Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe

UK/H/0234/002/DC
UK licence no: PL 06099/0012

Bracco SpA

LAY SUMMARY

The Medicine and Healthcare products Regulatory Agency (MHRA) granted Bracco SpA a Marketing Authorisation (licence) for the medicinal product MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe. This is a prescription-only medicine (POM) used for diagnostic purposes only.

MultiHance (gadobenate dimeglumine, 0.5 M injectable solution), is an approved gadolinium based contrast agent or special dye. It is used in magnetic resonance imaging (MRI) of the liver, the brain and spine. MultiHance is currently marketed in glass vials. The current application for a pre-filled syringe is a new presentation of the already approved product, i.e., the same solution for injection now being packaged in a plastic pre-filled syringe instead of a glass vial. MultiHance was first approved in the UK on 22nd July 1997.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	MutiHance 529mg/ml Solution for Injection in Pre-Filled Syringe
Type of Application	Full Dossier (or Extension), Article 8.3
Active Substance	Gadobenate dimeglumine
Form	Solution For Infusion
Strength	529mg/ml
MA Holder	Bracco SpA Via Egidio Folli 50-20134, Milan, Italy
RMS	UK
CMS	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Spain, Sweden.
Procedure Number	UK/H/0234/002/DC
Timetable	Day 210 – 11th February 2008

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
MultiHance 529 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution for injection contains: gadobenic acid 334 mg (0.5 mmol) as dimeglumine salt.
[Gadobenate dimeglumine 529 mg = gadobenic acid 334 mg + meglumine 195 mg].
10 ml of solution for injection contain: gadobenic acid 3340 mg (0.5 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 (0.5 mmol) as dimeglumine salt.
[gadobenate dimeglumine 7935= gadobenic acid 5010 mg + meglumine 2925]
20 ml of solution for injection contain: gadobenic acid 6680 mg (0.5 mmol) as dimeglumine salt.
[gadobenate dimeglumine 10580 mg = gadobenic acid 6680 mg + meglumine 3900]
For a full list of excipients, see Section 6.1'.

3 PHARMACEUTICAL FORM
Solution for injection in a pre-filled syringe.
Clear, colourless to slightly yellow, aqueous solution.
Osmolality at 37°C: 1.97 osmol/kg
Viscosity at 37°C: 5.3 mPa.s
pH: 6.9-7.3

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.
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.

4.2 Posology and method of administration
MRI 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.
MRI of the brain and spine : the recommended dose of MultiHance 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 used immediately after opening and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations.
To use the syringe, the threaded tip of the plunger rod clockwise should be screwed into the plunger and pushed forward a few millimetres to break any friction between the plunger and syringe barrel.
Whilst holding syringe erect (with the nozzle cap upwards), the nozzle cap should be removed aseptically from the tip of the syringe and either a sterile, disposable needle or 5/6 tubing with a compatible luer lock should be attached using a push-twist action.
While still holding the syringe erect, the plunger should be pushed forward until all the air is evacuated and the fluid either appears at the tip of the needle or the tubing is completely filled.
The injection should be completed following the usual aspiration procedure.
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 flush of sodium chloride 9 mg/ml (0.9%) solution for injection.

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.	

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.

4.3 Contraindications

MultiHance is contra-indicated in patients with hypersensitivity to the active substance or to any of the excipients.
MultiHance should not be used in patients with a history of allergic or adverse reactions to other gadolinium chelates.

4.4 Special warnings and precautions for use

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.
Small quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Thus 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.
Impaired renal function
There have been reports of Nephrogenic Systemic Fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR<30ml/min/1.73m^2). As there is a possibility that NSF may occur with MultiHance, it should be avoided in patients with acute or chronic severe renal impairment (GFR<30ml/min/1.73m^2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period unless the diagnostic information is essential and cannot be obtained through other means.
The risk for the development of NSF in patients with moderate renal impairment is unknown, therefore MultiHance should be used with caution in patients with moderate renal impairment (GFR 30-59ml/min/1.73m^2).
All patients should be screened, in particular patients over the age of 65, for renal dysfunction by obtaining a history and/or laboratory tests.
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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed during the clinical development of MultiHance. However no drug interactions were reported during the clinical development programme.

4.6 Pregnancy and lactation

There are no adequate data for the use of gadobenate dimeglumine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. MultiHance should not be used during pregnancy unless clearly necessary.
Although it is not known to what extent gadobenate dimeglumine is excreted in human milk, it is known from animal experiments that minimal amounts, less than 0.5% of the administered dose were transferred via milk from mother to new-born infants. Although the clinical relevance of this observation is unknown, breast-feeding should be discontinued prior to the administration of

MultiHance and should not be recommenced until at least 24 hours after the administration of MultiHance.

4.7 Effects on ability to drive and use machines

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.

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.
In marketed use, adverse reactions were reported in fewer than 0.1 % of patients.
Most commonly reported were: nausea, vomiting, signs and symptoms of hypersensitivity reactions including anaphylactic shock, anaphylactoid reactions, angioedema, laryngeal spasm and rash.
Injection site reactions due to extravasation of the contrast medium leading to local pain or burning sensations, swelling and blistering have been reported.
Isolated cases of NSF have been reported with MultiHance in patients co-administered other gadolinium-containing contrast agents (see Section 4.4).

4.9 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 has been shown to be dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media ATC code V08CA08
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.
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.
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.
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 in this indication, 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.

5.2 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.
Gadobenate ion does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.

5.3 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 section 4.2).
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years
From a microbiological point of view, the product should be used immediately after opening.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

10, 15 and 20 mL solution filled into a transparent plastic (cyclic polyolefin) syringe with chlorobutyl rubber plunger and tip cap.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.
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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

(Company) Name: Bracco SpA
Address:via Egidio Folli 50 – 20134 Milan
Country:Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 06099/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2008

10 DATE OF REVISION OF THE TEXT

19/02/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

BRACCO

MultiHance® 529 mg/ml solution for injection in pre-filled syringe

Gadobenate dimeglumine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT MULTIHANCE® IS AND WHAT IT IS USED FOR

MultiHance® is a special dye (or contrast agent) which contains the rare earth metal gadolinium and improves images of the liver, brain and spine during magnetic resonance imaging (MRI) scans. It helps your doctor to identify any abnormalities of your liver, brain or spine.
This medicine is for diagnostic use only.

2. BEFORE YOU USE MULTIHANCE®

Do not use MULTIHANCE®
- If you are allergic (hypersensitive) to gadobenate dimeglumine or any of the other ingredients of MultiHance®.
- If you have had any allergic reaction (hypersensitivity reaction) in the past such as rash, itching, urticaria (hives) or difficulty in breathing following injection of any special dye or contrast agent for a MRI scan.

Tell your doctor if you think any of the points in this section apply to you.

Take special care with MULTIHANCE®
MultiHance® should only be given to you in a hospital or clinic where there are equipment and medically trained staff able to deal with allergic reactions.

Before treatment with MultiHance® tell your doctor if:

- you suffer from **a heart problem** or have **raised blood pressure**
- you have a **cardiac pacemaker**, or you are aware of the presence in your body of any other metallic objects such as clips, screws or plates as these might interfere with the magnet of the MRI scanner
- you are under **18** years of age
- you suffer from **kidney problems** as use of some gadolinium-containing contrast agents in patients with these conditions has been associated with a disease called nephrogenic systemic fibrosis (NSF). NSF is a disease involving thickening of the skin and connective tissues. NSF may result in debilitating joint immobility, muscle weakness or impairment of the function of internal organs which may potentially be life threatening
- if you are allergic (hypersensitive) to benzyl alcohol, because small quantities of benzyl alcohol (a derivative of alcohol) can be released in the MultiHance® solution during storage.

Using other medicines
There are no reports of reactions between MultiHance® and other medicines.

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
MultiHance® should not be used during pregnancy unless clearly necessary. Ask your doctor for advice before being given this medicine.

If you are breast-feeding you should **stop before being given MultiHance®** and you should not start again **until 24 hours afterwards.**

Ask your doctor or pharmacist for advice before taking medicine.

Driving and using machines
There is no information about the effects of MultiHance® on driving, or using tools or machines. Ask your doctor if you can drive and if it is safe for you to use any tools or machines.

3. HOW TO USE MULTIHANCE®

MultiHance® is injected into a vein, usually in your arm just before the MRI scan. The amount in millilitre you will be injected depends on how much you weigh in kilogram of body weight.

The usual **dose for MRI of the liver** is: 0.1 ml per kilogram of body weight
The usual **dose for MRI of brain/spine** is: 0.2 ml per kilogram of body weight

The medical staff supervising your scan will administer your injection of MultiHance®. They should ensure that the needle is correctly positioned: tell them if you feel pain or a burning sensation at the site of the injection while it is being administered.

You should remain in the hospital environment for one hour after the time of the injection.
If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, MultiHance® can cause side effects, although not everybody gets them.
Most of the side effects that have been reported with MultiHance® have been mild and were not prolonged, and spontaneously resolved without residual effects.

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Most of the side effects that have been reported with MultiHance® have been mild and were not prolonged, and spontaneously resolved without residual effects.

Possible side effects	
Common: (More than 1 out of 100 persons and less 1 out of 10 persons)	- Headache - Nausea - Feeling hot - Local reactions where the injection was given such as: swelling, pain or an unusual sensation at the injection site
Uncommon: (More than 1 out of 1,000 persons and less than 1 out of 100 persons)	- Changes in blood pressure, and in heart rate or rhythm, abnormal electrocardiogram (a test that monitors changes in your heart beat) - Pain in the chest - Dry mouth, changes in taste, vomiting, diarrhoea - Dizziness, acute sensitivity to touch/pain/or other stimuli, generalised numbness, tingling - Sweating, feeling weak, chills, raised body temperature
	- Itching, skin rash, urticaria (hives) - Fainting - Heart burn, abdominal pain - Pain in the back or in muscles - Strange smell, increase in salivation - Leakage out of the vein that can cause a burning sensation and blistering around the injection site - Inflammation of nose or throat - Swollen face and neck - **Abnormal laboratory tests**, such as: - changes in liver function tests, - reduction of haemoglobin (the oxygen carrying component) in the blood, - abnormal blood and urine tests, blood in urine, - changes in the mineral composition of blood.
Rare: (More than 1 out of 10,000 persons and less than 1 out of 1,000 persons)	- **Allergic reaction**, which infrequently can lead to shock, may include, besides itching, skin rash, urticaria, fainting, swollen face and neck and inflammation of nose or throat, also: - Shortness of breath, throat spasm, wheezing - Inflammation of your eyes (conjunctivitis) - Tremor - Ringing in the ears (tinnitus) - Incontinence of urine and stool, urgency to urinate, difficulty in defecation - Inflammation of the pancreas (pancreatitis) - Fluid in the lungs (pulmonary oedema) - Increase in fluid pressure in the brain (intracranial hypertension) - Loss of strength in arm, leg and sometimes face on one side of the body (hemiparesis)

If you think you notice any side effects after receiving an injection of MultiHance®, immediately tell the medical staff supervising your scan.

If you have any other questions not answered in this leaflet please ask the medical staff supervising your scan.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE MULTIHANCE®

- Keep out of the reach and sight of children.
- Do not use MultiHance® after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Do not freeze.
- MultiHance® should be administered to you immediately after opening.
- Do not use MultiHance® if you notice that the container and closure have been damaged or the solution is discoloured or particulate matter is present.
- Medicines should not be disposed of via wastewater or household waste. The hospital pharmacist will dispose any unused product or waste material. These measures will help to protect the environment.

6. FURTHER INFORMATION

What MULTIHANCE® contains

1 ml of solution for injection contains: gadobenic acid 334 mg (0.5 mmol) as gadobenate dimeglumine (529 mg).
Quantity of gadobenate dimeglumine:
10 ml: 5290 mg
15 ml: 7935 mg
20 ml: 10580 mg

What MULTIHANCE® looks like and contents of the pack

MultiHance® is an aqueous solution for injection in pre-filled syringe (clear, colourless to slightly yellow colour).
MultiHance® is supplied in pre-filled syringes containing 10 ml, 15 ml, or 20 ml of solution for injection.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bracco s.p.a.
Via E. Folli, 50
20134 Milan (Italy)

Manufacturer

Bracco Imaging S.p.A
Via Ribes 5,
10010 Colleretto Giacosa (TO)
Italy

This leaflet was last approved in February 2008

The following information is intended for medical or healthcare professionals only.

To use the syringe, the threaded tip of the plunger rod clockwise should be screwed into the plunger and pushed forward a few millimetres to break any friction between the plunger and syringe barrel.

Whilst holding syringe erect (with the nozzle cap upwards), the nozzle cap should be removed aseptically from the tip of the syringe and either a sterile, disposable needle or 5/6 tubing with a compatible luer lock should be attached using a push-twist action.

While still holding the syringe erect, the plunger should be pushed forward until all the air is evacuated and the fluid either appears at the tip of the needle or the tubing is completely filled.

The injection should be completed following the usual aspiration procedure.

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.).

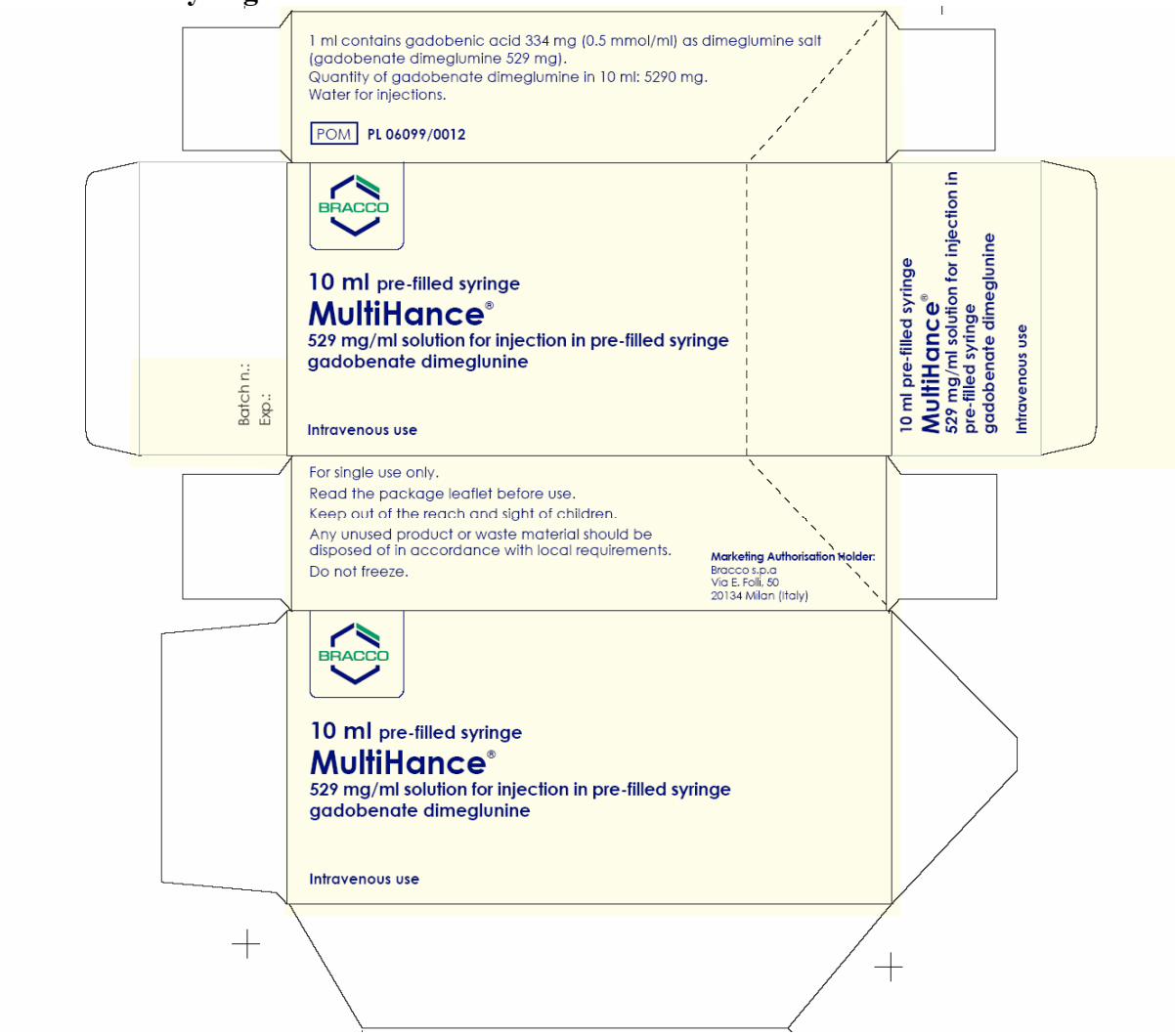
The injection should be followed by a flush of sodium chloride 9 mg/ml (0.9%) solution for injection.

Post-contrast imaging acquisition:

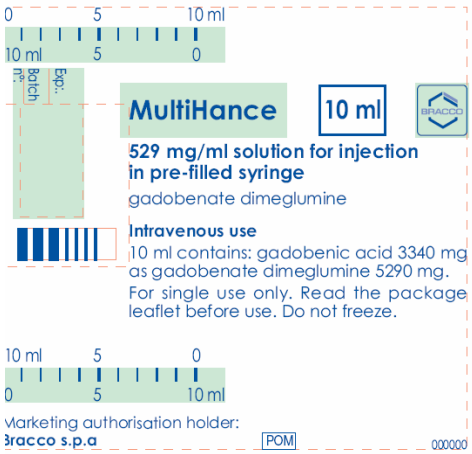
Liver	Dynamic imaging:	Immediately following bolus injection.
	Delayed imaging:	between 40 and 120 minutes following the injection, depending on the individual imaging needs.
Brain and Spine	up to 60 minutes after the administration.	

Module 4
Labelling

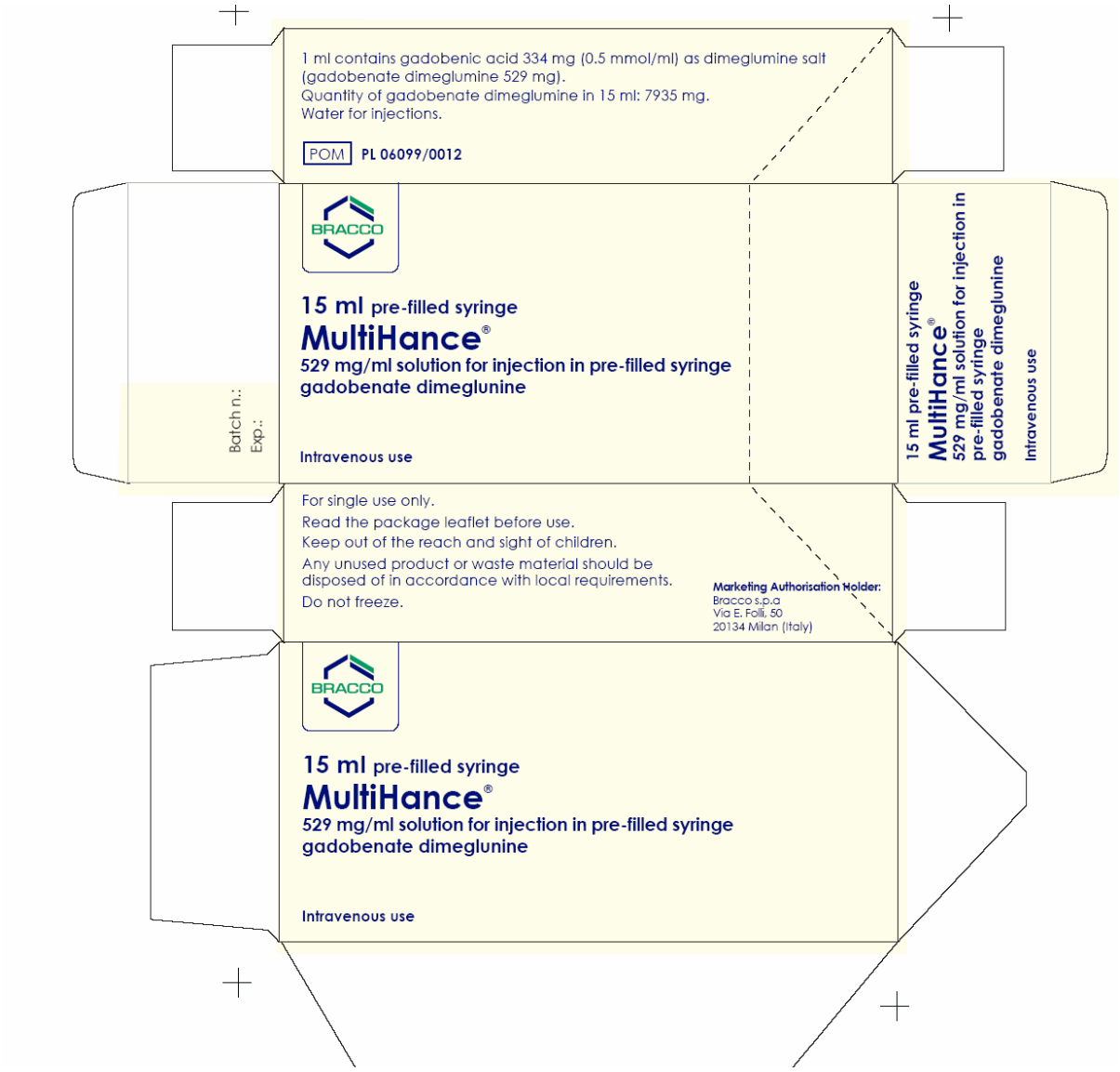
MultiHance 529mg/ml Solution for Injection
Carton-l0ml syringe



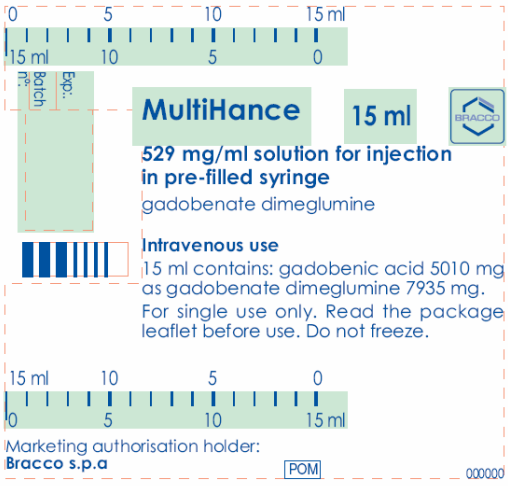
Label-10ml syringe



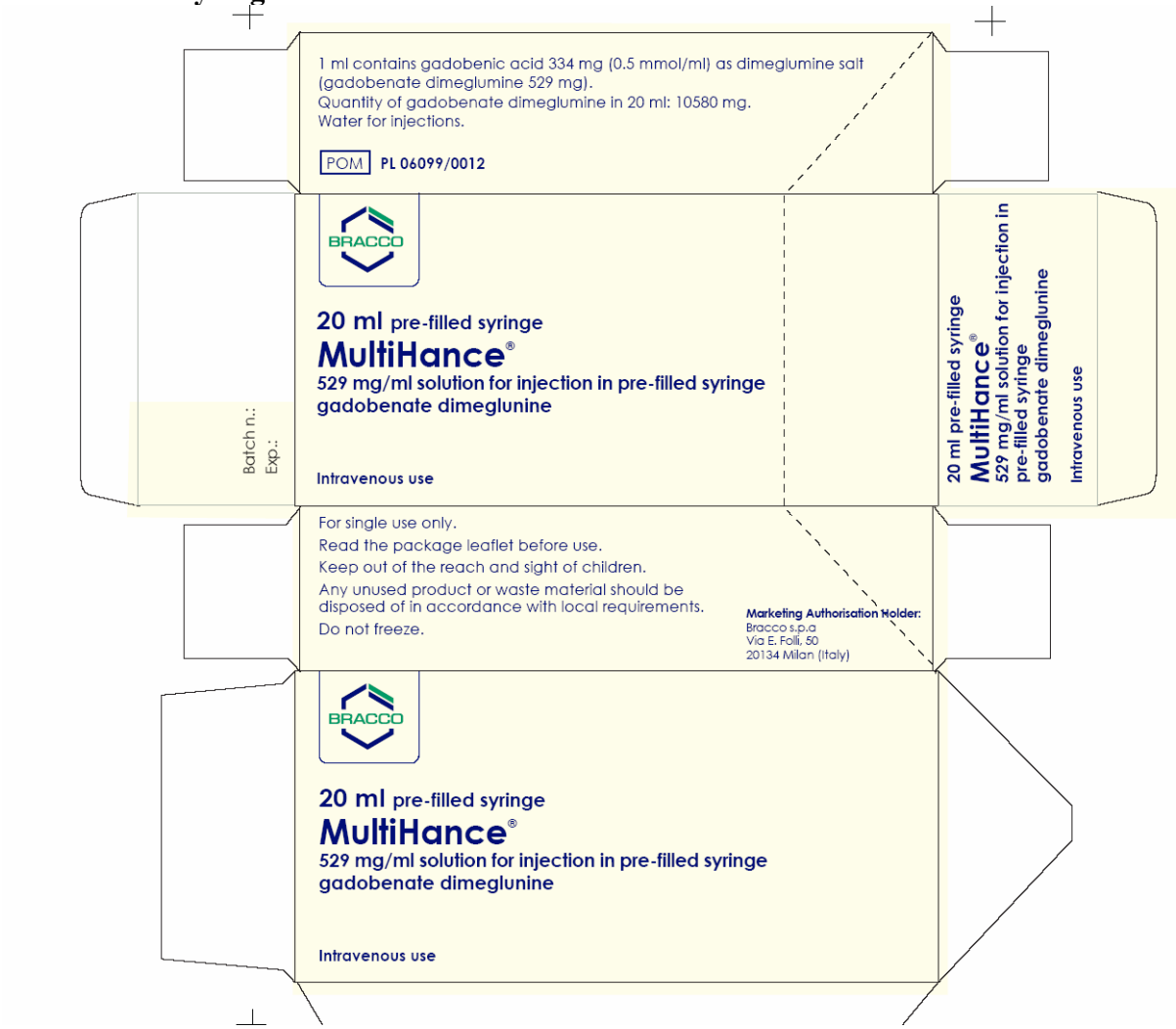
MultiHance 529mg/ml Solution for Injection
Carton-l5ml syringe



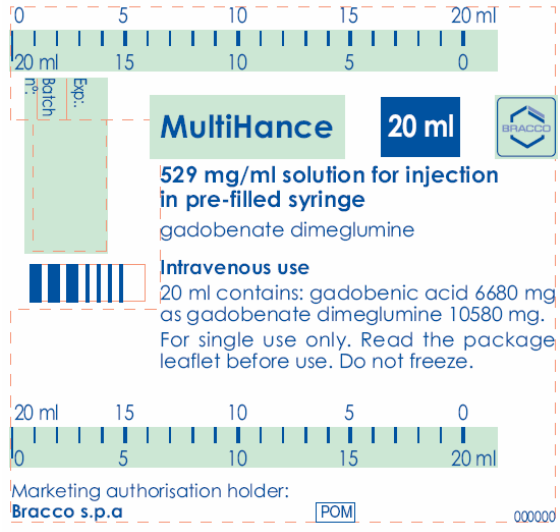
Label-15ml syringe



MultiHance 529mg/ml Solution for Injection
Carton-20ml syringe



Label-20ml syringe



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for MultiHance pre-filled syringe, used as a diagnostic contrast agent in MRI, is approvable.

This is an application for Marketing Authorisation in the UK submitted under Article 8(3) of Directive 2001/83 (as amended) concerning a line extension for a new pharmaceutical form to an existing product: pre-filled syringe of Gadobenic acid as the dimeglumine salt (gadobenate dimeglumine) solution for injection. The reference product is MultiHance 0.5M solution for injection, clear aqueous solution filled into colourless glass vials (PL 06099/0006) and was authorised in the UK, dated 22 July 1997.

MultiHance (gadobenate dimeglumine, 0.5 M injectable solution), is an approved gadolinium based contrast agent. This chelate complex of the gadolinium ion (GD3+) is used as a paramagnetic positive diagnostic contrast agent in magnetic resonance imaging (MRI) of the liver, the brain and spine. MultiHance is currently marketed in glass vials. The current application for a pre-filled syringe is a new presentation of the already approved product, i.e., the same solution for injection now being packaged in a plastic pre-filled syringe instead of a glass vial.

The application is in accordance with Article 8(3) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal Environmental Risk Assessment has not been performed as the product is another presentation of an already approved product. Hence no increase in environmental risk is to be expected compared to that of the reference product.

A Risk Management Plan has not been provided and one is not required for this application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No GCP certificate is required for this type of application.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	MutiHance 529mg/ml Solution for Injection in Pre-Filled Syringe
Name(s) of the active substance(s) (INN)	Gadobenate dimeglumine
Pharmacotherapeutic classification (ATC code)	Paramagnetic contrast media (V08CA)
Pharmaceutical form and strength(s)	529mg/ml Solution for Infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/0234/0021/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Spain and Sweden
Marketing Authorisation Number(s)	PL 06099/0012
Name and address of the authorisation holder	Bracco SpA Via Egidio Folli 50-20134, Milan, Italy

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Gadobenate Dimeglumine

The active substance gadobenate dimeglumine is not isolated for the manufacture of the drug product due to hygroscopic and deliquescent nature of the drug substance. Section 3.2.S of the dossier is therefore not submitted. This is considered acceptable.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely water for injection. An appropriate justification for the inclusion of the excipient has been provided.

The excipient used complies with its respective Ph.Eur monograph. A satisfactory certificate of analysis has been provided for the excipient.

Pharmaceutical Development

Gadobenic acid is the active substance but free gadolinium is toxic. Chelation with excess (carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid (BOPTA) is required to form a stable and non-toxic complex. The drug substance is not described in any pharmacopoeia. The composition of the test product is identical to the existing product. A satisfactory summary of the manufacturing process development is provided. There are no novel excipients used and no overages in the manufacture of the product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data for 3 commercial batches of each presentation have been provided.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in 10, 15 and 20ml transparent plastic (cyclic polyolefin) syringe with chlorobutyl rubber plunger and tip cap. Not all pack sizes may be marketed. Specifications and satisfactory certificates of analysis are provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months without the requirement of any special storage conditions is considered acceptable.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

Critical evaluation of the Non-Clinical Overview and Summary
This is an application for a change to an existing marketing Authorisation leading to an extension as referred to in Annex II of Regulations (EC) No 1084/2003 or 1085/2003. The applicant is seeking approval for the addition of a new pharmaceutical form: pre-filled syringe.

The originator product is MultiHance (gadobenate dimeglumine 0.5M solution for injection), which has been developed by Bracco and the formulation is currently marketed in glass vials since approval in 1997, via the mutual recognition procedure. Gadobenate dimeglumine is an octadentate chelate of gadolinium ion to be used as an MRI (Magnetic Resonance Imaging) contrast medium to provide contrast enhancement.

The proposed pre-filled syringe (PFS) is another presentation of the already approved product i.e. the same solution for injection is now being packaged in a plastic PFS instead of a glass vial.

The company's overview states that stability studies under ICH conditions confirmed that the impurity pattern of MultiHance in PFS is the same as that of vials, with no significant evidence of substances leaching from the syringe components. The non-clinical safety profile is unchanged to that previously submitted in the original Marketing Authorisation application.

The pharmacological, pharmacokinetic and toxicological properties of gadobenate dimeglumine are well known. Therefore no further studies are required and the applicant has provided none.

The overview has been written by a suitably qualified company employee. It is a brief statement dated December 2006 providing an acceptable rationale for the lack of further studies.

Conclusions
There are no objections to the approval of MultiHance PFS from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Introduction
No new clinical data have been submitted and none are required for this application.

The indications are:

MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver and Central Nervous System (CNS).
MultiHance is indicated, for the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease.
MultiHance is also indicated for the MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.

Assessor's comment:
The indications in the SPC for 'MultiHance pre-filled syringe formulation' are identical to the SPC for 'MultiHance glass vials'

The posology

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.

CNS: 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.

The product should be administered intravenously either as a bolus or slow injection (10 mL/min.) without dilution. Post-contrast imaging can be performed immediately following bolus injection (dynamic MRI).

In the CNS the imaging window has been shown to be up to 60 minutes after the administration. In the liver delayed imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

MultiHance prefilled syringe should be used immediately after opening 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 injection should be followed by a saline flush.

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.

Assessor's comment:
The dosing posology in the SPC for 'MultiHance pre-filled syringe formulation' is identical to the SPC for 'MultiHance glass vials'. Additional instructions for use are shown in *italics.*

Clinical Pharmacology

No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application. The pharmacodynamic and pharmacokinetic claims in the SPC are appropriately consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties of this product have been extensively studied in the past.

Clinical efficacy

No new data have been submitted and none are required for this application.

Clinical safety

No novel safety data are supplied for this application. The applicant has provided a review of the published literature confirming the safety of the product.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe is well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The use of MultiHance is well established. It has recognised efficacy and has an acceptable safety. Overall the risk: benefit analysis for MultiHance is considered favourable and the product is approvable.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome