NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	214993
Priority or Standard	Priority
Submit Date	5/19/2021
Received Date	5/19/2021
PDUFA Goal Date	02/19/2022
Division/Office	DIRM/OSM
Review Completion Date	02/08/2022
Established/Proper Name	Kit for the Preparation of Technetium Tc99m Succimer Injection
Trade Name	NephroScan
Pharmacologic Class	Radioactive Diagnostic Agent (for Gamma-Scintigraphy)
Applicant	Theragnostics Inc.
Dosage form	Powder for Injection
Applicant proposed Dosing Regimen	The recommended amount of radioactivity by intravenous injection (bolus) is: • For adults: 74 MBq to 222 MBq (2 mCi to 6 mCi) • For pediatric patients: 1.85 MBq/kg (0.05 mCi/kg) of body weight with a range of 19 MBq to 74 MBq (0.5 mCi to 2 mCi)
Applicant Proposed Indication/Population	For use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	767094002 | Disorder of renal parenchyma (disorder) |
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	NEPHROSCAN, after radiolabeling with technetium Tc 99m, is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients including term neonates.
Recommended SNOMED CT Indication Disease Term for Each Indication	767094002 | Disorder of renal parenchyma (disorder) |
Recommended Dosing Regimen	Adults: 74 MBq to 222 MBq (2 mCi to 6 mCi) by intravenous injection (bolus). Pediatric Patients: 1.85 MBq/kg (0.05 mCi/kg) with a range of 19 MBq to 74 MBq (0.5 mCi to 2 mCi) by intravenous injection (bolus).

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OPQ = Office of Pharmaceutical Quality
ATL = Application Technical Lead
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
ECG	electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

1. Executive Summary

1.1. Product Introduction

Theragnostics Inc. (Theragnostics) has developed the Kit for Preparation of Technetium Tc99m Succimer Injection (THG Kit), which upon radiolabeling with Technetium Tc 99m injection solution gives Technetium Tc99m Succimer Injection, a radioactive diagnostic agent proposed for use as an aid for the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients. The kit contining the active ingredient DMSA (dimercaptosuccinic acid injection) was initially manufactured by GE Healthcare [GE] and the kit for the preparation of Technetium Tc99m Succimer Injection (Tc99m DMSA Injection) was approved on 18 May 1982 (NDA 017944-MPI DMSA Kidney Reagent) for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults. Tc99m DMSA Injection is useful for assessment of the renal cortex because it binds to the sulfhydryl groups in proximal tubules. The product can be used to image the renal cortices with gamma scintigraphy for the detection of focal lesions such as pyelonephritic scars.

In 2014, GE discontinued commercial distribution of the GE Kit, not for efficacy or safety reasons, and the FDA placed the product on the Drug Shortage List on 15 October 2014. On 03 August 2017, the FDA granted Theragnostics permission to import DMSA drug product manufactured by ROTOP Pharmaka GmbH under the drug shortage program (Theragnostics Imported Kit). There are no differences in the active ingredients between the proposed THG Kit and the approved-but-discontinued GE Kit and the differences in inactive ingredients between them are not expected to result in any differences in in vivo performance or the safety of the proposed product..

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA determined that Tc99m DMSA (GE Kit) is safe and effective for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults in March 1982 (NDA 017944) [1]. Review of studies from the scientific literature provides supportive evidence for its effective and safe use in pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk profile for the use of Nephroscan as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients (including term neonates) is favorable. This assessment is based on the following –

- prior FDA approval for the safe and effective use of the GE Kit in adults
- supportive evidence from the scientific literature for its effectiveness in pediatric patients
- post-marketing data demonstrating a favorable safety profile in both adult and pediatric patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Causes of renal parenchymal disorders can be acquired or congenital. Acquired causes include infections, endocrine and autoimmune disorders, exposure to toxic agents, cancer, poorly controlled hypertension and hypovolemia. In pediatric patients, urinary tract infections including pyelonephritis are a common problem and can result in significant morbidity (i.e., renal scarring, chronic renal failure, hypertension). In children, renal scarring is usually caused by episodes of acute pyelonephritis related to vesicoureteral reflux. The presence of scarring in patients with vesicoureteral reflux may lead one to consider surgical options to treat vesicoureteral reflux to prevent further scarring and damage to the kidneys. Estimating split renal function (SRF), the relative contribution of each kidney to total renal function, can be helpful for evaluating and guiding the management of a wide range of renal disorders.	Given the high compensatory capacity of the kidneys manifestations of renal damage may be delayed. Therefore, timely diagnosis facilitated by laboratory evaluation and renal imaging is important.
Current Treatment Options	Several imaging techniques are available to evaluate renal parenchymal disease. These include ultrasound (US), renal scintigraphy, computerized tomography (CT), intravenous pyelography (IVP) and magnetic resonance imaging (MRI).	While MRI, CT and US can be used for renal cortical characterization, Tc-99m succimer renal cortical scintigraphy is still considered the gold standard in the detection of renal scarring by the American College of Radiology

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Each of these techniques has been found to be optimal in specific renal conditions. In contrast to anatomic imaging techniques such as CT, MRI and US, scintigraphic techniques can provide both anatomical and functional information.	https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RenalScint.pdf
Benefit	FDA had previously determined that Tc99m DMSA (GE Kit; NDA 17944) is safe and effective for the scintigraphic evaluation of renal parenchymal disorders in adults. Review of the scientific literature provides supportive evidence that Tc99m DMSA is also safe and effective for this indication in the pediatric population.	Review of seven published pediatric studies provides supportive evidence of the effectiveness of Tc99m DMSA in pediatric patients including neonates.
Risk and Risk Management	Tc99m DMSA (GE Kit) is a microdose product . Most reported adverse reactions were mild in intensity and resolved without sequelae. There were a few reports of hypersensitivity reactions, including anaphylaxis, pruritus, erythema, and urticaria with the use of Tc 99m DMSA. The time of onset of the reactions varied within 2 hours to several hours after administration (see Pharmacovigilance Review).	Text related to the possibility for Hypersensitivity Reactions to Tc-99m Succimer Injection was added to Section 6 (ADVERSE REACTIONS) of the prescribing information. Text related to the monitoring and management of Hypersensitivity Reactions was added to Section 5 (WARNINGS AND PRECAUTIONS) of the prescribing information.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application and is not needed.**			

2. Therapeutic Context

2.1. Analysis of Condition

Diseases effecting the renal cortex and renal medulla constitute renal parenchymal disease and the causes can be acquired or congenital (Barnett and Cummings 2019; Mayo Clinic 2022; Texas Children's Hospital 2022). Acquired causes include infections, endocrine and autoimmune disorders, exposure to toxic agents, cancer, poorly controlled hypertension and hypovolemia due to dehydration, poor fluid intake or diuretics (Barnett and Cummings 2019; Mayo Clinic 2022; Texas Children's Hospital 2022). Early on in the disease process the patients can be asymptomatic and diagnosis can be challenging (Mayo Clinic 2022; Texas Children's Hospital 2022). The nonspecific symptomatology of renal disease together with the high compensatory capacity of the kidneys make diagnosis difficult before irreversible renal damage occurs (Mayo Clinic 2022; Texas Children's Hospital 2022). Therefore, timely diagnosis and management of renal parenchymal disease is essential to preserve renal function.

In pediatric patients, urinary tract infections are a common problem. While infections involving the bladder and collecting system usually have a benign clinical course, pyelonephritis can lead to morbidity resulting from renal scarring, chronic renal failure and hypertension (Lim 2009; Merguerian et al. 2010; Koyle et al. 2011; Williams et al. 2012). In children, renal scarring can result from recurrent episodes of acute pyelonephritis (APN) related to vesicoureteral reflux (Ditchfield et al. 1994; Goldman et al. 2000; Gordon et al. 2003; Orellana et al. 2004; Lee et al. 2006; Polito et al. 2006). Higher grades of vesicoureteral reflux are generally associated with a greater risk for the development of pyelonephritis (Ditchfield et al. 1994; Goldman et al. 2000; Gordon et al. 2003; Orellana et al. 2004; Lee et al. 2006; Polito et al. 2006). However, APN can also be seen in the absence of vesicoureteral reflux. The presence of scarring in patients with vesicoureteral reflux may lead one to consider surgical options to treat vesicoureteral reflux to prevent further scarring and damage to the kidneys (Ditchfield et al. 1994; Goldman et al. 2000; Gordon et al. 2003; Orellana et al. 2004; Lee et al. 2006; Polito et al. 2006). Patients with pyelonephritis may present with fever, flank pain or tenderness, malaise, irritability, leukocytosis, and bacteriuria (Williams et al. 2012). However, neonates can present with nonspecific clinical findings (Williams et al. 2012). It should be noted that the commonly used clinical and laboratory parameters may not be adequate for the diagnosis of APN and a variety of imaging techniques could be used to aid in the diagnosis (Williams et al. 2012; UpToDate 2019) (see Section 2.2).

Differential renal function, termed split renal function (SRF), is the relative contribution of each of the two kidneys to total renal function. It is helpful for evaluating and guiding the management of a wide range of renal disorders and can be assessed by a variety of non-invasive imaging techniques (UpToDate 2019) (see Section 2.2).

2.2. Analysis of Current Treatment Options

A variety of radiologic studies can be used to evaluate patients with renal disease. These include US, renal scintigraphy, CT, IVP and MRI and each of these has been found to be optimal in specific renal disorders (UpToDate 2019). These modalities are either used alone or in combination. In contrast to anatomic imaging techniques such as CT, MRI, and US, scintigraphic techniques can provide both anatomical and functional information. While Tc99m Succimer Injection has been approved for the scintigraphic evaluation of renal parenchymal disorders in adults (NDA017944), it is being routinely used off-label in the pediatric population for renal cortical characterization including renal function. While there are reports in the scientific literature regarding the use of MRI, CT and US for renal cortical characterization in children, as a substitute for Tc-99m DMSA examinations, Tc-99m DMSA renal cortical scintigraphy is still considered the gold standard in the detection of renal scarring by the American College of Radiology (American College of Radiology 2017).

SRF is estimated in clinical practice with CT angiography (Summerlin et al. 2008; Miyazaki et al. 2010), dynamic contrast-enhanced MR urography (Claudon et al. 2014), DWI (Li et al. 2013), and renal scintigraphy performed with various radionuclides, (Piepsz et al. 1999; Piepsz et al. 2001; Smokvina et al. 2005; Ritchie et al. 2008; Miyazaki et al. 2010; Dostbil et al. 2011).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- **1982:** GE received initial FDA approval (NDA 017944) for DMSA (GE Kit)
- **2014:** GE ceased commercial distribution of GE Kit (not for efficacy or safety reasons) and it was placed on the FDA Drug Shortage List
- **2017:** FDA granted Applicant permission to import a DMSA drug product manufactured by ROTOP Pharmaka GmbH with marketing authorization in Germany (referred as "ROTOP Kit / THG Imported Kit" in this review) under the FDA Drug Shortage Program
- **2017-Present:** Applicant reports that over (b) (4) vials of the "ROTOP Kit / THG Imported Kit" have been distributed for use in adult and pediatric patients in the US under the FDA Drug Shortage Program

3.2. Summary of Presubmission/Submission Regulatory Activity

All regulatory communications related to NDA 214993 have been through Pre-IND 145176.

10/29/2019: Pre-NDA meeting to align with FDA on the content and format for the proposed 505(b)(2) NDA.

FDA advised the Applicant -"If you are able to provide an adequate scientific bridge between your product and the listed drug as described above, you may be able to rely in part on FDA's previous findings of safety and effectiveness for Tc99m-DMSA in adults (NDA 017944). However, since there are differences in the proposed formulation, population of use, and dose between your product and the listed drug, your literature search should include citations of any publication date that describe:

- studies of Tc99m-DMSA use in pediatric patients,
- studies specifically involving use of your formulation, and
- studies specifically using your proposed adult and pediatric dosing regimens

In addition to the above citations, your literature search should include any other studies of Tc99m-DMSA in adults that were published since FDA approval. You must provide adequate justification to establish that reliance upon the published literature is scientifically appropriate."

9/2/2020: In the initial pediatric study plan (iPSP) written comments on literature and the Statistical Analysis Plan (SAP), FDA advised -
"Limit your literature search for efficacy to the papers with the following study designs:

1. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., MRI or CT) in the detection of renal scarring. Studies similar to Freeman et al. (2018) may be of most value.
2. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., MRI or CT) in the detection of acute pyelonephritis.
3. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., Tc99m-MAG3) in split function measurement."

9/4/2020: Agreement between the FDA and Theragnostics on proposed iPSP.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable to this NDA.

4.2. Product Quality

The Kit for the Preparation of Technetium Tc99m Succimer Injection is supplied as a white - yellowish to off white, lyophilized powder for injection in a clear, 10 mL glass vial. Each kit vial is composed of 1.0 mg meso-2,3-dimercaptosuccinic acid [DMSA], 0.42 mg stannous chloride

dihydrate, 0.1 mg (b) (4) ascorbic acid, up to 0.2 mg sodium hydroxide and 0.02 mg of HCl (b) (4) (b) (4)

Subsequent to radiolabeling with up to 40 mCi of sodium pertechnetate Tc 99m injection solution from a Tc-99m generator, the technetium Tc99m succimer injection is obtained as a clear, colorless, sterile intravenous solution provided in 5 mL of solution. The volume of dose administered will vary depending on the radioactive concentration at the time of administration. The generator compatibility results demonstrate that when the labeling instructions are followed, any commercially available technetium generator can be used to prepare the Technetium Tc99m Succimer Injection drug product.

The applicant has provided sufficient information to assure the identity, strength, purity, quality, including sterility of the proposed drug product. The container closure system is appropriate for lyophilized drug products. The Kit for the Preparation of Technetium Tc99m Succimer Injection is to be stored at 5°C (refrigerator) and is not photosensitive. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, Kit for the Preparation of Technetium Tc99m Succimer Injection possesses the necessary attributes to ensure indicated safety and efficacy.

4.3. Clinical Microbiology

Not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

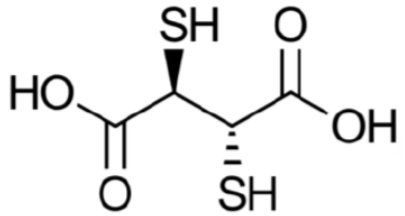
This NDA should be approved from a nonclinical perspective.

The Applicant conducted no new nonclinical studies on Tc99m DMSA to support this NDA submission. However, the Applicant is relying on the previous findings of safety for the listed drug described in the most recent labeling for DMSA Kit for the Preparation of Technetium Tc99m Succimer Injection (NDA 017944 approved in 1982) and data reported in the published nonclinical literature. Renal parenchymal disorder, also known as kidney disease, is caused by toxic agents, diuretic medications, as well as low fluid intake and dehydration found to impact kidney function. Kidney stones, cancer, sepsis, and congenital conditions such as autosomal

polycystic kidney disease can also impact kidney function (Barnett and Cummings 2019; Texas Children's Hospital 2022). Due to the compensatory capacity and the nonspecific symptomology of kidney disease, it is challenging to diagnose before irreversible damage has occurred. Kidney disease is commonly diagnosed by measurement of the following clinical chemistry parameters: blood urea nitrogen (BUN), creatinine clearance, glomerular filtration rate (GFR), and urinalysis, specifically presence of blood and/or protein in the urine.

The Structure of DMSA is shown in Figure 1:

Figure 1. Structure of DMSA



Molecular Formula = $C_4H_6O_4S_2$
Molecular Weight =182.22

Mechanism of Action

Following intravenous administration, Tc99m DMSA is rapidly distributed to several organs and tissues, with high concentrations of Tc99m DMSA demonstrated in the kidneys. Elimination occurs gradually over 24 hours from the blood, liver, and muscle. In line with FDA Guidance for Microdose Radiopharmaceutical Diagnostic Drugs, dedicated safety pharmacology studies were not conducted for Tc99m DMSA. The Applicant summarized findings from Klimmek et al. (1993) that evaluated in vitro effects of DMSA on oxygen consumption and ferrihemoglobin (MetHb) in vitro in whole blood and erythrocytes suspended in phosphate buffer as well as cardiovascular and respiratory effects following intravenous administration in Beagle dogs. No measurable ferrihemoglobin was produced following incubation of whole blood or erythrocytes with 1 mM DMSA for up to 150-minutes. The in vivo data did not demonstrate any cardiovascular and respiratory effects following intravenous administration of 12 mg/kg DMSA in beagle dogs (Klimmek et al. 1993).

PK/ADME studies

Pharmacokinetics data indicates that the uptake and excretion of the radiolabel occur via independent pathways in alignment with the suggestion that glomerular filtration and peritubular capillary uptake contribute to the renal handling of Tc99m DMSA (Müller-Suur and Gutsche 1995; Burckhardt et al. 2002). Metabolism of Tc99m DMSA might involve autoxidation, disulfide formation, thiol transfer, desulfurization, or a combination of the processes. For most species, the tracer is excreted unchanged and in humans, DMSA is mostly excreted in the urine in the form of mixed disulfides with cysteine, and only 2.5% is excreted as unchanged DMSA (Aposhian and Aposhian 1990).

Toxicology Studies

Published findings for single dose toxicity studies conducted in mice suggest that DMSA is not acutely toxic (Lin et al. 1974; Friedheim and Corvi 1975; Aposhian et al. 1984; Flora and Pachauri 2010); the median lethal dose (LD_{50}) values for DMSA in mice by various routes of administration ranged from 2.4 g/kg (intravenous) to 8.5 g/kg (oral), 116,750 to 413,491-fold respectively greater than the intended clinical dose based on a maximum dose of 100 µg mass dose. However, the LD_{50} is not considered appropriate and No-Observed-Adverse-Effect-Level (NOAEL) was not provided to estimate the safety margin for DMSA by the intravenous route. In a repeat-dose toxicity study in rats, no adverse clinical signs or histological findings were demonstrated in rats administered 0.55 mg/kg DMSA by intravenous injection for 14 days (Lin et al. 1974). In a repeat-dose toxicity study in dogs, intravenous administration of 0.34 mg DMSA/kg for 17 consecutive days did not result in any adverse clinical signs or adverse changes in clinical chemistry parameters. The toxicity data demonstrates that DMSA is well tolerated at very high doses and therefore no serious adverse effects are expected at the proposed microdose for the intended indication for Tc99m DMSA in this application. Genotoxicity studies and carcinogenicity studies were not conducted and are not required for radioactive diagnostic agents. The Applicant requested and was granted a waiver from conducting reproductive and developmental toxicity studies for Tc99m DMSA.

Therefore, no other nonclinical studies are necessary to support the safety of Tc 99m DMSA for the indication in the intended population. Based on the available nonclinical data with Tc99m DMSA, it is recommended that NDA 214993 for Tc99m DMSA be approved from a nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 017944
NDA 019998

5.3. Pharmacology

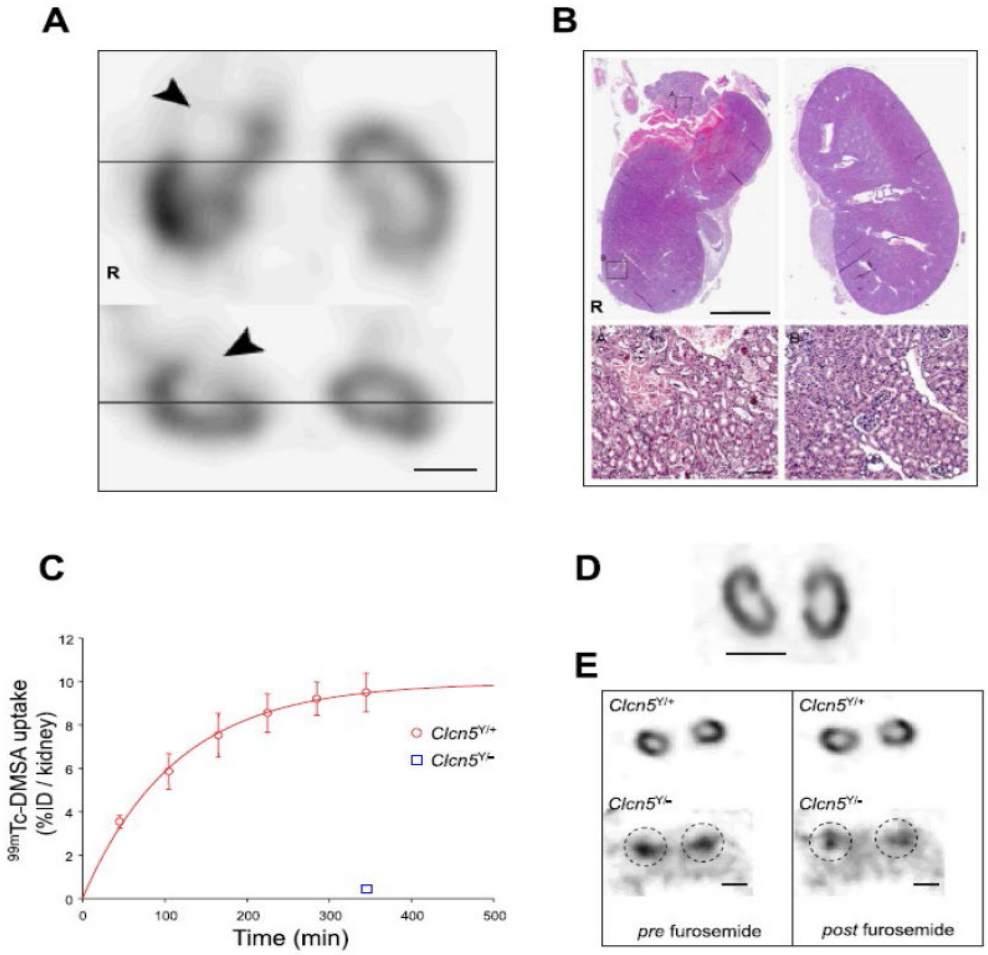
No pharmacology studies were conducted to support the efficacy or safety of Tc99m DMSA. The Applicant however provided the nonclinical pharmacology data below from relevant published nonclinical literature to support the NDA submission.

In Vitro Pharmacology:

Data from the literature suggests that Tc99m DMSA binds to the cortical region of kidneys. Tc99m DMSA remains bound to healthy cortical tissue for more than 24 hours post administration. Tc99m DMSA imaging has been evaluated for the assessment of the renal cortices and differential renal function and renal scarring (Farnsworth et al. 1991).

The applicant summarized studies on the uptake of Tc99m DMSA and other radiopharmaceuticals investigated at various time points, organs, and species. In a study by Arnold et al. (1975) that evaluated 17 renal imaging agents, the kidney/blood, kidney/liver, kidney/muscle, and cortex/medulla uptake ratios in New Zealand rabbits were 18.0 ± 4.40, 46.0 ± 12.00, 197 ± 74.0, and 17.00 ± 4.20, respectively for Tc99m DMSA. It was reported that the concentration of Tc99m DMSA remained high in the kidneys, but decreased over 24 hours in the blood, liver, and muscle. Similar concentrations of Tc99m DMSA were reported for the kidney of Mongrel dogs, specifically the cortex of the kidneys. In a published study by Jouret et al. (2010), Tc99m DMSA was used for imaging the kidney cortex and ^{123}I β2-microglobulin monitored receptor-mediated endocytosis in C57BL/6, normal and experimentally infarcted, as well as *Clcn5* knockout (KO) mice (Figure 2). It was reported that by 5 hours post-intravenous injection, the functional renal cortex was imaged in normal C57BL/6 mice with Tc99m DMSA SPECT. Infarcted and KO mice showed no cortical uptake of Tc99m DMSA. Progressive increase in renal uptake of Tc99m DMSA in normal mice was observed and the uptake then plateaued to a level that was approximately 10% of the injected dose (%ID). The results of this study suggest that Tc99m DMSA SPECT imaging in mice can identify functional tissue in the renal cortex with a spatial resolution of approximately 1 mm. There is reduced or absent uptake of Tc99m DMSA in functionally defective cortical tissue, caused either by insufficient perfusion (infarction) or proximal tubule dysfunction (*Clcn5* KO mice) which supports the clinical use of Tc99m DMSA for the scintigraphic evaluation of renal parenchyma.

Figure 2. SPECT Imaging of Tc99m DMSA in the Mouse



Abbreviations: %ID = percent of injected dose; KO = knock out (gene silenced); min = minute(s); SPECT = single-photon emission computer tomography.

Panel A: Tc99m DMSA SPECT image following apical infarction of the right (R) kidney of a wild-type mouse. Coronal (*top*) and transverse (*bottom*) sections/slices showing no Tc99m DMSA SPECT uptake in the infarction area (arrows). The bar = 3 mm. Panel B: Histological confirmation of the infarction in the right (R) kidney following hematoxylin-eosin (H&E) staining. Low magnification (top), the bar = 3 mm; high magnification (bottom), the bar = 100 µm. Panel C: Kinetics of Tc99m DMSA SPECT uptake in the kidney cortex from wild-type (Clcn5Y/+; red circles) and KO (Clcn5Y/-; blue square) measured using consecutive SPECT acquisitions (n=8 kidneys from 4 mice). Panels D and E: Representative coronal (D) and transverse (E) sections of kidneys from wild-type and KO mice before and after furosemide administration. In Panel D the bar = 3 mm.

Source: Jouret et al., 2010.

Source: Sponsor Figure 1 from Section 2.6.2. Pharmacology Written Summary

In a study by Moretti et al. (1984), Tc99m DMSA uptake and binding in rat kidney could be inhibited by the addition of unlabeled DMSA indicating that there are a limited number of binding sites. In the study, following co administration of Hg+ ion, there was inhibition of uptake and binding in the kidneys with increased urinary excretion of Tc99m DMSA (Table 1). However, Hg+ ion did not affect Tc99m DMSA uptake and binding to the same extent in the liver, spleen, heart, and blood, suggesting that Hg+ ion and Tc99m DMSA compete for the same binding site in the proximal tubules.

Table 1. Effect of Mercury Ion on the Uptake/Binding of Tc99m DMSA

Treatment	Kidneys	Liver	Spleen	Heart	Blood
Tc99m DMSA	48.8 ± 3.6[a]	1.8 ± 0.09	0.38 ± 0.02	0.15 ± 0.01	0.12 ± 0.01
Tc99m DMSA + Hg^{+}	1.74 ± 0.12	0.11 ± 0.01	0.06 ± 0.01	0.024 ± 0.002	0.033 ± 0.003

Abbreviations: %ID = percent of the injected dose; SD = standard deviation.

[a] Values presented are the %ID; as the mean ± SD (n=5).

Source: Moretti et al., 1984b.

Source: Sponsor Table 1 from Section 2.6.2. Pharmacology Written Summary

In a biodistribution study of Tc99m DMSA and other renal imaging agents (Arnold et al. 1975), the biodistribution of Tc99m was evaluated in rabbits (Table 2) and dogs (Table 3) at one hour, following intravenous administration. The Tc99m DMSA distribution in various organs indicated that Tc99m DMSA was predominantly located in the kidneys.

Table 2. One-Hour Distribution of Tc99m DMSA in Rabbits[1]

Percent Dose/1% Body Weight in Whole Organ					Ratios			
2 Kidneys	Blood	Liver	Muscle	Urine	Kidney/ Blood	Kidney/ Liver	Kidney/ Muscle	Cortex/ Medulla
20.0 ± 4.00	17.0 ± 1.90	3.2 ± 0.49	9.8 ± 2.20	15.0 ± 5.2	18.0 ± 4.40	46.0 ± 12.00	197 ± 74.0	17.00 ± 4.20

[1] (n=6).

Source: Sponsor Table 4 from 2.6.2. Pharmacology Written Summary

Table 3. One-Hour Distribution of Tc99m DMSA in Mongrel Dogs[1]

Percent Dose in Whole Organ:	Normal Kidney (one)	8.30 ± 5.20
Percent Dose/1% Body Weight:	Blood	0.77 ± 0.51
	Liver	0.77 ± 0.47
	Muscle	0.16 ± 0.09
	Small Bowel and Contents	0.41 ± 0.18
	Kidney	33.00 ± 20.00
	Cortex of Kidney	33.00 ± 23.00
	Medulla of Kidney	8.00 ± 8.40
Ratios:	Kidney/Blood	58.00 ± 42.00
	Kidney/Liver	53.00 ± 38.00
	Kidney/Muscle	229.00 ± 120.00
	Cortex/Medulla	7.10 ± 7.40

[1] (n=6).

Source: Sponsor Table 5 from 2.6.2. Pharmacology Written Summary

In a study by Arnold et al. (1990), SPECT imaging of renal scarring by Tc99m DMSA was evaluated in a porcine model of unilateral vesicoureteral reflux (VUR) induced by inoculation with bacteria to induce a urinary tract infection (UTI). The sensitivity and specificity for Tc99m DMSA imaging for renal scarring was 85% and 97%, respectively based on renal histology (macroscopic renal scarring). In a porcine model of unilateral VUR the uptake of administered Tc99m DMSA in the normal and VUR kidney were evaluated (Godley et al. 1999). Prior to infection, all groups had normal Tc99m DMSA images and a mean differential uptake of 50%. The mean values for the absolute percent dose uptake for the VUR kidney ranged between 20% and 22%.

The Applicant summarized the findings from another VUR study conducted in pigs designed to evaluate renal scarring (Rossleigh et al. 1998). In this study, Tc99m DMSA was evaluated 3 months after unilateral VUR to ensure no residual inflammation was present in the kidneys and only reflux nephropathy (RN) was observed in the scans. Each pig was imaged using a high-resolution-hole collimator (planar), pinhole collimator (pinhole), and SPECT methods and compared to ultrasound. The three Tc99m DMSA imaging techniques were better than ultrasound for imaging RN (Table 4).

Table 4. Sensitivity, Specificity, PPV, and NPV of Imaging Methods (%)

Imaging Technique	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
Planar	62	100	100	88	90
Pinhole	74	99	96	91	92
SPECT	59	98	91	87	87
Ultrasound	29	92	59	78	75

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; SPECT = single photon emitting computer tomography.

Results are from 18 kidneys evaluated.

Source: Rossleigh et al., 1998.

Source: Sponsor Table 7 from 2.6.2. Pharmacology Written Summary

The Applicant summarized the findings from a quantitative study of Tc99m DMSA renal uptake in a porcine model of unilateral VUR-related pyelonephritis (Godley et al. 1999). In this study, the changes in the absolute percent of the dose uptake as well as differential uptake during pyelonephritis induction and after treatment compared very well with the DMSA imaging results and renal histopathology at necropsy.

In a study by Majd et al. (2001), the ability of Tc99m DMSA SPECT to identify acute pyelonephritis was compared to histopathology in pigs and included spiral computerized tomography (CT), magnetic resonance imaging (MRI), and power Doppler ultrasound imaging modalities for the diagnosis of acute pyelonephritis. After imaging, the kidneys were removed for histology and evidence of pyelonephritis in 38 of the 70 kidneys was found in a total of 102 zones. The sensitivity and specificity for identifying pyelonephritis in the kidney were 92% and

94% and zonally 94% and 95%, respectively (Majd et al. 2001). In a meta-analysis of nonclinical studies across various species to analyze the performance of all Tc99m DMSA imaging modalities (Craig et al. 2000), the overall sensitivity and estimated specificity were 86% and 91%, respectively.

Secondary Pharmacology:

No secondary pharmacology studies with DMSA were conducted by the Applicant. However, DMSA is currently approved (NDA 019998 in 1991) for the treatment of heavy metal poisoning (particularly lead) at 10-12.5 mg/kg by oral route every 8 hours for 5 days for adult and pediatric population (Recordati Rare Diseases Inc. 2018). The orally administered dose is greater than the intended clinical dose for Tc99m DMSA (not more than 100 µg) to be administered to patients for the detection of kidney disease. In a study that evaluated metal chelation and excretion in Swiss Webster mice following daily DMSA administration (Cantilena and Klaassen 1982), a significant increase in the urinary excretion of endogenous copper was reported following once daily (3 consecutive days) or twice daily (7 consecutive days) DMSA administration at 0.74 g/kg (1/4th of the LD_{50} dose). However, the urinary excretion of zinc, iron, magnesium, calcium, and manganese was not affected by DMSA administration in this study.

Safety Pharmacology:

Safety Pharmacology studies of Tc99m DMSA were not conducted by the Applicant and are not recommended for microdose radioactive diagnostic agents. However, the Applicant summarized the findings from a study (Klimmek et al. 1993) on the respiratory and cardiovascular effects of DMSA. In the study, the effect of nonchelated DMSA on oxygen consumption and ferrihemoglobin (MetHb) produced was evaluated by in vitro assay on whole blood and erythrocytes suspended in phosphate buffer. No measurable MetHb was produced by incubation with DMSA which would suggest that there would be no potential for respiratory and cardiovascular effects of DMSA through oxidation. In Beagle dogs administered 12 mg/kg DMSA by intravenous injection, there were no significant changes reported in the mean central venous pressure (CVP) mean aortic pressure (AOP), femoral mean arterial pressure (MAP), femoral mean venous pressure (MVP), and left ventricular pressure (LVP), left ventricular differential pressure (LVdp/dt), cardiac output (COU), effective perfusion pressure (EPP), femoral blood flow (Vfem), and electrocardiogram (ECG).

Drug Interactions:

The Applicant summarized findings from published studies on potential drug-drug interactions with Tc99m DMSA. In a study by Gomes et al. (2001), pre-treatment of female Balb/c mice with Mitomycin C (MMC) caused a decrease in Tc99m DMSA uptake in the uterus, heart, pancreas, bone, liver, thyroid, lung, stomach, ovary, spleen, thymus, and kidney compared to mice not pre-treated with MMC. In a published study by Mattos et al. (2001), pretreatment of mice with

vincristine, an anticancer drug, increased the %ID/g of tissue in the lung, liver, heart, thyroid, brain, and bone.

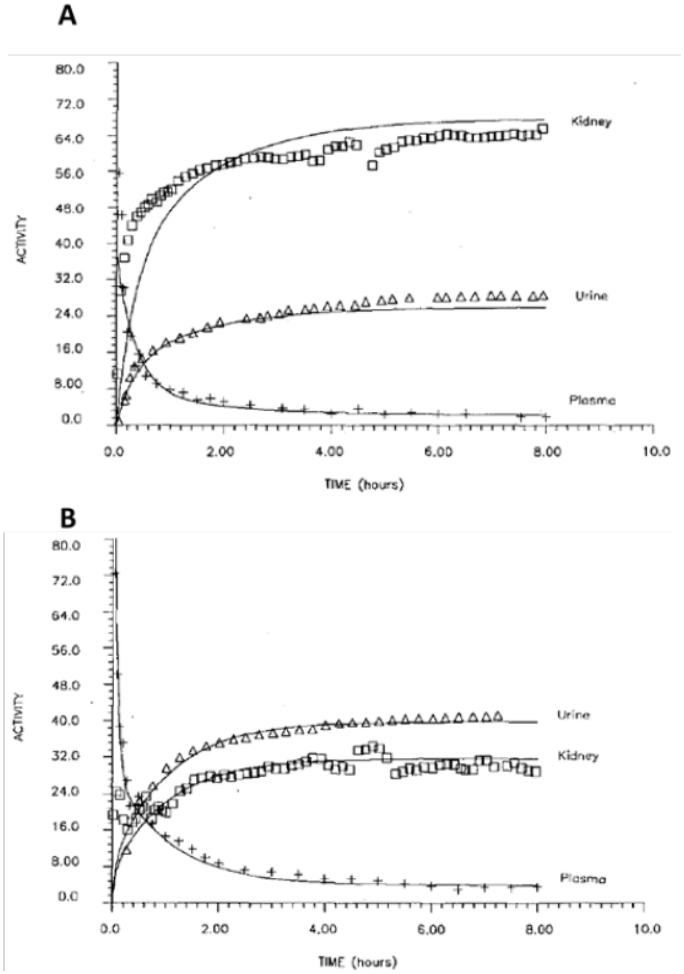
5.4. ADME/PK

The Applicant did not conduct any nonclinical pharmacokinetic (PK) or absorption, distribution, metabolism, excretion (ADME) studies of Tc99m DMSA to support this application. However, the Applicant summarized findings from published studies on PK/ADME properties of Tc99m DMSA to support the NDA submission.

Table 5. Summarized Study Findings on PK/ADME Properties of Tc99m DMSA

N	Major Findings
Absorption	
N/A	N/A
Distribution	
*"A kinetic model for 99mTc-DMSA in the rat" (*Maneval et al. 1990*)*	A PK model was developed to study the distribution, tissue uptake, and elimination of intravenous Tc99m DMSA in rats using plasma, kidney, and urine data. The Authors stated that the PK model accurately predicted the data for plasma and urine, for both control and the animals co-administered unlabeled DMSA The data suggested that the uptake and excretion of the radiolabel occur via independent pathways, that glomerular filtration and peritubular capillary uptake contribute to the renal handling of Tc99m DMSA (See also (Müller-Suur and Gutsche 1995; Burckhardt et al. 2002).

Figure 3. Pharmacokinetic Modeling Results for Tc99m DMSA in the Rat



Source: Sponsor Figure 4 from Section 2.6.4. Pharmacokinetics Written Summary

Panel A and B are control animals and animals co-administered unlabeled DMSA, respectively where (+) = plasma; (□) = kidney; (Δ) = urine. Kidney and urine data are expressed as % injected dose (%ID), and plasma is 1/10th the ordinate value in %ID/mL.

	The role of the renal Na+-dependent dicarboxylate transporter (NaDC-3) in the translocation of DMSA and DMSA chelates of mercury and lead was investigated by electrophysiological methods on cultured proximal tubule cells (NaDC-3 is found on the basolateral plasma membrane of proximal tubule cells). The study indicated that DMSA was translocated, but mercury or lead chelates of DMSA were not. The Sponsor stated that while the cited study was not conducted with Tc99m DMSA, the findings were consistent with studies demonstrating that peritubular extraction accounts for Tc99m DMSA uptake in the proximal tubular cells of the renal cortex. This reviewer agrees with this assessment.
"The renal Na+-dependent dicarboxylate transporter, NaDC-3, translocates dimethyl- and sulfhydryl-compounds and contributes to renal heavy metal detoxification" (Burckhardt et al. 2002)	Serum T_{max} following subcutaneous and oral administration of S35-labeled DMSA in rats was 15 and 30 min, respectively. In this study, the majority of the radiolabel in the blood was undetectable after 2 hours and 95% of the radiolabel was eliminated from the body by 24 hours after dosing.
*"DMSA and DMPS - water soluble antidotes for heavy metal poisoning."(*Aposhian 1983*)*	Tc99m DMSA biodistribution and organ uptake (kidneys, liver, spleen, carcass) in Wistar rats did not vary significantly between two different labeling kits and formulations (excipients ascorbic acid and inositol present in 1 kit) at high (3700 MBq) and low activity (555 MBq) (Table 6). **Table 6. Biodistribution of Tc99m DMSA Produced Using 2 Different Kits in Wistar Rats** Abbreviations: %IA = percent of injected activity; IPEN = Instituto de Pesquisas Energéticas e Nucleares (Nuclear and Energy Research Institute) in São Paulo, Brazil. Source: Sponsor Table 1 from Section 2.6.4. Pharmacokinetics Written Summary
*"Study of 99mTc-DMSA biodistribution in experimental animals." (*de Castro et al. 2017*)*	Tc99m-DMSA uptake (radioactivity concentration) was greatest in the kidneys, regardless of the formulation conditions (Table 7). Formulation conditions were administration 10 (Group 1) or 60 min (Group 3) following kit preparation and exposure to air (Group 2).

Organ (USP Criteria)	%IA/Organ for Tc99m DMSA (IPEN Kit)		%IA/Organ for Tc99m DMSA (Other Kit)	
	185 MBq/3 mL (Low)	3700 MBq/3 mL (High)	185 MBq/3 mL (Low)	3700 MBq/3 mL (High)
Kidneys (≥40 % IA)	55.10 ± 1.36	44.87 ± 1.62	43.15 ± 1.62	41.25 ± 0.61
Liver (no criterion)	2.82 ± 0.53	3.86 ± 0.31	6.58 ± 0.49	6.01 ± 0.81
Spleen (no criterion)	0.17 ± 0.10	0.15 ± 0.02	0.40 ± 0.04	0.28 ± 0.05
Carcass (no criterion)	22.79 ± 4.51	27.29 ± 4.80	33.78 ± 1.01	31.68 ± 1.61
Kidneys/ (Liver + Spleen) (≥6)	18.84 ± 3.58	11.22 ± 0.51	6.19 ± 0.20	6.64 ± 0.90

Table 7. Tissue Distribution of Tc99m DMSA in Rats as a Function of Time After Formulation and Aeration of the Formulation

Tissue	Group 1 (% Dose/Organ)	Group 2 (% Dose/Organ)	Group 3 (% Dose/Organ)
Blood[1]	7.0 ± 0.41	5.3 ± 0.65	8.9 ± 4.4
Liver	7.5 ± 1.9	17 ± 2.9	7.1 ± 2.1
Spleen	0.16 ± 0.04	0.4 ± 0.09	0.19 ± 0.06
One Kidney	25 ± 1.4	20 ± 2.6	24 ± 1.8
Muscle[1]	3.1 ± 0.21	3.0 ± 0.3	3.6 ± 0.3
Stomach[2]	0.15 ± 0.02	0.15 ± 0.06	0.15 ± 0.03
Intestine[2]	1.2 ± 0.2	1.0 ± 0.06	1.0 ± 0.2

Source: Sponsor Table 5 from Section 2.6.4. Pharmacokinetics Written Summary

In the table, tissue distribution was calculated based on estimates of % body weight ([1]blood and [1]muscle estimated to 7% and 40% of the total body weight, respectively) and radioactivity of the [2]stomach and [2]intestine included content (mean ± SD, n=5)

Kidney uptake in rats was approximately 50% at 30 minutes after dosing and remained essentially constant out to 24 hours after intravenous administration (Table 8).

Table 8. Tissue Distribution of Tc99m DMSA in Rats as a Function of Time After Administration

Tissue	Group 4 (% dose/organ) 0.5 hr After Dosing	Group 1 (% dose/organ) 2.0 hr After Dosing	Group 5 (% dose/organ) 24.0 hr After Dosing	Group 4 (% dose/g) × 100 0.5 hr After Dosing	Group 1 (% dose/g) × 100 2.0 hr After Dosing	Group 5 (% dose/g) × 100 24.0 hr After Dosing
Blood[1]	14 ± 0.87	7.0 ± 0.41	1.1 ± 0.89	54 ± 14	24 ± 0.9	3.7 ± 0.42
Liver	11 ± 3.3	7.5 ± 1.9	3.4 ± 0.23	71 ± 28	44 ± 12	20 ± 2.9
Spleen	0.17 ± 0.07	0.16 ± 0.04	0.11 ± 0.03	27 ± 9.4	21 ± 5.2	18 ± 6.2
Kidney	27 ± 2.3	25 ± 1.4	27.0 ± 1.1	2000 ± 420	1600 ± 150	1800 ± 63
Muscle[1]	4.8 ± 0.33	3.1 ± 0.21	1.9 ± 0.26	3.3 ± 0.63	1.9 ± 0.16	1.2 ± 0.1
Stomach[2]	0.24 ± 0.08	0.15 ± 0.02	0.12 ± 0.09	—	—	—
Intestine[2]	1.3 ± 0.18	1.2 ± 0.2	0.77 ± 0.10	—	—	—
Feces			0.95 ± 0.19			
Kidney/Blood Ratio	—	—	—	37	67	487
Kidney/Liver Ratio	—	—	—	28	36	90
Kidney/Muscle Ratio	—	—	—	606	842	1500

Source: Sponsor Table 6 from Section 2.6.4. Pharmacokinetics Written Summary
In the table, tissue distr bution was calculated based on estimates of % body weight (blood[1] and muscle[1] estimated to 7% and 40% of the total body weight, respectively) and radioactivity of the stomach[2] and intestine[2] included content (mean ± SD, n=5).

"Optimal handling of dimercaptosuccinic acid for quantitative renal scanning." (Taylor et al. 1980)	In male Wistar rats that were administered Tc99m DMSA by intravenous route or by micropuncture technique, Tc99m DMSA was largely bound to plasma protein and there is very little glomerular filtration, with all the Tc99m DMSA in the tubule fluid being excreted and not reabsorbed. The Authors stated that peritubular extraction accounted for the uptake of Tc99m DMSA in the proximal tubular cells of the renal cortex.

*"Tubular reabsorption of technetium-99m-DMSA." (*Müller-Suur and Gutsche 1995*)*	Fetotoxic and embryotoxic effects of nonchelated DMSA were reported in pregnant Swiss mice in two studies. The Applicant stated that the toxicological effects seen at these doses would suggest that there is placental transfer of DMSA from the maternal blood (DMSA levels in the placenta, amniotic fluid, the embryo, or fetus were not measured in the study). The Applicant further stated that no placental transfer of Tc99m DMSA is expected at such a low dose exposure in the proposed indication. The reviewer agrees with this assessment.
*"Developmental toxicity of subcutaneously administered meso-2,3-dimercaptosuccinic acid in mice." (*Domingo et al. 1988*); "Oral meso-2, 3-dimercaptosuccinic acid in pregnant Sprague-Dawley rats: teratogenicity and alterations in mineral metabolism." (*Domingo et al. 1990*)*	
Metabolism	Metabolism of DMSA is complex and varies among different species. Available data suggests that it might involve autoxidation, disulfide formation, thiol transfer, desulfurization, or a combination of the processes. It has been reported that DMSA can autoxidize in solution, leading to formation of disulfides (Knudsen and McGown 1988).
*"Gas chromatographic analysis of urinary dimercaptosuccinic acid" (*Knudsen and McGown 1988*)*	Male New Zealand rabbits were intramuscularly administered 0.20 mml/kg of uniformly labeled DMSA [U-C14]DMSA. Analysis of the radioactivity uptake and HPLC showed that 73% of the DMSA was excreted in the urine unaltered, 7% as MSA, and as 2 unknown compounds comprising 6% and 14% of the injected dose. Bromobimane treatment of urine collected from treated rabbits inhibited the autoxidation of DMSA. Cysteine was only found in the urine from DMSA treated rabbits following electrolytic reduction and the amount of cysteine was only 6% DMSA.
*"Determination and metabolism of dithiol chelating agents IV. Urinary excretion of meso-2,3-dimercaptosuccinic acid and mercaptosuccinic acid in rabbits given meso-2,3-dimercaptosuccinic acid" (*Maiorino and Aposhian 1989*)*	
Excretion	In most species, DMSA is excreted unchanged in the urine. Mice Whole-body radiography of mice administered C14-DMSA by intravenous route, demonstrated moderate uptake in the gallbladder, suggesting biliary excretion in mice.
*"Disposition of [14C]Dimercaptosuccinic acid in mice" (*Liang et al. 1986*)*	Rats Neither unaltered nor altered DMSA was found in the bile of male Sprague-Dawley rats following intravenous administration of 0.20 mmol DMSA/kg.
*"Determination and metabolism of dithiol chelating agents: VII. Biliary excretion of dithiols and their interactions with cadmium and metallothionein" (*Zheng et al. 1990*)*	Monkeys By oral administration of C14 DMSA, 16% of the radiolabel was excreted in the urine, 70% was excreted in the feces, and 1.6% as CO_2. However, intravenous administration

	resulted in 82% being excreted in urine, 0.3% excreted in the feces, and 0.8% being excreted as CO_2.
*"DMSA and DMPS - water soluble antidotes for heavy metal poisoning" (*Aposhian 1983*)*	Humans DMSA is predominately excreted in the urine in the form of mixed disulfides with cysteine, with only 2.5% is excreted as unchanged DMSA.
*"Meso-2.3-dimercaptosuccinic acid: chemical, pharmacological, and toxicological properties of an orally effective metal chelating agent" (*Aposhian and Aposhian 1990*)*	Not Applicable
TK data from general toxicology studies *Study not conducted*	Not Applicable
TK data from reproductive toxicology studies *Study not conducted*	

5.5. Toxicology

5.5.1. General Toxicology

The Applicant did not conduct any toxicity studies to support the safety of Tc99m DMSA and is relying on previous findings of safety for Tc99m DMSA under NDA 017-944 and published nonclinical studies to support this application.

Single-Dose Toxicity Study:

The Applicant summarized findings from toxicity studies in mice, however the no-observed adverse effect level (NOAEL) values were not provided and the safety margins for the product could not be estimated. The Applicant provided a table (Table 9) of the LD_{50} values for DMSA in mice by oral, intravenous, intramuscular, and intraperitoneal routes of administration, which ranged from 2.4 g/kg (intravenous) to 8.5 g/kg (oral) indicating DMSA is not acutely toxic (Lin et al. 1974; Friedheim and Corvi 1975; Aposhian et al. 1984; Flora and Pachauri 2010).

Table 9. LD_{50} Values for DMSA by Various Routes of Administration

Species	Route	LD_{50}	Citation
Mouse	Oral	8.5 g/kg	Flora and Pachauri, 2010
	Intravenous	2.4 g/kg	
	Intramuscular	3.8 g/kg	
	Intraperitoneal	4.4 g/kg	
	Intraperitoneal	2.5 g/kg	Aposhian et al., 1984
	Intraperitoneal	3.163 g/kg	Lin et al., 1974
	Intraperitoneal	>3 g/kg	Friedheim and Corvi, 1975

Abbreviations: DMSA = dimercaptosuccinic acid; LD_{50} = medial lethal dose.
Source: Applicant Table 2 from Section 2.6.6. Toxicology Written Summary

The LD_{50} values in the table are not informative in determining a NOAEL to estimate the safety margin based on current FDA and ICH Guidances.

Repeated-Dose Toxicity Study:

Repeated-dose toxicity studies are not recommended for microdose radiopharmaceuticals and were not conducted. The Applicant summarized findings from a study by Lin et al. (1974) where rats and dogs were administered DMSA by intravenous injection. No adverse clinical signs or histological findings were reported in rats that were intravenously administered 0.55 mg/kg DMSA as Tc99m DMSA for 14 days. There were also no adverse clinical signs or changes in clinical chemistry parameters in dogs following intravenous administration of 0.34 mg DMSA/kg for 17 consecutive days.

5.5.2. Genetic Toxicology

Genotoxicity studies are not recommended for microdose radiopharmaceuticals and were not conducted by the Applicant or identified in the peer-reviewed scientific literature.

5.5.3. Carcinogenicity

Carcinogenicity studies are not required for microdose radiopharmaceuticals. No carcinogenicity studies were identified in the peer-reviewed scientific literature or conducted by the Applicant.

5.5.4. Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies for Tc99m DMSA were conducted or identified in the peer-reviewed scientific literature.

The Applicant requested a waiver for reproductive and developmental toxicology studies. The waiver request was justified because Tc99m DMSA is a radiopharmaceutical diagnostic drug that will be administered as a single microdose (<100 µg), corresponding to a sub-pharmacologic dose level, no signs of toxicity and rapid elimination from the body. The waiver

request was granted based on the proposed single-use indication, mass dose, and no evidence of any potential toxicity.

5.5.5. Other Toxicology Studies

Not conducted

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant (THG) submitted 505(b)(2) NDA to obtain marketing approval for NephroScan (kit for the preparation of technetium Tc99m succimer injection) (referred as "THG Kit" in this review). The Applicant proposed the following in this NDA for THG Kit:

- **Proposed Indication:** as an aid in the scintigraphic evaluation of renal parenchymal disease in adults and pediatrics
- **Dosage and Administration**
    - **Adult patients:** 74 to 222 MBq (2-6 mCi)
    - **Pediatric patients:** 1.85 MBq/kg (0.05 mCi/kg) with a dose range of 19 to 74 MBq (0.5-2.0 mCi)
- **Dosage Forms and Strengths:** single-dose vial containing up to 1480 MBq (40 mCi) Tc99m succimer injection in 5 mL of solution at calibration time

The listed drug is GE Healthcare's DMSA (dimercaptosuccinic acid injection) Kit for the preparation of Technetium Tc99m succimer injection (referred as "GE Kit" in this review). The following history is noted for the GE Kit:

- **1982:** received FDA approval (NDA 017944)
- **2014:** GE Healthcare ceased commercial distribution of GE Kit (not for efficacy or safety reasons), thus GE Kit was placed on the FDA Drug Shortage List
- **2017:** FDA granted the Applicant permission to import a DMSA drug product manufactured by ROTOP Pharmaka GmbH with marketing authorization in Germany (referred as "ROTOP Kit / THG Imported Kit" in this review) under the FDA Drug Shortage Program
- **2017-Present:** Applicant states that over (b) (4) vials of the "ROTOP Kit / THG Imported Kit" have been distributed for use in adult and pediatric patients in the US under the FDA Drug Shortage Program

Note the similarities between the THG Kit and the ROTOP / THG Imported Kits (b) (4) (b) (4) As part of the 505(b)(2) regulatory pathway, a scientific bridge needed to be established between the three

formulations (THG/ROTOP Kits, GE Kit) in order for the Applicant to rely on data obtained from the two other Kits. Refer to Biopharmaceutics Review (Integrated Quality Assessment - Chapter VI: BIOPHARMACEUTICS) in regarding the determination that the differences in the inactive ingredients between the THG/ROTOP Kits and the GE Kit do not contribute to differences in their in vivo performance.

The Applicant is relying on FDA's previous determinations of safety and efficacy for the GE Kit in adult patients, including its most recent labeling. The Applicant is also relying on other data reported in scientific literature, including its use in pediatric patients. The Applicant has not conducted any clinical studies to support this NDA. The Applicant requested a biowaiver for in vivo bioavailability studies by providing information for a scientific bridge to show that differences in inactive ingredients between THG Kit and GE Kit do not contribute to differences in their in vivo performance (refer to Biopharmaceutics review).

The clinical pharmacology review focused on the evaluations of the proposed dosing regimens, especially in pediatric patients, biodistribution, dosimetry, and pharmacokinetics.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and literature data contained in NDA 214993. This NDA is approvable from a Clinical Pharmacology perspective.

REVIEW ISSUE	RECOMMENDATIONS / COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness in adult patients derives from efficacy demonstrated for the GE Kit. The evidence of effectiveness in pediatric patients derives from extrapolation from adult data and supportive efficacy demonstrated in the scientific literature.
General dosing instructions	The proposed dosing in adult (74-222 MBq, 2-6 mCi, based on GE Kit) and pediatric patients (1.85 MBq/kg (0.05 mCi) with a range of 19-74 MBq (0.5-2.0 mCi), based on scientific literature) are acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed in patients with intrinsic or extrinsic factors.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the labeling.
Initial bridge between the to-be-marketed and clinical trial formulations	N/A – the Applicant requested a biowaiver for in vivo bioavailability studies between THG Kit and GE Kit (refer to Biopharmaceutics review).

Post-Marketing Requirements (PMR) or Commitments (PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

See Section 6.3.

6.2.1. Pharmacology and Clinical Pharmacokinetics

See Section 6.3.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant did not conduct a formal dose-finding study.

Adults

In adult patients, the proposed recommended dose is 74-222 MBq (2-6 mCi), which is based on the FDA-approved adult dose of the GE Kit in adult patients.

Pediatrics

In pediatric patients, the proposed dose is 1.85 MBq/kg (0.05 mCi/kg) (with a dose range of 19-74 MBq (0.5-2.0 mCi)), which is based used on the scientific literature. The Applicant referenced multiple studies that used Tc99m succimer injection for the evaluation of acute pyelonephritis (APN), renal scarring (RS), and split renal function (SRF). In the analyzed studies that reported technetium Tc99m DMSA dose, the doses were generally within the range of 1.5-3.0 MBq/kg with a minimum dose of 10 MBq and a maximum dose of 110 MBq. Specifically, in patients <3 years of age, multiple studies used either the same dose or very similar dose as the Applicant's proposed dose in pediatric patients (Table 10).

Table 10. Published Scientific Literature That Support Dosing in Pediatric Patients ≤3 Years of Age

Article	# Pediatric Patients	Age	Dose
Simren et al., 2020; Sweden	25	Median: 1.7 mos Range: 0.7-5.5 mos	0.5 mCi (19 MBq)
Bykov et al., 2003; Israel	40	Mean: 25.9 mos Range: 1-68 mos	0.04-0.05 mCi/kg (1.5-1.85[a] MBq/kg) min: 0.4 mCi (15 MBq)
Nguyen et al., 2000; USA	23	<6 mos	0.05 mCi/kg (1.85 MBq/kg) min: 0.3 mCi (11 MBq)[c]
Barry et al., 1998; UK	300	Mean: 3.89 yrs Range: 18 days-13.6 yrs	Dose fraction of 2.2 mCi (80 MBq) based on weight min: 0.49 mCi (18 MBq)
Zaki et al., 1996; Kuwait	50	Mean: 3.5 yrs Range: 6 mos-12 yrs	0.07 mCi/kg (2.6 MBq/kg) Range: 0.5 -2 mCi (19-74 MBq)
Hansen et al., 1995; Denmark	90	Females median: 4.3 yrs Females range: 0-13 yrs Males median: 5 mos, Males range: 0-12 yrs	0-1 yr: 0.8 mCi (30 MBq), 1-5 yr: 1.6 mCi (60 MBq)
Bjorgvinsson et al., 1991; USA / Ireland	91	Mean: 2.7 yrs Median: 1.5 yrs Range: 1 wk-10 yrs	0.05 mCi/kg (1.85 MBq/kg) min: 0.3 mCi (11 MBq)
Farnsworth et al., 1991; Australia	113	<1 yr	1.1 mCi (40 MBq)
Rossleigh et al., 1990; Australia	63	<1 yr	1.1 mCi (40 MBq)

Abbreviations: EANM = European Association of Nuclear Medicine; min = minimum; mo(s) = month(s); UK = United Kingdom; USA = United States of America; yr(s) = year(s).

[a] Article rounds 1.85 MBq to 2 MBq.

[b] Article specifies they followed EANM guidelines. For patients up to 10 kg, EANM guidelines specify a dose of 0.5 mCi (19 MBq). Refer to Agreed Pediatric Study Plan, Appendix 1.

[c] Minimum dose used for patients weighing <6 kg.

Source: Table 5 from Applicant's response to FDA Information Request (response dated 7-19-21).

Note that the proposed pediatric dose also follows the current North American Consensus Guidelines for Pediatric Administered Radiopharmaceutical Activities as well as the Society of Nuclear Medicine and Molecular Imaging (SNMMI) for technetium Tc99m DMSA products in pediatric patients.

Therapeutic Individualization

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant did not conduct any clinical pharmacology studies.

Biodistribution and Dosimetry

The Applicant referenced biodistribution and dosimetry data of technetium Tc99m succimer DMSA from the scientific literature. Summary of biodistribution and dosimetry studies from the scientific literature is given in Table 11.

Table 11. Summary of Biodistribution and Dosimetry Studies

Study/Data Source	Study Objective	# Subjects / Injected Tc99m DMSA Dose	Results
In Vitro Studies: Related to Plasma Protein Binding			
ROTOP DMSA PI, 2019	Plasma protein binding of Tc99m DMSA in humans.	NA	In the human plasma and is 70% bound to the α2-microglobulin.
Biodistribution: Tracer Uptake in Normal and Diseased Tissues in Adults			
Groshar et al., 1989	To determine the ability of SPECT to quantitate renal uptake of Tc99m DMSA in adults.	88 subjects, 25 were normal subjects with respect to kidney function, 16 patients had a single normal kidney, 30 patients had unilateral nephropathy, and 17 patients had bilateral nephropathy / 2-4 mCi	Kidney phantom evaluation via SPECT measurement demonstrated excellent correlation (r = 0.99) with actual concentrations. Kidney uptake at 6 hours after injection in normal subjects was the same for both kidneys (~20%). In patients with unilateral nephropathy there was a significantly lower uptake in the diseased kidney, but the contralateral kidney uptake the same as subjects with 2 normal kidneys (~20%/kidney). Patients with bilateral nephropathy, significantly lower uptake (~6%) for both the left and right kidneys was found. In this group of patients, total kidney uptake (right + left) was inversely correlated with serum creatinine. SPECT is a reliable and reproducible technique to quantitate ARU of Tc99m DMSA.
Lopes de Lima et al., 2008	To evaluate a simplified method for determining the ARU of Tc99m DMSA prior to nephrectomy, using the radioactivity counts of nephrectomy specimens as the gold standard.	17 patients (12 females; ranging in age from 22 to 82 yr old; [mean age 50.8 yr]) / 188.7 MBq (5.1 mCi)	Reference method and ARU measurements were very similar (linear regression, r2 = 0.96)

Arnold et al., 1975	To determine the distribution, defined as blood clearance and renal concentration, tissue/organ dosimetry, and the excretion of Tc99m DMSA and other Tc99m-labelled ligands were assessed in male adults.	Seven normal healthy adult volunteers/ 0.5-1 mCi	The high absolute renal concentration of Tc99m DMSA is about 2-fold greater than the other Tc99m-complexes, approaching that of labeled chlormerodrin. The plasma clearance of Tc99m DMSA is similar to that of chlormerodrin, but its blood clearance is slower. The urinary excretion of Tc99m DMSA is very slow so it is not good for imaging the pelvocalyceal but is an excellent agent for delayed imaging of the parenchyma for the detection of small focal lesions such as masses, infarcts, or pyelonephritic scars.
Ghione et al., 1987	To determine the renal responses to physical and mental effort in essential hypertension using Tc99m DMSA imaging.	8 essential hypertensive and 2 normal healthy adults / 2 mCi	In non-stressed subjects DMSA uptake rate increased regularly over time. Stressors such as isometric exercise and mental effort (arithmetic) induced an abrupt reduction of the uptake rate, which returned to pre-stress levels at rest. These results suggest a reduction in renal blood flow during stressful conditions.
Rajić et al., 2002	To determine the relationship between Tc99m DMSA biodistribution and its ability to serve as a marker of renal function in adult patients with glomerular kidney diseases.	23 healthy adult volunteers, 42 patients with glomerulonephritis with normal serum creatinine, and 25 patients with glomerulonephritis with elevated serum creatinine / 1.85 MBq/kg	Glomerulonephritis induces quantitative perturbations in the biodistribution of Tc99m DMSA. The changes in biodistribution suggest they are the result of tubular dysfunction, but a role for altered glomerular filtration may also play a role.

Biodistribution: Tracer Uptake in Normal and Diseased Tissues in Adults and Children			
Peters et al., 1988	To assess the relative roles of binding to plasma proteins and renal extraction efficacy in the renal uptake of Tc99m DMSA.	Children and adult patients with various renal indications and 1 normal adult volunteer / Dose not reported	In this study, the percent of plasma protein binding found for Tc99m DMSA was 76%. Based on 24% unbound (free) Tc99m DMSA the renal extraction efficacy by glomerular filtration is about 5%, consistent with glomerular filtration followed by tubular reabsorption rather than by direct extraction from peritubular blood. Fitting of the kinetic data for both Tc99m DMSA and Tc99m-DTPA, along with the effects of captopril in patients with RVH support that glomerular filtration followed by tubular reabsorption is the predominant route for DMSA uptake by the kidney.
Van Luijk et al., 1986	To assess the relative roles of glomerular filtration and proximal tubular reabsorption in the renal handling of Tc99m DMSA.	NA	The finding for the relative clearance of both I125-iothalamate and Tc99m DMSA, the effect changes in the GFR, and extent of protein binding, are consistent with glomerular filtration and proximal tubular reabsorption in the renal handling of Tc99m DMSA.
de Lange et al., 1989	To assess the relative roles of glomerular filtration and proximal tubular reabsorption in the renal handling of Tc99m DMSA.	13 healthy volunteers, 2 renal transplant patients, and 2 children with proximal tubular dysfunction / 75 MBq (2 mCi)	Peritubular uptake accounted for ~65% and glomerular filtration for ~35% of the renal handling of Tc99m DMSA.

Biodistribution: Tracer Uptake in Normal and Diseased Tissues in Children			
Groshar and Gorenberg, 1999a	To determine the normal range of renal uptake of Tc99m DMSA in children.	A total of 135 children, 87 girls and 48 boys with UTI, aged 2 wk-15 yr (mean, 53 ± 51 mo), / 0.750-2 mCi	There was a significant correlation between age and functional renal volume, a significant inverse correlation between age and %ID/cm^3, and no significant correlation between age and kidney uptake, suggesting that the normal changes that occur during maturation of infants and newborns have no impact on the renal uptake Tc99m DMSA. Therefore, quantitative uptake of Tc99m DMSA is amenable for the assessment of changes in renal function of children 2 wk to 15 yr of age.
Moorin, 2001	To determine if normal ARU values of Tc99m DMSA can be predicted accurately over the optimal time for imaging.	44 children with a median age of 4 yr / Dose not reported	The ARU of Tc99m DMSA can be accurately predicted by linear regression modeling incorporating the amount of DMSA injected in milligrams and the patient's age. The time between injection and imaging appeared to be of little importance in the determination of the ARU of Tc99m DMSA over the time range of 2-4 hr after injection.
Arnello et al., 1999	To evaluate the functional changes occurring during the acute phase of UTI in children.	A total of 247 pediatric patients, 180 with both normal kidneys, 56 with clear unilateral abnormalities on DMSA scintigraphy and 11 with 2 abnormal kidneys / Dose not reported	In unilateral acute UTI, renal clearance as measured by Cr51-EDTA (considered a good marker of GFR) is lower in the affected kidney than the healthy contralateral kidney. In such cases, contralateral compensatory mechanisms often come into play, resulting in normal overall clearance. Hyperfiltration may be operative in many cases of acute UTI.

Groshar et al., 1999b	To determine the renal volume and individual renal uptake of Tc99m DMSA in infants with unilateral UPJ obstruction compared to infants with normal kidneys.	A total of 13 infants (10 males, 3 females; mean age 2.8 ± 2.8 mo, (range 3 wk-10 mo) with moderate to severe unilateral hydronephrosis and unilateral UPJ obstruction / 27.8-55.5 MBq (0.750-1.5 mCi)	A significantly lower %ID/mL of renal tissue in UPJ obstructed kidneys may be the result of renal dysfunction, however the significantly increased functional volume of obstructed kidneys may be a compensatory mechanism as evidenced by the overall renal function of the obstructed kidneys being similar to that of the contralateral and control kidneys.
Tsukamoto et al., 1999	To determine the normal range of renal uptake of Tc99m DMSA in children.	A total of 238 children (103 girls and 135 boys) with VUR and/or ureteral or urethral abnormalities (0-13 yr in age) / 26-95 MBq	The %ID per kidney and for both kidneys combined (global) in children with normal kidneys was found to be ~20% and 41%, respectively. There was no significant correlation between renal uptake and age. These findings were consistent with other reported in the scientific literature.
Baillet et al., 1985	To determine the renal uptake of Tc99m DMSA and creatinine clearance as measure of renal function was assessed in children.	A total of 15 children (10 boys and 5 girls) ranging from 2 mo to 14 yr of age (6.8 ± 4.4 yr old), all with a single kidney / 0.74 MBq (20 µCi)/kg	A significant correlation was found between creatine clearance and renal uptake of Tc99m DMSA. In the range for normal creatinine clearance (80-120 mL/min/1.73 m^2), the range for Tc99m DMSA uptake was 36% to 60%.
Anninga et al., 1994	To determine the ability of quantitative Tc99m DMSA scintigraphy to detect renal dysfunction in pediatric patients undergoing ifosfamide based cancer chemotherapy.	A total of 11 children (4 female and 7 male) with a number of different malignancies and ranging in age at diagnosis from 0.6 to 12.9 yr of age / 20 to 100 MBq	Tc99m DMSA was found to be sensitive method to monitor ifosfamide-induced tubular dysfunction both during and after treatment. Tc99m DMSA scintigraphy appeared to be superior to clinical chemistry measurements and detect subclinical injury and may predict potentially high risk at retreatment.

Groshar et al., 1994	To determine the ability of quantitative SPECT to determine the functional renal volume, percent of injected dose/unit of renal functional volume, and the percent renal uptake of Tc99m DMSA in both normal and children with Grade 3 of higher VUR.	A total of 30 children (22 female and 8 male) with a mean age of 59 mo (range 12 to 132 mo) with previous UTI / 0.750-2 mCi	Normal kidneys had a function volume of ~100 cc, the %ID/cc was 0.27, and Tc99m DMSA uptake in 1 kidney was ~25%. Kidneys affected with VUR had a significantly reduced renal uptake (~16%) of Tc99m DMSA ($p<0.001$). The healthy contralateral kidney had a significantly increased uptake (~33%) of Tc99m DMSA compared to normal healthy kidneys ($p<0.01$). However, the global uptake (~49%) was not different from control kidneys.
Peters et al., 1994	To determine the relationship between intracellular, extracellular concentration and the plasma clearance of Tc99m DMSA.	11 adults / Dose not reported	The extravascular concentration of Tc99m DMSA as a function of time was found to be equal to injected dose remaining following subtraction of the intravascular concentration and the total amount of the label cleared from the plasma. Protein binding for Tc99m DMSA was 86%, compared to 0%, 30%, and 88% for Tc99m-labeled EDTA, hippuran, and MAG3 respectively. Therefore, the idea that highly protein bound radiotracers, like Tc99m DMSA, will result in very little extravascular concentration relative to the intravascular concentration cannot be simply assumed to be the case.
Biodistribution: Elimination			
Evans et al., 1996	To determine the biokinetic behavior, including urinary excretion, of Tc99m DMSA in children of various ages and with different degrees of renal dysfunction.	A total of 24 children (15 boys, 9 girls) that ranged in age from 5 wk to 14.8 yr (mean 5.6 yr) with suspected renal impairment / based on a body surface area scaling factor for the adult dose activity of 100 MBq.	In children with normal renal function, global renal uptake of Tc99m DMSA was ~42% with a half-time for uptake being ~1 hr. The amount of label renally excreted over 24 hr after injection was 18%. In children with abnormal renal function there was the expected reduction in renal Tc99m DMSA uptake. There was little evidence of age-dependent biokinetic factors other than reduced urinary excretion and lower uptake in knees in children aged <1 year, so a single biokinetic model may be adequate for radiation dosimetry purposes in normal children regardless of age.
Stabin and Breitz, 2000	To assess excretion of radiopharmaceuticals into breast milk	NA	Overall, the absorbed dose to the mother's breast milk was quite low (0.33% to 5%). However, the author's advised to take breast milk samples and measure the activity to determine when breast feeding could safely resume and have the infant ED be below the 1 mSv (100 mrem) dose criterion.

Dosimetry			
Saunders et al., 2002	Comparison of the maternal and fetal dosimetry of various Tc99m radiodiagnostics administered to pregnant women.	NA	During both the first and third trimesters the fetal dose ranged from 0.77 to 5.2 µGy/MBq. For DMSA, the maternal contribution to the fetal dose was always >93%.
Arteaga et al., 2018	To determine the absorbed dose in kidneys of infants, and 1-year-old children, during renal function studies using ^{99m}Tc-DTPA, ^{99m}Tc-DMSA, and ^{99m}Tc-MAG3 to ascertain which of these 3 radiodiagnostic agent delivers the lowest radiation dose.	Newborns and 1-yr old children / NA	Based on the calculated doses to the kidneys of newborns and 1-yr old children, the largest dose to the kidneys was the self-dose, with the lowest dose to the kidneys obtained for Tc99m-MAG3 and the greatest dose found for Tc99m DMSA.
Bagheri et al., 2020	To determine the biodistribution and dosimetry of Tc99m DMSA in pediatric patients.	12 pediatric patients (4 boys and 8 girls) that ranged from 3 to 12 yr of age with genitourinary abnormalities / 86-170 MBq	The relative percent uptake of Tc99m DMSA in the kidney was 22%. Across the 12 patients the effective dose ranged from 0.00342 to 0.0207 mGy/MBq, and the effective dose equivalents ranged from 0.00507 to 0.0365 mGy/MBq.

Teles et al., 2018	To determine the biokinetics and radiation dosimetry Tc99m DMSA in infants.	8 infants (6 boys and 2 girls) ranging in age from 0.42 to 2.00 yr of age / Dose not reported	This study demonstrated that specific biokinetic models derived are better model for organ function in infants. The dose values calculated in this study are lower than the reference ICRP 128 doses by 32.1% in the kidneys, and 18.4% in the liver. The determination of an effective dose in pediatric population is important due the high radiosensitivity and frequency of renal imaging in this population
Smith et al., 1997a	To establish a simple mathematical relationship for estimating a uniform effective dose based only on body weight	NA	A simple formula for calculating the effective dose per unit of administered radioactivity (expressed as mSv/MBq) based only on body weight was established. By choosing the appropriate administered activity schedule it is possible to calculate the effective dose of Tc99m DMSA and other radiodiagnostic agents for children of any age.
Bagheri et al., 2018	To determine the Tc99m DMSA dosimetry in pediatric patients.	A total of 10 children, 3 boys and 7 girls ranging in age from 3 to 12 yr of age, with genitourinary abnormalities / 86-170 MBq	The mean percent uptake of Tc99m DMSA in the kidney was ~18%. The mean absorbed organ dose to the kidney was ~0.06 mGy/MBq.
Teles et al., 2017	To utilize Monte Carlo simulations and VOXEL phantoms to calculate the absorbed dose in pediatric patients with normal renal function following administration of Tc99m DMSA.	A total of 17 pediatric patients (2 wk to 16 yr of age) / Doses ranged from 25.16 to 129.50 MBq	The dose to the kidney from Tc99m DMSA is primarily due to self-irradiation. The results of the calculations suggested that a more convenient parameter for providing ICRP values for adsorbed dose in pediatric patients is mass, rather than age. Because ICRP models tend to be an average for a typical infant or child within a specific age range, the dose coefficients calculated by ICRP methodology can either under- or overestimate the absorbed dose.

Abbreviations: ARU = absolute renal uptake; DMSA = meso-2,3-dimercaptosuccinic acid; DTPA = diethylenetriamine pentaacetic acid; ED = effective dose; EDTA = ethylenediaminetetraacetic acid; GFR = glomerular filtration rate; hr = hour(s); %ID = percent injected dose; ICRP = International Commission on Radiological Protection; MAG3 = mercaptoacetyltriglycine; min = minute(s); mo = month(s); NA = not available or not applicable; SPECT = single photon emission computed tomography; UPJ = unilateral ureteropelvic junction; UTI = urinary tract infection; VUR = vesicoureteral reflux; wk = week(s); yr = year(s).

Source: Table 2 from Applicant's 2.7.2 Summary of Clinical Pharmacology Studies.

Pharmacokinetics (PK)

Technetium Tc99m succimer is distributed in the plasma, bound to plasma proteins following IV administration. In humans, 53% to 70% of the intravenously administered technetium Tc99m succimer is protein bound. There is negligible activity in the red blood cells. At six hours, about 20% of the dose is concentrated in each kidney.

Approximately 16% of the technetium Tc99m succimer activity is excreted in the urine within two hours.

Overall Comparative Data (Scientific Bridge)

As part of the 505(b)(2) regulatory pathway, a scientific bridge needed to be established between the three formulations (THG/ROTOP Kits, GE Kit) in order for the Applicant to rely on data obtained from the two other Kits. Refer to Biopharmaceutics Review regarding their determination that the differences in the inactive ingredients between the THG/ROTOP Kits and the GE Kit do not contribute to differences in their in vivo performance.

Additionally, the Applicant also provided comparative biodistribution, clinical PK and dosimetry data between THG Kit and GE Kit to further support a scientific bridge between the Kits. Based on the data, GE Kit and THG Kit appear comparable in biodistribution, clinical PK and dosimetry (Table 12).

Table 12. Comparative Summary of Biodistribution, Clinical PK and Dosimetry Between THG Kit and GE Kit

Parameter	GE Kit	THG Kit	Comment
Kidney uptake (rat)	Spefication: ≥40%	Spefication: ≥40% Results: 42% to 61%	The THG Kit results meet the specification that the GE Kit was tested to.
Kidneys/(liver and spleen) ratio (rat)	Specification: the ratio is >6:1	Specification: Liver ≤10% Result: Worst case ratio is 8.4:1	While the activity in the spleen is not measured, the THG Kit results should meet the specification that the GE Kit was tested to.
Plasma clearance (human)	$t_{1/2}$ ~ 1 hour	70% to 30% from 5 minutes to 1 hour	The data are presented differently, but both are equivalent.
Kidney uptake (human)	~20% of the activity in each kidneys at 6 hours	50% of the activity in renal cortex at 3 hours (~25% / kidney)	The data are presented differently, but are consistent with the literature as presented in 2.7.2 Clinical Pharmacology.[a]
Excretion (human)	~16% of the activity in urine at 2 hours	10% of the activity in urine at 1 hour	The data are presented differently, but are consistent with the literature as presented in 2.7.2 Clinical Pharmacology.[b]
Absorbed Dose per Unit of Activity Administered (mGy/MBq) of selected organs (human)	Kidneys: 0.17 Bladder wall: 0.018 Bone marrow/surface: 0.0058 Liver: 0.0085 Ovaries: 0.0036 Testes: 0.0018	Kidneys: 0.18 Bladder wall: 0.018 Bone marrow/surface: 0.0050 Liver: 0.0095 Ovaries: 0.0035 Testes: 0.0018	The human dosimetry data show equivalent distribution of the GE Kit and the THG Kit.

[a] Literature references include Bagheri et al., 2020; Rajic et al., 2002; Groshar et al., 1999b; Groshar and Gorenberg 1999a; Groshar et al., 1989.

[b] Literature references includes Arnold et al., 1975.

Source: Table 4 from Applicant's response to FDA Information Request (response dated 7-19-21).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, refer to Section 6.2.2 (General Dosing and Therapeutic Individualization). For additional details, refer to Section 8 (Statistical and Clinical and Evaluation).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the intended patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen is required for subpopulations based on intrinsic patient factors. However, patients with renal impairment are likely to have reduced renal uptake of technetium Tc99m succimer. In patients with very poor renal function, implementing a waiting period of up to 6 hours (delayed imaging time) should be observed.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No.

Question on clinically relevant specifications (TBD)?

No.

7. Sources of Clinical Data and Review Strategy

7.1. Sources of Clinical Data

The Applicant did not conduct any clinical studies with Nephroscan. To support this 505(b)(2) NDA submission, the applicant is relying on FDA's previous findings of safety and efficacy of the GE Kit (NDA 017944) for the evaluation of renal parenchymal disorders in adult patients since the THG kit is identical to the approved GE Kit with only minor differences in inactive ingredients (refer to Biopharmaceutics Review). In addition, the Applicant is relying on evidence from clinical studies reported in the public domain to extend the use of the THG kit in the evaluation of renal parenchymal disorders to pediatric patients.

For identifying studies in the scientific literature related to imaging performance, FDA advised the Applicant (refer to 1.6.3 Correspondence Regarding Meetings - iPSP Written Comments 02 September 2020 / Literature and SAP) to limit literature search for papers on:

1. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., MRI or CT) in the detection of renal scarring
2. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., MRI or CT) in the detection of acute pyelonephritis
3. Comparison between Tc99m-DMSA scan and other imaging tests (e.g., Tc99m-MAG3) in split renal function measurement

For assessing imaging performance in pediatric patients, the Applicant submitted results for each study as well as meta-analysis results for pooled studies for each of the 3 clinical contexts listed above. However, due to issues with the quality of several of the studies included by the applicant in their meta-analysis we did not further evaluate the applicant's analysis. Our review focuses on analysis of individual studies (see Section 8.3) for each of the three clinical contexts selected using the following criteria -

- patient population of intended clinical use
- prospective study design
- conducted at multiple study sites
- independent blinded imaging readers with evaluation of performance per reader
- adequate sample size
- comparison of imaging interpretation to a reliable reference standard (e.g., MRI, CT, US, MAG)
- achievement of pre-specified success thresholds for diagnostic performance endpoints

For assessing safety of the THG Kit, per agreement with the FDA at the pre-sNDA meeting (refer to 1.6.3 Correspondence Regarding Meetings), the applicant did not perform any clinical

studies. The Applicant is relying in part on the FDA's previous determination that Tc99m DMSA Injection prepared with the GE Kit is safe for use in the evaluation of renal parenchymal disorders in adults. In addition, the applicant submitted the following additional evidence to support the safety of the THG Kit in adult and pediatric patients:

- Published clinical studies with the GE Kit;
- Experience with the Theragnostics Imported Kit sold in the United States under the drug shortages program;
- Post-marketing experience related to the GE Kit from GE;
- Experience with the ROTOP Kit marketed in Germany.

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7.2. Review Strategy

For assessing efficacy in pediatric patients, we focused our review on analysis of individual studies we identified from the applicant's selected studies for each of the three clinical contexts (see Section 7.1).

See Section 8.2.1 for details on the strategy for the review of safety of Tc99m DMSA in adult and pediatric patients.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Evidence to Support Efficacy

In this 505(b)(2) submission there is no specific study or protocol name as the applicant did not perform any clinical studies per agreement with the FDA at the pre-IND meeting (refer to 1.6.3 Correspondence Regarding Meetings). For adult patients, the applicant did not conduct any clinical studies stating the reasons that (i) FDA has previously determined that Tc99m DMSA is safe and effective, and (ii) additional support for the use of THG Kit in adult patients is derived from the previously approved product distributed by GE and scientific bridge showing comparability between the THG Kit and the GE Kit by demonstrating that any differences in the inactive ingredients between the proposed (THG Kit) and listed (GE Kit) drug products do not contribute to differences in their in vivo performance while the active ingredient is identical between the products.

For pediatric patients, instead of carrying out new clinical studies, the Applicant proposed to re-analyze clinical studies reported in the public domain to derive evidence to support the diagnostic efficacy of the THG Kit. The Applicant performed statistical analyses of the data

collected from articles (a total of 74 unique articles) evaluating the use of Tc99m DMSA in pediatric patients. Specifically, data were collected from articles related to three clinical contexts: acute pyelonephritis (APN, 34 articles), renal scarring (RS, 40 articles) and split renal function (SRF, 3 articles). The primary endpoint included the zone-level, kidney-level or patient-level percent agreement. Sensitivity and specificity using Tc99m DMSA as the reference standard are secondary endpoints. The analyses for primary and secondary endpoints were performed for each paper, overall (meta-analysis) and by imaging modality. The reason for proposing percent agreement as the primary endpoint appears to be because DMSA is the assumed gold standard, which is an off-label standard of care in practice.

Although the applicant provided the analysis results for each study and the meta-analysis results for pooled multiple studies, we noted the following –

- the statistical analysis plans (SAPs) for each of the three clinical contexts, APN, RS and SRF, submitted in this NDA 214993 were not previously submitted for FDA review in the associated IND 145176
- in these SAPs, no success criterion was specified for the primary analysis
- many of the studies selected by the applicant are not adequate for reasons including retrospective study design, unblinded image readers, sample size too small

Therefore, our review focuses on analysis of individual studies selected for each of the three clinical contexts (see Section 7.2). More details about the selected papers, demographic characteristics of the patients studied in each of the selected papers and the corresponding primary analyses in zonal-level, kidney-level, and/or patient-level are provided in Section 8.3.

8.1.2. Compliance with Good Clinical Practices

Compliance with Good Clinical Practices is not applicable to this submission as it is based on published clinical studies that were not conducted or contributed to by the Applicant.

8.1.3. Financial Disclosure

This 505(b)(2) NDA relies upon published literature for which the applicant did not provide drug or financial support. Furthermore, the applicant was not the sponsor of the published clinical studies.

Please see Section 8.3 on Statistical Issues for details on the seven publications selected by the clinical and statistical review teams for this NDA review.

Data Quality and Integrity

Not applicable as the applicant did not conduct any new clinical studies nor submit any data from published studies.

Dose/Dose Response

See Section 6.2.2.

Adult patients - The proposed adult dose of THG kit is same as GE Kit. The labeling states "The recommended amount of radioactivity of Technetium Tc 99m Succimer Injection for renal parenchymal imaging in adults is 74 MBq to 222 MBq (2 mCi to 6 mCi) by intravenous injection (bolus)."

Pediatric Patients - The labeling states "The recommended amount of radioactivity of Technetium Tc 99m Succimer Injection for renal parenchymal imaging in pediatric patients is 1.85 MBq/kg (0.05 mCi/kg) of body weight with a range of 19 MBq to 74 MBq (0.5 mCi to 2 mCi) by intravenous injection (bolus)." Weight based pediatric dosing is shown in Table 13.

Table 13. Recommended Dose for Pediatric Patients

Body Weight (kg)	Recommended Radioactivity MBq (mCi)	Body Weight (kg)	Recommended Radioactivity MBq (mCi)
less than 11 kg	19 MBq (0.5 mCi)	25 to 26	49 MBq (1.3 mCi)
11 to 12	21 MBq (0.6 mCi)	27 to 28	52 MBq (1.4 mCi)
13 to 14	26 MBq (0.7 mCi)	29 to 30	56 MBq (1.5 mCi)
15 to 16	30 MBq (0.8 mCi)	31 to 32	59 MBq (1.6 mCi)
17 to 18	33 MBq (0.9 mCi)	33 to 34	63 MBq (1.7 mCi)
19 to 20	37 MBq (1 mCi)	35 to 36	67 MBq (1.8 mCi)
21 to 22	41 MBq (1.1 mCi)	37 to 38	70 MBq (1.9 mCi)
23 to 24	44 MBq (1.2 mCi)	39 kg or greater	74 MBq (2 mCi)

Source: Prescribing information.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) issued 3 guiding documents on pediatric DMSA scan procedure from 1997 to 2011, which specify the pediatric dosage. Please note that the proposed dose for the THG kit is similar to the recommended pediatric dose in the publication by (Gelfand et al. 2011).

Table 14. DMSA Pediatric Dose Recommended by the SNMMI

Literature article author, Year	Publication	Pediatric Dose	Reference
Mandell, GA, et al., 1997	Procedure Guideline for Renal Cortical Scintigraphy in Children	The minimal dose is about 0.3 mCi. The maximum is about 3.0 mCi.	2
Mandell, GA, et al., 2003	Society of Nuclear Medicine Procedure Guideline for Renal Cortical Scintigraphy in Children	The minimal dose is about 0.3 mCi. The maximum is about 3.0 mCi.	3
Gelfand, MJ, et al., 2011	Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines	0.05 mCi/kg, minimal the dose 0.5 mCi.	4
THG Kit proposed		0.05 mCi/kg, with a range of 0.5-2.0 mCi	

Radiation Dosimetry (see Section 6.3.1)

Tc-99m DMSA is a technetium (Tc-99m) radiopharmaceutical; Tc99m decays by isomeric transition with a physical half-life of 6.02 hours.

DMSA (GE):
The estimated absorbed radiation doses to an average adult (70 kg) are shown in Table 15.

Table 15. Absorbed Radiation Dose - DMSA (GE)

Tissue	mGy / 222 MBq	rads / 6 mCi
Bladder Wall	4.2	0.42
Kidneys (total)	37.8	3.78
Renal Cortices	51.0	5.10
Liver	1.9	0.19
Bone Marrow	1.3	0.13
Ovaries	0.8	0.08
Testes	0.4	0.04
Total Body	0.9	0.09

Source: DMSA (GE) labeling. The original source from:
Method of Calculation: A schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD Pamphlet No. 1, J. Nucl. Med., p. 7, 1968.
Biological Data: Arnold, R.W; Subramanian, G.; McAfee, J.G.; Blair, R.J.; Thomas, F.D.; Comparison of Tc99m complexes for renal imaging, J. Nucl. Med., 16, pp. 357- 367, 1975.

Proposed THG Kit:
The estimated absorbed radiation doses to an average adult (70 kg) are shown in Table 16. In an adult (70 kg), after intravenous injection of 70 MBq (maximum dose) technetium Tc 99m succimer injection, the effective dose is approx. 0.62 mSv. The absorbed dose in the target organ kidney is approximately 12.6 mGy and is 1.26 mGy in the critical organ bladder wall.

Table 16. Estimated Radiation Absorbed Dose per Injection Activity in Selected Organs and Tissues of Adults After a Technetium Tc 99m Succimer Injection Dose

Absorbed Dose per Unit of Activity Administered (mGy/MBq)					
Organ	**Adults**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.012	0.016	0.024	0.035	0.060
Bladder wall	0.018	0.023	0.029	0.031	0.057
Bone surface	0.0050	0.0062	0.0092	0.014	0.026
Brain	0.0012	0.0015	0.0025	0.0040	0.0072
Breasts	0.0013	0.0018	0.0028	0.0045	0.0084
Gall bladder	0.0083	0.010	0.014	0.022	0.031
Stomach wall	0.0052	0.0063	0.010	0.014	0.020
Colon	0.0050	0.0063	0.010	0.014	0.024
Intestine	0.0043	0.0055	0.0082	0.012	0.020
Upper large intestine	0.0050	0.0064	0.095	0.014	0.023
Lower large intestine	0.0035	0.0043	0.0065	0.0096	0.016
Heart	0.0030	0.0038	0.0058	0.0086	0.014
Kidneys	0.18	0.22	0.30	0.43	0.76
Liver	0.0095	0.012	0.018	0.025	0.041
Lungs	0.0025	0.0035	0.0052	0.0080	0.015
Muscles	0.0029	0.0036	0.0052	0.0077	0.014
Oesophagus	0.0017	0.0023	0.0034	0.0054	0.0094
Ovaries	0.0035	0.0047	0.0070	0.011	0.019
Pancreas	0.0090	0.011	0.016	0.023	0.037
Red marrow	0.0039	0.0047	0.0068	0.0090	0.014
Skin	0.0015	0.0018	0.0029	0.0045	0.0085
Spleen	0.013	0.017	0.026	0.038	0.061
Testes	0.0018	0.0024	0.0037	0.0053	0.010
Thymus	0.0017	0.0023	0.0034	0.0054	0.0094
Thyroid	0.0015	0.0019	0.0031	0.0052	0.0094
Uterus	0.0045	0.0056	0.0083	0.011	0.019
Remaining organ	0.0029	0.0037	0.0052	0.0077	0.014
Effective Dose per unit of activity administered (mSv/MBq)	**0.0088**	**0.011**	**0.015**	**0.021**	**0.037**

Source: The proposed THG kit labeling. The original source from "ICRP. Radiation dose to patients from radiopharmaceuticals addendum. Annals of the ICRP Publication 80. 1998; 28(3)."

Summary:

1. The dosimetry table (Table 15) of DMSA (GE) is for adults only.
2. The dosimetry table of the proposed THG kit is for adult and pediatric patients and also lists more organs than those listed in the DMSA (GE) labeling dosimetry table.
3. Based on the proposed labeling for the THG kit, the ED will be from 0.65 to 1.95 mSv per dosing (2-6 mCi) for an adult subject with body-weight of 70 Kg.
4. The proposed dosimetry information submitted by the Applicant for the adult and pediatric patients is acceptable

Additional Analyses Conducted

Please refer to Section 8.3 for additional analyses conducted by the FDA statistical team for individual studies selected from the scientific literature for each of the 3 clinical contexts.

Integrated Review of Effectiveness

8.1.4. Assessment of Efficacy Across Trials

Not applicable

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant did not perform clinical studies to evaluate the safety of the THG Kit, a plan that was endorsed by the FDA at the pre-NDA meeting (10/29/2019). For assessing safety, we reviewed the following evidence submitted by the applicant to support the safety of the THG Kit in adult and pediatric patients:

- Clinical studies using the GE DMSA Kit reported in the scientific literature;
- Experience with the Theragnostics Imported Kit sold in the United States under the drug shortages program;
- Post-marketing experience with the GE Kit from GE;

In addition, we conducted a pharmacovigilance review that included assessing the FDA Adverse Event Reporting System (FAERS), medical literature, VigiBase, and Periodic Adverse Drug Experience Reports (PADERs) for safety data and adverse events (AEs) reported with Tc99m Succimer Injection (see Pharmacovigilance Review).

8.2.2. Review of the Safety Database

Overall Exposure

FDA determined that DMSA is safe and effective for use in adults (NDA017944). Tc99m DMSA safety is assessed from GE post-approval data, the Theragnostics Imported Kit use in the US, and from the use of the ROTOP Kit in Germany -

- Assuming each distributed GE Kit was used for unique patient dose, at least (b) (4) patients received the FDA-approved labeled adult dose of 74-222 MBq between 1984 and 2014.
- Between 03 August 2017 and 30 April 2021, Theragnostics distributed (b) (4) single-dose units of the Theragnostics Imported Kit in the US under the drug shortages program. It is estimated that >60% of the Theragnostics Imported Kits were distributed to pediatric imaging centers. Therefore, at least (b) (4) patients received the pediatric dose of 15 MBq to 70 MBq based on a body weight-dose calculation (the remaining 40% of Kit distributions likely also included pediatric administrations of the product).
- Approximately (b) (4) ROTOP single-use Kits were distributed in Germany from 2005 to 2020a mixed population of adults and children, have received the ROTOP recommended

target adult dose of 70 MBq or the pediatric dose of 15 MBq to 70 MBq based on a body weight-dose calculation.

Among the studies submitted by the Applicant (77 publications) describing the use of Tc99m DMSA in humans, in the pediatric and adult populations, only 3 publications reported safety information related to DMSA. These publications included a total of 149 pediatric patients and 79 adult patients, and the patients' ages ranged from 7 months to 88 years. The 79 adult subjects were administered 80 MBq (Farmer et al. 1999) and 45 pediatric subjects were administered 5 MBq/kg per body weight (minimum 25 MBq) (Schiepers et al. 2001). One safety study in pediatric patients did not include information about the administered dose (Michaud et al. 2016).

Table 17. Published Studies That Reported on the Safety of Tc99m DMSA

Literature Article Author, Year	Product Used/ Manufacturer/ Time from Dose to Scan	Administered Dose and Weight	Clinical Indication Studied/Study Design/Number of Study Sites	Age	Gender	Number of Subjects	Reported Safety
Farmer et al., 1999	Tc99m DMSA/ unknown manufacturer/ 2 hours	80 MBq; weight not included	Renovascular disease and potential renal artery stenosis/prospective/ 1 site	Mean 68.9 yrs Range 25.2-88.2 yrs	35 females; 44 males	79	Tc99m DMSA was well tolerated.
Michaud et al., 2016	Tc99m DMSA/ unknown manufacturer/ time unknown	Administered dose not included; weight not included	Febrile urinary tract infections/ retrospective/ 1 site	Median age at scan time: 10.6 mos Age range: 6.8-18.4[a] mos	89 females; 15 males	104 total (42 sedated)	Multiple IV attempts made in 10 sedated subjects (24%); no anesthesia-related complications; no other safety mentioned.
Schiepers et al., 2001	Tc99m DMSA/ Nephroscint DMSA, DuPont Pharma, Belgium/ 6 hours	5 MBq/kg (minimum 25 MBq); weight not included	Vesicoureteral reflux requiring surgery/ retrospective / unknown	Baseline mean: 6.7 yrs (range 1.5-14.7 yrs) Follow-up mean: 11.3 yrs (range 6.5-19.1 yrs)	31 females; 14 males	45	No adverse reactions; Tc99m DMSA was well tolerated.

Abbreviations: IV = intravenous; mos = month(s); yrs = year(s).

Source: The table 1 of Summary of Clinical Safety.Adequacy of the Safety Database

Collectively, the safety data submitted by the Applicant and the pharmacovigilance review conducted by FDA/OSE/DPVII (see Pharmacovigilance Review) are adequate to evaluate the safety of Tc99m Succimer injection for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients including term neonates.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Not applicable as the applicant did not conduct any clinical studies to assess safety and none were needed.

8.2.4. Safety Results

Deaths

While the Applicant's submission did not report any deaths, a pediatric patient was identified in the FAERS database (see Pharmacovigilance Review for details) who experienced an episode of tachcardia during administration of Tc99m DMSA and another episode a day later. Following the episode of tachycardia the next day the patient expired. Based on the WHO Causality criteria, causality between tachycardia and death and exposure to Tc99m DMSA was deemed "possible". However, the patient was born premature and had been hospitalized since birth confounding the reason for the tachycardiac events and death. As the event of tachycardia accompanying the death occurred the following day, they are likely related to other factors and not to the administration of Tc99m DMSA. It is also important to note that another infant received Tc99m DMSA from the same vial without effect.

Serious Adverse Events

While the Applicant's submission did not report any serious adverse events (SAEs), we identified 15 serious cases including one death (see above), prolonged hospitalization (n=6), and "other" serious (n=8) (see Pharmacovigilance Review for details).

Dropouts and/or Discontinuations Due to Adverse Effects

The applicant did not conduct any clinical studies. Additionally, there were no reports in the literature of discontinuation due to AEs. .

Significant Adverse Events

While the Applicant's submission did not report any significant AEs, we identified 15 SAEs including one death, and cases of prolonged hospitalization from adverse events following Tc99m DMSA administration (see Serious Adverse Events). Five of these cases occurred within 2 hours following administration, eight occurred within the 24 hours following administration, and two did not report a time-to-onset (see Pharmacovigilance Review for details).

Treatment-Emergent Adverse Events and Adverse Reactions

We identified a total of 30 cases in the pharmacovigilance review from all data sources (FAERS [n =9], VigiBase [n =20] PADERs [n =1], literature [n =0]) (see Pharmacovigilance Review for details). Three of these 30 cases were included in the 29 cases reported in the Applicant's Summary of Clinical Safety- Post Marketing Submission.

Of the 15 serious cases we identified in the pharmacovigilance review (see Pharmacovigilance Review for details), we deemed causality between product exposure and the outcome as "probable" in three cases (tachycardia (n=1), pruritus (n=1), and circulatory collapse with

hypotension, loss of consciousness, and sinus bradycardia (n=1). We deemed the other twelve serious cases as “possible”, based on the WHO-UMC causality criteria (WHO-UMC 2013).

We identified 56 preferred terms in the 30 cases of the case series (Table 18). The following preferred terms were identified in two or more cases; pruritus, erythema, cough, cases included PTs within the Hypersensitivity Standardized MedDRA Query (SMQ), including the events of rash, pruritus, erythema, hypersensitivity, anaphylactic reaction, circulatory collapse, drug eruption, flushing, injection site rash, rash erythematous, skin necrosis, skin swelling, and urticaria. Hypersensitivity reactions are now cited as a warning in the labeling. The following preferred terms were reported in two or more cases and did not represent hypersensitivity: cough, feeling abnormal, headache, pallor, tachycardia, and vomiting.

Table 18. Preferred Terms for All Adverse Events with Tc99m Succimer in the FAERS, PADER, and VigiBase Case Series, Received by FDA for All Dates Through June 30, 2021 (N=30)

	FAERS/ PADER (n=10) *	VigiBase (n=20)	Total (n=30)
Rash†	1	4	5
Pruritus†	2	2	4
Drug ineffective	0	3	3
Erythema†	1	2	3
Renal scan abnormal	1	2	3
Feeling abnormal	1	2	3
Cough	0	2	2
Headache	0	2	2
Hypersensitivity†	1	1	2
Pallor	1	1	2
Tachycardia	2	0	2
Vomiting	0	2	2
Anaphylactic reaction†	1	0	1
Anaphylactoid reaction‡	0	1	1
Anxiety	0	1	1
Asthmatic crisis	0	1	1
Circulatory collapse†	1	0	1
Diarrhea	0	1	1
Drug eruption†	0	1	1
Dyspnea	1	0	1
Flushing†	0	1	1
Hyperkalemia	1	0	1
Hypotension	1	0	1
Hypotonia	0	1	1
Injection site rash†	0	1	1
Loss of consciousness	1	0	1
Malaise	0	1	1
Peripheral coldness	1	0	1
Pyrexia	1	0	1
Rash erythematous†	0	1	1
Sinus bradycardia	1	0	1
Skin necrosis†	0	1	1
Skin swelling†	0	1	1
Therapeutic product effect decreased	1	0	1
Urticaria†	1	0	1

* FAERS (n=9), PADER (n=1) The one case identified in the March – May 1984 PADER, not found in FAERS.
† Preferred Terms from the case series found in the Hypersensitivity SMQ include rash, pruritus, erythema, hypersensitivity, anaphylactic reaction, circulatory collapse, drug eruption, flushing, injection site rash, rash erythematous, skin necrosis, skin swelling, urticaria
‡ Although anaphylactoid reactions resemble generalized anaphylaxis, they are not caused by IgE-mediated allergic reaction but rather by a nonimmunologic mechanism (Miller-Keane 2003).
Source - (see Pharmacovigilance Review for details)

Laboratory Findings

The applicant did not conduct any clinical studies. No clinically significant changes in any laboratory parameters were reported by the Applicant nor did we identify any in the pharmacovigilance review (see Pharmacovigilance Review for details).

Vital Signs

The applicant did not conduct any clinical studies. No data related to vital signs in adult or pediatric patients were submitted with this sNDA.

Electrocardiograms (ECGs)

The applicant did not conduct any clinical studies. Further, there is no electrocardiogram data in subjects receiving Tc99m DMSA available in the literature.

Immunogenicity
In the pharmacovigilance review (see Pharmacovigilance Review for details), we identified cases that included PTs within the Hypersensitivity SMQ, including urticaria, rash, pruritus, and erythema.

8.2.5. Analysis of Submission-Specific Safety Issues

Not applicable

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

Age

None of the literature containing safety information included term and preterm neonates. The youngest patient in any publication identified in the literature was 6.8 months old. In the pharmacovigilance review (see Pharmacovigilance Review for details), among the 27 of the 30 cases that reported age, the majority were pediatric patients, with 23 cases reporting an age of less than 17 years. The labeling states that clinical studies of technetium Tc 99m succimer did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. The labeling states that this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with decreased renal function.

Gender

There is no information in the Applicant's submission or in the pharmacovigilance review (see Pharmacovigilance Review for details) to suggest the safety profile of Tc99m DMSA differs by gender.

Race

There is no information in the Applicant's submission or in the pharmacovigilance review (see Pharmacovigilance Review for details) to suggest the safety profile of Tc99m DMSA differs by race.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No long-term animal studies were performed to evaluate the carcinogenicity potential of technetium Tc 99m succimer.

Human Reproduction and Pregnancy

The following description summarizes information related to human reproduction and pregnancy from DPMH Maternal Health Review in sections 8.1 and 8.2 of the labeling**:**

8.1 Pregnancy
Risk Summary
Available data with Technetium 99m Succimer use in pregnant women are insufficient to evaluate for a drug-associated risk for major birth defects and miscarriage. Animal reproduction studies with Technetium 99m Succimer have not been conducted. Although all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose, the radiation exposure to the fetus from Technetium 99m Succimer is expected to be low (less than 0.50 mGy) *(see Data)* .
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data
Human Data
No adverse fetal effects of radiation risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 10mGy fetal doses.

8.2 Lactation
Risk Summary
Technetium 99m succimer is present in breast milk. There are no data on the effects of Technetium 99m succimer on the breastfed infant or the effects on milk production.

Technetium 99m succimer is used for imaging in infants with renal disease; exposure to technetium 99m succimer via breastmilk is expected to be lower. Based on clinical guidelines, exposure of technetium Tc 99m succimer to a breastfed infant may be minimized by advising a lactating woman to pump and discard breast milk for a minimum of 24 hours after administration of technetium Tc 99m succimer. The developmental and health benefits of breastfeeding should be considered along with a mother's clinical need for NEPHROSCAN, any potential adverse effects on the breastfed child from technetium Tc 99m succimer or from the underlying maternal condition.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the event of an overdose, measures should be taken to reduce the absorbed dose to the patient to the maximum extent possible. Hydration and frequent voiding of the bladder will help increase elimination of the radionuclide from the body. Use of a diuretic might also be considered.

NEPHROSCAN is intended as a single administration in a hospital or clinic/imaging center setting. No data suggestive of a potential for abuse, withdrawal or rebound effects have been identified.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Per the Applicant, in the Postmarketing annual report setting, GE received a total of 50 AE reports (see Table 19) for 29 subjects out of an estimated 270,500 administrations of DMSA for which there is safety information available. The following events occurred in >5% of the 50 total AEs reported: rash (n=8), urticaria (n=4), headache (n=4), nausea/vomiting (n=4), and fever (n=5). Syncope occurred in 2% of the 50 total AEs reported. Based on the number of AEs in relation to the number of distributed vials, all AEs would be considered rare occurrences. No information was provided as to when the patients experienced the AE (i.e., immediately following administration of DMSA or some period of time thereafter).

Table 19. Summary of Adverse Events Reported to GE From 1982-January 2003

Type of Event	Number of Events Reported: Age <65 yrs	Number of Events Reported: Age ≥65 yrs	Number of Events Reported: Age Unknown
Rash	7		1
Urticaria	4		
Pruritus			1
Chills	1		
Flushing	1		
Edema	1		
Sneezing	1		
Respiratory Disorder	1		1
Vasovagal Attack	2		
Tachycardia	1		
Syncope	1		
Dizziness	2		
Somnolence	1		
Tiredness	1		
Hypotonia			1
Convulsions	1		
Headache	4		
Paresthesia	1		
Nausea/Vomiting	4		
Diarrhea	1		
Fever	5		
Dyspnea	1		
Tonsilitis	1		
Ear Inflammation	1		
Arthralgia	1		
Serum Potassium Increase			1
Lack of Effect	1		

Abbreviations: yrs = year(s)
Source: Amersham Health (the sponsor then) 3/18/2003 sNDA labeling submission on 3/18/2003.

Additionally, as noted above under Significant Adverse Events (see Section 8.2.4), we identified 30 cases with 56 preferred terms (see Table 18 above) in the Postmarket Setting of any adverse events with Tc99m Succimer in the FAERS, VigiBase, and Periodic Safety Reports (see Pharmacovigilance Review for details).

Expectations on Safety in the Postmarket Setting

The clinical review team does not anticipate any significant safety issues in the Postmarket Setting.

8.3. Statistical Issues

In this section, FDA statistical review focuses on analysis of individual studies selected for the three clinical contexts: 4 papers for RS, 2 papers for APN and 1 paper for RSF. For the selected

papers, depending on information available, the percent agreement could be zonal-level, kidney-level, and/or patient-level. More details about the selected papers under each of the three clinical contexts and the corresponding primary analyses are provided below.

8.3.1. Renal Scarring (RS)

Four articles among the 40 articles under renal scarring clinical context are identified by clinical reviewers to have relevance to the proposed indication. Statistical comments are on the diagnostic efficacy of THG Kit (Nephroscan) for use as an aid in the scintigraphic evaluation of renal scarring in pediatrics:

Below are the summaries of the four selected papers and the re-analysis results of the primary endpoint of percent agreement between Tc99m DMSA and comparator.

1. **Freeman Paper** (Freeman et al. 2018): *Unenhanced MRI as an Alternative to 99m Tc-Labeled Dimercaptosuccinic Acid Scintigraphy in the Detection of Pediatric Renal Scarring*

Study Objective: To determine if unenhanced MRI can be used as a substitute for Tc99m DMSA scintigraphy in the detection of renal scars in pediatric patients.

Overview: Thirteen pediatric patients, with ages ranging from 5 years to 19 years, suspicious for kidney scarring (on the basis of symptoms or histories consistent with urinary tract infections) underwent Tc99m DMSA Imaging and MRI for the detection of kidney scars. The Images were subsequently read, in blinded fashion, by radiologists – two readers for Tc99m DMSA and two different readers for MRI. The focus of these reads was the detection of scars. Each kidney was partitioned into three zones (upper, middle, and lower kidney), and each zone was assigned a score of 1 if scarring was detected, or 0 otherwise. The two Tc99m DSMA scores, and the two MRI scores for each zone were collapsed into a single consensus score (scarring, no scarring). Thus, each patient was provided with six consensus binary scores by zone for each modality. These scores could then be further collapsed by level, as follows:

A kidney was scored = 1 if at least one zone was scored = 1
A patient was scored = 1 if at least one kidney was scored = 1

Note that the focus of the study was the performance of MRI with respect to a standard of truth of Tc99m DMSA. Table 20 shows the number of zones with scars detected by consensus read with Tc99m DMSA and MRI for each of the 13 patients.

Table 20. DMSA Versus MRI Detections of Zones with Scars (Consensus Read)

Patient	# Zones with scars	
	Tc99m DMSA	MRI
1	1	1
2	2	2
3	3	3
4	0	0
5	0	0
6	3	3
7	1	1
8	2	1
9	0	0
10	0	0
11	0	0
12	4	4
13	0	0
Total	16	15

Source: (Freeman et al. 2018).

Summary:

In the author's re-analysis, patient-level precent agreement between Tc99m DMSA and MRI was 100% with two-sided 95% exact CI (75.3%, 100%), see statistical-report-for-ise.pdf. Tc99m DMSA showed scarring in 16 of the 78 zones and MRI showed scarring in 15 of the 78 zones. However, zonal-level and kidney-level percent agreement were not reported and seems difficult to obtain based on the information provided in Freeman et al. (2018).

2. **Kavanagh Paper** (Kavanagh et al. 2005): *Can MRI replace DMSA in the detection of renal parenchymal defects in children with urinary tract infections.*

Study Objective: To compare Tc99m DMSA with MRI for the detection of renal parenchymal defects in children presenting for radiological investigation after a first UTI.

Overview: This paper is similar in intent and methods to the Freeman paper.
Pediatric patients with urinary tract infections undergo imaging with Tc99m DMSA and MRI for the detection of kidney scarring. A total of 37 patients (19 boys, 18 girls) aged from 4 months to 13 years were imaged with Tc99m DMSA and MRI. Three blinded readers read both sets of images and recorded, by consensus within each Image type, the presence/absence of scarring in 12 zones per patient (six zones per kidney: lateral and medial in upper, middle, and lower thirds per kidney), and each zone was assessed for presence/absence of scarring on Tc99m DMSA and MRI. As with Freeman, the focus of the study was the performance of MRI with respect to a standard of truth of Tc99m DMSA. Table 21 and Table 22 gives comparison of Tc99m DMSA vs. MRI at kidney and zonal levels.

Table 21. Kidney Level Consensus Presence/Absence of Scars: Comparison of MRI vs. DMSA for the Detection of Renal Scaring on a Kidney-by-Kidney Comparison Using DMSA as the Gold Standard.

	Scar on Tc99m DMSA	No Scar on Tc99m DMSA	Total
Scar on MRI	10	3	13
No Scar on MRI	3	21	24
Total	13	24	37

Source:(Kavanagh et al. 2005).

Table 22. Zonal Level Consensus Presence/Absence of Scars: Comparison of MRI vs. DMSA for the Detection of Renal Scaring on a Zonal Basis, Using DMSA as the Gold Standard.

	Scar on Tc99m DMSA	No Scar on Tc99m DMSA	Total
Scar on MRI	30	6	36
No Scar on MRI	10	398	408
Total	40	404	444

Source: (Kavanagh et al. 2005).

Summary:

In the sponsor's re-analysis, kidney-level precent agreement between Tc99m DMSA and MRI was 83.8% with two-sided 95% exact CI (68.0%, 93.8%), see statistical-report-for-ise.pdf. One limitation of the author's report is that there were only 37 kidneys in the kidney-level analysis even through there were 74 kidneys in 37 patients.

In the sponsor's re-analysis, zonal-level precent agreement between Tc99m DMSA and MRI was 96.4% with two-sided 95% exact CI (94.2%, 97.9%), see statistical-report-for-ise.pdf.

3. **Chan Paper** (Chan et al. 1999): *Potential utility of MRI in the evaluation of children at risk of renal scarring.*

Study Objective: To evaluate the potential utility of MRI using fat-saturated T1-weighted and post-gadolinium STIR sequences in detecting renal scarring by comparison with Tc99m DMSA scintigraphy in children at risk of renal scarring.

Overview: A total of 24 children suspected of renal scarring but with no symptoms of acute urinary tract infections underwent Tc99m DMSA and MRI imaging in order to evaluate the performance of MRI as a substitute for Tc99m DMSA in the detection of kidney scarring. Tc99m DMSA and MRI scans were each separately interpreted by consensus agreement between two pairs of radiologists blinded to the results of the other pair. One pair of readers evaluated the Tc99m DMSA scans and another pair evaluated the MRI scans. Each kidney was partitioned into 6 zones (12 zones per patient), with each zone graded as normal or abnormal for renal scarring. Note MRI included fat-saturated T1-weighted MRI and post-gadolinium STIR sequences MRI, and Tc99m DMSA was used as the gold standard. The comparisons of Tc99m DMSA and MRI (T1 + STIR) for scar detections at both the zonal and kidney levels are presented in Table 23 below.

Table 23. Kidney Level Presence/Absence of Scars

	Scar on Tc99m DMSA	No Scar on Tc99m DMSA	Total
Scar on MRI	16	7	23
No Scar on MRI	0	25	25
Total	16	32	48

Source: (Chan et al. 1999).

Table 24. Zonal Level Presence/Absence of Scars

	Scar on Tc99m DMSA	No Scar on Tc99m DMSA	Total
Scar on MRI	48	32	80
No Scar on MRI	9	199	208
Total	57	231	288

Source: (Chan et al. 1999).

Summary:

In the sponsor's re-analysis, kidney-level precent agreement between Tc99m DMSA and MRI was 85.4% with two-sided 95% exact CI (72.2%, 93.9%), see statistical-report-for-ise.pdf.

In the sponsor's re-analysis, zonal-level precent agreement between Tc99m DMSA and MRI was 85.8% with two-sided 95% exact CI (81.2%, 89.6%), see statistical-report-for-ise.pdf.

4. **Cerwinka Paper** (Cerwinka et al. 2014): *Comparison of magnetic resonance urography to dimercaptosuccinic acid scan for the identification of renal parenchyma defects in children with vesicoureteral reflux.*

Study Objective: To compare the accuracy of Tc99m DMSA renal scan to magnetic resonance urography (MRU) in the identification of renal parenchyma defects (RPD).

Overview: 25 children (5 boys and 20 girls, aged from 0.25 to 143 months) with history of acute pyelonephritis and vesicoureteral reflux underwent Tc99m DMSA scan and MRU to determine the presence of RPD. Tc99m DMSA scans and MRUs were each evaluated by two radiologists and agreement achieved by consensus. Discordant Tc99m DMSA-MRU findings were re-evaluated in a side-by-side comparison and an ultimate consensus reached. The kidney was divided into 12 segments and the number of abnormal segments was recorded. Renal parenchymal injury was classified as negative (0 RPD), mild (1-2 RPDs), moderate (3-4 RPDs), and severe (>4 RPDs). The comparisons of Tc99m DMSA and MRU for RPD at both kidney and patient levels are derived, see Table 25 and Table 26.

Table 25. Kidney Level Presence/Absence of Renal Parenchyma Defects (RPDs)

	RPD on Tc99m DMSA	No PRD on Tc99m DMSA	Total
RPD on MRU	18	0	18
No RPD on MRU	1	31	32
Total	19	31	50

Source: derived from Table 1 of (Cerwinka et al. 2014) by statistical reviewer.

Table 26. Patient Level Presence/Absence of Renal Parenchyma Defects (RPDs)

	RPD on Tc99m DMSA	No RPD on Tc99m DMSA	Total
RPD on MRU	15	0	15
No RPD on MRU	1	9	10
Total	16	9	25

Source: derived from Table 1 of (Cerwinka et al. 2014) by statistical reviewer.

Summary:

In the sponsor's re-analysis, kidney-level precent agreement between Tc99m DMSA and MRU was 98.0% with two-sided 95% exact CI (89.4%, 99.9%), see statistical-report-for-ise.pdf.

The sponsor didn't provide patient-level percent agreement summary. FDA statistical reviewer performed the analysis and found that patient-level precent agreement between Tc99m DMSA and MRU was 96.0% with two-sided 95% exact CI (79.6%, 99.9%).

Overall Summary of Renal Scarring Context:

- For the four renal scarring papers, the studies were conducted in prospective manner, the results were based on consensus read regarding MRI/MRU and Tc99m DMSA. All the readers were independent. In Freeman et al. (2018) "readers were blinded to the patients' clinical information and other imaging findings". In Cerwinka et al. (2014), "^{99m}Tc-DMSA and MRI scans were each separately interpreted by consensus agreement between two pairs of radiologists blinded to the results of the other pair".
- In Kavanagh et al. (2005) and Chan et al. (1999), the patient-level agreement analysis was not provided and cannot be derived. In Freeman et al. (2018), kidney-level agreement was not provided and cannot be derived based on summary-level data. In Freeman et al. (2018) and Cerwinka et al. (2014), zone-level agreement was not provided.
- The results of these four papers are summarized in Table 27. Among the reportable estimates, the smallest value of the lower bound of the 95% CI of percent agreements between Tc99m DSMA and MRI was 81.2% for the zonal level, 68.0% for the kidney level and 75.3% for the patient-level.

Table 27. Zone/Kidney/Patient Levels Percent Agreement Analysis for the Four RS Papers.

	Zone-level Point estimate (95% CI)	Kidney-level Point estimate (95% CI)	Patient-level Point estimate (95% CI)
Freeman et al.(2018) n = 13	NA	NA	100% (75.3%, 100%)
Kavanaugh et al. (2005)* n=37	96.4% (94.2%, 97.9%)	83.8% (68.0%, 93.8%)	NA
Chan et al. (1999) n = 24	85.8% (81.2%, 89.6%)	85.4% (72.2%, 93.9%)	NA
Cerwinka et al. (2014) n = 25	NA	98% (89.4%, 99.9%)	96% (79.6%, 99.9%)

Source: FDA statistical review team's summary of the papers selected for review.
*: One limitation : there were only 37 kidneys in the kidney-level analysis even through there were 74 kidneys in 37 patients.

8.3.2. Acute Pyelonephritis (APN) and Split Renal Function (SRF)

Three papers are additionally identified by clinical and statistical reviewers that have relevance to the context of APN and SRF. Simrén et al. (2020) and Hung et al. (2016) are for Acute Pyelonephritis clinical context. Gordon et al. (1992) is for Split Renal Function clinical context. Below is the summary of the three additional papers and the re-analyses of the primary endpoint of percent agreement between Tc99m DMSA and comparator performed by the Applicant.

5. **Simrén Paper** [**APN** context] (Simrén et al. 2020): *Diffusion weighted imaging is a promising method to detect acute pyelonephritis in non-sedated free breathing infants*

Study Objective: To prospectively assess the feasibility and performance of diffusion weighted magnetic resonance imaging (DWI) for detection of pyelonephritis in non-sedated free breathing infants.

Overview: 25 out of 32 children <6 months of age (median age of 1.7 (0.7-5.5) months) with first-time symptomatic urinary tract infection (UTI) completed the examination with DWI and Tc99m DMSA scintigraphy. Pyelonephritic lesions were registered for both methods by independent observers – three pediatric radiologists analyzed MRI images and one nuclear medicine specialist reviewed all Tc99m DMSA images where all the four observers were blinded to the other data. The criterion for pyelonephritis on the DWI images was any presence of focal signal increase in the parenchyma. A kidney fulfilling the criteria for pyelonephritis was classified as abnormal. The criterion for pyelonephritis in the Tc99m DMSA images was the presence of focal uptake reduction. A kidney fulfilling the criteria for pyelonephritis was classified as abnormal. Kidney-level agreement between DWI and Tc99m DMSA was evaluated. There was no zonal-level assessment. Table 28 compares detection of pyelonephritis in 50 kidneys between DWI versus Tc99m DMSA scanning.

Table 28. Kidney Level Detection of Pyelonephritis Between DWI Versus DMSA Scanning

	Tc99m DMSA +	Tc99m DMSA -	Total
DWI +	6	2	8
DWI -	6	36	42
Total	12	38	50

+: abnormal; - normal.
Source: Table 2 of (Simrén et al. 2020).

Summary:

There was no zonal-level assessment in Simrén et al. (2020).

In the Applicant's re-analysis, kidney-level precent agreement between Tc99m DMSA and DWI was 84% with two-sided 95% exact CI (70.9%, 92.8%), see statistical-report-for-ise.pdf.

In this single center study of 25 children less than 6 months of age (median age of 1.7 (0.7-5.5) months) with first-time symptomatic urinary tract infection (UTI) completed the examination with DWI and Tc99m DMSA scintigraphy, it is not clear whether the kidney-level summary table was generated by using consensus MRI reads. Assuming the kidney-level summary table was based on consensus MRI reads, this reviewer derived patient-level summary table from Simrén et al. (2020) and found that patient-level precent agreement between Tc99m DMSA and MRU was 72.0% with two-sided 95% exact CI (50.6%, 87.9%), see Table 29.

Table 29. Patient Level Detection of Pyelonephritis Between DWI Versus Tc99m DMSA Scanning

	Tc99m DMSA +	Tc99m DMSA -	Total
DWI +	4	1	5
DWI -	6	14	20
Total	10	15	25

+: abnormal; - normal.
Source: derived from (Simrén et al. 2020) by statistical reviewer.

No data were submitted for review. Based on the information provided in the paper, the 95% CI interval was wide due to small sample size. The lower bound of 95% CI of agreement measure between DMSA and MRU was 50.6%, which is a little better than 50:50 agreement: no-agreement. The weight of the evidence appears minimal.

6. **Hung Paper** [**APN** context] (Hung et al. 2016): *Role of renal ultrasonography in predicting vesicoureteral reflux and renal scarring in children hospitalized with a first febrile urinary tract infection*

Study Objective: To examine the capability of renal ultrasonography (US) for predicting vesicoureteral reflux (VUR) and renal scarring (RS), and to assess, using initial US, the urologic abnormalities that impact management of children hospitalized with a first febrile urinary tract infection (UTI).

Overview: 310 hospitalized children aged <= 2 years (195 boys, 115 girls; median age of 5 (0.5-24) months) with a first febrile UTI were prospectively evaluated using imaging studies, including DMSA scan, US, and voiding cystourethrography. There were no zonal-level or kidney-level assessments. No reader(s) information was provided. All abnormal US findings were recorded, including >= 7 mm anteroposterior diameter of the renal pelvis, and/or any grade of dilatation of the calyces or ureters irrespective of anteroposterior diameter; pelvic or ureteral wall thickening; absence of corticomedullary differentiation; irregular renal outline and signs of renal hypoplasia; duplicated renal collecting system, abnormal kidney size, renal cysts, dysplastic kidney, stenosis of the ureteropelvic junction, or ureterovesical junction and ureterocele. An abnormal acute Tc99m DMSA scan suggesting APN was defined as the presence of focal or diffuse areas of decreased uptake, with preservation of the renal contour. The study compared the performances of US with Tc99m DMSA. Table 30 presents comparison of DMSA vs. US at patient level.

Table 30. Patient Level Abnormal/Normal Findings in Children with a First Febrile UTI: Comparison of US vs. DMSA Findings of APN.

	Abnormal on Tc99m DMSA	Normal on Tc99m DMSA	Total
Abnormal on US	89	16	105
Normal on US	105	100	205
Total	184	116	310

Source: Table 1 of (Hung et al. 2016).

Summary:

These 310 children aged ≤ 2 years (195 boys, 115 girls; median age of 5 (0.5-24) months) with a first febrile UTI were prospectively evaluated using imaging studies, including Tc99m DMSA scan, US, and voiding cystourethrography. There was no information about US and Tc99m DSMA reads and whether readers were blinded. There were no zonal-level or kidney-level assessments in Hung et al. (2016).

In the Applicant's re-analysis, patient-level percent agreement between DMSA and US was 61.0% with two-sided 95% exact CI (55.3%, 66.4%), see statistical-report-for-ise.pdf. The lower bound of the 95% CI for agreement measure was 55.3%.

7. **Gordon Paper** [**Split Renal Function** context] (Gordon et al. 1992): *Can technetium-99m-mercaptoacetyltriglycine replace technetium-99m-dimercaptosuccinic acid in the exclusion of a focal renal defect?*

Study Objective: To evaluate the potential of ^{99m}Tc-mercaptoacetyltriglycine (MAG3) to assess differential renal function and detect focal renal parenchymal abnormalities by comparing the differential function by MAG3 and Tc99m DMSA and investigating the sensitivity and specificity of MAG3 in the detection of a parenchymal renal defect.

Overview: 59 children, between the ages of 0.1 - 14 years (28 boys, 31 girls; median 5.3 years) with previous (12 – 24 weeks earlier) urinary tract infection underwent ^{99m}TC-DMSA and MAG3 within 4 weeks of each other. The DMSA images, functional and summed MAG3 images were reviewed independently with knowledge of the other investigation. Each kidney in each investigation was scored as either normal, uncertain, or abnormal, those eight kidneys regarded as uncertain were excluded, leaving 110 kidneys for analysis. No further reader information was provided. The results of the Tc99m DMSA images were considered as the reference method in declaring the kidney as normal or abnormal. The comparison of Tc99m DMSA and MAG3 functional images at kidney level is presented in Table 31. There was no zonal-level or patient-level assessment.

Table 31. Kidney-Level Comparison Between DMSA and MAG3 Functional Images

	Tc99m DMSA Abnormal	Tc99m DMSA Normal	Total
MAG3 Abnormal	44	7	51
MAG3 Normal	6	53	59
Total	50	60	110

Source: Table 1 of (Gordon et al. 1992). 8 kidneys with uncertain assessment were excluded for the analysis.

Summary: There was no zonal-level assessment in Gordon et al. (1992) And patient-level assessment seems difficult to obtain based on the information provided in Gordon et al. (1992).

In the Applicant's re-analysis, kidney-level precent agreement between Tc99m DMSA and MAG3 was 88.2% with two-sided 95% exact CI (80.6%, 93.6%), see statistical-report-for-ise.pdf.

Overall Summary of APN and SRF Contexts:

- The two APN papers (Simrén et al. 2020) and (Hung et al. 2016):

1. It is not clear whether the results were based on consensus read regarding MRI, and there was only one reader for Tc99m DMSA in Simrén et al. (2020). There was no reader information in Hung et al. (2016).
2. Both papers had no zonal-level data. The paper by Hung et al. (2016) had no kidney level data.
3. Patient-level agreements were low in both papers as shown in Table 32.

Table 32. Kidney/Patient Levels Percent Agreement Analysis for the Two APN Papers

	Kidney-level Point estimate (95% CI)	Patient-level Point estimate (95% CI)
Simrén et al. 2020	84% (70.9%, 92.8%)	72% (50.5%,87.9%)
Hung et al. 2016	N.A.	61% (55.3%, 66.4)

Source: FDA statistical review team's summary of the two papers selected for review.

- The SRF paper (Gordon et al. 1992)

  The readers appeared to be not blinded when reading Tc99m DMSA images. It is unclear whether the percent agreement result was based on consensus read. Patient-level

agreement analysis was not provided and could not be derived. On its face, if the above facts are not of major concern, the lower bound of the 95% CI on kidney level percent agreement between Tc99m DMSA and MAG3 was 80.6%, which appeared reasonable, see Table 33.

Table 33. Kidney Level Percent Agreement Analysis for the SRF Paper

	Kidney-level Point estimate (95% CI)
Gordon et al. (1992)	88.2% (80.6%, 93.6%)

Source: FDA statistical review team's summary of the paper selected for review.

8.4. Conclusions and Recommendations

We recommend approval of this 505(b)(2) application for Nephroscan. Our recommendation for approval of the use of proposed Tc99m Succimer product (NEPHROSCAN) in adult patients is based on the following –

- the approval of Tc-99m-DMSA in adults (NDA 017944) in 1982 which is cross-referenced in this application,
- assessment of an adequate scientific bridge indicating that there are no differences in the active ingredients between the proposed Tc99m Succimer product and Tc-99m-DMSA (NDA 017944). This document is the basis for the conclusion that the differences in inactive ingredients between the proposed Tc99m Succimer product and Tc99m DMSA are not expected to result in any differences in in vivo performance.
- review of literature and post marketing safety data of Tc-99m-DMSA and Tc-99m Succimer (ROTOP kit) in adult patients

Our recommendation to extend the use of Nephroscan to pediatric patients is based on –

- extrapolating the findings of its efficacy in adult patients (prior NDA 017944)
- additional supporting evidence of its efficacy in pediatric patients from the literature. We reviewed selected publications from the sponsor's submitted review of literature that evaluate the efficacy and pharmacokinetics of Tc-99m Succimer. From extensive reviews of the seven papers selected for pediatric population, we found the four papers addressing the agreement performance between Tc99m DMSA and MRI/MRU for renal scarring disorder provide reasonable agreement performance, although there was no prespecified study success threshold of agreement measure. For APN and RSF disorders, there were concerns on the potential bias of image reads, the quality of the paper and the close to 50:50 agreement vs no-agreement reported. The review team concluded that collectively, the literature review of the seven pediatric studies provides supportive evidence of reasonable Tc99m DMSA agreement performance. The primary diagnostic performance may need to rely on the evidence shown in the adult studies in the original DMSA labeling.

- review of literature and post marketing safety data of Tc-99m-DMSA and Tc-99m Succimer (ROTOP kit) in pediatric patients

We conclude that the data provide adequate evidence of favorable risk-benefit for Nephroscan in pediatric patients.

Based upon findings of the pharmacovigilance review (see Pharmacovigilance Review), of an association between Tc99m Succimer and Hypersensitivity Reactions (e.g.: rash, pruritus, erythema, hypersensitivity, urticaria, flushing, etc.), Hypersensitivity Reactions were added to ADVERSE REACTIONS (Section 6) of the proposed labeling. In addition, the following text was included in the WARNINGS AND PRECAUTIONS (Section 5.1) of the proposed labeling –

> **Hypersensitivity Reactions**
> Hypersensitivity reactions, including urticaria, rash, pruritus, and erythema have been reported with the use of technetium Tc 99m succimer injection in adults and pediatric patients. The time of onset of the reactions varied within 2 hours to several hours after the injection. Have appropriate instruments and medications necessary for immediate treatment of allergic reactions and monitor patients for hypersensitivity reactions during and after administration [see Adverse Reactions (6)].

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultations are needed.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The proposed prescribing information (PI) for Nephroscan relies on NDA 017944, DMSA by GE Healthcare (herein referred to as GE kit). The labeling of the GE kit is in old format (non-PLR) and the Nephroscan labeling is updated to include a new indication and safety information as well as to conform to Physician Labeling Rule (PLR) (71 FR 3922, January 24, 2006).

Highlights of the final labeling includes:

a) Indications and Usage: The indication of the current drug (THG kit) is for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in both adults and pediatric patients including term neonates whereas the GE kit was approved for use in adults only [1].
b) Dosage and Administration
    i. The recommended amount of radioactivity of the THG kit for adults is the same as the GE kit (i.e., 74 MBq to 222 MBq); for pediatric patients, a weight adjusted dose of 1.85 MBq/kg of body weight (0.05 mCi/kg) with a range of 19-74 MBq (0.5-2.0 mCi) is added per published literature. See section 6.2.2 for the cited references.
    ii. A dosing table for pediatric patients is included to show the weight-adjusted doses with 2 kg increments, 19 MBq for less than 11 kg, and 74 MBq for 39 kg or greater.
    iii. The section also includes a recommendation to delay imaging up to 6 to 24 hour in patients with severely reduced glomerular filtration rate (eGFR) to enable the acquisition of satisfactory images..
c) Warnings and Precautions: A new warning regarding hypersensitivity reactions including urticaria, rash, pruritus, and erythema is added based on the FDA post-marketing reports of technetium Tc 99m succimer. The following mitigations are added: i) Have appropriate instruments and medications necessary for immediate treatment of allergic reactions; ii) monitor patients for hypersensitivity reactions during and after administration.
d) Adverse Reactions: This section is updated to include hypersensitivity reactions as the new post-marketing adverse reactions in addition to syncope, fever, and nausea from the GE kit.
e) Use in Specific Populations
    i. The Pregnancy and Lactation sections (8.1, 8.2) are revised to conform to the final rule “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling” (79 FR 72064, December 4, 2014).

    ii. The Pediatric Use section (8.4) is added to include –

"NEPHROSCAN, after radiolabeling with technetium Tc 99m, is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in pediatric patients, including term neonates. Use of NEPHROSCAN in this age group for this indication is supported by evidence from effectiveness established in adult studies and data from published pediatric studies supporting the safety and effectiveness of weight-based dosing of Technetium Tc 99m Succimer Injection in renal parenchymal imaging in pediatric patients including term neonates *[see Dosage and Administration (2.3)].*

The recommended amount of radioactivity in pediatric patients, 1.85 MBq/kg (0.05 mCi/kg) with a range of 19 MBq to 74 MBq (0.5 mCi to 2 mCi), is based on published studies that used technetium Tc 99m succimer for the evaluation of acute pyelonephritis, renal scarring, and split renal function in pediatric patients *[see Dosage and Administration (2.2)]*.

Hypersensitivity reactions, including urticaria, rash, pruritus, and erythema have been reported with the use of technetium Tc 99m succimer in pediatric patients *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*."

iii. The Geriatric Use section (8.5) is the same as the GE kit and consistent with 21 CFR 201.57(c)(9)(v)(B)(1) except the geriatric use verbatim statement being modified to accurately reflect the use of technetium Tc 99m succimer injection in geriatric patients: i.e., "administering at the lower end of the dosing range" instead of "starting at the low end of the dosing range" of the verbatim statement.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are needed.

12. Postmarketing Requirements and Commitments

No Postmarketing requirements and commitment are needed.

13. Division Director (Clinical) Comments

I concur with the determination by the NDA reviewers that the differences in the inactive ingredients between the Theragnostics Kit for the preparation of Technetium Tc99m Succimer injection (THG Kit) and the Kit manufactured by GE Healthcare (GE Kit) do not have an impact on their in vivo performance.

The Applicant provided biodistribution, clinical PK and dosimetry data to provide a scientific bridge between the THG Kit and the GE Kit. I concur with the reviewers' assessment that the THG Kit and the GE Kit are comparable in biodistribution, clinical PK and dosimetry.

I concur with the reviewer's conclusion that the use of Technetium Tc 99m Succimer in pediatric patients including term neonates is supported by the extrapolation of evidence of effectiveness established in adult studies and by data from published pediatric studies supporting the safety and effectiveness of weight-based dosing for renal parenchymal imaging.

I concur with the unanimous recommendation for approval of this application by the NDA review team.

14. Appendices

14.1. References

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14.2. Financial Disclosure

No personnel from the sponsor were involved in the published studies cited in the NDA submission.

Covered Clinical Study (Name and/or Number): NDA 214993

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 0		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15. Supplemental Documents

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10 Pages have been withheld in full as duplicate copy of DMPH 2.9.22 review in OtherR immediately following this page

9 Pages have been withheld in full as duplicate copy of DMPH 10.22.21 review in OtherR immediately following this page

207 Pages have been withheld in full as duplicate copy of OPQ IQA review in ChemR 2.9.22 immediately following this page

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	November 5, 2021
Reviewers:	Samantha Cotter, PharmD, BCPS, FISMP Division of Pharmacovigilance II (DPV II)
Team Leader (Acting):	Mallika Mundkur, MD, MPH DPV II
Division Director:	S. Christopher Jones, PharmD, MS, MPH DPV II
Product Name(s):	NephroScan (Kit for the Preparation of Technetium Tc 99m Succimer Injection)
Subject:	All Adverse Events
Application Type/Number:	NDA 214993
Applicant/Sponsor:	Theragnostics, Inc.
OSE RCM #:	2021-1170

Acknowledgements: Thank you to Dr. Jessica Weintraub for her expertise and assistance in searching the VigiBase data for this review.

****This document contains information obtained by FDA using VigiLyze, a tool for searching VigiBase, the World Health Organization-Uppsala Monitoring Centre's global database of individual case safety reports (ICSRs). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information included does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization. Use of VigiBase data in any document or publication, in whole or in part, must be accompanied by this statement.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In this review, the Division of Pharmacovigilance (DPV) II assessed the FDA Adverse Event Reporting System (FAERS), published medical literature, VigiBase, Periodic Adverse Drug Experience Reports (PADERs), and sponsor materials ("Clinical Safety Data") for safety data and adverse events (AEs) reported with NephroScan™ (Kit for the preparation of Tc99m Succimer Injection—Theragnostics, Inc.) in adult and pediatric patients. The review was prompted by a consult from the Division of Imaging and Radiation Medicine (DIRM) that was received on June 11, 2021, which sought to identify and evaluate any available Tc99m Succimer safety data in adults and pediatric patients.

DPV identified 30 cases of any AE with Tc99m Succimer from all sources. The most frequently reported AEs were hypersensitivity reactions. Although several cases described AEs other than hypersensitivity, the totality of the evidence did not provide adequate support for signals other than hypersensitivity.

Based upon findings from this review, DPV recommends the addition of Hypersensitivity Reactions to the Section 6 Adverse Reactions section of the proposed label. In addition, Hypersensitivity Reactions could be further characterized by including preferred terms from the case series such as rash, pruritus, erythema or urticaria.

1 DEFINITIONS

Due to the number of technetium-99m (Tc99m) Succimer injection products discussed in this review, we define the following and hereinto reference them:

- **Tc99m DSMA** - DMSA- dimercaptosuccinic acid injection, powder, lyophilized, for solution (DMSA Kit for the Preparation of Tc99m Succimer Injection) initially approved on May 18, 1982 under the NDA 017944 (MPI DMSA Kidney Reagent) for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults
- **Tc99m ROTOP DEU** – sodium Tc99m Succimer Injection solution (Tc99m DMSA) drug product manufactured by ROTOP Pharmaka GmbH for use in Germany
- **Tc99m ROTOP Import** - sodium Tc99m Succimer Injection solution (Tc99m DMSA) drug product manufactured by ROTOP Pharmaka GmbH and imported to US by Theragnostics under the drug shortage program
- **Tc99m Theragnostics** - NephroScan (Kit for the Preparation of Tc99m Succimer Injection) submitted by Theragnostics under NDA 214993 505(b)(2) for use as a radioactive diagnostic agent indicated as an aid for the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients.
- **Tc99m Succimer** – non-specific formulation of Tc99m Succimer Injection

2 INTRODUCTION

In this review, the Division of Pharmacovigilance (DPV) II assessed the FDA Adverse Event Reporting System (FAERS) database, medical literature, VigiBase (See Appendix A), Periodic Adverse Drug Experience Reports, and sponsor materials ("Clinical Safety Data") for safety data and adverse events (AEs) reported with NephroScan (Kit for the preparation of Tc99m Succimer Injection) in adult and pediatric patients. This review was prompted by a consult request from the Division of Imaging and Radiation Medicine (DIRM) received on June 11, 2021, which sought to address Tc99m Succimer safety data in adults and pediatric patients.

2.1 BACKGROUND

Product Characteristics

Tc99m is a radionuclide isotope that is used primarily for imaging and diagnostic purposes (Papagiannopoulou 2017). Tc99m was isolated in 1938 from molybdenum-99 (Mo-99) decay and is the most common radioactive isotope tracer used for single-photon emission computerized

tomography (SPECT) imaging (Adams 2020, Green 2012). [a] Numerous Tc99m-labeled radiopharmaceutical agents have been formulated by radiolabeling the radionuclide Tc99m to various compounds (e.g., Tc99m mebrofenin, Tc99m medronate, Tc99m sestamibi) (Povoski 2009). The formulation of the radiopharmaceutical determines the organ or organs that can be imaged (brain, kidneys, thyroid, liver, etc.) (Adams 2020).[e] Tc99m succimer binds the cortical region of the kidneys and in conjunction with gamma scintigraphy[b] or SPECT is used to image the renal cortices and for the detection of small focal lesions such as pyelonephritic scars. Tc99m succimer has a physical half-life of 6.02 hours (Theragnostics 2021).

2.2 REGULATORY HISTORY

The dimercaptosuccinic acid injection, powder, lyophilized, for solution (DMSA) Kit for the Preparation of Tc99m Succimer Injection (herein referred to as (Tc99m DSMA) was initially approved on May 18, 1982 under the NDA 017944 (MPI DMSA Kidney Reagent) for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults. The product was discontinued by the manufacturer (GE Healthcare [GE]) for business/commercial reasons (not efficacy or safety reasons) and was placed on the FDA Drug Shortage List on October 15, 2014. On August 3, 2017, the FDA granted Theragnostics permission to import sodium Tc99m succimer injection solution (herein referred to as Tc99m ROTOP DEU), a product manufactured by ROTOP Pharmaka GmbH and imported to US by Theragnostics under the drug shortage program (herein referred to as the Tc99m ROTOP Import). Tc99M ROTOP DEU is approved for adult and pediatric use in Germany. To remove Tc99m Succimer from the Drug Shortages List, FDA recommended Theragnostics submit an NDA.

On May 19, 2021, Theragnostics submitted NDA 214993 505(b)(2) for NephroScan (Kit for the preparation of Technetium Tc99m Succimer Injection, herein referred to as Tc99m Theragnostics) the radioactive diagnostic agent indicated as an aid for the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients.

For this submission, Theragnostics did not perform any clinical studies to evaluate the safety of Tc99m. The Agency agreed with this approach at the pre-IND meeting[c]. FDA previously determined that Tc99m DMSA is safe for use in the evaluation of renal parenchymal disorders in adults. The NDA application submitted by Theragnostics relies on FDA's previous findings of the safety of Tc99m DMSA, clinical studies reported in the global public domain, experience with the Tc99m ROTOP Import, post-marketing experience from GE with Tc99m DMSA, experience with the Tc99m ROTOP DEU, and testimonial from a United States clinical expert on the use of Tc99m Succimer.

[a] SPECT is a nuclear medicine tomographic imaging technique, where radioisotopes attached to drugs travel to a specific organ or tissue (radiopharmaceuticals) and emitted gamma radiation that is captured using gamma rays and is able to provide true 3-dimensional images (NIH 2021).
[b] Scintigraphy (gamma scan) a diagnostic test in nuclear medicine, where radioisotopes attached to drugs travel to a specific organ or tissue (radiopharmaceuticals) and emitted gamma radiation that is captured by gamma cameras to form two-dimensional images (Dorland 2007).
[c] date

2.3 RELEVANT PRODUCT LABELING

Relevant Contraindications, Warnings and Precautions, and Adverse Reactions in the proposed draft labeling for Tc99M Theragnostics can be found in Table 1. The comparative labeling information from *Tc99M DMSA and Tc99M ROTOP-DEU is provided in Appendix B.*

Table 1. Proposed Draft Label for NephroScan (Kit for the Preparation of Technetium Tc 99m Succimer Injection), for intravenous use

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

(b) (4) **Radiation Risks**

(b) (4)

6 ADVERSE REACTIONS

(b) (4)

3 METHODS AND MATERIALS

In this review, we reviewed FAERS reports, the medical literature, VigiBase and the Sponsor's Clinical Safety data for all AEs following use of Tc99m Succimer. Details of this methodology are described below. Of note, our assessment focused on identifying all adverse events associated with the Sponsors Tc 99m Theragnostics.

3.1 CASE SELECTION

We included all report meeting the search criteria described below. We reviewed all PTs in FAERS case reports for new potential safety signals.

Inclusion Criteria:

- All FAERS reports that included technetium Tc99m succimer or dimercaptosuccinic acid (DMSA), or mentioned "ROTOP-DMSA", "MPI DMSA", or "Theragnostics imported kit" anywhere in the report (e.g.: narrative, sender manufacturer organization, product manufacturer, etc.)

Exclusion Criteria:

- Reports of other formulations of Technetium Tc99M, other than succimer (i.e.: albumin, diphosphonate, sestamibi, sulfur colloid, mebrofenin, medronate, pentetate, etc.)

3.2 CAUSALITY CRITERIA

We evaluated selected cases for a causal relationship (between Tc99 exposure and the occurrence of an AE) utilizing the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment (See Appendix C) (WHO-UMC 2013).

Reports obtained without a narrative could not achieve a level of probable (only possible, unassessable, or unlikely). Cases where we deemed causality as unassessable or unlikely were excluded from the case series.

3.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 4.

Table 4. FAERS Search Strategy*	
Date of search	July 14, 2021
Time period of search	All dates to June 30, 2021
Search type	FBIS Quick Query
Product terms	Product Name - Technetium Tc-99m Succimer; Rotop - DMSA; Dimercaptosuccinic Acid DMSA; MPI DMSA Kidney Reagent Product Active Ingredient - Technetium Tc-99m Succimer; 2,3-Dimercaptosuccinic Acid Product Verbatim - DMSA; DMSA (Succimer); DMSA Powder (Succimer); MPI DMSA; MPI DMSA Kidney Reagent; Succimer (DMSA); Succimer DMSA; Technescan DMSA; Technetium (99m Tc) DMSA; Technetium (99m Tc) DMSA (Technetium (9m Tc) DMSA); Technetium (99m Tc) Succimer (Technescan DMSA); Technetium Tc99m DMSA NDA # - 017944 Reporter Narrative (verbatim) – THERAGNOSTICS, NEPHROSCAN
MedDRA search terms (Version 24.0)	All Preferred Terms
* See Appendix D for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, SOC=System Organ Class, HLGT=High Level Group Term, HLT=High Level Term, PT=Preferred Term, DMSA = dimercaptosuccinic acid	

In addition, DPV reviewed all reports submitted by the following sender organizations (GE Healthcare, MPI, ROTOP, Theragnostics, (b) (4)) for reports with reference to TC 99M succimer.

3.4 VIGIBASE SEARCH STRATEGY

DPV II searched the VigiBase database (See Appendix A) with the strategy described in Table 5. VigiBase is a global database of more than 20,000,000 ICSRs maintained by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC 2013).

Table 5. VigiBase Search Strategy*	
Date of search	July 13, 2021
Time period of search	All dates through July 11, 2021
Search type	VigiLyze
Product terms	Drug: Technetium tc 99m succimer (Active ingredient)
MedDRA search terms (Version 24.0)	All adverse events
* See Appendix A for a description of the VigiBase database MedDRA-Medical Dictionary for Regulatory Activities	

3.5 LITERATURE SEARCH

DPV searched PubMed and Embase using the strategies described in Table 6 to identify published case reports of adverse events occurring with Tc99m Succimer.

Table 6. Literature Search Strategy – PubMed and Embase	
Literature Search Strategy – PubMed	
Date of search	August 2, 2021
Search terms	(("technetium"[MeSH Terms] OR "technetium"[All Fields]) AND ("succimer"[MeSH Terms] OR "succimer"[All Fields])) AND ("case reports"[All Fields] OR "case report"[All Fields])
Years included in search	All dates
Literature Search Strategy – Embase	
Date of search	August 2, 2021
Search terms	('succimer tc 99m'/exp OR 'succimer tc 99m') AND ('case report'/exp OR 'case report') AND ('adverse event'/exp OR 'adverse event')
Years included in search	All dates

3.6 PERIODIC SAFETY REPORTS

DPV screened the following 14 periodic safety reports submitted by GE for NDA 017944, for periodic reports of any adverse events with Tc99m DMSA use:

- New/Periodic Safety Report: (NDA 17944), [June 1983 – November 1983]
- New/Periodic Safety Report: (NDA 17944), [December 1983 - May 1984]
- New/Periodic Safety Report: (NDA 17944), [March 1984 - May 1984]
- New/Periodic Safety Report:2 (NDA 17944), SDN 16 [May 1986 - May 1987]
- New/Periodic Safety Report: 3 (NDA 17944), SDN 19 [May 1987 - April 1988]
- New/Periodic Safety Report: 5 (NDA 17944), SDN 34 [May 1990 - April 1991]
- New/Periodic Safety Report: 6 (NDA 17944), SDN 37 [May 1991-April 1992]
- New/Periodic Safety Report: 7 (NDA 17944), SDN 43 [May 1992 - April 1993]
- New/Periodic Safety Report: 8 (NDA 17944), SDN 48 [May 1993 – April 1994]
- New/Periodic Safety Report: 9 (NDA 17944), SDN 51 [May 1994 - April 1995]
- New/Periodic Safety Report: 10 (NDA 17944), SDN 56 [May 1996 - April 1997]
- New/Periodic Safety Report: 13 (NDA 17944), SDN 63 [May 1998 - April 1999]
- New/Periodic Safety Report: 17 (NDA 17944), SDN 81 [May 2001 - May 2002]
- New/Periodic Safety Report: 18 (NDA 17944), SDN 87 [May 2002 - May 2003]

3.7 OTHER DATA SOURCES - THERAGNOSTICS INC. - KIT FOR THE PREPARATION OF TECHNETIUM TC99M SUCCIMER INJECTION - 2.7.4 SUMMARY OF CLINICAL SAFETY-POSTMARKETING DATA- MAY 2021

DPV II reviewed Section 2.7.4. Summary of Clinical Safety - PostMarketing Data NDA 214993 for kit for the preparation of technetium tc99m succimer injection submitted on May 19, 2021.

4 RESULTS

A total of 30 cases were identified from all data sources (FAERS [n= 9], VigiBase [n=20] PADERs [n=1], literature [n= 0]). The Sponsor's Summary of Clinical Safety- Post Marketing Submission identified 26 reports; these were not included in DPV cases series, however, given the lack of case-level data (See Section 4.5). Additional detail is provided below.

4.1 FAERS, VIGIBASE, PADER CASE SELECTION

Figure 1 depicts selection of cases from FAERS, VigiBase and PADERs.

Figure 1. FAERS Case Selection

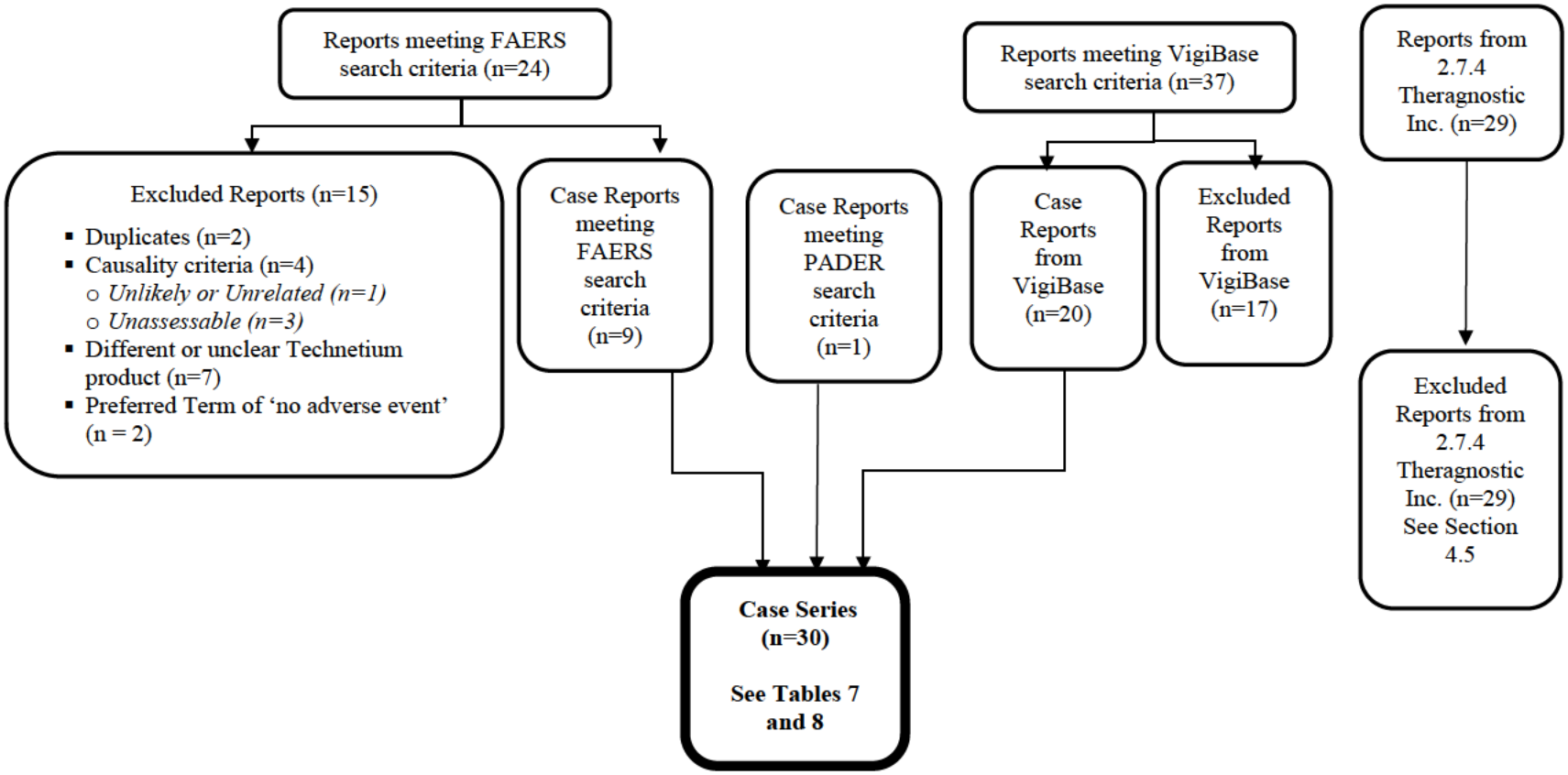

Table 7 summarizes case characteristics (See Appendix E for line listing of cases).

Table 7. Descriptive Characteristics of All Adverse Events with Tc99m Succimer in This FAERS, PADER, and VigiBase Case Series, Received by FDA for all Dates through June 30, 2021 (N=30)			
	FAERS/PADER (n=10) *	VigiBase (n=20)	Total (n=30)
Age (years)			
Mean	22.4	9.3	13.3
Median	11	7	7.5
Range	0.33-67	0.07-67	0.07-67
NR	2	1	3
Sex			
Female	5	15	20
Male	2	5	7
NR	3	0	3
Report type			
Expedited	3	0	3
Non-Expedited	7	0	7
Direct	0	0	0
NR	0	20	20
Country Derived			
Domestic	8	0	8
Foreign	2	22	28
Initial year received			
1982-2003	9	3	12
2004-2010	0	4	4
2011-2015	0	8	8
2016-2021	1	5	6
Time to Onset			
During procedure	1	0	1
Less than 15 mins	3	0	3
Within 2 hours	3	0	3
Same day as procedure	1	20	21
NR	2	0	2
Serious outcome(s) †			
DE	1	0	1
HO	1	5	6
OT	6	2	8
Not Serious	2	10	12
NR	0	3	3
Causality assessment			
Probable	4	0	4
Possible‡	6	20	26

Table 7. Descriptive Characteristics of All Adverse Events with Tc99m Succimer in This FAERS, PADER, and VigiBase Case Series, Received by FDA for all Dates through June 30, 2021

(N=30)

* One case identified in PADER March – May 1984 and was not in FAERS

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

Among the 27 cases reporting an age, the majority were pediatric patients, with 23 cases reporting an age of less than 17 years. Cases identified in FAERS/PADER were mostly domestic (8 of 10 cases), contrary to cases identified in VigiBase which were all from foreign sources (n=20). The FDA initial received date spanned from 1982 to 2021. Of the 28 reports with a time-to-onset, all events occurred within the same day of administration and seven events occurred within 2 hours of the administration.

We identified 15 serious cases including death (n=1), hospitalization (n=6), and "other" serious (n=8). Of the serious cases, we deemed causality between product exposure and the outcome as "probable" in three cases (tachycardia (n=1), pruritus (n=1), and circulatory collapse with hypotension, loss of consciousness, and sinus bradycardia (n=1). We deemed the other twelve serious cases as "possible", based on the WHO-UMC causality criteria (WHO-UMC 2013).

Table 8 provides the preferred terms identified in the 30 cases of any adverse event with Tc99m Succimer in our case series. Preferred terms that are part of the Hypersensitivity SMQ, are further identified in the Table. Labeled preferred terms in the proposed label for Tc99m Theragnostics are also identified.

Table 8. Preferred Terms for All Adverse Events with Tc99m Succimer in This FAERS, PADER, and VigiBase Case Series, Received by FDA for all Dates through June 30, 2021

(N=30)

	FAERS/ PADER (n=10) *	VigiBase (n=20)	Total (n=30)	Proposed Labeling (Label Location)
Rash†	1	4	5	Yes–(AR) 'maculopapular'
Pruritus†	2	2	4	No
Drug ineffective	0	3	3	Yes – (W/P) 5.2
Erythema†	1	2	3	No
Renal scan abnormal	1	2	3	Yes – (W/P) 5.2
Feeling abnormal	1	2	3	No
Cough	0	2	2	No
Headache	0	2	2	No
Hypersensitivity†	1	1	2	No
Pallor	1	1	2	No
Tachycardia	2	0	2	No
Vomiting	0	2	2	No

Anaphylactic reaction†	1	0	1	No
Anaphylactoid reaction‡	0	1	1	No
Anxiety	0	1	1	No
Asthmatic crisis	0	1	1	No
Circulatory collapse†	1	0	1	No
Diarrhea	0	1	1	No
Drug eruption†	0	1	1	No
Dyspnoea	1	0	1	No
Flushing†	0	1	1	No
Hyperkalaemia	1	0	1	No
Hypotension	1	0	1	No
Hypotonia	0	1	1	No
Injection site rash†	0	1	1	No
Loss of consciousness	1	0	1	No
Malaise	0	1	1	No
Peripheral coldness	1	0	1	No
Pyrexia	1	0	1	Yes–(AR) 'fever'
Rash erythematous†	0	1	1	No
Sinus bradycardia	1	0	1	No
Skin necrosis†	0	1	1	No
Skin swelling†	0	1	1	No
Therapeutic product effect decreased	1	0	1	Yes – (W/P) 5.2
Urticaria†	1	0	1	No

* FAERS (n=9), PADER (n=1) The one case identified in the March – May 1984 PADER, not found in FAERS.
† Preferred Terms from the case series found in the Hypersensitivity SMQ include rash, pruritus, erythema, hypersensitivity, anaphylactic reaction, circulatory collapse, drug eruption, flushing, injection site rash, rash erythematous, skin necrosis, skin swelling, urticaria and in Section 5.2 Advanced Renal Failure: Some patients with advanced renal failure may exhibit poor renal intake of technetium Tc 99m succimer injection. It has been reported that satisfactory images may be obtained in some of these patients by delaying imaging for up to 24 hours.
‡ Although anaphylactoid reactions resemble generalized anaphylaxis, they are not caused by IgE-mediated allergic reaction but rather by a nonimmunologic mechanism (Miller-Keane 2003).
AR – Adverse Reactions; W/P – Warnings and Precautions

DPV reviewed all 30 cases in the case series and read through narrative data where available[d]. As presented in Table 8, there were 56 preferred terms identified in the 30 cases of the case series. The case series only identified two PTs in the proposed label, rash (n=5) and fever ('pyrexia') (n=1). However, more specifically, our case series identified cases of rash, and were not specific for maculopapular rash, as proposed by the sponsor. The following preferred terms were identified in two or more cases and are not in the proposed label; pruritus, erythema, cough,

[d] VigiBase cases do not include case narrative data

feeling abnormal, headache, hypersensitivity, pallor, tachycardia, and vomiting. Fifteen of the 30 cases included PTs within the Hypersensitivity Standardized MedDRA Query (SMQ), including the events of rash, pruritus, erythema, hypersensitivity, anaphylactic reaction, circulatory collapse, drug eruption, flushing, injection site rash, rash erythematous, skin necrosis, skin swelling, and urticaria. These cases were reviewed for inclusion of a modified version of Hypersensitivity Case Definition.[e] For the 15 cases with a PT from the Hypersensitivity SMQ (list of PTs available in Appendix F), seven had a serious outcome (other serious n=4, hospital n =3).

The following unlabeled preferred terms[f] were reported in two or more cases and did not represent hypersensitivity: cough, feeling abnormal, headache, pallor, tachycardia, and vomiting. Of these reports with unlabeled events, only two were considered serious. These two cases (tachycardia [FAERS Case # 5392300] and pallor [FAERS Case # 11961899] are described below.

We highlight the following FAERS cases of events with preferred terms for hypersensitivity in patients exposed to Tc99m Succimer.

- **FAERS Case # 3490545 (GBR) [HO] 2000**
  PTs: circulatory collapse: feeling abnormal: hypotension: loss of consciousness: pallor: peripheral coldness: sinus bradycardia

  An 8-year-old male received Technetium Tc99M DMSA injection for scan of renal scarring. His past medical history included a recurrent urinary tract infection. Following the administration of Tc99m DMSA, the patient experienced "a funny feeling" and 30 seconds later lost consciousness. He "awoke" after another 30-45 seconds. Additional symptoms experienced by the patient included cold to touch, pallor, hypotension, and sinus bradycardia.

  Reviewers Comments: This pediatric patient experienced circulatory collapse, loss of consciousness, and sinus bradycardia almost immediately after receiving Tc99M DMSA. Circulatory collapse is preferred term in the SMQ for Hypersensitivity.

  WHO Causality: Probable

[e] Modified version of Hypersensitivity Case Definition: We referred to the Office of Surveillance and Epidemiology (OSE) anaphylaxis case definition (OSE Case Definition 2014) which includes a subsection addressing hypersensitivity. We included reports that described an event of hypersensitivity (symptoms of urticaria, rash, pruritus, or erythema/flushing) or anaphylaxis in relation to Tc99M Succimer exposure, with a time-to-onset within one day of exposure to Tc99m Succimer. Cases were not categorized as hypersensitivity if they did not describe an event of hypersensitivity, or reports classified as unassessable or unlikely based on causality assessment (Section 3.3).

[f] Labeled terms in Adverse Reaction section of the proposed label include: syncope, fever, nausea, and maculopapular skin rash; and Warnings and Precautions (b)(4) mentions some patients may exhibit poor renal intake, which can affect the image quality.

- **FAERS Case # 4406178 (USA) [Not Serious] 1984**
  PTs: hypersensitivity: pyrexia: tachycardia

  A seven-month-old female infant received Tc99m DMSA injection for a renal scan. Past medical history included lipomyelocele[g], sacral agenesis[h] and no motor control of lower extremities, however otherwise normal for age. No past medical history of allergies. Thirty minutes after the administration of Tc99m DMSA, the infant became irritable, flushed, tachycardic (220 beats per minute without arrhythmias), and developed a temperature reported between 104 – 105.8 (units not specified). Treatment included intravenous diphenhydramine and hydrocortisone. Events resolved completely within three hours. The physician stated it was an allergic reaction that responded immediately to treatment.

  Reviewers Comments: This pediatric patient experienced hypersensitivity, pyrexia, and tachycardia 30 minutes after receiving Tc99m DMSA. Events resolved after treatment with diphenhydramine and hydrocortisone.

  WHO Causality: Possible

We also highlight the only case of death in our FAERS cases of a patient exposed to Tc99m Succimer.

- **FAERS Case # 5392300 (USA) [DE] 1996**
  PT: tachycardia

  A 4-month-old infant (sex not reported) received 500 μCi of Tc99m DMSA for evaluation of renal parenchymal disorders. Past medical history included premature and hospitalized since birth. During administration of technetium, the infant experienced an episode of tachycardia. One day later, the infant had another tachycardia event and subsequently expired. Autopsy was completed but results were not available. The reporter noted that a second infant (age not reported) received a dose from the same vial of product with no adverse experience.

  Reviewers Comments: This pediatric patient was the only death in our case series. The patient experienced tachycardia during administration of Tc99m DMSA. The patient was born premature and had been hospitalized since birth confounding the reason for the events and death. The event of tachycardia accompanying the death occurred the following day and may have been related to other factors. It is important to note that another infant received Tc99m DMSA from the same vial without effect.

  WHO Causality: Possible

[g] A lipomyelocele is a type of lipoma that occurs with Spina Bifida. A lipoma is a fatty, fibrous tissue mass in the spinal column that extends on the backside through a Spina Bifida defect and connects to the spinal cord against the skin. (SBA 2021)
[h] Sacral agenesis is a congenital disorder in which the fetal development of the l caudal partition of the spine is abnormal. (ISUOG 2019)

4.2 VIGIBASE

The VigiBase search retrieved 37 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 20 VigiBase cases were included in the case series of all adverse events reported with Tc99m Succimer use. The information from these 20 cases is included above in Section 4.1, and in Table 7 and Table 8. All cases identified in VigiBase were foreign reports. Due to a lack of narrative case level details, all cases obtained from VigiBase were categorized as possible, based on the WHO-UMC causality criteria (WHO-UMC 2013).

We highlight the following VigiBase case of an event with preferred terms for hypersensitivity in a patient exposed to Tc99m Succimer.

- **UMC Report VigiBase Case # 12205815 (FRA) [HO] 2013**
  PTs: Injection site rash, Rash

  An 8-year-old female patient received Renocis (technetium tc 99m succimer). Her past medical history included pyelonephritis and atrophic kidney. On the date of administration of Tc99m Succimer, she experienced injection site rash. The patient recovered from the events. No further information was provided.

  Reviewers Comments: This pediatric patient experienced injection site rash on the same date that she received the Tc99m Succimer. There was no narrative data provided as this case was obtained from VigiLyze.

  WHO Causality: Possible

We highlight the following VigiBase case of an unlabeled PT (pallor) reported in two or more cases with a serious outcome.

- **UMC Report VigiBase ID Case # 11961899 (France) [HO] 1999**
  PT: pallor, anaphylactoid reaction, malaise, hypotonia

  A 26-day-old female patient received Renocis (technetium tc 99m succimer) 0.3 mL intravenous for an unknown indication. Past medical history was not included. On the date of administration of Tc99m Succimer, she experienced pallor, anaphylactoid reaction, malaise, and hypotonia. The patient recovered from the events. No further information was provided.

  Reviewers Comments: This pediatric patient experienced unlabeled events of pallor, anaphylactoid reaction, malaise, and hypotonia on the same date that she received the Tc99m Succimer. We note that the case was coded as an anaphylactoid reaction. Although anaphylactoid reactions resemble generalized anaphylaxis, they are not caused by IgE-mediated allergic reaction but rather by a nonimmunologic mechanism (Miller-Keane 2003). However, we appreciated that the term anaphylaxis and anaphylactoid reaction may be incorrectly used interchangeably. In addition, this case is difficult to interpret due to lack of narrative data from VigiBase.

4.3 LITERATURE SEARCH

DPV did not identify additional literature cases of any event associated with Tc99m Succimer.

4.4 PERIODIC SAFETY REPORTS

DPV manually reviewed 14 Periodic Safety Reports submitted by the Applicant (GE) for Tc99m DMSA between 1983 – May 2003. DPV identified one additional case (manufacture (MNF) report # DMSA00499000l) in periodic safety report 13 (May 1998 - April 1999), which could not be found in the FAERS database. This one case is added to the FAERS/ PADER columns in Table 7 and Table 8 above in section 4.1.

We provide details of this one PADER case of hypersensitivity in a patient exposed to Tc99m Succimer.

- **MNF Case # DMSA004990001 (USA) [Not Serious] 1999**
  PTs: Rash

  A 34-year-old male patient received Tc99m DMSA for renal study. Past medical history was not provided. Five to six minutes after administration, he developed a rash on his face, arm, and chest. No therapy to treat the events was given and the patient recovered completely.

  Reviewers Comments: This patient experienced rash on multiple body sites (face, arm, and chest) within six minutes of receiving Tc99m DMSA. He recovered from the events completely with no treatment and the case was considered non-serious.

  WHO Causality: Probable

4.5 OTHER DATA SOURCES - THERAGNOSTICS INC. - KIT FOR THE PREPARATION OF TECHNETIUM TC99M SUCCIMER INJECTION - 2.7.4 SUMMARY OF CLINICAL SAFETY-POSTMARKETING DATA- MAY 2021

As discussed previously, the Sponsor's NDA application for Tc99m Theragnostics safety data relies on the post-marketing experience from GE with Tc99m DMSA (NDA 017944). The Sponsor submitted information from GE's March 18, 2003 Annual Report (Theragnostics 2021). Per Theragnostics submission, GE documented that there was a total of 29 reports that included 50 PTs from 1982 to January 2003[i] with Tc99m DMSA. Details of subject ages corresponding to the specific adverse events were not available. Theragnostics stated that of the 29 reports, 26 occurred in patients under 65 years old and three reports, age was not reported. No further information was provided regarding patient demographics, narrative information, or other event details. Theragnostics reported

[i] GE received approval on 18 May 1982, although Theragnostics only has US distribution data for the GE Kit from 1984 onward (through 2014). Further, Theragnostics only has AE data from 1982-January 2003, from the GE Annual Report.

that were no deaths, serious adverse events, or other significant adverse events "reported in the literature or received in postmarketing reports by Theragnostics, ROTOP DEU, or GE".

DPV attempted to identify duplicate reports in the data as presented by Theragnostics. We utilized date information (1982 – 2003) and PTs to find duplicates from either FAERs or VigiBase cases. Three reports were clear duplicates of reports from FAERS. We classified the remaining 26 reports as unassessable due to a lack of case-level data, based on WHO-UMC causality criteria. Despite the lack of data to fully analyze these 26 reports, we consolidated the list of the 43 PTs represented from the reports in Table 9. Information provided includes PTs, PTs that are part of the Hypersensitivity SMQ, and PTs that are in the proposed label for Tc99m Theragnostics.

Table 9. Preferred Terms for All Adverse Events with Tc99m DMSA Submitted in the Sponsor's Clinical Safety Data Submitted May 20, 2021 (Theragnostics 2021) **(N=26)**

Preferred Terms	Number of Reports	Proposed Labeling (Label Location)
Rash†	7	Yes-(AR) 'maculopapular'
Fever	5	Yes-(AR)
Urticaria†	3	No
Headache	2	No
Dizziness	2	No
Nausea	2	Yes-(AR)
Respiratory disorder	2	No
Vasovagal attack	2	No
Pruritus†	1	No
Dyspnea	1	No
Flushing†	1	No
Hypotonia	1	No
Tachycardia	1	No
Arthralgia	1	No
Chills	1	No
Convulsions	1	No
Diarrhea	1	No
Ear inflammation	1	No
Edema	1	No
(b) (4)	1	Yes – (b) (4)
Paresthesia	1	No
Sneezing†	1	No
Somnolence	1	No
Syncope	1	Yes-(AR)
Tiredness	1	No
Tonsilitis	1	No

Table 9. Preferred Terms for All Adverse Events with Tc99m DMSA Submitted in the Sponsor's Clinical Safety Data Submitted May 20, 2021 (Theragnostics 2021) **(N=26)**
* Per the Sponsor, the ages of 2 subjects (3 PTs) were unknown and none of the subjects reporting AEs were over 65 years old. † Preferred Terms from Theragnostics data found in the Hypersensitivity SMQ include rash, urticaria, pruritus, flushing, and sneezing AR – Adverse Reactions; (b) (4)

Reviewers Comments: Information submitted by the sponsor was difficult to interpret due to lack of case level data. Despite this, we note a few differences and similarities to the cases in our case series. First, although the Sponsor stated that they had not identified any serious cases, to the contrary, DPV identified 15 serious cases including one death, and many cases of prolonged hospitalization from adverse events following Tc99m DMSA administration. We note that the PTs in the Sponsor's data are similar to those in the case series and note that five are part of the Hypersensitivity SMQ, including rash, urticaria, pruritus, flushing, and sneezing. However, with such limited information, data in this section lacks any certainty that a reported event was due to Tc99m DMSA.

5 DISCUSSION

DPV identified 30 cases of any adverse event with Tc99m Succimer in FAERS, VigiBase, and Periodic Safety Reports. No additional cases were identified in the medical literature or the Sponsor's Clinical Safety Data.

Of the 30 cases, hypersensitivity reactions were the most frequently reported event. Although several cases described AEs other than hypersensitivity, the totality of the evidence did not provide adequate support for signals other than hypersensitivity. We note that although the GE label for NDA 017944 does not mention hypersensitivity reactions, the Summary of Product Characteristics for ROTOP states "*In very rare cases (< 0.01 %) after intravenous injection of the ready-to use solution, hypersensitivity reactions have occurred such as locally confined or general rashes, itching, drop in blood pressure, headache, dizziness, nausea and vomiting. Reactions can occur up to 24 hours after the injection. Although such reactions are very rare and usually very minor, appropriate instruments and medications for immediate treatment of allergic reactions (adrenaline, corticosteroids and antihistamines) should be within reach for possible emergency treatment at all times*."

Our review provided key safety information in pediatric patients. Although the information provided by the Sponsor in the Clinical Safety Data suggested that the majority of patients were under 65 year of age, our case series was more specific and further characterized the majority of cases in patients under 17 years of age (n=26). This information could be helpful as the Sponsor is seeking approval for Tc99m Theragnostics as an aid for the scintigraphic evaluation of renal parenchymal disorders in both adult and pediatric patients.

Serious cases were documented in our case series, contrary to the information provided by the Sponsor. The Sponsor stated that they had not identified any serious cases from the data that they

reviewed, however DPV identified 15 serious cases including one death, and many cases of prolonged hospitalization from adverse events following Tc99m DMSA administration. Of these serious cases, five occurred within 2 hours following administration, eight occurred within the 24 hours following administration, and two didn't not report a time-to-onset. Of these serious cases, we deemed several as possibly or probably related to the administration of Tc99m Succimer.

Our analysis is subject to several limitations. We note that spontaneous reporting databases are subject to the problem of underreporting, potentially leading to incomplete capture of relevant cases. Most importantly, submitted cases may often lack relevant detail, such as information on route, drug formulation or manufacturer, so misclassification of cases by manufacturer is possible. Reports from VigiBase lack narrative data, making it difficult to fully interpret the drug event relationship. In addition, we identified at least one Tc99m DMSA periodic report that was not available in the FAERS database.

6 CONCLUSION

In conclusion, based on our review of FAERS, VigiBase, Periodic Safety Reports, medical literature, and the Sponsor's Clinical Safety Data, we find an association between Tc99m Succimer and Hypersensitivity Reactions (e.g.: rash, pruritus, erythema, hypersensitivity, urticaria, flushing, etc.).

7 RECOMMENDATIONS

Based upon findings from this review, DPV recommends the addition of Hypersensitivity Reactions to ADVERSE REACTIONS (Section 6) of the proposed label. In addition, Hypersensitivity Reactions could be further characterized by including preferred terms from the case series such as rash, pruritus, erythema and/or urticaria.

8 REFERENCES

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9 APPENDICES

9.1 APPENDIX A. VIGIBASE DATABASE

VigiBase is a global database of individual case safety reports (ICSRs) received by the Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. VigiLyze is a tool used to search and analyze VigiBase. VigiBase includes ICSRs submitted by over 130 countries, including the U.S., for allopathic medicines, traditional medicines (herbals), and biological medicines, including vaccines. The FDA does not have access to case narratives in VigiBase but may request them from the regulatory authorities that submitted the ICSRs. Some cases in VigiBase may also be in the FDA Adverse Event Reporting System (FAERS). The limitations and qualifications that apply to VigiBase information and its use include:

> Tentative and variable nature of the data
> *Uncertainty:* The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication
> *Variability of source:* Reports submitted to national centers come from both regulated and voluntary sources. Practice varies: some national centers accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.
> *Contingent influences:* The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.
> *No prevalence data:* No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.
> *Time to VigiBase:* Some national centers make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national center until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centers.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

9.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

9.3 APPENDIX C. WORLD HEALTH ORGANIZATION-UPPSALA MONITORING CENTRE (WHO-UMC) CAUSALITY ASSESSMENT CATEGORIES

World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Categories	
Causality term	**Assessment criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

9.4 APPENDIX D. PRESCRIBING INFORMATION FOR TC99M DMSA AND TC99M ROTOP-DEU

Relevant prescribing information for the most recent label for Tc99M DMSA by GE Healthcare can be found below.

Relevant Labeling for DMSA (dimercaptosuccinic acid injection) Kit for the Preparation of Technetium Tc99m Succimer Injection

CONTRAINDICATIONS

None known.

WARNINGS

None.

PRECAUTIONS

General

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to ensure minimum radiation exposure to occupational workers.

DMSA should be used between 10 minutes and 4 hours following reconstitution (see "Preparation" section). Any unused portion should be discarded after that time.

Some patients with advanced renal failure may exhibit poor renal intake of Tc99m DMSA. It has been reported that satisfactory images may be obtained in some of these patients by delaying imaging for up to 24 hours.

The contents of the kit vials are intended only for use in the preparation of DMSA Injection and are not to be directly administered to the patient.

The contents of the kit vials are not radioactive. However, after Tc99m is added, adequate shielding of the final preparation must be maintained.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

ADVERSE REACTIONS

Rare instances of syncope, fever, nausea, and maculopapular skin rash have been reported.

Relevant information from the Package Leaflet and Summary of Product Characteristics for Tc99M ROTOP-DEU can be found below.

Relevant information from the Package Leaflet and Summary of Product Characteristics

for ROTOP - DMSA, 1.0 mg Kit for radiopharmaceutical preparation Succimer

Contraindications

ROTOP-DMSA should not be used in case of hypersensitivity to the active substance or to any of the excipients listed in section 6.

4. POSSIBLE SIDE EFFECTS

As all medicinal product s, ROTOP - DMSA can cause side effects, although not everybody gets them.

For assessing the side effects the frequency is classified as follows:

Very common:	observed in more than 1 patient in 10
Common:	observed in less than 1 patient in 10, but more than 1 patient in 100
Uncommon:	observed in less than 1 patient in 100, but more than 1 patient in 1,000
Rare:	observed in less than 1 patient in 1,000, but more than 1 patient in 1 0,000
Very rare:	observed in less than 1 patient in 10,000 or not known

In very rare cases (< 0.01 %) after intravenous injection of the ready-to use solution, hypersensitivity reactions have occurred such as locally confined or general rashes, itching, drop in blood pressure, headache, dizziness, nausea and vomiting. Reactions can occur up to 24 hours after the injection.

Although such reactions are very rare and usually very minor, appropriate instruments and medications for immediate treatment of allergic reactions (adrenaline, corticosteroids and antihistamines) should be within reach for possible emergency treatment at all times.

Since the administered amounts of active substances are very low, the risks of use are mainly related to radiation exposure. Ionising radiation can cause cancer and genetic mutations.

Since most radiopharmaceutical examinations are conducted with low effective radiation doses of less than 20 mSv, the probability of such effects occurring is expected to be low.

The effective radiation dose is 0.62 mSv when the maximum recommended activity of this medicinal product is applied.

9.5 APPENDIX E. LINE LISTING OF CASES FROM FAERS, VIGIBASE, AND PADER LINE LISTING OF ALL EVENTS WITH TC99M SUCCIMER CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Mnf. Control #	Case Type	Age (years)	Sex	Country Derived	All Preferred Terms	Serious Outcome(s)*
1	9/8/1982	5632891	1	0264	Non-E	NR	NR	USA	Pruritus	OT
2	4/11/1984	4406178	1	1089	Non-E	0.417	F	USA	Hypersensitivity: Pyrexia: Tachycardia	Not Serious
3	6/27/1986	4497851	1	1629	Non-E	67	F	USA	Dyspnoea	OT
4	6/25/1991	4803848	1	2781	Non-E	NR	NR	USA	Hyperkalaemia	OT
5	5/6/1996	5392300	1	3689	Expedited	0.333	NR	USA	Tachycardia	DE
6	3/3/1998	3183173	1	3705	Non-E	3	F	USA	Renal scan abnormal: Therapeutic product effect decreased	OT
7	3/3/1998	3183174	1	3718	Non-E	11	F	USA	Urticaria	OT
8	6/22/1999	No FAERS Number – PADER 1999	1	DMSA004990001	Non-E	34	M	USA	Rash	Not Serious
9	6/23/2000	3490545	1	DMSA-UK-0006S-0001(0)	Expedited	8	M	GBR	Circulatory Collapse: Feeling Abnormal: Hypotension: Loss of Consciousness: Pallor: Peripheral Coldness: Sinus Bradycardia	HO
10	8/2/2018	15233036	1	FR-TEVA-2018-FR-	Expedited	45	F	FRA	Anaphylactic reaction: Pruritus	OT

				932885						
	Initial VigiBase Received Date	**VigiBase Case #**	**Version #**	**Mnf. Control #**	**Case Type**	**Age (years)**	**Sex**	**Country Derived**	**All Preferred Terms**	**Serious Outcome(s)***
11	2001-11-15	1427727	N/A	NR	N/A	6	F	GBR	Vomiting: Headache	NR
12	2001-11-15	1428890	N/A	NR	N/A	5	F	GBR	Vomiting: Diarrhoea: Headache	NR
13	2001-11-15	1434454	N/A	NR	N/A	4	M	GBR	Rash	NR
14	2005-12-18	2421967	N/A	FR-AFSSAPS-NT0200038	N/A	3	M	FRA	Cough: Anxiety	Not Serious
15	2006-03-21	2468796	N/A	FR-AFSSAPS-NT0400289	N/A	11	F	FRA	Pruritus: Drug eruption	Not Serious
16	2008-03-06	2518778	N/A	FR-AFSSAPS-MA0700226	N/A	5	M	FRA	Drug ineffective	HO
17	2008-03-06	2518785	N/A	FR-AFSSAPS-MA0700227	N/A	2	F	FRA	Drug ineffective	HO
18	2014-10-14	11961899	N/A	FR-AFSSAPS-AN99LM176	N/A	0.071 (26 days)	F	FRA	Pallor: Anaphylactoid reaction: Malaise: Hypotonia	HO
19	2014-10-15	11967931	N/A	FR-AFSSAPS-DJ20070578	N/A	7	F	FRA	Cough	Not Serious

20	2014-10-16	12083332	N/A	FR-AFSSAPS-BX20100877	N/A	10	M	FRA	Rash	Not Serious
21	2014-10-18	12245145	N/A	FR-AFSSAPS-AN20140418	N/A	9	F	FRA	Renal scan abnormal	Not Serious
22	2014-10-18	12223737	N/A	FR-AFSSAPS-NY20140326	N/A	6	F	FRA	Renal scan abnormal	OT
23	2014-10-18	12214910	N/A	FR-AFSSAPS-LY20131458	N/A	0.42	M	FRA	Skin necrosis	HO
24	2014-10-18	12205815	N/A	FR-AFSSAPS-NY20131249	N/A	8	F	FRA	Injection site rash: Rash	HO
25	2015-09-30	14875393	N/A	FR-AFSSAPS-NY20151138	N/A	67	F	FRA	Drug ineffective	Not Serious
26	2016-08-10	17653576	N/A	FR-AFSSAPS-MP20160886	N/A	7	F	FRA	Asthmatic crisis	Not Serious
27	2018-05-20	23524247	N/A	FR-AFSSAPS-MP20181313	N/A	NR	F	FRA	Rash erythematous	Not Serious
28	2018-12-	25611926	N/A	GB-MHRA-	N/A	9	F	GBR	Erythema: Skin	Not Serious

	30			EYC 00192002					swelling: Flushing: Rash: Pruritus: Feeling abnormal	
29	2019-04-16	26270326	N/A	GB-MHRA-ADR 24392020	N/A	9	F	GBR	Erythema: Feeling abnormal: Eczema: Flushing: Pruritus	Not Serious
30	2/1/2020	30396066	N/A	FR-AFSSAPS-MA20200145	N/A	9	F	FRA	Hypersensitivity	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.

Abbreviations: DE=death, F = female, FRA = France, GBR = Great Britain, HO=hospitalization, M = male, Mnf. = manufacturer; N/A = not applicable, Non-E = non-expedited, NR = not reported, OT=other medically significant, USA = United States of America

9.6 APPENDIX F. HYPERSENSITIVITY (SMQ) NARROW PTS - MEDDRA VERSION 24.0

Acute respiratory failure
Administration site photosensitivity reaction
Airway remodeling
Allergy to chemicals
Allergy to fermented products
Alpha tumour necrosis factor increased
Alveolitis
Antibody test abnormal
Antibody test positive
Anti-insulin antibody increased
Anti-insulin antibody positive
Anti-insulin receptor antibody increased
Anti-insulin receptor antibody positive
Application site photosensitivity reaction
Asthma
Asthma late onset
Asthma-chronic obstructive pulmonary disease overlap syndrome
Asthmatic crisis
Auricular swelling
Blister
Blister rupture
Blood immunoglobulin A abnormal
Blood immunoglobulin A increased
Blood immunoglobulin D increased
Blood immunoglobulin G abnormal
Blood immunoglobulin G increased
Blood immunoglobulin M abnormal
Blood immunoglobulin M increased
Bronchial hyperreactivity
Bronchial oedema
Bullous impetigo
Caffeine allergy
Capillaritis
Charcot-Leyden crystals
Cheilitis
Childhood asthma
Choking
Choking sensation
Complement factor C1 decreased
Complement factor C2 decreased
Complement factor C3 decreased
Complement factor C4 decreased
Complement factor decreased
Conjunctivitis
Corneal exfoliation
Cough variant asthma
Cytokine release syndrome
Cytokine storm
Ear swelling
Eosinophil count abnormal
Eosinophil count increased
Eosinophil percentage abnormal
Eosinophil percentage increased
Eosinophilia
Eosinophilia myalgia syndrome
Eosinophilic bronchitis
Eosinophilic oesophagitis
Eosinophilic pneumonia
Eosinophilic pneumonia acute
Eosinophilic pneumonia chronic
Erythema
Flushing
Gastrointestinal oedema
Generalised oedema
Genital rash
Genital swelling
Haemolytic transfusion reaction
HLA marker study positive
Human anti-hamster antibody increased
Human anti-hamster antibody positive
Immune complex level increased
Immunoglobulins abnormal
Immunoglobulins increased
Immunology test abnormal
Implant site photosensitivity
Infusion site photosensitivity reaction
Injection site panniculitis
Injection site photosensitivity reaction
Interstitial lung disease
Laryngeal dyspnoea
Laryngeal obstruction
Leukotriene increased
Lip exfoliation
Localised oedema
Macrophage inflammatory protein-1 alpha increased
Mechanical urticaria
Medical device site photosensitivity reaction
Mesenteric panniculitis
Monocyte chemotactic protein-2 increased
Mouth ulceration
Mucocutaneous

ulceration
Mucosa vesicle
Mucosal erosion
Mucosal exfoliation
Mucosal necrosis
Mucosal ulceration
Nasal crease
Necrotising panniculitis
Neurodermatitis
Neutralising antibodies positive
Noninfective conjunctivitis
Non-neutralising antibodies positive
Occupational asthma
Occupational dermatitis
Oedema mucosal
Oral mucosal exfoliation

Orbital oedema
Panniculitis
Penile exfoliation
Penile oedema
Penile rash
Penile swelling
Perineal rash
Perivascular dermatitis
Photosensitivity reaction
Pneumonitis
Prurigo
Pruritus
Pulmonary eosinophilia
Reactive airways dysfunction syndrome
Respiratory arrest
Respiratory distress
Respiratory failure
Respiratory tract

oedema
Reversible airways obstruction
Rhinitis perennial
Scrotal exfoliation
Scrotal swelling
Seasonal allergy
Septal panniculitis
Skin erosion
Skin exfoliation
Skin oedema
Skin swelling
Sneezing
Status asthmaticus
Stomatitis
Streptokinase antibody increased
Stridor
Suffocation feeling
Sunscreen sensitivity
Throat tightness

Tongue exfoliation
Tracheal obstruction
Tracheostomy
Transplantation associated food allergy
Upper airway obstruction
Vaccination site photosensitivity reaction
Vaginal oedema
Visceral oedema
Vulval oedema
Vulvovaginal exfoliation
Vulvovaginal swelling
Wheezing

9.7 APPENDIX G. HYPERSENSITIVITY (SMQ) BROAD PTS - MEDDRA VERSION 24.0

Acquired C1 inhibitor deficiency
Acute generalised exanthematous pustulosis
Administration related reaction
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site rash
Administration site recall reaction
Administration site urticaria
Administration site vasculitis
Allergic bronchitis
Allergic colitis
Allergic cough
Allergic cystitis
Allergic eosinophilia
Allergic gastroenteritis
Allergic hepatitis
Allergic keratitis
Allergic oedema
Allergic otitis externa
Allergic otitis media
Allergic pharyngitis
Allergic reaction to excipient
Allergic respiratory disease
Allergic respiratory symptom

Allergic sinusitis
Allergic stomatitis
Allergic transfusion reaction
Allergy alert test positive
Allergy test positive
Allergy to immunoglobulin therapy
Allergy to surgical sutures
Allergy to vaccine
Anal eczema
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Antiallergic therapy
Antiendomysial antibody positive
Anti-neutrophil cytoplasmic antibody positive vasculitis
Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site rash
Application site recall reaction
Application site urticaria

Application site vasculitis
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopic cough
Atopy
Blepharitis allergic
Blood immunoglobulin E abnormal
Blood immunoglobulin E increased
Bromoderma
Bronchospasm
Bullous haemorrhagic dermatosis
Catheter site dermatitis
Catheter site eczema
Catheter site hypersensitivity
Catheter site rash
Catheter site urticaria
Catheter site vasculitis
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Circulatory collapse
Circumoral oedema
Circumoral swelling
Conjunctival oedema
Conjunctivitis allergic
Contact stomatitis

Contrast media allergy
Contrast media reaction
Corneal oedema
Cutaneous vasculitis
Dennie-Morgan fold
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Dermatitis infected
Dermatitis psoriasiform
Device allergy
Dialysis membrane reaction
Distributive shock
Documented hypersensitivity to administered product
Drug eruption
Drug hypersensitivity
Drug provocation test
Drug reaction with eosinophilia and systemic symptoms
Eczema
Eczema infantile

Eczema nummular
Eczema vaccinatum
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Eosinophilic granulomatosis with polyangiitis
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Epiglottic oedema
Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Giant papillary conjunctivitis
Gingival oedema
Gingival swelling
Gleich's syndrome
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Heparin-induced thrombocytopenia
Hereditary angioedema
Hereditary angioedema with C1 esterase inhibitor deficiency
Hypersensitivity
Hypersensitivity myocarditis
Hypersensitivity pneumonitis
Hypersensitivity vasculitis
Idiopathic urticaria
Immediate post-injection reaction
Immune thrombocytopenia
Immune tolerance induction
Implant site dermatitis
Implant site hypersensitivity
Implant site rash
Implant site urticaria
Incision site dermatitis
Incision site rash
Infusion related hypersensitivity reaction
Infusion related reaction
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site rash
Infusion site recall reaction
Infusion site urticaria
Infusion site vasculitis
Injection related reaction
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash
Injection site recall reaction
Injection site urticaria
Injection site vasculitis
Instillation site hypersensitivity
Instillation site rash
Instillation site urticaria
Interstitial granulomatous dermatitis
Intestinal angioedema
Iodine allergy
Kaposi's varicelliform eruption
Kounis syndrome
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Mast cell degranulation present
Medical device site dermatitis
Medical device site eczema
Medical device site hypersensitivity
Medical device site rash
Medical device site recall reaction
Medical device site urticaria
Mouth swelling
Mucocutaneous rash
Multiple allergies
Nephritis allergic
Nikolsky's sign
Nodular rash
Nutritional supplement allergy
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema mouth
Oral allergy syndrome
Oropharyngeal blistering
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Palisaded neutrophilic granulomatous dermatitis
Palpable purpura
Pathergy reaction
Perioral dermatitis
Periorbital oedema
Periorbital swelling
Pharyngeal oedema
Pharyngeal swelling
Procedural shock
Pruritus allergic
Radioallergosorbent

test positive
Rash
Rash erythematous
Rash follicular
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to azo-dyes
Reaction to colouring
Reaction to excipient
Reaction to food additive
Reaction to preservatives
Red man syndrome
Rhinitis allergic
Scleral oedema

Scleritis allergic
Scrotal dermatitis
Scrotal oedema
Serum sickness
Serum sickness-like reaction
Shock
Shock symptom
SJS-TEN overlap
Skin necrosis
Skin reaction
Skin test positive
Solar urticaria
Solvent sensitivity
Stevens-Johnson syndrome
Stoma site hypersensitivity
Stoma site rash
Swelling face
Swelling of eyelid
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Therapeutic product cross-reactivity

Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria contact
Urticaria papular
Urticaria physical
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial dermatitis
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site

eczema
Vaccination site exfoliation
Vaccination site hypersensitivity
Vaccination site rash
Vaccination site recall reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaginal ulceration
Vasculitic rash
Vernal keratoconjunctivitis
Vessel puncture site rash
Vessel puncture site vesicles
Vulval eczema
Vulval ulceration
Vulvovaginal rash
Vulvovaginal ulceration
Vulvovaginitis allergic

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