The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

CPMP/1361/00

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

OPINION FOLLOWING A REFERRAL FOR ARBITRATION ACCORDING TO ARTICLE 7(5) OF COMMISSION REGULATION (EC) No 541/95 AS AMENDED, FOR

MultiHance

International Nonproprietary Name (INN): **gadobenic acid**

BACKGROUND INFORMATION

MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI), containing the active substance gadobenic acid 334 mg/ml, as the dimeglumine salt. The indication when first authorised in a number of Member States related to imaging 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.

In November 1998, Bracco s.p.a. submitted applications for a Type II variation in the Mutual Recognition procedure, with the United Kingdom as Reference Member State, for MultiHance. The scope of the variation was to extend the indication to include MRI imaging of the CNS, in addition to the liver. The Mutual Recognition Variation procedure started on 8 December 1998. The Concerned Member States were Austria, Belgium, Denmark, Germany, Finland, Greece, France, Ireland, Italy, Luxembourg, The Netherlands and Sweden. The Concerned Member State, France, not agreeing to the conclusions and proposals in the Reference Member State's final variation assessment report referred the reasons for disagreement to the EMEA on 5 October 1999, with a request to initiate an arbitration procedure in order to clarify the matter.

The objections raised by France related to the main Phase III trials designed to show non-inferiority of MultiHance to an authorised comparator product. In summary, the referral notification stated that it was not possible to conclude non-inferiority of MultiHance to the comparator product in the main Phase III trials, mainly due to a major problem of external validity of the comparator, and to methodological biases.

The CPMP prepared a list of questions for the Marketing Authorisation Holder, including the above issues, and the arbitration procedure started on 21 October 1999. The Applicant's response to this list of questions was received in February 2000 and the CPMP started the clock on 18 February 2000.

The CPMP having considered the written responses provided by the Applicant, the joint Rapporteur/Co-Rapporteur's assessment report, an oral explanation by the Marketing Authorisation Holder and the comments from CPMP members was of the opinion that the objections raised by France should not prevent the approval of the variation applied for.

The CPMP therefore adopted a positive opinion on 25 May 2000 CPMP recommending the granting of the variation of the Marketing Authorisation for MultiHance, and the amendment of the Summary of Product Characteristics.

An overall summary of the scientific evaluation is provided, together with the amended SPC.

A Decision was issued by the European Commission on 15 September 2000.

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SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MULTIHANCE

The supporting data for the extension of the indication to include imaging of the CNS included 13 Phase II studies and two main Phase III trials. The main trials were multicentre, randomised, double-blind, parallel group comparisons of the safety and efficacy of different single and cumulative doses of MultiHance with single and cumulative doses of a validated active (gadolinium-based) comparator product authorised in the EU for imaging of the CNS. The trials were conducted in adult patients of either gender who were highly suspected of having CNS lesions; a total of 680 patients were evaluable for safety and 665 were evaluable for efficacy. Both trials were conducted as non-inferiority studies, and diagnostic equivalence criteria were defined.

Images obtained in the respective arms of the trials were assessed by two groups of readers, i.e. 'on-site' by the investigators and independently by 'off-site' neuroradiologists unaffiliated with any of the centres in either study. The on-site assessors were blinded to the dose and nature of the test compound; off-site investigators were blinded to all patient data and to the results of the imaging procedures.

Following review in the mutual recognition procedure the main scientific questions which initiated arbitration were as follows:

1. The *a priori* choice of a confidence interval with an upper limit of 20% of the difference between results obtained in each treatment group has not been clinically justified; this is in disagreement with the current ICH E9 guideline.The above maximum expected difference and sample size calculation were based on published information for the reported effect (80%) of other gadolinium chelates, rather than the reference comparator product; this is in disagreement with the current ICH E9 guideline.
2. The observed effect of the comparator product in the submitted studies was far below the expected effect (mean 50% compared to 80%) leading to a conclusion that it was not the right comparator product.

During the arbitration procedure, the CPMP considered the supporting information provided by the Marketing Authorisation Holder but the following concerns arising from the Phase III trials were still evident and were put to the company:

1. The non-inferiority of MultiHance when compared to the chosen comparator in the claimed indication should be demonstrated. The company should provide justification that in the worst-case scenario represented by the upper confidence limit, MultiHance still retains a sufficient degree of clinical benefit to make it clinically valuable.
2. The Applicant should comment on why other more relevant comparators were not chosen as the active control when more relevant data with regard to the adequacy of the methodology used (both drug and clinical blinding, percentage patients with increase in the level of diagnostic information as a primary endpoint) were available for these.

The MAH was instructed that the above issues were to be presented during an oral explanation. In addition, the MAH was notified to discuss a number of residual minor concerns in the form of a written response. The evaluation of the written response was satisfactory in general. However, there was an additional concern as follows:

3. For both the level of diagnostic information and the increase in level of diagnostic information, there is evidence that the degree of consistency between the two readers is low. This is disappointing, as it suggests that although overall diagnostic improvements have been found with both MultiHance and the comparator in the two trials, there is little consistent pattern to these improvements. Readers could be responding to different aspects of the images, or they could be aware of a general improvement in image but finding it difficult to associate this with specific images. The values of

kappa for the detection of disease are, not surprisingly, better but still not overwhelming. This must reflect an appreciable number of instances of disagreements between readers. As a result, these studies cannot reasonably be claimed to have shown satisfactory consistency across readers.

This concern was notified to the company, with a request for this also to be addressed at the oral hearing, in order to clarify whether or not the assessment of the clinical efficacy of MultiHance was compromised by the poor inter-reader consistency.

At the oral hearing the company initially presented images showing examples of the clinical effects of MultiHance in MRI of the CNS. The company then addressed the non-inferiority issue, highlighting the improvement in image quality achieved with MultiHance and the active comparator, and the similarity in overall results between the 2 agents. The company presented the various analyses that were conducted (as discussed earlier in this report), but did not attempt to justify an appropriate value for the upper limit of the 97.23% confidence interval. However, they argued that in the worst case scenario, 20-58% of images from MultiHance recipients and 23-58% of those from comparator product recipients would show an increase in level of diagnostic information. In view of the approximately 30% of pre-dose unenhanced images that were judged to be 'excellent', the company argued that these figures represented a 'worthwhile gain'. The company also argued that the chosen comparator was appropriate, as it has been shown to have a similar degree of efficacy to that of other MRI contrast agents, i.e. those agents from which the predicted efficacy in the phase III studies was obtained.

The company next discussed the inter-reader consistency in the pivotal phase III studies, focusing on consistency in terms of detection of disease, rather than level of diagnostic information (the primary end-point). A question was asked in relation to the company's failure to discuss the inter-reader consistency for the primary end-point, which was far lower. The company argued that the detection of disease was the more clinically relevant parameter.

In response to a question, the company presented data relating to the stability of the active complex of MultiHance, together with details of the apparent lack of protein binding.

Benefit/risk considerations

The efficacy and safety of gadolinium-based compounds has been established in MRI of the CNS, and several are now licensed within the European Union. These products have been shown to improve the quality of images, increase the level of diagnostic information and improve diagnostic decision-making relative to non-enhanced scans. The chosen active comparator in the Phase III trials is one such agent, currently approved in all EU Member States for this indication at the dosage used in the pivotal phase III clinical trials of MultiHance.

Following discussion, the CPMP accepted the non-inferiority of MultiHance relative to the chosen active comparator because there was a reasonable likelihood that in the worst-case scenario, MultiHance would retain a sufficient proportion of the effect of the comparator to be clinically relevant. The CPMP noted that although the delta value for non-inferiority had not been adequately defined in terms of clinical relevance, there are currently no available data to guide such an assessment, and that a judgement in clinical terms would have to be made.

The stability of the active complex of MultiHance was considered to be acceptable following the oral hearing. Similarly, concerns over the degree of protein binding associated with the complex were deemed to have been resolved.

Thus, the CPMP considered that the efficacy of MultiHance in MRI of the CNS was acceptable, and that the outstanding safety concerns had been fully addressed by the company.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- It was appropriate to use the chosen reference product as an active comparator in the main Phase III trials in CNS imaging.
- In the worst-case scenario, it is likely that MultiHance retains a sufficient proportion of the activity of the chosen active comparator product to be clinically relevant in the context of CNS imaging.
- The stability of the active complex of MultiHance was acceptable for use in MRI of the CNS.
- There was no evidence of significant binding to plasma proteins.

the CPMP recommended the amendment of the Summary of Product Characteristics as set out in the Annex to this report.

ANNEX

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

1. TRADE NAME OF THE MEDICINAL PRODUCT

MultiHance, 334 mg/ml solution for injection

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].

Osmolality at 37°C: 1.970 osmol/kg
Viscosity at 37°C: 5.3 mPa.s

For excipients see 6.1

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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 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 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

4.3 Contra-indications

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

There are no studies with MultiHance in patients with impaired renal function (creatinine clearance $\leq$ 30 ml/min.). Therefore, MultiHance cannot be recommended for use in this group of patients.

The safety and efficacy of MultiHance have not been established in pregnant women and, therefore, MultiHance cannot be recommended for use during pregnancy (see section 4.6).

4.4 Special warnings and special precaution 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.
Patients with a history of allergy or hypersensivity should be kept under observation. 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.

4.5 Interaction with other medicaments 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.

4.6 Pregnancy and lactation

The use of MultiHance cannot be recommended in pregnant women because there are no clinical data to support its use in this group of patients (information regarding findings in reproductive toxicity studies can be found in section 5.3).
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 neonates. 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

None known.

4.8 Undesirable effects

The following adverse events were seen during the clinical development of MultiHance:
more than 1%: hypertension;
0.5 – 1%: altered sensation or pain at injection site, tachycardia, headache, nausea, vomiting;
less than 0.5%: pruritus, diarrhoea, dry mouth, vasodilation, skin rash, dizziness, tremor, abdominal pain, hypotension, arrythmia, taste perversion, localized edema.

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.

During the clinical development of MultiHance, one possible moderate anaphylactic reaction (dyspnoe and laryngeal spasm) has been reported. Also reported were single incidents of myalgia, convulsion, urinary incontinence and faecal incontinence.

Laboratory abnormalities, such as albuminuria, leukokytosis, glucosuria, decrease in total iron and increases in serum transaminases, alkaline phosphatase, serum creatinine and serum iron were reported in less than 1% of patients following the administration of MultiHance. However these findings were mostly seen in patients with evidence of pre-existing impairment of hepatic function.

4.9 Overdose

There have been no cases of overdose reported. Therefore, the signs and symptoms of overdosage have not been characterised. In the event of overdosage, the patient should be carefully monitored and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group, ATC code V08CA

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 CNS imaging, 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

Toxicity
After repeated administration of high doses to rats and dogs haematological and blood chemistry changes (mainly in dogs) were observed which were shown to be reversible after cessation of treatment.
In the kidneys of both species there was evidence of tubular epithel cell vacuolisation which was still present after a recovery period of 4 weeks in some rats of the highest dose group. Nearly all dog showed lymphatic infiltration of the liver and 2 out of 6 male dogs of the highest dose group developed liver necrosis.
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).

Mutagenicity
Gadobenate dimeglumine showed no effects in a range of in vitro and in vivo tests.

Carcinogenicity
Carcinogenicity studies were not conducted because MultiHance is for single dose administration and has no mutagenic potential.

Impairment of fertility
No changes in reproductive performance and outcome of pregnancy were caused in rats by daily intravenous administration of gadobenate to parent animals before and during gestation

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

MultiHance should not be admixed with any other drug.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

5 ml, 10 ml, 15 ml and 20 ml of a clear aqueous solution filled into colourless type I glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps.

6.6 Instruction for use/handling

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
Any unused product should be discarded.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER.

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

10. DATE OF PARTIAL REVISION OF THE TEXT