclinical safety data***). MultiHance should not be used during pregnancy unless the clinical condition of the woman requires use of gadobenate dimeglumine.
Lactation
Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see ***Preclinical safety data***). 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.

Effects on ability to drive and use machines
On the basis of the pharmacokinetics and pharmacodynamics profiles, no or negligible influence is expected with the use of MultiHance on the ability to drive or use machines.

Undesirable effects
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, Dizziness, Taste perversion	Convulsion, Syncope, Hypoaesthesia, Tremor, Parosmia	Loss of consciousness
Eye disorders			Visual impairment	Conjunctivitis
Cardiac disorders		First-degree atrioventricular block, Tachycardia	Myocardial ischaemia, Bradycardia	Cardiac arrest, Kounis syndrome***, Cyanosis
Vascular disorders		Hypertension, Hypotension, Flushing		
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Dyspnoea, Laryngospasm, Wheezing, Rhinitis, Cough	Respiratory failure, Laryngeal oedema, Hypoxia, Bronchospasm
Gastrointestinal disorders	Nausea	Diarrhoea, Vomiting, Dry mouth	Salivary hypersecretion, Abdominal pain	Oedema mouth
Skin & subcutaneous tissue disorders		Urticaria, Rash including erythematous rash, macular and maculo-papular rash, Pruritus	Face oedema, Sweating increased	Angioedema
Musculoskeletal, connective tissue and bone disorders			Myalgia	

SENSO MACCHINA LETTURA CODICE

SENSO MACCHINA LETTURA CODICE

16 DIC 2024
CROMinFOTO s.n.c.
GRAFICA - FOTOCOMPOSIZIONE
Via G. Tartini, 2 - 20158 - MILANO
AZIENDA CERTIFICATA UNI EN ISO 9001:2015

FCI00K9-10 PIL MULTI VIAL
Versione interna: 01

Impianto di proprietà della: BRACCO — Bracco s.p.a. via E. Folli, 50 - 20134 Milano - Italy
patheon by Thermo Fisher Scientific — Patheon Italia S.p.A. viale G.B. Stucchi, 110 - 20900 Monza (MB)- Italy — Cliente: BRACCO s.p.a.
Prodotto: MULTIHANCE VIAL (MALAYSIA)

SPECIFICA RIFERIMENTO: SF 0003 IS + P	Materiale: Istruzione	Codice Patheon: 000000	Codice Patheon superato: 256808	Codice Bracco: CI00K9-10	Codice Bracco superato: CI00K909

Dimensioni: 150x560 mm — Stesa ☒ Piegata ☒ Bobina ☐ Pre taglio ☐ Passo di taglio a mm
CODICE LAETUS
Apri nota digitale se presente

Colori n°:	Pantone Reflex Blu					
01						

Modifica rispetto la versione precedente: UPDATE OF PACKAGE INSERT IN LINE WITH EU SPC/PIL

Packaging Development	Data Emissione	Data Obsolescenza	Status

I colori su questa prova sono approssimativi, questa è una stampa a 600 dpi ottenuta con colori a base acqua CMYK. Definizione e colori non riflettono il risultato finale della produzione stampata.

RETRO - Font size heading c.19.5 - Font size subheading c.10 - Font size main text c.8 - Font size line-spacing 9.1

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**
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions		Pyrexia, Feeling hot, Injection Site Reaction including injection site pain, inflammation, burning, warmth, coldness, discomfort, erythema, paraesthesia and pruritus	Chest pain, Asthenia, Malaise, Chills	Injection site swelling, Injection site vesicles
Investigations		Electrocardiogram abnormalities*, Blood bilirubin increased, Increases in serum transaminases, gamma-glutamyl-transferase and creatinine	Blood albumin decreased, Alkaline phosphatase increased, Blood iron increased, Increase in lactic dehydrogenase	

* 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 5,712 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.
*** Allergic acute coronary syndrome

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 **Special warnings and precautions for use**). 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 **Special warnings and precautions for use**).

Paediatric population

System Organ Class	Adverse Reactions — Clinical Trials	
	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)
Nervous system disorders		Dizziness
Eye disorders		Eye pain, Eyelid oedema
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting	Abdominal pain
Skin and subcutaneous tissue disorders		Rash, Sweating increased
General disorders and administration site conditions		Chest pain, Injection site pain, Pyrexia

The adverse reactions reported among paediatric patients treated with MultiHance during clinical trials and tabulated above were non-serious. The adverse reactions identified during post-marketing surveillance indicate that MultiHance safety profile is similar in children and adults.

Overdose
There have been no cases of overdose reported. Therefore, the signs and symptoms of overdosage have not been characterised. Doses up to 0.4 mmol/kg were administered to healthy volunteers, without any serious adverse events. However, doses exceeding the specific approved dosage are not recommended. In the event of overdosage, the patient should be carefully monitored and treated symptomatically.
MultiHance can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: paramagnetic contrast media, ATC code V08CA08

Mechanism of action and pharmacodynamic effects
The gadolinium chelate, gadobenate dimeglumine, shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons.
The relaxivities of gadobenate dimeglumine in aqueous solution are r_1 = 4.39 and r_2 = 5.56 $mM^{-1}s^{-1}$ at 20 MHz.
Gadobenate dimeglumine experiences a strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins, r_1 and r_2 values were 9.7 and 12.5 respectively in human plasma.

Clinical efficacy and safety
In liver imaging, MultiHance may detect lesions not visualised in pre-contrast enhanced MRI examination of patients with known or suspected hepatocellular cancer or metastatic disease. The nature of the lesions visualised after contrast enhancement with MultiHance has not been verified by pathological anatomical investigation. Furthermore, where the effect on patient management was assessed, the visualisation of post-contrast-enhanced lesions was not always associated with a change in the patient management.
In the liver MultiHance provides strong and persistent signal intensity enhancement of normal parenchyma on T1-weighted imaging. The signal intensity enhancement persists at high level for at least two hours after the administration of doses of either 0.05 or 0.10 mmol/kg. Contrast between focal liver lesions and normal parenchyma is observed almost immediately after bolus injection (up to 2-3 minutes) on T1-weighted dynamic imaging. Contrast tends to decrease at later time points because of non-specific lesion enhancement. However, progressive washout of MultiHance from the lesions and persistent signal intensity enhancement of normal parenchyma are considered to result in enhanced lesion detection and a lower detection threshold for lesion site between 40 and 120 minutes after MultiHance administration.
Data from pivotal Phase II and Phase III studies in patients with liver cancer indicate that, compared with other reference imaging modalities (e.g. intraoperative ultrasonography, computed tomographic angio-portography, CTAP, or computed tomography following intra-arterial injection of iodized oil), with MultiHance enhanced MRI scans there was a mean sensitivity of 95% and a mean specificity of 80% for detection of liver cancer or metastasis in patients with a high suspicion of these conditions.

Pharmacokinetic properties
Modelling of the human pharmacokinetics was well described using a biexponential decay model. The apparent distribution and elimination half-times range from 0.085 to 0.117 h and from 1.17 to 1.68 respectively. The apparent total volume of distribution, ranging from 0.170 to 0.248 L/kg body weight, indicates that the compound is distributed in plasma and in the extracellular space.
Gadobenate ion is rapidly cleared from plasma and is eliminated mainly in urine and to a lesser extent in bile. Total plasma clearance, ranging from 0.098 to 0.133 L/h/Kg body weight, and renal clearance, ranging from 0.082 to 0.104 L/h/Kg body weight, 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.
Disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.
Population pharmacokinetic analysis was performed on systemic drug concentration-time data from 80 subjects (40 adult healthy volunteers and 40 paediatric patients) aged 2 to 47 years following intravenous administration of gadobenate dimeglumine. The kinetics of gadolinium down to the age of 2 years could be described by a two-compartment model with standard allometric coefficients and a covariate effect of creatinine clearance (reflecting glomerular filtration rate) on gadolinium clearance. The pharmacokinetic parameter values (referenced to adult body weight) were consistent with previously reported values for MultiHance and consistent with the physiology presumed to underlie MultiHance distribution and elimination: distribution into extracellular fluid (approximately 15 L in an adult, or 0.21 L/kg) and elimination by glomerular filtration (approximately 130 mL plasma per minute in an adult, or 7.8 L/h and 0.11 L/h/kg). Clearance and volume of distribution decreased progressively for younger subjects due to their smaller body size. This effect could largely be accounted for by normalising pharmacokinetic parameters for body weight. Based on this analysis, weight based dosing for MultiHance in paediatric patients gives similar systemic exposure (AUC) and maximum concentration (Cmax) to those reported for adults, and confirms that no dose adjustment is necessary for the paediatric population over the proposed age range (2 years and above).
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.

Preclinical safety data
Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
Indeed, preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Animal experiments revealed a poor local tolerance of MultiHance, especially in case of accidental paravenous application where severe local reaction, such as necrosis and eschars, could be observed.
Local tolerance in case of accidental intra-arterial application has not been investigated, so that it is particularly important to ensure that the i.v. needle or cannula is correctly inserted into a vein (see ***Posology and method of administration***).

Pregnancy and lactation
In animal studies no untoward effects on the embryonic or foetal development were exerted by daily intravenous administration of gadobenate dimeglumine in rats. Also, no adverse effects on physical and behavioural development were observed in the offspring of rats. However, after repeated daily dosing in rabbit, isolated cases of skeletal variations and two cases of visceral malformations were reported.

PHARMACEUTICAL PARTICULARS

List of excipients
Water for injections.

Incompatibilities
MultiHance should not be mixed with any other drug.

Shelf life
3 years
From a microbiological point of view, the product should be used immediately after drawing into the syringe.

Special precautions for storage
Store below 30°C. Do not freeze.

Nature and contents of container
5 mL, 10 mL, 15 mL and 20 mL of a clear aqueous solution filled into single dose colourless type I glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps.
Not all pack sizes may be marketed.

Special precautions for disposal and other handlings
MultiHance should be drawn up into the syringe immediately before use and should not be diluted.
Before use, examine the product to assure that the container and closure have not been damaged, the solution is not discoloured and no particulate matter is present.
When MultiHance is used in conjunction with an injector system, the connecting tubes to the patient and the relevant disposable parts should be disposed after each patient examination. Any additional instructions from the respective equipment manufacturer must also be adhered to.
For single use only. Any unused product or waste material should be discarded.

Manufactured For: Bracco Imaging s.p.a., Via Egidio Folli 50, 20134 Milan, Italy

By: Patheon Italia S.P.A, 2° Trav. SX Via Morolense 5, 030313 Ferentino (FR), Italy.

DATE OF PARTIAL REVISION OF THE TEXT: January 2025

CI00K9-10 - 000000