יולי 2013

MultiHance® 0.5 M, Solution for injection

צוות רפואי נכבד,

חברת דקסל פארמה מבקשת להודיעכם על עדכון בעלון לרופא של התכשיר
.MultiHance®, 0.5 M solution for injection

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פנייה
לבעל הרישום: דקסל בע"מ, רח' דקסל 1, אור – עקיבא 3060000, ישראל, טל': 04-6364000.

הרכב:

Gadobenic Acid (as dimeglumine salt) 334 mg/ml

התוויות מאושרות:

MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) indicated for:

- MRI of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease.
- MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.
- Contrast-enhanced MR- angiography where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries.

העלון לרופא עודכן במאי 2013, העדכון הינו בסעיפים הבאים:

2. 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].

5 ml of solution for injection contain: gadobenic acid 1670 mg (2.5 mmol) as dimeglumine salt. [gadobenate dimeglumine 2645 mg = gadobenic acid 1670 mg + meglumine 975 mg].

10 ml of solution for injection contain: gadobenic acid 3340 mg (5 mmol) as dimeglumine salt. [gadobenate dimeglumine 5290 mg = gadobenic acid 3340 mg + meglumine 1950 mg]
15 ml of solution for injection contain: gadobenic acid 5010 mg (7.5 mmol) as dimeglumine salt. [gadobenate dimeglumine 7935 mg = gadobenic acid 5010 mg + meglumine 2925 mg].
20 ml of solution for injection contain: gadobenic acid 6680 mg (10 mmol) as dimeglumine salt. [gadobenate dimeglumine 10580 mg = gadobenic acid 6680 mg + meglumine 3900 mg].

For excipients, see 6.1.

4.2 Posology and Method of Administration

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

MRI of the brain and spine: the recommended dose of MultiHance injection in adult and in paediatric patients greater than 2 years of age is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution.

MRA: the recommended dose of MultiHance injection in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution.

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.

Liver and Brain and Spine: the product should be administered intravenously either as a bolus or slow injection (10 mL/min.).

MRA: the product should be administered intravenously as a bolus injection, either manually or using an automatic injector system.

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.
Brain and Spine	up to 60 minutes after the administration.	
MRA	immediately after the administration, with scan delay calculated on the basis of test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection ≤2 mL of the agent should be used to calculate the appropriate scan delay.	

Special Populations

Impaired renal function

Use of MultiHance should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of MultiHance cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine or MR-angiography and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. 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 section 4.4).

~~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.~~

Paediatric population

No dosage adjustment considered necessary.

Use for MRI of the brain and spine is not recommended in children less than 2 years of age.

Use for MRI of the liver and MRA is not recommended in children less than 18 years of age.

4.4 Special warnings and special precautions for use

~~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.~~

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4.6 Pregnancy and lactation

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Lactation

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

4.8 Undesirable effects

The following adverse events were seen during the clinical development of MultiHance among 2637 adult subjects. There were no adverse reactions with a frequency greater than 2%.

System organ classes	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Infections and infestations		Nasopharyngitis	
Nervous system disorders	Headache	Paraesthesia, dizziness, syncope, parosmia	Hyperaesthesia, tremor,intracranial hypertension, hemiplegia
Eye disorders			Conjunctivitis
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Tachycardia, atrial fibrillation, first-degree atrioventricular block, ventricular extrasystoles, sinus bradycardia	Arrhythmia, myocardial ischaemia, prolonged PR interval
Vascular disorders		Hypertension, hypotension	

Respiratory, thoracic and mediastinal disorders		Rhinitis	Dyspnoea N.O.S., laryngospasm, wheezing, pulmonary congestion, pulmonary oedema
Gastrointestinal disorders	Nausea	Dry mouth, taste perversion, diarrhoea, vomiting, dyspepsia, salivation, abdominal pain	Constipation, faecal incontinence, necrotising pancreatitis
Skin & subcutaneous tissue disorders		Pruritus, rash, face oedema, urticaria, sweating	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia	
Renal and urinary disorders			Urinary incontinence, urinary urgency
General disorders and administration site conditions	Injection Site Reaction, feeling hot	Asthenia, fever, chills, chest pain, pain, injection site pain, injection site extravasation	injection site inflammation
Investigations		Abnormal laboratory tests, abnormal ECG, prolonged QT	

Laboratory abnormalities cited above include hypochromic anaemia, leukocytosis, leukopenia, basophilia, hypoproteinaemia, hypocalcaemia, hyperkalaemia, hyperglycaemia or hypoglycaemia, albuminuria, glycosuria, haematuria, hyperlipidaemia, hyperbilirubinaemia, serum iron increased, and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, and in serum creatinine and were reported in equal or less than 0.4% of patients following the administration of MultiHance. However these 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.

paediatric
In paediatric patients enrolled in clinical trials the most commonly reported adverse reactions included vomiting (1.4 %), pyrexia (0.9%) and hyperhydrosis (0.9%). The frequency and nature of adverse reactions was similar to that in adults.
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5.1 Pharmacodynamic properties

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In MRI of the brain and spine, MultiHance enhances normal tissues lacking a blood-brain barrier, extra axial tumours and regions in which the blood-brain-barrier has broken down. In the pivotal phase III clinical trials conducted in adults for ~~in~~ this indication, designed as parallel-group comparisons, off-site readers reported an improvement in level of diagnostic information in 32-69% of images with MultiHance, and 35-69% of images with the active comparator.

In two studies designed as intra-individual, crossover comparisons of 0.1 mmol/kg body weight MultiHance vs 0.1 mmol/kg body weight of two active comparators (gadopentetate dimeglumine or gadodiamide), conducted in patients with known or suspected brain or spine disease undergoing MRI of the central nervous system (CNS), MultiHance provided significantly ($p<0.001$) higher increase in lesion signal intensity, contrast-to-noise ratio, and lesion-to-brain ratio, as well as significantly ($p<0.001$) better visualisation of CNS lesions in images obtained with 1.5 Tesla scanners as tabulated below.

Visualisation of CNS Lesions Endpoints	Improvement Provided by MultiHance Over gadopentetate dimeglumine (Study MH-109) (n=151)	p-value	Improvement Provided by MultiHance Over gadodiamide (Study MH-130) (n=113)	p-value
Definition of extent of CNS Disease	25% to 30%	<0.001	24% to 25%	<0.001
Visualisation of Lesion Internal Morphology	29% to 34%	<0.001	28% to 32%	<0.001

Delineation of Borders of Intra- and Extra-axial Lesions	37% to 44%	<0.001	35% to 44%	<0.001
Lesion Contrast Enhancement	50% to 66%	<0.001	58% to 67%	<0.001
Global Diagnostic Preference	50% to 68%	<0.001	56% to 68%	<0.001

In the trials MH-109 and MH-130, the impact of improved visualization of CNS lesions with MultiHance versus gadodiamide or gadopentetate dimeglumine on diagnostic thinking and patient management was not studied.

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5.2 Pharmacokinetic properties

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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).

5.3 Preclinical safety data

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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.

In animal studies minimum amounts (less than 0.5% of the administered dose) were passed from the mother to the newborn through the breast milk.

6.5 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.