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APPLICATION NUMBER:

202158Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	202-158
Submission Dates	January 4, 2013 SDN 1 January 22, 2013 SDN 2 February 15, 2013 SDN 6 June 24, 2013 SDN 12 July 10, 2013 SDN 13
Type/Category	Original-1 (Type 5 - New Formulation or New Manufacturer)
Brand Name	Sodium Pertechnetate Tc99m Injection USP
Generic Name	Sodium Pertechnetate Tc99m Injection USP
Proposed Indication	<p>Sodium Pertechnetate Tc99m Injection produced by a TechneGen Generator System is a diagnostic radiopharmaceutical agent intended for use in children and adults for the following indications:</p> <p>Brain Imaging (including cerebral radionuclide angiography) Thyroid Imaging Salivary Gland Imaging Placenta Localization Blood Pool Imaging (including radionuclide angiography) Urinary Bladder Imaging (direct isotopic cystography) for detection of vesico-ureteral reflux.</p> <p>In addition, it is indicated for use in adults for Nasolacrimal Drainage System Imaging (dacryoscintigraphy).</p> <p>Sodium Pertechnetate Tc99m Injection is also used to reconstitute a variety of reagent kits, commonly referred to as Technetium Tc99m Kits, and with each reconstituted kit used for specified diagnostic imaging indications.</p>
Dose	(b) (4) (depending on indication)
Route of Administration	Intravenous Injection; oral; instillation in bladder or eyes
Applicant	Northstar Medical Radioisotopes, LLC

Reviewing Division	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division	Division of Medical Imaging Products (DMIP)
Primary Reviewer	Christy S. John, Ph.D.
Secondary Reviewer	Gene Williams, Ph.D.

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1. Executive Summary

The applicant has submitted an Original 505(b)(2) NDA for the TechneGen Generator System. The TechneGen Generator System is a computer monitored and controlled automated synthesis module used to prepare Sodium Pertechnetate Tc99m Injection using low specific activity potassium molybdate Mo99 solution as starting material.

Sodium pertechnetate Tc-99m is used for several indications including brain imaging (including cerebral radionuclide angiography), thyroid imaging, salivary gland imaging, placenta localization, and blood pool imaging (including radionuclide angiography). Sodium pertechnetate Tc-99m is also used for the formulations of kits to prepare drugs for imaging a variety of conditions including renal function, myocardial perfusion, and brain.

Two Tc-99m generators have been approved by FDA. They are Ultra-Technekow DTE (NDA 017-243) and Technelite (NDA 017-771). These approvals occurred decades ago and Sodium Pertechnetate Tc-99m has been in continual routine use for decades.

There were no clinical pharmacology or clinical studies conducted for this NDA. The proposed package insert uses the same language (verbatim) as the package inserts for Ultra-Technekow and Technelite. The application will not be approved due to microbiology and chemistry issues. As a result the package insert was not reviewed.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5 has reviewed NDA 202-158. The application is acceptable from a clinical pharmacology standpoint.

1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

There are no clinical pharmacology and biopharmaceutics findings as there are no clinical pharmacology studies associated with this submission.

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

There are no clinical pharmacology studies associated with this submission.

2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Sodium Pertechnetate Tc99m Injection contains a variable range of radioactive concentrations ranging from less than 1 mCi/mL up to greater than 1000 mCi/mL. A representative qualitative and quantitative composition statement is provided in **FDA Table 1**. Review by the Office of New Drug Quality Assurance will verify, but it appears that the quality and purity of the Sodium Pertechnetate Tc99m Injection meets all requirements specified in the current revision of the USP monograph for this item. The Sodium Pertechnetate Tc99m is dispensed into 20 mL vials.

FDA Table 1. Qualitative and Quantitative Composition of Sodium Pertechnetate Tc99m Injection* (Derived from TechneGen Generator System)

Component	Concentration (mCi/mL)	Amount per Vial (Elution)	Function
Na ^{99m} TcO ₄	(b) (4)	(b) (4)	Active pharmaceutical ingredient
NaCl	(b) (4)	(b) (4)	(b) (4)
Water for Injection	(b) (4)	(b) (4)	(b) (4)

2.2.2. What are the proposed mechanism of action and therapeutic indications?

The following (indented) is reproduced from the proposed package insert.

(b) (4)

2.2.3. What are the proposed dosages and routes of administration?

According to Dr. Kasliwal, the Drug Product Quality Reviewer, there is no specification for the mass amount of Tc-99m. This reviewer used the radioactive dose in MBq and the decay rate of Tc-99m (half-life = 6.006 h), to calculate that the dose range of (b) (4) MBq corresponds to a mass dose range of (b) (4) ng.

The following text and tables (indented) are reproduced from the proposed package insert. The first value in the first table (8.5 MBq) is an error by the applicant: it should be 18.5 MBq.

(b) (4)

The suggested dose ranges employed for various diagnostic indications in the average ADULT PATIENT (70 kg) are as follows:

Indication	Recommended Dose
Vesico-ureteral imaging	8.5 to 37 MBq (0.5 to 1 mCi)
Brain imaging	370 to 740 MBq (10 to 20 mCi)
Thyroid gland imaging	37 to 370 MBq (1 to 10 mCi)
Salivary gland imaging	37 to 185 MBq (1 to 5 mCi)
Placenta localization	37 to 111 MBq (1 to 3 mCi)
Blood pool imaging	370 to 1110 MBq (10 to 30 mCi)
Nasolacrimal drainage system	Maximum dose of 3.7 MBq (100 μ Ci)

The recommended dosages in PEDIATRIC PATIENTS are:

Indication	Recommended Dose
Vesico-ureteral imaging:	18.5 to 37 MBq (0.5 to 1 mCi)
Brain imaging:	5.18 to 10.36 MBq (140 to 280 μ Ci) per kg body weight
Thyroid gland imaging:	2.22 to 2.96 MBq (60 to 80 μ Ci) per kg body weight
Blood pool imaging:	5.18 to 10.36 MBq (140 to 280 μ Ci) per kg body weight

2.2.4 What is the radiation absorbed dose associated with the proposed dose of Sodium Pertechnetate Tc99m Injection?

The following (indented text and tables) are excerpted from the proposed package insert.

The estimated absorbed radiation doses¹ to an average **ADULT** patient (70 kg) from an intravenous injection of a maximum dose of 1110 megabecquerels (30 millicuries) of Sodium Pertechnetate Tc99m distributed uniformly in the total body of subjects not pretreated with blocking agents, such as pharmaceutical grade potassium perchlorate, are shown in Table 3. For placental localization studies, when a maximum dose of 111 megabecquerels (3 millicuries) is used, it is assumed to be uniformly equilibrated between maternal and fetal tissues.

¹Modified from: Summary of Current Radiation Dose Estimates to Normal Humans from Tc99m as Sodium Pertechnetate. MIRDO Dose Estimate Report No. 8. J. Nucl. Med., 17 (1):74-7, 1976.

Absorbed Radiation Doses from Intravenous Injection (ADULTS)

Tissue	1110 MBq (30 mCi) Dose				111 MBq (3 mCi) Dose	
	Resting Population		Active Population		mGy	rads
	mGy	rads	mGy	rads		
Bladder Wall	15.9	1.59	25.5	2.55		
Gastrointestinal Tract:						
Stomach wall	75.0	7.50	15.3	1.53		
Upper large intestine wall	20.4	2.04	36.0	3.60		
Lower large intestine wall	18.3	1.83	33.0	3.30		
Red Marrow	5.7	0.57	5.1	0.51		
Testes	2.7	0.27	2.7	0.27		
Ovaries	6.6	0.66	9.0	0.90		
Thyroid	39.0	3.90	39.0	3.90		
Brain	4.2	0.42	3.6	0.36		
Total Body	4.2	0.42	3.3	0.33		
Placenta					0.5	0.05
Fetus					0.5	0.05

In **PEDIATRIC** patients, the maximum radiation doses when a dose of 185 megabecquerels (5 millicuries) Sodium Pertechnetate Tc99m is administered to a neonate (3.5 kg) for brain or blood pool imaging with radionuclide angiography are shown in Table 6.

In pediatric patients, an average 30 minute exposure to 37 megabecquerels (1 millicurie) of Sodium Pertechnetate Tc99m following instillation for direct cystography, results in an estimated absorbed radiation dose of approximately 300 micrograys (30 millirads) to the bladder wall and 40 to 50 micrograys (4 to 5 millirads) to the gonads².

Absorbed Radiation Doses from Intravenous Injection (PEDIATRIC)

Tissue	37 MBq (1 mCi) Dose		185 MBq (5 mCi) Dose	
	mGys	rads	mGys	rads
Thyroid (without perchlorate)	46.0	4.60	230.0	23.0
Thyroid (with perchlorate)	9.7	0.97	48.5	4.85
Large Bowel (with perchlorate)	19.0	1.90	95.5	9.55
Testes	1.0	0.10	5.1	0.51
Ovaries	2.2	0.22	11.0	1.10
Total Body	1.5	0.15	7.6	0.76

²Conway, J.J., et al., Direct and indirect radionuclide cystography. J. Urol. 113:689-693, May 1975.

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

Two other Tc-99m generators have been approved by FDA. They are Ultra-Technekow DTE (NDA 017-243) and Technelite (NDA 017-771). The indications proposed in the current NDA are the same as those for the two approved generators.

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

There were no clinical pharmacology studies conducted to support dosing or claims.. The dosing is the same as that for the two approved Sodium pertechnetate Tc-99m generators (see **2.2.4**).

2.4. Exposure-Response

2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?

2.4.2. What are the characteristics of the exposure-response relationships for safety?

There are no clinical pharmacology studies associated with this submission. The dosing is the same as that for the two approved Sodium pertechnetate Tc-99m generators (see **2.2.4**). The following (indented) is reproduced from Section 12.2 of the proposed package insert.

Pertechnetate concentrates in the thyroid gland, salivary glands, stomach and choroid plexus. After intravenous administration it remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

Following the administration of Sodium Pertechnetate Tc99m as an eye drop, the drug mixes with tears within the conjunctival space. Within seconds to minutes it leaves the conjunctival space and escapes into the inferior meatus of the nose through the nasolacrimal drainage system. During this process the pertechnetate ion passes through the canaliculi, the lacrimal sac and the nasolacrimal duct. In the event of any anatomical or functional blockage of the drainage system there will be a backflow resulting in tearing (epiphora). Thus the pertechnetate escapes the conjunctival space in the tears.

While the major part of the pertechnetate escapes within a few minutes of normal drainage and tearing, it has been documented that there is some degree of transconjunctival absorption with turnover of 1.5% per minute in normal individuals, 2.1% per minute in patients without any sac and 2.7% per minute in patients with inflamed conjunctiva due to chronic dacryocystitis. Individual values may vary but these rates are probably representative and indicate that the maximum possible pertechnetate absorbed will remain below one thousandth of that used in other routine diagnostic procedures.

2.4.3. Does this drug prolong QT/QTc Interval?

There are no clinical pharmacology studies associated with this submission. Sodium pertechnetate Tc-99m has been used for several decades around the world. QT/QTc prolongation is not expected for a micro-dose (maximum mass dose of (b) (4) ng) administered only once.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

There are no clinical pharmacology studies associated with this submission. The package insert doses of Sodium pertechnetate Tc-99m has been in routine clinical use for several decades.

2.5. Pharmacokinetics

2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

2.5.4. What are the characteristics of drug absorption?

2.5.5. What are the characteristics of drug distribution?

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

2.5.8. What are the characteristics of drug metabolism?

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?

2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

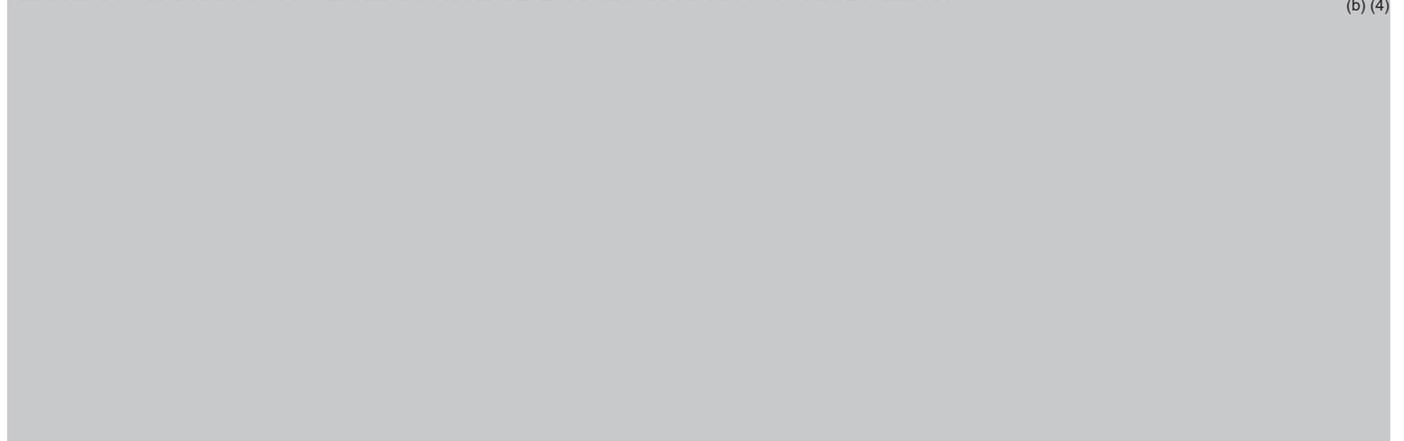
2.5.11. What are the characteristics of drug excretion in urine?

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

2.5.13. How do the PK parameters change with time following chronic dosing?

2.5.14. Is there evidence for a circadian rhythm of the PK?

There are no clinical pharmacology studies associated with this submission. The following (indented) is reproduced from Section 12.2 of the proposed package insert



2.6. Intrinsic Factors

2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

2.6.2.1. Severity of Disease State

2.6.2.2. Body Weight

See section **2.6.2.4.**

2.7. Extrinsic Factors

- 2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**
- 2.7.2. Is the drug a substrate of CYP enzymes?**
- 2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?**
- 2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**
- 2.7.5. Are there other metabolic/transporter pathways that may be important?**
- 2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**
- 2.7.7. What are the drug-drug interactions?**
- 2.7.8. Does the label specify co-administration of another drug?**
- 2.7.9. What other co-medications are likely to be administered to the target population?**

2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

(b) (4)

2.8 General Biopharmaceutics

2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

2.9. Analytical Section

2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

2.9.2. Which metabolites have been selected for analysis and why?

2.9.3. For all moieties measured, is free, bound, or total measured?

2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?

2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting *techniques* were used?

2.9.5.1. What are the lower and upper limits of quantitation?

2.9.5.2. What are the accuracy, precision, and selectivity at these limits?

2.9.5.3. What is the sample stability under conditions used in the study?

2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

There are no clinical pharmacology studies associated with this submission -- no bioanalytical methods are reported.

3. Detailed Labeling Recommendations

The labeling of Sodium Pertechnetate Tc99m Injection is not been reviewed as the application will not be approved due to microbiology and product quality issues.

4. Appendices

4.1. Applicant's Proposed Package Insert (final submitted version – applicant's changes from the original were not the result of negotiation with the FDA)

4.2. Cover sheet and OCPB Filing/Review Form

4.1. Applicant's Proposed Package Insert (final submitted version – applicant's changes from the original were not the result of negotiation with the FDA)

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTY S JOHN
02/07/2013

GENE M WILLIAMS
02/07/2013

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	202-158	Brand Name	TechneGen™ Sodium Pertechnetate Tc99m Injection
OCP Division (I, II, III, IV, V)	V	Generic Name	Sodium Pertechnetate Tc- 99m Injection
Medical Division	Division of Medical Imaging Products	Drug Class	Imaging
OCP Reviewer	Christy S. John, Ph.D.	Indication(s)	<p>Sodium Pertechnetate is used for following:</p> <ul style="list-style-type: none"> - Brain Imaging (including cerebral radionuclide angiography) - Thyroid Imaging - Salivary Gland Imaging - Placenta Localization - Blood Pool Imaging (including radionuclide angiography) - Urinary Bladder Imaging (direct isotopic cystography) for detection of vesico-ureteral reflux <p>In addition, it is indicated for use in adults for Nasolacrimal Drainage System Imaging (dacryoscintigraphy). Sodium Pertechnetate Tc99m Injection is also used to reconstitute a variety of reagent kits, commonly referred to as Technetium Tc99m Kits, and with each reconstituted kit used for specified diagnostic imaging indications.</p>
OCP Team Leader	Gene Williams, Ph.D.	Dosage Form	Clear Solution
		Dosing Regimen	

Date of Submission	January 4, 2013	Route of Administration	Intravenous Injection
Estimated Due Date of OCP Review	June 10, 2013	Sponsor	Northstar Medical Radioisotope, LLC
PDUFA Due Date	July 3, 2013	Priority Classification	P
Division Due Date	June 10, 2013		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		None		

Fileability and QBR comments		
	“X” if yes	Comments
Application fileable ?	X	
Comments sent to firm ?	None	This is a 505(b)(2) application for Sodium Pertechnetate Tc99m Injection prepared using a new TechneGen Generator System Utilizing non-fission produced Mo99
QBR questions (key issues to be considered)	There are no key issues to be considered; there is no clinical pharmacology section in this NDA.	
Other comments or information not included above	The proposed package insert was derived from the PIs of approved Tc-99m generators. The package insert requires review, as the PIs from which it was derived were approved many years ago.	
Primary reviewer signature	Christy S. John, Ph.D.	
Secondary reviewer Signature and date	Gene Williams, Ph.D.	

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/s/

CHRISTY S JOHN
09/26/2013

GENE M WILLIAMS
09/26/2013