PRODUCT MONOGRAPH

TESLASCAN*

(mangafodipir trisodium) Injection
37.9 mg/mL (50 μmol/mL)

For intravenous injection only

Contrast Enhancement Agent for

Magnetic Resonance Imaging (MRI)

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*Trade Mark

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THERAPEUTIC CLASSIFICATION

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ACTION AND CLINICAL PHARMACOLOGY

TESLASCAN Injection (mangafodipir trisodium) is a complex formed between a chelating agent (fodipir) and a metal ion, manganese, which has paramagnetic properties and is responsible for the contrast enhancement effect in MRI. Mangafodipir shortens the spin lattice (longitudinal) relaxation time (T_1) of targeted tissues during MRI, leading to an increase in signal intensity (brightness) of the tissues.

Mangafodipir enhances T1 signal intensity. In a study of 12 healthy volunteer men, mangafodipir began to increase the signal intensity of liver tissue within 1-3 minutes, and steady-state enhancement was reached in about 5-10 minutes. Liver enhancement after TESLASCAN Injection administration is detectable in patients up to 24 hours after injection. After mangafodipir trisodium administration, liver lesions may present in a number of different patterns of contrast enhancement.

INDICATIONS AND CLINICAL USE

TESLASCAN (mangafodipir trisodium) injection is indicated for intravenous administration as an adjunct to MRI in patients to enhance the T1-weighted images used in the detection, localization, characterization, and evaluation of lesions of the liver.

CONTRAINDICATIONS

TESLASCAN (mangafodipir trisodium) Injection is contraindicated in patients with known allergic or hypersensitivity reactions to manganese, fodipir or any of the inert ingredients.

WARNINGS

Patients with history of drug reactions to contrast media, other allergies, or immune system disorders should be observed for several hours after drug administration.

A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating anaphylactic reactions should be available.

Caution should be exercised before administering TESLASCAN (mangafodipir trisodium) to patients who have or cannot tolerate nausea or vomiting. The possibility of complications from nausea and vomiting should be considered when administering TESLASCAN Injection to patients who cannot tolerate vomiting, who have reflux esophagitis (especially if it is increased in a supine position) or who cannot roll over to prevent aspiration.

PRECAUTIONS

GENERAL - THE DECISION TO USE CONTRAST ENHANCEMENT SHOULD

INCLUDE A CONSIDERATION OF THE RISK OF THE DRUG, THE RISK OF THE PROCEDURE, THE EXPECTED BENEFIT OF THE IMAGE AND THE PATIENTS UNDERLYING DISORDER. THE DECISION TO USE TESLASCAN (MANGAFODIPIR TRISODIUM) INJECTION SHOULD BE BASED UPON CAREFUL EVALUATION OF CLINICAL DATA, OTHER RADIOLOGIC DATA AND THE RESULTS OF UNENHANCED MRI.

Diagnostic procedures involving the use of contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as, for emergency treatment of severe reactions to the contrast agent itself.

Although more lesions are generally visualized on contrast-enhanced images than on unenhanced images, lesions seen on unenhanced images may not all be seen on contrast-enhanced images. Possible causes include changes in imaging parameters, patient motion, misregistration, and effects of the contrast agent.

Since TESLASCAN Injection is cleared from the body partially by glomerular filtration and partially by hepatobiliary excretion, caution should be exercised in patients with impaired renal or impaired hepatobiliary function. Dose adjustments in renal or hepatic impairment have not been studied.

The safety of repeated doses has not been studied. If the physician determines that imaging needs to be repeated, repeat images could be obtained up to 24 hours after the original injection without reinjection.

DRUG INTERACTIONS

Drug interactions with other contrast agents and other drugs were not studied.

LABORATORY TEST INTERACTIONS

Transmetalation of manganese may occur. The extent of which this might affect laboratory assays of ferritin, iron, bilirubin, and zinc is not known.

USE IN PREGNANT WOMEN

TESLASCAN may cause harm to the fetus when administered to a pregnant woman. Adequate and well-controlled studies were not conducted in pregnant women. If TESLASCAN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be told of the potential hazard to the fetus.

NURSING MOTHERS

The rate and extent to which manganese or mangafodipir is excreted in human milk after TESLASCAN Injection has not been studied. In the literature, there are reports that manganese is excreted in human milk. The relationship between the bioavailability of manganese from human milk and subsequent toxicity in developing infants is not known.

Because of the potential risk to nursing infants from manganese exposure, consideration should be given to temporarily discontinuing nursing to allow clearance of mangafodipir and manganese (see Action and Clinical Pharmacology - Elimination section).

PEDIATRIC USE

Safety and effectiveness of TESLASCAN Injection in adolescents are expected to be the same as in adults.

Safety and effectiveness or pharmacokinetics of TESLASCAN Injection in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

In clinical trials, a total of 637 subjects (57 healthy volunteers and 580 patients with known or suspected liver lesions) received the contrast agent at a dose of 5 μmol/kg. Of these subjects, there were 387 men and 250 women with a mean age of 56 years (19 to 86). There were 497 (78%) Caucasian, 72 (11%) Black, 32 (5%) Oriental, and 36 (6%) in other racial groups.

Of these 637 subjects, 481 (76%) reported at least one adverse event. In clinical trials, there were 4 deaths and 2 serious events. The serious events included prolonged vomiting in one patient. The deaths occurred in patients with advanced multisystem disease (hepatocellular carcinoma, esophageal variceal bleeding, sepsis, and

pneumonia), and were attributed to underlying disorders.

The most commonly noted adverse experiences were injection site discomfort 430 (67%), headache - 32 (5%), and any gastrointestinal event - 79 (12%). (See Table 1 for details.)

Table 1

ADVERSE EVENTS REPORTED IN ≥0.5% OF PATIENTS WHO RECEIVED TESLASCAN IN CLINICAL TRIALS

Patients Exposed to TESLASCAN	637
Patients with Any Adverse Event	481 (76%)
Patients with Any Injection Site Discomfort	430 (67%)
Gastrointestinal Nausea Vomiting Abdominal Pain	79 (12%) 67 (11%) 17 (3%) 14 (2%)
Body as a Whole Headache Chest Pain	25 (4%) 32 (5%) 4 (0.6%)
Central and Peripheral Nervous System Dizziness	48 (8%) 9 (1%)
Skin and Appendages Pruritus	12 (2%) 7 (1%)

As with other contrast media, patients receiving TESLASCAN (mangafodir trisodium) reported injection-associated discomfort. Overall 430 (67%) of the patients receiving TESLASCAN reported mild to moderate injection associated discomfort. Of these, the discomfort was described as heat - 266 (42%), flushing - 234 (36%), pressure - 26 (4%),

pain - 19 (3%) and cold 9 (1%).

The following selected adverse events occurred in <0.5% of the subjects. The majority (93%) of these adverse events were of mild to moderate intensity: chest pain, dizziness, hot flushes, hypersensitivity, hypertension, palpitation, pruritus, rash, taste perversion, urticaria.

In another 798 subjects who received the contrast agent in foreign clinical studies, similar types and rates of adverse events were reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinical consequences of overdosage with TESLASCAN (mangafodipir trisodium) Injection have not been reported. Treatment of an overdose is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. The minimum lethal dose of mangafodipir trisodium when administered intravenously to mice as a bolus was >2000 μmol/kg (400 times the recommended human dose of 5 μmol/kg based on body weight and 17 times based on body surface area).

The dialyzability of TESLASCAN Injection and its metabolites has not been studied. Mangafodipir itself does not undergo protein binding *in vitro*; however, manganese(II) and manganese(III) are known to bind to plasma proteins *in vitro*.

DOSAGE AND ADMINISTRATION

TESLASCAN (mangafodipir trisodium) Injection should be administered as a peripheral intravenous injection at a dose of 5 μmol/kg (0.1 mL/kg) over approximately one minute. The maximum dose should not exceed 15 mL (See the Dosage Chart).

TESLASCAN Injection should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. Unused portions of the drug must be discarded.

Imaging can begin within minutes after TESLASCAN Injection. If it is determined that imaging needs to be repeated, repeat images could be obtained up to 24 hours after the original injection without reinjection. The safety of repeat doses has not been studied.

DOSAGE CHART

BODY WEIGHT		VOLUME
kg	lb	(mL)
40	88	4
50	110	5
60	132	6
70	154	7
80	176	8
90	198	9
100	220	10
110	242	11
120	264	12
150	330	15

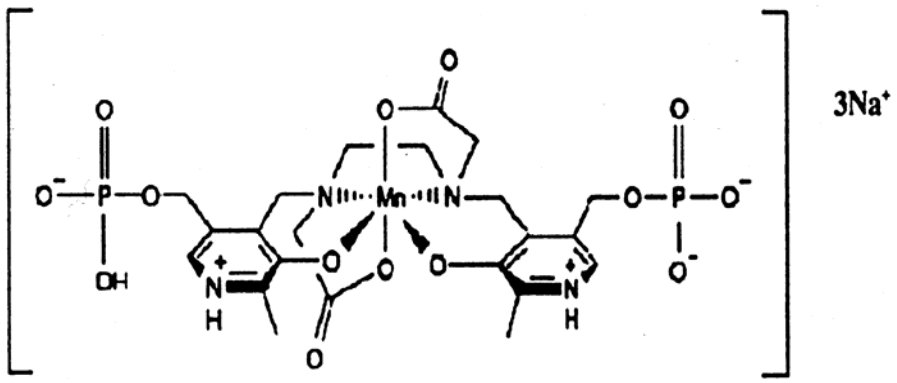
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name (USAN): Mangafodipir Trisodium

Chemical name: Trisodium trihydrogen (*OC*-6-13)-[[*N*,*N*'-1,2-ethanediylbis[*N*-[[3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato]](8-)] manganate (6-)

Structural Formula:



Molecular Formula: $C_{22}H_{27}MnN_4Na_3O_{14}P_2$ (anhydrous)

Molecular Weight: 757.33 (anhydrous)

Physical Form: Mangafodipir trisodium is a yellow solid.

Solubility: Mangafodipir trisodium is freely soluble in water, sparingly soluble in methanol, slightly soluble in chloroform, and very slightly soluble in ethanol and acetone.

The pH of a 1.0 weight % solution: 6.3 - 6.8

Partition Coefficient (Octanol:water): 2.4×10^{-6}

Melting Point: A distinct melting point has not been observed. Mangafodipir trisodium decomposes between 230°C and 240°C.

Composition:

TESLASCAN Injection is a sterile, clear yellow solution. Each milliliter of TESLASCAN Injection contains 37.9 mg (or 50 μmol/mL) mangafodipir trisodium; ascorbic acid, 2.0 mg; sodium chloride, 2.0 mg; fodipir, 0.25 mg; and Water for Injection. The pH is adjusted to 8.8 ±0.4 with hydrochloric acid and/or sodium hydroxide. The osmolality is 298 mOsmol/kg water. TESLASCAN Injection does not contain a preservative.

Pertinent physicochemical data for TESLASCAN are provided below:

PHYSICOCHEMICAL DATA

	@ 37°C
Viscosity (cp)	0.8
Density (g/mL)	1.02
Specific Gravity	1.03
Osmolality (mOsmol/kg water)	298

Stability and Storage Recommendations:

Store in the original, unopened container between 15°C to 30°C. **Protect from freezing**. Do not use product if it has been frozen. Freezing may compromise the package integrity.

Parenteral Products:

Other drugs should not be physically mixed with contrast agents because of the potential for chemical incompatibility. If the injection is made through tubing, the injection should be followed by a 5 mL flush with 0.9% sodium chloride.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the solution is other than clear yellow or if particulate matter is present.

AVAILABILITY OF DOSAGE FORMS

TESLASCAN (mangafodipir trisodium) Injection is supplied in 10 mL vials, in boxes of 5.

PHARMACOLOGY

Mangafodipir administered intravenously to dogs produced no physiologically significant hemodynamic changes at up to 46 times the anticipated clinical dose of 5 μmol/kg following a single administration. Changes observed following administration at a dose of 463 μmol/kg (92 times the anticipated clinical dose) included transient decreases in aortic and left ventricular pressures, and systemic and pulmonary vascular resistances in the presence of essentially minimal changes in heart rate and filling pressure. Values for these parameters returned to pretreatment levels within 12 minutes.

Studies in both intact and bile duct cannulated rats and dogs have shown distribution primarily to the liver, gastrointestinal tract, kidneys and pancreas.

In pregnant rats who received ^{54}Mn, radioactivity was detected in the placenta and in the fetus.

Pharmacokinetics

Mangafodipir has two components: Fodipir and a manganese(II) ion. Each has different pharmacokinetics, metabolism, and modes of elimination. After intravenous administration of TESLASCAN, the pharmacokinetics of each component were investigated.

Fodipir: When TESLASCAN is labeled with the ^{14}C-label residing in the fodipir, after a single intravenous dose of 5 μmol/kg of ^{14}C-TESLASCAN in 6 healthy male volunteers,

the mean ±SD area under the radioactivity plasma concentration curve (AUC) is 22.7 ±3.2 μg*h/mL.

Manganese (II) ion: Generally, the total body store of manganese in adults is 20 mg. Most of this is from dietary intake (2-5 mg/day). TESLASCAN Injection contains 2.75 mg/ml of chelated manganese. In a 70 kg adult, 5μmol/kg of TESLASCAN Injection contains 19.2 mg of chelated manganese. Therefore, a single injection of TESLASCAN will approximately double the total body store of manganese before excretion occurs. In a study of 31 healthy volunteers (16 men & 15 women), after a single intravenous dose of 5 μmol/kg TESLASCAN, areas under the manganese serum concentration versus time curves (AUC) were 15.8 ±5.8 μM*h (mean ± SD) and 16.0 ±2.9 μM*h (mean ± SD), respectively. (See Elimination section for details on excretion).

Distribution

Mangafodipir itself does not bind to plasma proteins *in vitro*; however, manganese(II) and manganese(III) are known to bind to plasma proteins *in vitro*.

Metabolism

After intravenous injection, mangafodipir trisodium is metabolized by the removal of two phosphate groups and the exchange of the manganese ion for an endogenous zinc ion. This produces two major metabolites, manganese dipyridoxyl ethylenediamine diacetic acid (MnPLED) and zinc dipyridoxyl ethylenediamine diacetic acid (ZnPLED).

In plasma, the mangafodipir trisodium is not detected after 2 hours. The MnPLED

concentration peaks within ten minutes and is not detected after 1 hour. The ZnPLED metabolite reaches maximum concentration 20 minutes after injection and then decreases slowly. By 24 hours, the two major metabolites (MnPLED and ZnPLED) represent 12% and 57% of the administered dose, respectively.

Elimination

Fodipir: When TESLASCAN is labeled with ^{14}C in the fodipir, after intravenous administration of 5 μmol/kg ^{14}C-mangafodipir trisodium to six healthy volunteer men, approximately 92% of the radioactivity administered is eliminated in the urine over 24 hours. Negligible amounts (0.3%) are recovered in feces over 168 hours. The total plasma clearance of radioactivity was 11.6 ±2.1 L/h (0.15 ±0.02 L/h/kg, mean ± SD). The apparent terminal half-life (mean ± SD) of elimination of radioactivity from plasma is 2.09 ± 0.47 hours.

Manganese (II) ion: After intravenous administration of TESLASCAN, the initially high serum manganese concentrations drop rapidly and approach detection limits (or baseline levels) within a few hours. Approximately 15% of the dose administered of the manganese(II) ion of mangafodipir is eliminated in the urine within the first 24 hours after injection and an additional 59% is excreted in the feces over the following 5 days. The remainder is eliminated in urine and feces gradually.

The dialyzability of TESLASCAN Injection and its metabolites has not been studied.

Special Populations

Hepatic Insufficiency: A single intravenous dose of 5 μmol/kg of TESLASCAN was administered to 31 subjects with normal hepatic function (16 men and 15 women) and 10 subjects with impaired hepatic function (5 men and 5 women). In the patients with impaired hepatic function (5 men and 5 women), after a single intravenous dose of 5 μmol/kg TESLASCAN, for manganese, AUCs were 23.3 ±4.3 μM*h (mean ± SD) and 24.6 ±4.0 μM*h (mean ± SD), respectively. (See Pharmacokinetics of Manganese Ion for comparative values in healthy volunteers).

Manganese (II) ion serum levels at 1 hour after injection were 10% or less of maximal values.

Manganese (II) ion half-life: In both healthy subjects and subjects with hepatic impairment, the immediate distribution half-life (determined over the interval from 5 minutes to 2 hours after injection) was 24.4 ±7.7 min (mean ±SD). However, the terminal half-lives were longer, $t_{\square}$ = 10.1 ±20.3 hrs and $t_{\square}$ = 26.7 ±19.0 hrs, respectively for healthy and hepatically impaired subjects).

Gender

Statistically significant differences were not detected in the elimination half-lives between men and women who were either healthy or had hepatic impairments, nor were there differences in the overall urinary or fecal recovery of manganese(II) ion in men and

women who were either healthy or had hepatic impairments. (See Table 2 for details.)

TABLE 2

SIMILARITY IN ELIMINATION PROFILES OF NORMAL AND HEPATICALLY IMPAIRED MEN AND WOMEN (mean ± S.D.)

Population	Elimination T $\frac{1}{2}$ (hours)		Urine or Fecal Recovery*	
	Men	Women	Men	Women
Healthy Volunteers	13.9 ± 27.4	5.8 ± 4.0	73.9 ± 22.8	73.4 ± 22.9
Hepatically Impaired	30.6 ± 16.6	22.9 ± 22.3	77.8 ± 14.7	66.6 ± 9.8
* Collected over 0-5 days				

Age

Pharmacokinetic differences due to age in adults or in pediatric patients after intravenous TESLASCAN were not studied.

Race

Pharmacokinetic differences due to race after intravenous TESLASCAN were not studied.

Drug-Drug Interactions

Drug interactions were not studied.

Dietary Effects

Pharmacokinetic studies with intravenous TESLASCAN were performed with nonfasted volunteers or patients.

TOXICOLOGY

Acute Toxicity

The minimum lethal intravenous dose of TESLASCAN in mice was greater than 2000 μmol/kg, greater than 400 times the anticipated clinical dose. Beagle dogs tolerated an intravenous dose up to 1806 μmol/kg, greater than 360 times the anticipated clinical dose.

Subacute and Long-Term Toxicity

No rats died when injected with mangafodipir in doses of 289 μmol/kg three days a week for 3 weeks, 58 times the anticipated clinical dose (520 times cumulatively), and no effects were observed at doses up to 116 μmol/kg, 24 times the anticipated clinical dose (216 times cumulatively). At 289 μmol/kg, treatment-related effects included a significantly elevated mean eosinophil count in the females at Week 3, a significantly lower absolute testes weight for males compared to control, and an increased incidence of hepatic microgranulomas in females.

In a three-week intravenous toxicity study in Beagle dogs, the NOEL of mangafodipir was 10 μmol/kg (210 μg/kg, cumulatively). At higher doses, multiple signs of toxicity were found in the liver and kidneys.

Cynomolgus monkeys received mangafodipir intravenously at doses of either 29 or 289 μmol/kg, three times per week for three weeks. No effects were observed at 29 μmol/kg, six times the anticipated clinical dose (52 times cumulatively). At the higher dose, there

was evidence of reversible hepatic changes. One male in the high-dose group was killed on Day 18 in a moribund condition, with signs of liver toxicity.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of TESLASCAN (mangafodipir trisodium) Injection.

Mutagenicity

Mangafodipir trisodium did not demonstrate mutagenic potential in 3 *in vitro* tests (the Ames test, the CHO/HGPRT forward mutation assay, and the Chromosomal Aberration Frequency assay in CHO cells), or in an *in vivo* mouse micronucleus test.

TESLASCAN was positive in an *in vitro* mouse BALB/c-3T3 assay, but negative when the test was repeated; the assays were performed with the same final concentrations of TESLASCAN in the culture medium.

Reproduction and Teratology Studies

TESLASCAN did not affect male or female rat reproductive performance when administered at daily doses up to 100 μmol/kg (3.33 times the clinical dose based on body surface area, 20 times based on body weight).

Animal studies have shown that ^{54}Mn manganese crosses the placenta and locates in the fetus. At least 24 hours after injection, radioactivity is detected in liver and bones of the fetus. It has been reported that manganese enters nerve terminals, accumulates in

nervous tissue and could be associated with neurotoxicity in fetuses.

Manganese causes embryo toxicity and fetal toxicity in various animal species. In rats, mangafodipir was teratogenic (increased incidence of skeletal malformations) and fetotoxic (decreased fetal body weight) after 12 consecutive daily injections with 10, 20 and 40 μmol/kg (days 6 through 17 of gestation). These doses did not produce toxicity in the dams.

When female rats received TESLASCAN intravenously at doses of 2, 5 or 20 μmol/kg on Days 6 through 17 of gestation, adverse effects were not observed in fetal rats at doses of 5 μmol/kg/day (each daily dose was 0.16 of the single imaging dose based on body surface area and the same as the imaging dose based on body weight).

In another developmental study of rats injected with TESLASCAN for 3 consecutive days, 20-60% of the litters at the lowest daily dose tested (20 μmol/kg; each daily dose was 0.64 times the single imaging dose based on surface area, 4 times based on body weight) had skeletal abnormalities observed at each of the four 3-day intervals studied.

Rabbits received TESLASCAN intravenously at doses of 5, 20, 40 or 60 μmol/kg from days 6 to 18 of gestation. The maternal NOEL was >60 μmol/kg, and the NOEL for developmental toxicity was 40 μmol/kg. At 60 μmol/kg, there was an increased number of postimplantation losses and resorptions, and a decreased number of viable fetuses. In rabbits receiving up to 20 μmol/kg of mangafodipir (each daily dose was 1.33 times the

single imaging dose based on body surface area, 4 times based on body weight), there were no signs of maternal or fetal toxicity.

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