Public Assessment Report

Scientific discussion

Omniscan 0.5 mmol/ml solution for injection
Omniscan 0.5 mmol/ml solution for injection, pre-filled syringes
Gadodiamide

SE/H/428/01/MR, SE/H/428/02/MR

This module reflects the scientific discussion for the approval of Omniscan. The procedure was finalised at 13 June 2006. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

GE Healthcare AS has applied for a marketing authorisation for Omniscan 0.5 mmol/ml solution for injection. The active substance is Gadodiamide, a non-ionic paramagnetic contrast medium for magnetic resonance imaging (MRI). The product is indicated for:

“This medicinal product is for diagnostic use only.

Omniscan is a contrast medium for cranial and spinal magnetic resonance imaging (MRI). Omniscan is also indicated for whole body MRI including head and neck region, thoracic space including the heart, extremities, abdomen and pelvis (prostate and bladder), female breast, abdomen (pancreas and liver), retroperitoneal space (kidney), musculoskeletal system and vessels (angiography) by intravenous administration.

Omniscan facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.”

II. QUALITY ASPECTS

II.1 Introduction

Omniscan 0.5 mmol/ml, solution for injection is presented in glass vials/bottles, polypropylene bottles and polypropylene pre-filled syringes. It is dissolved in water for injections at pH 6.0-7.0 and contains, apart from the active substance, an excess of the chelating agent caldiamide sodium. Sodium hydroxide or hydrochloric acid solutions are used for pH adjustment.

II.2 Drug Substance

The drug substance used in Omniscan 0.5 mmol/ml, solution for injection is gadodiamide, a gadolinium chelate of diethylenetriaminepentaacetic acid bis(methylamide), GdDTPA-BMA. It is a non-ionic paramagnetic contrast medium for magnetic resonance imaging (MRI). Gadodiamide is an odourless, white powder. It is freely soluble in water and methanol, soluble in ethanol, and slightly soluble in acetone and chloroform.

The structure of gadodiamide has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been appropriately described and satisfactory specifications have been provided for starting materials, reagents and solvents. The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated. Relevant stability studies have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

The excipients used in Omniscan 0.5 mmol/ml solution for injection, except caldiamide sodium, are described in Ph. Eur. Suitable in-house specifications has been presented for caldiamide sodium. No materials within the scope of the TSE/BSE Note for Guidance are used in the manufacture of Omniscan injection and compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform
Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) is thus achieved.

The product development has taken into relevant consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. The finished product is terminally sterilised in an autoclave and the sterilisation process has been suitably validated.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC, 3 years. The product is light sensitive and should be kept in its outer carton. In addition, freezing of the product should be avoided.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Pharmacodynamic studies were performed to demonstrate that gadodiamide is useful as a contrast agent in MRI. Safety pharmacology studies were in the original application limited to cardiovascular safety studies. Later, additional safety pharmacology studies addressing CNS, cardiovascular, respiratory, gastrointestinal, renal and skeletal muscle function have been performed without any important adverse effect. Non-clinical studies addressing the potential for QT prolongation have not been reported. Such studies were not required at the time of the original application.

III.2 Pharmacokinetics

Pharmacokinetic studies in rats, rabbits and monkeys showed that gadodiamide was rapidly distributed into a volume similar to the extracellular fluid. The major proportion of the injected dose, typically >95%, was excreted unchanged in the urine within the first 24 hours after administration. No metabolites of the complex were identified. Placental transfer was studied in rats. It was demonstrated that about 0.01% of the dose could be recovered in the foetus. Very low concentrations of gadodiamide were found in milk from nursing rats injected with gadodiamide. In light of the very limited transfer of gadodiamide to milk and the low likelihood of oral absorption, no restriction in the use of gadodiamide in breast-feeding women is considered necessary.

III.3 Toxicology

Single dose toxicity studies were performed in mice and rats. LD\textsubscript{50} values were between 25 and 35 mmol/kg in mice and >20 mmol/kg in rats. This give safety margins of >67 on a mmol/kg basis in relation to the maximal clinical dose of 0.3 mmol/kg.

Gadodiamide induced vaculation of the renal proximal tubules in rats after single and repeated dosing, and in monkeys after repeated dosing. Similar findings have been observed with other contrast media and are suggested to represent a storage phenomenon of limited toxicological significance. These changes were not associated with altered kidney physiology. Reversibility was demonstrated in the single dose toxicity study.
Repeated daily dosing in rats was associated with urinary bladder pathology, comprising cystitis and urothelial hyperplasia. This appears to be a rat specific phenomenon, possibly due to irritation after prolonged treatment, and has not proven to be a problem in clinical use.

Gastric mineralization, skin lesions and testicular changes were observed in rats after repeated dosing. These changes were not observed in other species and have not been observed in the clinic. It is hypothesized that these changes are the result of an alteration in Zn status, as a result of chelation of Zn by the excess caldiamide sodium ligand present in the gadodiamide formulation.

Gadodiamide showed no clastogenic or mutagenic potential in standard in vitro and in vivo assays. No carcinogenicity studies have been performed. This is considered appropriate for this single administration product.

Gadodiamide reduced the fertility of male rats at 1.0 mmol/kg. This was directly related to the testicular changes observed in several toxicity studies with repeated daily dosing as discussed above.

Studies on embryo-foetal toxicity were performed in rats and rabbits. No evidence for teratogenicity was observed. However, in rats there was an increased frequency of a skeletal variation (decreased ossification of 5th sternebrae) and in rabbits there was an increased frequency of skeletal anomalies (bulbous ribs and fused sternebrae). In rabbits these findings coincided with some evidence for maternal toxicity (decreased body weight gain). It is concluded that repeated treatment with gadodiamide during pregnancy may cause embryotoxicity, with skeletal changes indicative of developmental retardation. Although the clinical relevance of these findings is considered limited, they should be mentioned in the SPC with a recommendation not to use Omniscan in pregnancy.

Studies on peri- and postnatal toxicity in rats gave no evidence for adverse effects.

Gadodiamide was judged nonirritating when administered intravenously (rabbit), intramuscularly (dog), subcutaneously (dog), paravenously (dog), or topically to the skin (rabbit) or eye (rabbit). Gadodiamide crystalline powder was found to be minimally irritating when applied on the eye (rabbit).

An environmental risk assessment for gadodiamide did not suggest any risk for the environment from the intended clinical use of the product.

**IV. CLINICAL ASPECTS**

**IV.1 Pharmacokinetics**

After intravenous administration of single doses of gadodiamide, serum levels of gadolinium declined rapidly with time. The distribution volume is of the same magnitude as the extra cellular fluid (14 L). The pharmacokinetics were linear, as evidenced by the finding that AUC$_0$-$\infty$, C$_{max}$ were dose proportional, whereas t$_{1/2}$, V$_d$ and Cl$_S$ were dose-independent.

Gadodiamide was quickly eliminated via urinary excretion. Approximately 90% of the injected dose was recovered in urine by 8 hours after administration. The results demonstrate that urinary excretion of parent drug was the major elimination route. In subjects with impaired
renal function the elimination half-life is prolonged. There is no significant metabolism of gadodiamide in vivo.

IV.2 Pharmacodynamics

IV.3 Clinical efficacy

Studies of the efficacy in CNS

A total of 26 studies in patients with known or suspected lesions in the CNS have been submitted in support of this application. Among these 19 were performed in adults (n=1516) and 7 studies in paediatric subjects (n=495). One of the paediatric studies was performed on children less than 6 months of age. The studies in adults used a dose range from 0.1 to 0.3 mmol/kg and in children the dose was 0.1 mmol/kg.

Studies of efficacy outside the CNS

The following has been studied: Head and neck; Extremities; Abdomen and Pelvis; Breast; Various other body areas; Angiographic studies; Paediatric studies (other than CNS). Of the 30 studies performed to support these indications, 23 were done in adults, 2 in paediatric populations and 5 studies in patients with various degrees of renal impairment. In all 2420 adults, 100 children and 50 adult patients with renal impairment were included.

IV.3.1 CNS studies

Results

CNS, standard dose, adults

One non-drug comparative open study with the standard dose of Omniscan has been performed in adult subjects. Efficacy data was obtained in 439 subjects with 351 (80%) evaluated for abnormalities of the brain and 88 (20%) for abnormalities of the spine. Omniscan provided contrast enhancement or facilitated visualisation of lesions on T1-weighted images in 266 (207 head, 59 spine) of the remaining 353 subjects (75%). The investigator indicated that contrast enhancement facilitated diagnosis by disclosing findings not apparent on pre-contrast scans in 190 (145 head, 45 spine) of these subjects, and that the diagnosis was actually changed as a result of new findings on post-contrast scans in 76 (54 head, 22 spine) of these 266 subjects (29%).

In addition five drug-comparative studies have been performed in adult subjects. Data from these five studies has been combined in order to make an overall comparison of the results obtained with the three contrast media. A total of 314 subjects completed the examination in the 5 studies, and was evaluated for efficacy. Of these 314 subjects, 155 received Omniscan, 99 received Magnevist and 60 received Dotarem.

Table 1 Abnormal structures in pre- and post-contrast T1-weighted images in adult subjects

<table>
<thead>
<tr>
<th>Contrast medium</th>
<th>Abnormal structure; Pre-contrast</th>
<th>Abnormal structure; Post-contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N</td>
<td>Yes n [%]</td>
</tr>
<tr>
<td>Dotarem 0.1</td>
<td>59</td>
<td>43 [73]</td>
</tr>
</tbody>
</table>
In thirty subjects more lesions were observed post contrast while in only three subjects more lesions were seen on the pre-contrast images.

Based on these results it is concluded that Omniscan at the standard dose, provided significant assistance in the evaluation of lesions in the CNS. There were no clinically relevant difference between Omniscan and the control drugs, Magnevist and Dotarem at doses of 0.1 mmol/kg, was observed.

**CNS, high dose, adults**

Thirteen drug-comparative clinical studies have been performed to document the safety and efficacy of Omniscan at the high dose in subjects with lesions in the CNS.

### Table 2 Abnormal structures on T1-weighted scan – studies with limited efficacy evaluation of the high dose

<table>
<thead>
<tr>
<th>Omniscan Dose</th>
<th>Pre-contrast</th>
<th>Post-contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Yes [%]</td>
</tr>
<tr>
<td>High dose [0.3]</td>
<td>145</td>
<td>102 [70]</td>
</tr>
<tr>
<td>Standard dose [0.1]</td>
<td>142</td>
<td>105 [74]</td>
</tr>
<tr>
<td>Total</td>
<td>287</td>
<td>207 [79]</td>
</tr>
</tbody>
</table>

1. One subject had pre-contrast scans made in sagittal orientation and post-contrast scans in the axial; thus only a general efficacy evaluation could be made.
2. One subject had no pre-contrast scan performed.

### Table 3 Number of subjects with more diagnostic information post-contrast and grading of the information

<table>
<thead>
<tr>
<th>Omniscan dose</th>
<th>No. of subjects</th>
<th>Yes n [%]</th>
<th>Grading of additional information, n [%]</th>
<th>No. n [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose 0.3</td>
<td>145</td>
<td>112 [77]</td>
<td>5 [4]</td>
<td>33 [23]</td>
</tr>
</tbody>
</table>

Based on the results, it is concluded that the high dose of Omniscan provided at least the same diagnostic information compared to the standard dose. Especially in subjects with known brain metastases the high dose demonstrated the presence of significantly more metastases, resulted in better delineation of lesions and made it easier to distinguish between metastases and oedema.

**CNS studies in paediatric subjects**

Seven clinical studies have been performed in paediatric subjects up to 18 years of age, six of these studies were conducted in paediatric subjects between 6 months and 18 years of age.

In total in the six studies in “older” children, 431 subjects were evaluated for efficacy; of these 303 received Omniscan standard dose and 128 received Magnevist 0.1 mmol/kg. Totally, 208 (69%) and 215 (71%) of the subjects in the Omniscan group showed abnormal structures on respectively pre- and post-contrast scans. In the Magnevist group, 75 (59%) and 78 (61%) of the subjects showed abnormal structures on respectively pre- and post-contrast scans.

Omniscan was effective in MRI examinations of the CNS in children and adolescents from 6 months up to 18 years of age and comparable to Magnevist.

**CNS study in children below 6 months of age**
The main objective of this study was to evaluate the safety of Omniscan standard dose with the results of a control group of subjects undergoing MR examination without contrast. 39 subjects were evaluated. In the Omniscan group, no differences were found between pre- and post-contrast images in the number of subjects with lesions or the number of lesions in each subject, but Omniscan provided more diagnostic information for 20 subjects (51.3%) according to the on-site investigator and 13 subjects (33.3%) according to the independent reader. This additional information was rated as significant in 8 of the 20 subjects in the on-site investigator’s evaluation and in 5 of the 13 subjects in the independent reader’s evaluation. Comparing the paediatric studies to those performed in adults, it is obvious that although advantages of contrast medium could be shown, the efficacy results are somewhat lower and are more variable. In these studies, however the main focus of the studies was on safety issues, which will be described below.

IV.3.2 Studies "outside" the CNS (whole body)

Whole body studies

1. ENT region

Three studies were performed in subjects with soft tissue lesions in the head and neck region. Post-contrast images provided more diagnostic information than pre-contrast images for 39 (51%) of the subjects in the 0.1 dose studies. In the 0.3 dose group, post-contrast images provided significantly more diagnostic information than pre-contrast images for all the subjects. It was concluded that Omniscan injection at both doses (0.1 and 0.3 mmol Gd/kg) is efficacious in subjects with soft tissue lesions in the head and neck region referred to MR examinations.

2. Extremities

Two open non-drug comparative studies of subjects with known or suspected bone or soft tissue tumours in the extremities were performed. Omniscan was given at doses of 0.1 and 0.3 mmol Gd/kg respectively. Post-contrast images compared with pre-contrast images provided additional diagnostic information and assisted in subject management in subjects with bone and soft tissue tumours in the extremities. In the 0.1 dose study, Omniscan was useful in the assessment of possible recurrence of aggressive soft tissue tumours. Dynamic images obtained in the 0.3 dose study showed statistically significant differences between benign and malignant tumours regarding contrast enhancement. The retrospective independent evaluations performed confirmed the trends in the results from the on-site evaluations.

3. Abdomen and pelvis

Five studies were performed with Omniscan to evaluate safety and efficacy of Omniscan in subjects examined for tumours in the abdomen and pelvis. Omniscan was found to be useful for the differentiation between recurrence and no recurrence in dynamic MR imaging of subjects with suspected recurrence of pelvic neoplasm. Both Omniscan and Dotarem had a sensitivity above 94% and an accuracy around 90%, demonstrating that there was no statistically significant difference between the performances of the two contrast media. The comparison of pre- and post-contrast MRI clearly demonstrated the superiority of post-contrast dynamic MRI. Both contrast media provided more diagnostic information in about 70% of the subjects and, as a result of this additional information, 50-70% of these subjects had changes in the management of their condition.

4. Breasts

Four studies were conducted in female subjects to evaluate the ability of Omniscan used for MR examinations to differentiate between malignant and benign tumours of the breast. The
MR results were compared either to histopathological findings performed after biopsy or surgery or to results from a one-year post-examination follow-up questioning procedure. Omniscan at a dose of 0.2 mmol Gd/kg was found to be equivalent to Magnevist at the same dose, with regard to the accuracy of differentiation between malignant and benign breast lesions, both with accuracy values around 90%. X-ray mammography was found to give clearly inferior results in comparison to contrast-enhanced MRI.

5. Various body areas
Three studies were conducted including subjects with abnormalities in various body areas. A wide spectrum of patho-physiological processes and clinical diagnoses were accurately determined by contrast-enhanced MRI with Omniscan 0.3 mmol Gd/kg. Generally, metastasis, primary tumours, cysts, inflammatory and structural abnormalities were consistently and successfully delineated. Altogether, the diagnosis changed post contrast in 8% of the subjects, while new post-contrast information assisted in management of 42% of the subjects. The results of both studies were consistent.

6. Angiography
Six studies have been conducted to support the use in angiography. The post-contrast images provided more diagnostic information than the pre-contrast images for 56 (56%) and 62 (62%) of the subjects, according to the on-site investigator and independent reviewer, respectively.

IV.3.3 Clinical studies in special populations

1. Studies in paediatric subjects (mainly outside CNS)
Two open, non drug-comparative, single centre studies were performed in paediatric subjects up to 18 years of age, referred for MR examination of the body. In both studies the subjects received Omniscan at a dose of 0.1 mmol Gd/kg. A total of 100 subjects were enrolled in the studies. Contrast enhancement in the region of interest was observed for approximately 80% of the 81 body subjects. The post-contrast images provided new information that affected subject management for 25% of the subjects and diagnosis was modified for 11 (14%) of the 81 subjects with body examinations. The post-contrast scan provided more diagnostic information than the pre-contrast scan in 64 (79%) of the body subjects.

2. Subjects with renal impairment
Five studies were conducted in subjects with impaired renal function, including a total of 48 subjects at various stages of renal impairment. The main objective with these five studies was the safety assessment, and this will be further commented on below.

IV.3.4 Conclusions on clinical efficacy
The results show that Omniscan contributes to the diagnosis by providing additional information which is not obtained by un-enhanced MRI. There were no trends to indicate that age, type of disease, location of disease, size of lesions or any other definition of the study cohorts was of importance for the efficacy of the product.

IV.4 Clinical safety
The safety of a standard and high dose of Omniscan in adult subjects for the examinations of suspected CNS lesions was assessed in 19 studies. The safety of the standard dose (0.1 mmol Gd/kg) in paediatric subjects for CNS examinations was assessed in 7 studies. The safety of a standard and a high dose when examining the “whole” body in adult were assessed in 28
studies, and in 5 of these studies subjects with renal impairment received 0.1 mmol Gd/kg. Paediatric subjects were examined in 2 studies.

**IV.4.1 Patient exposure**

In all 47 studies were performed in adults with known or suspected lesions, these studies enrolled 3,928 subjects evaluable for safety assessment, of these 3,338 received Omniscan and 590 reference therapy (Magnevist or Dotarem). Of the 3,928 dosed subjects, 1,493 were investigated for suspected CNS lesions and 2,435 for lesions elsewhere in the body.

In the paediatric studies 520 subjects were enrolled, all with known or suspected lesions in the CNS. Three hundred and ninety two received Omniscan, the rest Magnevist. Mean age was 8 years and 57 % were males.

**IV.4.2 Adverse events**

1. **Adults subjects with CNS lesions**

The proportion of subjects receiving Omniscan that experienced at least one AE was 8.8% for the 0.1 mmol dose, 5.85 for 0.3 mmol. Corresponding figures for Magnevist 0.1 mmol was 5.5% and for Dotarem 0.1 mmol 6.7%. The proportion of subjects having a SAE was low, 0.2% across all dose groups.

**Deaths**

Three deaths were reported, but only one had a temporal relation to Omniscan administration. This death involved a 42 year old female who received one dose each of Omniscan 0.1 and 0.3 mmol/kg in a cross-over study and died due to bleedings from an oesophageal ulcer. The responsible investigator deemed that this death had no relation to Omniscan.

**Other SAEs**

Only one SAE was reported and that was acute renal failure in a 67 year old male who received 0.3 mmol/kg. This event was not considered related to Omniscan by the investigator.

2. **Adults subjects with “whole body” lesions**

In the Omniscan 0.2 mmol/kg dose group 11.5% of the subjects experienced an AE compared to 16% in the Magnevist group. The majority (60%) of the AEs was of mild or moderate intensity, and only 32% were deemed related to Omniscan. The most common events were nausea, headache, taste perversion and micturation urgency. These events occurred at a frequency of 2% of subjects or less.

**Deaths**

Six subjects died after receiving Omniscan but none of these deaths were considered related to Omniscan.

**Other SAEs**

Three subjects in the Omniscan group experienced a total of five events. These included convulsions, shortness of breath and enuresis in one subject. Analyses of these events did not, however, reveal any safety concerns.

3. **Paediatric subjects with CNS and whole body lesions**

Analyses of the adverse events from the eight paediatric studies showed that most AEs were of mild to moderate intensity (80%) and most of them (63%) were considered as unrelated to
Omniscan administration. The most common events were fever, and diarrhoea, both occurring at a frequency of 0.6%. There were three SAEs but these could be attributed to co-morbidities. In children of 6 months age or less, there were two subjects that showed three AEs, but none of these events were considered as related to Omniscan. No deaths or SAEs were reported.

4. Patients with renal impairment

Five studies were conducted in subjects with impaired renal function, including a total of 48 subjects at various stages of renal impairment. The conclusions drawn point to an acceptable safety profile, for Omniscan administration in subjects with renal impairment. Subjects with varying degrees of renal impairment did not experience a substantial worsening of their baseline renal function.

5. Other “special populations”

Ischaemic heart disease

The safety assessment is based on 233 subjects with ischaemic heart disease. There was no evidence of any clinically significant change in results from physical examinations and vital signs, no overall trends in laboratory parameters indicative of a clinically relevant adverse effect of Omniscan.

Transmetallation

In 18 healthy volunteers the risk of transmetallation was measured by three laboratory parameters, serum zinc, serum alkaline phosphatase, and urine zinc. The results showed that decreases in serum zinc levels following both Omniscan and Magnevist administration were of short duration and that the levels returned to baseline within 72 hours. Urine zinc concentration increased during a short term, the effects of Omniscan was 4.5 times greater that that of Magnevist, which is consistent with Omniscan’s known behaviour. In conclusion, there were no safety concerns regarding the theoretical risk for transmetallation.

IV.4.3 Laboratory findings

Clinical laboratory data was collected for approximately 2,200 adults in 21 studies and for 187 children in 5 studies.

Adult subjects

All observed changes in laboratory parameters were with in the well-reported fluctuations seen after the administration of any gadolinium agent. None of these changes were deemed as clinically relevant. There were no dose related effects, and there were no measurable risk differences between the different treatment groups.

Paediatric subjects

Laboratory data was collected for 98 subjects who received Omniscan and 89 who received Magnavist. The observed changes were small and not considered as clinically relevant, none of them required any medical intervention or resulted in a prolonged observation after the examination.

IV.4.4 Conclusions on clinical safety

The safety of Omniscan has been evaluated in several clinical studies. These results give no cause for concerns. Omniscan-aided MR imaging using doses from 0.1 to 0.3 mmol /kg was well tolerated in different clinical situations and in different patient populations. It appears that Omniscan could also be used safely in the paediatric population undergoing both CNS and whole body examinations without increased risk compared to adults.
V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Omniscan 0.5 mmol/ml solution for injection is recommended for approval.
## Public Assessment Report – Update

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