SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Teslascan and has been updated until 1 July 2002. For information on changes after this date please refer to module 8B.

1. Introduction

Detection and characterisation of focal liver lesions are essential in order to plan effective treatment in patients with known extrahepatic or primary hepatic tumours. The number and size of lesions are for certain tumour types (in particular hepatocellular carcinoma and metastases of colonic cancer) a major factor in decisions on surgical treatment, including transplantation. The lack of a possibility for accurate quantification and size estimation of liver metastases often hinders the assessment of response to medical treatment. A special problem is the presence of liver tumours in abnormal liver tissue, particularly in patients with cirrhosis of the liver who have an increased risk of developing hepatocellular carcinoma.
Several imaging techniques can be used to visualise liver lesions such as ultrasonography, Computer Tomography (CT)-scanning, contrast-enhanced CT-scanning, angiography, radioisotope scanning and Magnetic Resonance Imaging (MRI). Paramagnetic magnetic resonance contrast media can be used for contrast enhancement, by changing the signal intensity of either normal or abnormal tissue, depending on the agent used. In general, these agents predominantly shorten the T_1 relaxation time of surrounding water protons. This results in an increase in signal intensity (SI) on T_1-weighted magnetic resonance images. A problem with all imaging techniques, with or without contrast, is that they cannot give certainty with regard to a specific diagnosis of the nature of the tumour.

Teslascan is an intravenous paramagnetic contrast medium for MRI. The active substance of Teslascan is mangafodipir trisodium, a manganese (Mn^{2+}) chelate with the ligand fodipir (dipyridoxyl diphosphate or DPDP). Mangafodipir trisodium is metabolised (dephosphorylated) and partially transmetallated (manganese exchanged for zinc) after intravenous administration. Manganese that is released from mangafodipir is taken up by hepatocytes thereby increasing the SI of normal liver tissue. This may result in an improvement of the detection of liver metastases, which usually have no hepatocytes. The metabolites of fodipir are renally excreted, whilst the biliary route mainly excretes manganese.

Manganese is a trace element with a normal daily dietary requirement of 3-8 µmol and a normal serum level of 0.001 µmol/l. Manganese toxicity is rare and has only been seen after long-term exposure resulting in neurological symptoms.

2. Chemical, pharmaceutical and biological aspects

Composition

Mangafodipir is supplied as a sterile aqueous solution containing 0.01 mmol/ml mangafodipir trisodium (anhydrous) 7.57 mg/ml corresponding to mangafodipir (anhydrous) 6.91 mg/ml. Excipients include ascorbic acid, sodium chloride, sodium hydroxide or hydrochloric acid and water for injections. The solution is filled into 50 ml injection vials with a 20 mm neck and a nitrogen headspace. The vials are made of sulphur treated uncoloured Type I glass, closed with rubber stoppers and sealed with aluminium caps.

Method of preparation

Formulation: The solution contains ascorbic acid to prevent oxidation, sodium chloride to obtain an isotonic formulation and water for injections as the solvent. Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to 7.5-7.8. Nitrogen is present in the headspace gas to prevent oxidation. The glass vials are pre-treated with sulphur to prevent transmetallation. Development studies focused on critical aspects of the formulation and justified the choice of the final formulation.

Manufacturing: The manufacturing process is described satisfactorily.

Control of starting materials

Drug substance: The synthetic route is described satisfactorily. An overview of potential impurities from synthesis and degradation is presented. All detected synthetic impurities are controlled in the drug substance specifications. The limits proposed have been satisfactorily justified according to the batches used in the toxicological studies. Analytical results from batches used in the toxicological, clinical and production batches have been presented. Production batch results justified an adjustment for assay of mangafodipir and water, which has been implemented by the applicant.

Mangafodipir trisodium is not described in a pharmacopoeia. Specifications for drug substance include physical characteristics, identity and assay of mangafodipir, total maganese and sodium, purity and microbiological tests. The specification limits for unspecified peaks and total unknowns have been adjusted in line with the ICH guideline "Impurities in new drug substances". The tests and specifications proposed were considered appropriate to control the drug substance in view of the synthetic route applied.

Stability: Drug substance stability studies, conducted according to ICH guidelines, identified the main degradative pathways. The proposed retest period and storage conditions are supported satisfactorily by the data presented.

Excipients and packaging materials: All excipients used complied with Ph.Eur.. Specifications for the packaging materials presented were satisfactory and complied with the appropriate Ph. Eur. specifications.

Control tests on the finished product

Satisfactory finished product specifications are proposed for release. The proposed limits for related substances and the lower limit for assay of ascorbic acid were adjusted in line with the presented batch analysis results. Extractable volume testing was amended in line with the Ph.Eur.. All methods have been adequately validated and the results justify the proposed specifications.

Stability test on the finished product

The formal stability programme included three production batches from the proposed manufacturing site packed in sulphur treated glass vials. A range of temperature/relative humidity storage conditions was examined in addition to the effects of light and freeze-thaw cycling. The results of the formal stability studies showed no significant changes at any condition. End-of-shelf-life specifications were presented. The lower limits for assay of mangafodipir and ascorbic acid were adjusted in line with stability data. The claimed shelf life for the finished product (24 months when stored protected from light) was considered acceptable following review of the 12-month results of the formal ongoing stability studies.

Inspection Status

The Norwegian Board of Health and Belgian Inspectorates inspected sites for the finished product manufacture of Teslascan. The facilities were considered satisfactory for the finished product manufacture of Teslascan.

3. Toxico-pharmacological aspects

Pharmacodynamics

On the basis of literature references it was demonstrated that mangafodipir enhances the MRI signal in rabbits, rats (including rats with chemically induced liver tumours) and pigs. Results from in vivo studies demonstrated that manganese ions are exchanged with zinc ions and that the MRI enhancing properties of mangafodipir are probably partly due to the release of manganese. In vivo uptake into rabbit hepatocytes was also demonstrated. Unlike manganese chloride, mangafodipir possesses sufficient stability to reduce the exposure to manganese in most tissues.

A linear dose-dependent relationship between signal and manganese tissue levels was observed following intravenous administration. A dose of 5 µmol/kg appeared to be sufficiently effective in rat

imaging studies. The duration of contrast enhancement in rats was increased by biliary obstruction as a result of impaired excretion of manganese.

Safety pharmacology studies mainly focused on the expected toxicity effects of manganese i.e. effects on the central nervous system (CNS) and cardiovascular system. Acute IV doses up to 70 times the expected clinical dose had no significant effects on the CNS in mice. In view of the potentially serious adverse effects of manganese itself mangafodipir has been extensively studied both in vivo and in vitro (anaesthetised dogs, conscious dogs and Langedorff perfused rat heart model). The dog studies produced no evidence of significant haemodynamic effects at doses up to 60 times the clinical dose although transient effects on blood pressure and heart rate were observed. In the rat heart model, mangafodipir, manganese dichloride and fodipir caused a dose dependent reduction of contractile function.

Pharmacokinetics

Single dose kinetic studies were conducted in rats, pregnant rats, bile obstructed dogs and monkeys as well as human volunteers. At similar dose levels the AUC of manganese was greater in man than in rats or dogs reflecting a more rapid elimination from plasma in these species. No repeat dose kinetic studies were performed.

Distribution: Radiolabelled fodipir was distributed rapidly throughout the body with the highest levels observed in the kidneys, lung, blood and liver with a low affinity in the myocardium and brain. Manganese was mainly distributed to the kidney initially and to the liver, spleen and pancreas at later time points. In vitro protein binding studies showed no significant binding with fodipir and approximately 26% binding with manganese at a concentration of 86 uM.

Biotransformation: Mangafodipir is subject to two processes of transformation dephosphorylation and transmetallation (exchange of manganese with zinc). No inter-species differences were observed with respect to the extent to which these processes take place.

Excretion: Excretion was studied mainly in rats and dogs. In both dogs and man fodipir was almost exclusively excreted through the urine whereas in rats up to 25 % was excreted in the faeces. In rats, dogs and humans 10-25% of the manganese dose is excreted in the urine within the first few hours, thereafter the remaining dose is excreted in the faeces.

Toxicology

Acute toxicity studies in mice, rats and dogs using IV administration showed mangafodipir to have low to moderate toxicity. Repeat dose toxicity studies were conducted in rats, cynomologous monkeys and dogs. The liver and to a lesser extent the kidney were target organs of toxicity. No-Observed-Effect-Level's (NOEL) were determined in rats (116 µmol/kg) and monkeys (29 µmol/kg), which on a dose for dose basis represent safety margins of approximately 23 and 6 respectively. In dogs severe toxicity was observed at a dose level of 100 µmol/kg with evidence of liver cell necrosis, cholestasis and important histopathological changes e.g. cholangiohepatitis. A further risk assessment was requested to address these toxic effects. In their response the applicants referred to a study examining single doses of mangafodipir (10-50 µmol/kg) administered to dogs with total common bile duct obstruction. No significant toxicity findings were reported and these data were considered adequate to address this issue.

Segment I/II reproductive toxicity studies were conducted in rats and rabbits. Skeletal malformations were observed in rats at the lowest doses tested together with embryotoxicity and foetotoxicity in rabbits. Teslascan administration is therefore contraindicated in pregnant women. Information on the excretion of mangafodipir into breast milk is lacking and it is recommended in the SPC to discontinue breast feeding for at least 14 days after administration.

Genotoxicity was studied in a standard battery of in vitro and in vivo tests as well as in cell transformation assays. Mangafodipir was devoid of any genotoxic potential in the standard tests. Some positive results were seen in the cell transformation assays, which were adequately addressed by the applicant in their response to questions. Mangafodipir is considered to be non-genotoxic. In view of it's single use administration there is no need to perform carcinogenicity studies.

Miscellaneous

Local tolerance was extensively studied in rabbits and dogs with no evidence of irritant effect.

The environmental risk assessment has been performed satisfactorily in compliance with Guideline III 5504/94 Draft 6 version 1. Even in the worst-case scenario the predicted environmental concentration in water (PEC_{water}) of mangafodipir is a factor of 15 below that requiring further action?

Good Laboratory Practice (GLP): All pivotal preclinical studies have been performed in compliance with GLP.

4. Clinical aspects

The clinical programme was carried out from May 1989 to December 1995. It consisted of 18 clinical trials including four Phase I studies, three Phase II studies and eleven Phase III studies set up as two multiple independent trials (MIT1 & MIT2). An overview of these trials is presented in Table 1.

Table 1: Overview of clinical documentation

	Study/ Report No.	**Description**	**Conc. µmol/ml**	**Dose, µmol/kg b.w.**	**Administration rate**	
					as given in report	in µmol/min*
Phase I Studies						
	727	Safety, tolerance, pharmacokinetics. 54 subjects	145	0**, 3, 10, 15, 20, 25	0.016, 0.08, 0.12, 0.16, 0.20, 0.25 ml/s	139.2, 696, 1044, 1392, 1740, 2175
	MNV015	Safety, pharmacokinetics, imaging. 13 subjects	10	5, 10	Admin. time: 1 min, 20 min	
	1587 (suppl. study)	Plasma profile, bio-transfor-mation, excretion of radiola-belled drug (^{14}C-ligand). 6 subjects	50	5	0.25 ml/s	750
	1774 (suppl. study)	Safety, iron metabolism, zinc metabolism. 30 subjects	50	0**, 5	0.25ml/s	750
Phase II Studies						
	2514	Pharmacokinetics in healthy volunteers and in patients with impaired liver function (cirrhosis), men and women. 41 subjects	50	5	0.1 ml/s	300
	BY017/ MR310	Dose ranging, safety and efficacy. 161 patients	10, 50	5, 10	2 - 3 ml/min	20-30, 100-150
	293	Dose ranging, safety and efficacy, 96 patients	145	3, 5, 8, 10	0.25 ml/s, 1 ml/min	2175, 145

Phase III Studies						
	MIT1 (n=5)	Safety and efficacy. 322 patients	10	5	2 - 3 ml/min	20-30
	MIT2 (n=6)	Safety and efficacy. 295 patients	10	5	2 - 3 ml/min	20-30
	Four US studies	Safety and efficacy. 546 patients (total)	50	5	1 min slow injection	-

* Obtained by multiplying rate in ml/min by concentration in µmol/ml

** placebo (received saline)

NA: not attached

Pharmacodynamics

Two Phase I studies in healthy male volunteers were conducted to study the safety and efficacy of mangafodipir in increasing doses and different concentrations. In **Study 727** SI increases of 27-63% at 3 µmol/kg and 82%-140% at 10-15 µmol/kg were found. The increase occurred within 1-3 min of administration and remained high during the 30 min scanning period. In **Study MNVO15** peak SI was reached in the liver 15-20 min after administration, enhancement lasted for 4 hr and returned to baseline after 48 hrs. Mean maximum SI enhancement for the liver was 77% and 110% at 5 and 10 µmol/kg respectively. Enhancement of SI was also seen in the pancreas, spleen, renal medulla, renal cortex and choroid plexus. No enhancement of T2 imaging was seen. In both studies adverse events reported in some patients included warmth, flushing and dose associated discomfort.

Pharmacokinetics

Five trials were performed for elucidating the pharmacokinetics of mangafodipir in man. Two phase I studies (**Study 727** dose ranging finding study & **Study MNVO15** effect of infusion time), one phase II study (**Study 2514** pharmacokinetics in males and females and patients with impaired liver function) and two supporting phase I studies performed in the US (**Study 1587** plasma concentration time profiles biotransformation and excretion of C^{13} labelled ligand & **Study 1774** interactions with iron and zinc metabolism).

These studies indicated that the protein binding of manganese is approx. 27% with negligible binding of fodipir being observed in in vitro studies. Mangafodipir trisodium is rapidly metabolised (dephosphorylated) and partially transmetallated following intravenous administration. Manganese is predominantly released from mangafodipir by exchange with plasma zinc. Free manganese is taken up by different organs e.g. liver, pancreas, and spleen by an undefined mechanism. The mean initial plasma half-life of manganese is 20 min or less with significant uptake into the liver, pancreas, kidney and spleen. The initial plasma half-life of fodipir is 50 min. Manganese and the ligand fodipir have different elimination routes. Initial renal elimination of manganese occurs in the form of manganese pyridoxylethylenediamine (MnPLED 15-20% over 24 hr) and further elimination occurs in the faeces via biliary excretion (over 4 days). The majority of the ligand fodipir (DPDP) is excreted as ZnPLED. Fodipir is metabolised by means of dephosphorylation to PLED.

In patients with impaired liver function due to liver cirrhosis the mean terminal elimination half-life was about three times longer than in healthy volunteers. In patients with impaired liver function obstruction of the hepatobiliary flow is of more importance than impairment of the metabolic capacity of the liver. Use of Teslascan in obstructive biliary disease is therefore contraindicated (as well as use in severely reduced liver function). No specific studies were performed in the elderly, children or patients with renal insufficiency. The lack of specific data in the elderly, which was not considered clinically relevant, and the lack of experience in children are suitably addressed in the SPC. The use of Teslascan is contraindicated in patients with severe renal insufficiency. Gender did not affect the metabolism of mangafodipir. The administration of Teslascan caused a statistically significant increase

in zinc excretion. This increase amounted to less than 1.3% of the total body zinc and was not considered clinically relevant.

Clinical Studies / Experience

Phase II studies: **Studies BY017/MR310** and **293** were designed as open non-controlled ascending dose studies examining safety and tolerability in patients with focal liver disease and evaluating efficacy. Safety evaluation included vital signs, ECG and laboratory parameters. Efficacy parameters were SI, technical quality, and diagnostic utility and lesion delineation. Only SI is considered an objective determination. In **Study BY017/MR310** SI increased more in normal tissue than in "tumour" tissue. In **Study 293** SI increased more in normal tissue with a significant dose response up to 8 µmol/kg. There was no difference between groups with respect to rate of administration or concentration. In **Study BY017/MR310** 30% of patients reported adverse events with an increased incidence with concentration and administration rate. In **Study 293** 64% patients reported adverse events, primarily warmth and flushing.

Definition of Optimal dose: Results from the Phase I/II clinical programme indicated that 5 µmol/kg was considered an adequate dose for efficacy as it produced a >50% increase in SI of normal liver tissue. Higher doses did not increase SI significantly and were associated with a higher incidence of side effects. Concentration or flow rate did not have an effect on efficacy but fewer side effects were seen with the lowest concentration and lowest administration rate. Based on these results a concentration of 10 µmol/ml and a flow rate of 2-3 ml/min were chosen for the phase III studies.

Phase III studies

Two "multiple independent" trials, **MIT1** & **MIT2** each consisting of 5 or 6 separate open non-controlled studies respectively, were performed in Europe. Formally these were not multi-centre trials but similar protocols and the same primary efficacy parameter were used throughout. However in separate studies different secondary parameters were examined.

Patients included were aged 18 or over and were referred for MRI of the liver with 1-5 liver lesions demonstrated in an examination (CT, MRI or ultrasound) within the last 4 weeks. All patients received 5 µmol/kg mangafodipir using a 10 µmol/ml solution, infused in 10-20 minutes (max. 50 ml per patient). MR machines with 0.5 to 2.0 Tesla field strengths were used according to standard protocols. The following sequences were performed: pre-contrast T1, SE, -T1GE, -T2SE and post contrast T1SE and -T1 GE sequence (no post contrast T2).

Primary efficacy parameters were similar for all studies i.e. the difference in the number of liver lesions detected per patient with post versus pre contrast MRI. Secondary efficacy parameters were investigated in separate studies e.g. diagnostic utility in detection and characterisation of lesions, optimal sequence for lesion characterisation, level of confidence in the final diagnosis etc.

For all studies separate "on site evaluations" were performed and these were integrated for each MIT. For each MIT as a whole an "independent evaluation" was performed. In all studies the main safety parameters collected up to 24 hr post dose were occurrence of adverse events and infusion associated discomfort. Secondary safety parameters included vital signs and blood chemistry.

Results: The number of lesions detected was compared for the different types of pre and post contrast images separately and for all pre and post contrast images taken together. Table 2 provides a summary of the change in the total number of lesions seen with post vs. pre contrast MRI for all images. In the on-site analysis 17% more lesions were found after contrast but in 75% of patients the number was unchanged and in 8% less lesions were found. In patients with more lesions, 1-2 more lesions were detected in most cases. In the independent analysis 33% of patients had more lesions after contrast but 20% of patients had fewer lesions? If diagnosis were taken into account the overall analysis of all images showed that both for metastases and hepatocellular carcinoma contrast resulted in more lesions being detected. However fewer lesions were detected in haemangioma.

Table 2: Change in total number of lesions post vs. pre-contrast, all images

	MIT1	MIT2	Total
	On-site evaluation		
All diagnosis	322	298	620
post>pre	62 (20%)	43 (14%)	108 (17%)
post<pre	30 (9%)	19 (6%)	49 (8%)
p value	=0.005	=0.05	=0.005
Metastases	101	88	189
post>pre	26 (26%)	15 (17%)	41 (22%)
post<pre	8 (8%)	3 (3%)	11 (6%)
p value	=0.05	=0.05	=0.005
Hepatocellular carcinoma (HCC)	65	92	157
post>pre	11 (17%)	13 (14%)	24 (15%)
post<pre	5 (8%)	3 (3%)	8 (5%)
p value	ns	=0.05	=0.005
Haemangioma	34	26	60
post>pre	0	2 (8%)	2 (3%)
post<pre	8 (24%)	3 (12%)	11 (18%)
p value	=0.05	ns	=0.05
	Independent analysis		
All diagnoses	294	293	587
post>pre	100 (34%)	94 (32%)	194 (33%)
post<pre	59 (20%)	58 (20%)	117 (20%)
p value	0.0014	0.0044	0.0001

Analyses of secondary end-points indicated that hepatic lesions = 5 mm in diameter were detected on post contrast MR images in an increased number of patients (66 vs. 47). The investigators judged diagnostic utility subjectively. Pre- and post- mangafodipir images were compared to those of previous examinations. Since the T_2 sequence was not repeated post contrast, there was a bias toward pre-examination. Diagnostic utility in detection of lesions was greater post contrast in 120 (20%) of cases and better pre-contrast in 81(14%) of cases. This was statistically significant in MIT1 but not in MIT2. Diagnostic utility in characterisation of lesions was better post-contrast in 132 (22%) of cases and better pre-contrast in 166 (28%) of cases.

Investigators considered that the enhanced images contained additional diagnostic information in 279 (45%) of the 621 patients examined and in 76 patients (12%) the additional diagnostic information was considered to have affected patient management. When considering all sequences, a post contrast sequence was most frequently considered best for lesion characterisation. In the delayed images (up to 24 hours post injection) in 129 patients, more lesions were detected than on the pre contrast images in 28 patients (22%). More lesions were seen in 8 cases (6%) when comparing delayed and immediate post contrast and in MIT2 this difference was considered to be statistically significant.

In comparing mangafodipir enhanced MRI scans with contrast enhanced computerised tomography (CECT) scans in 137 patients, more lesions were seen in the MR images in 40 patients, while more were seen in the CT images in 23 patients.

Pre-contrast images were used to determine diagnoses in 75% of the 621 patients and post-contrast images in 81% of patients. Diagnoses were described as extremely confident in 56% of the 729 diagnoses and as very confident in 26% of cases.

Two-phase III studies were submitted in support of a new indication "as an adjunct to MRI in the investigation of focal pancreatic lesions". These studies demonstrated that results with contrast enhanced MRI are comparable to those with spiral enhanced CT. There is however no clinically or statistically significant difference between the two methods and the results do not suggest a clear benefit with one method rather than another in the diagnosis of a particular pathology. The results of the studies are considered to support the indication as an adjunct to MRI in the investigation of focal pancreatic lesions.

Safety in Phase III trials

In the combined MIT trials 624 patients were evaluable for adverse events. Infusion associated discomfort was reported in 4% of patients (n=24) a feeling of warmth of mild (n=22) to moderate (n=2) intensity. Six serious adverse events occurred in 5 patients. Two were considered possibly/likely to be drug related and occurred in one patient. These were reported as exanthema of the left arm in the presence of pre-existing lymphedema followed by a septicaemia after a superficial cut of the left hand.

Vital signs were monitored in 321 patients and clinically important changes in blood pressure were recorded in two patients, one with an increased systolic blood pressure of 70 mmHg the other with increased systolic/diastolic pressures of 50/40 mmHg respectively. Monitoring of blood chemistry indicated increases in bilirubin levels and ALAT in one patient and high total serum iron in 5 patients.

Special populations: No specific interaction, renal impairment, high risk patient studies were submitted. Subjects less than 18 years old were excluded in the trials. In the phase III studies, 216 of the 624 patients were over 65. The rate of adverse events was lower in this sub-group (4% vs. 9.3%). Bilirubin was measured in 257 patients and was abnormal in 30 of them although severe obstructive hepatobiliary disease was an exclusion criterium. 138 patients were recorded as having cirrhosis. No increased adverse event rate was found in either sub-group. 86 out of the 624 patients had unspecified cardiovascular disease. No difference in adverse event rate was observed with this sub-group.

5. Conclusions

Risk Benefit Assessment

The quality of the product applied for has been well documented and is generally considered acceptable with satisfactory answers being provided to questions raised regarding the manufacturing process, drug substance specifications for related substances and finished product specifications.

Preclinical pharmacodynamics indicated that mangafodipir enhances the MRI signal in the species tested, which included rats with chemically induced tumours of the liver.

Results of in vivo studies demonstrated that manganese ions are exchanged with zinc ions, and that the MRI enhancing properties of mangafodipir are probably partly due to the release of manganese.

Acute toxicity was low to moderate. Target organs in repeated dose toxicity studies were the liver and to a lesser extent the kidney. Teratogenicity in rats and embryo- and foetotoxicity in rabbits have been observed. Mangafodipir is considered non-genotoxic. Local tolerance was good.

Mangafodipir is subject to two processes of transformation, dephosphorylation and transmetallation. No significant interspecies differences were observed with respect to the extent to which these processes take place. The metabolites of fodipir are renally excreted, whilst the biliary route mainly excretes manganese.

Dose, concentration and infusion rate have been appropriately selected as those associated with optimum efficacy and safety of this preparation.

The open uncontrolled Phase III studies in over 600 patients showed that mangafodipir enhanced MRI (at a dose of 0.5 ml/kg equivalent to 5 µmol/kg administered at 2-3 ml /min) revealed an increased number of lesions compared to unenhanced MRI. This applied particularly to metastases and hepatocellular lesions but not to haemangiomas. Overall on-site evaluation showed an increase in the total number of lesions in 17% of patients while this figure increased to 33% in the independent evaluation. In most of these cases 1 or 2 extra lesions were detected.

Assessment of secondary parameters was for the most part subjective e.g. diagnostic confidence, confidence in the presence of lesions, conspicuity of lesions. Diagnostic utility (the investigator's overall assessment) in detection of lesions was greater post contrast in MIT1 and the total analysis.

On comparing mangafodipir enhanced MRI with CECT scans, more lesions were seen in MR images in 31% of patients and more lesions in CT scan in 13% of patients.

The studies showed that there was a low rate of adverse events in general and in particular infusion related discomfort was noted in less than 5% of cases. No anaphylaxis was reported but the occurrence of an urticarial reaction in one patient indicates a possibility of allergic reactions to mangafodipir. No specific interaction studies were performed.

Overall Conclusion

Mangafodipir has been shown to be an effective contrast medium for diagnostic MRI for the detection of liver lesions due to metastatic disease or to hepatocellular carcinoma. The data presented have not clearly demonstrated a clear benefit in the characterisation of liver lesions. When administered at the proposed rate and concentration (2-3 ml/min & 0.01 mmol/ml) it was associated with a low incidence of infusion related discomfort or other adverse effects. The CPMP on the basis of this benefit risk ratio adopted a positive opinion on the granting of a marketing authorisation for Teslascan for the following indication:

"Contrast medium for diagnostic Magnetic Resonance Imaging (MRI) for the detection of lesions of the liver suspected to be due to metastatic disease or hepatocellular carcinomas."

The indication was extended in March 2001 to include the use of Teslascan as an adjunct to MRI to aid in the investigation of focal pancreatic lesions.