CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214657Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date: May 2, 2022
From: Emily F. Wearne, PhD
Pharmacologist
Division of Hematology Oncology Toxicology for Division of Oncology 2
Through: Claudia P. Miller, PhD
Acting Pharmacology/Toxicology Supervisor/Team Leader
Division of Hematology Oncology Toxicology for Division of Oncology 2
To: File for NDA 214657
Pemetrexed Injection
Re: Supporting Document (SD) 27, Resubmission/Class 2

On July 7, 2020, Sandoz submitted a New Drug Application (NDA) for Pemetrexed Injection under the 505(b)(2) pathway, identifying the listed drug as ALIMTA under NDA 021462 held by Eli Lily (approved on February 4, 2004). Pemetrexed is a folate analog metabolic inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. Sandoz's Pemetrexed Injection (25 mg/mL) is a ready-to-dilute formulation of pemetrexed with different excipients than the listed drug, ALIMTA. Sandoz submitted limited pharmacokinetic and toxicology studies comparing its Pemetrexed Injection formulation to ALIMTA to support the safety of the proposed formulation and qualify any novel impurities present in the Sandoz pemetrexed formulation. The nonclinical review of this NDA was completed by Dr. M. Anwar Goheer and was uploaded to DARRTS on March 15, 2021. The Office of Pharmaceutical Manufacturing Assessment (OPMA) subsequently consulted the Pharmacology/Toxicology team regarding the potential risk of the level of an extractable (b) (4) produced in the extractable studies (refer to Dr. Emily Wearne's review uploaded to DARRTS on March 31, 2021). There were no outstanding issues from a nonclinical perspective that prevented approval of Sandoz's Pemetrexed Injection. NDA 214657 received tentative approval on May 6, 2021, with final approval subject to expiration of a period of patent protection and/or exclusivity.

On November 26, 2021, Sandoz submitted a Request for Final Approval and Gratuitous Amendment for final approval of NDA 214657 upon the expiry of the pediatric exclusivity (May 24, 2022) associated with U.S. Pat. No. 7,772,209 which is the sole patent listed in the Orange Book for the RLD. This submission also includes a proposal to widen the release and shelf life specification limits for (b) (4) (b) (4) total impurities) in all three presentations (100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL) of the Drug Product (DP) specifications. The current and proposed impurity specifications are shown in Table 1.

Table 1: Current and Proposed DP Impurity Specifications

	Present (release and shelf life specification limits) 100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL	Proposed (release and shelf life specification limits) 100 mg/4 mL, 500 mg/20 mL, 1000 mg/40 mL
		(b) (4)

(Table excerpted from Applicant's submission)

The Applicant did not submit any new nonclinical studies with the current submission. Although nonclinical toxicology Study #31777 entitled "28-Day Repeated Dose Toxicity Study of Pemetrexed and Related Impurities by Intravenous Bolus Injection to CD®-1 Mice" was included in this submission, this GLP-compliant study was previously reviewed by Dr. M. Anwar Goheer under the original NDA submission (see nonclinical review uploaded to DARRTS on March 15, 2021). The Applicant used this toxicology study and a statistical evaluation of long term stability data to justify widening the specification limits for Pemetrexed Injection. In toxicology Study #31777, once weekly intravenous (IV) bolus injection of pemetrexed disodium with or without related impurities at (b) (4)% (based on clinical pemetrexed dose) for 5 doses did not cause any treatment-related mortality or changes in clinical signs, clinical chemistry, or hematology in CD1 mice at pemetrexed doses approximately equal to the 500 mg/m^2 clinical dose of the listed drug. The major target organs were the male reproductive organs. Overall, there were no clear toxicological differences between the pemetrexed active control and pemetrexed enriched with related impurities, suggesting the presence of these impurities did not change the toxicity profile of pemetrexed. The Applicant's new proposed specifications for (b) (4) (b) (4) at levels above the ICH Q3B thresholds are justified by the available nonclinical toxicology data. See Table 2 for justification of the proposed specifications.

Table 2: Impurity Specification Justification (FDA Table)

Impurity	New Proposed specification	Daily delivered dose of impurity at pemetrexed clinical dose of 500 mg/m^{2*}	Delivered dose of impurity to mice[a] at highest non-lethal dose of pemetrexed	Specification justified by nonclinical data?
[redacted] (b) (4)				Yes
				Yes
				Yes

NMT = No more than; * = Recommended clinical dose of Pemetrexed Injection is 500 mg/m^2 IV on the first day of each 21-day cycle;
[a] = 28-day mouse qualification Study #31777

The nonclinical team reviewed the submitted Pemetrexed Injection label and made minor edits in Sections 2.7, 5.7, 8.3, 12.1, 13.1, 15, 16, and 17 to reflect current labeling practices, including revising [redacted] (b) (4) to "hazardous" in Sections 2.7 and 16 to be consistent with OSHA, and updating the OHSA Hazardous Drugs website in Section 15. In addition, the exposure ratio in Section 13.1 was revised from [redacted] (b) (4) to 0.0006 times to reflect the correct exposure calculation [0.1 mg/kg in mice (0.3 mg/m^2) is approximately 0.0006 times the recommended human dose of 500 mg/m^2 based on BSA]. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent final approval of this 505(b)(2) application for the proposed indications.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY F WEARNE
05/02/2022 04:49:04 PM

CLAUDIA P MILLER
05/02/2022 04:59:46 PM

MEMORANDUM

Date: March 31, 2021
From: Emily F. Wearne, PhD
Pharmacologist
Division of Hematology Oncology Toxicology (DHOT) for Division of Oncology 2
Through: John K. Leighton, PhD
DHOT Division Director
To: File for NDA 214657
Pemetrexed Injection
Re: Supporting Document (SD) 3, New/NDA

On July 7, 2020, Sandoz submitted NDA 214657 for Pemetrexed Injection under the 505(b)(2) pathway. The nonclinical review of this NDA was completed by Dr. M. Anwar Goheer and was uploaded to DARRTS on March 15, 2021. At that time, the CMC team did not identify any leachables or extractables at levels that required a nonclinical assessment of safety.

OPMA consulted with Pharmacology/Toxicology on March 29, 2021 regarding the potential risk of (b) (4) mg / device (b) (4) produced in the extractable studies, which is calculated to be (b) (4) µg/mL (b) (4) in the drug product and slightly above AET at (b) (4) µg/mL. The Applicant identified the (b) (4) to be (b) (4) Assuming a maximum pemetrexed dose of 1000 mg IV once every 3 weeks (drug concentration = 25 mg/mL), patients could receive up to (b) (4) µg of (b) (4) once every 3 weeks. (b) (4) . The oral LD50 (IV not determined) of (b) (4) in rats is (b) (4) mg/kg (b) (4) mg/m^2 or (b) (4) mg in humans assuming a 60 kg body weight), and the oral LD50 (IV not determined) of (b) (4) in rats is (b) (4) mg/kg (b) (4) mg/m^2 or ~ (b) (4) mg in humans assuming a 60 kg body weight). The oral high LD50 values indicate very low acute toxicity by this route. Both of these LD50s are much higher than (b) (4) µg. Given the indication for pemetrexed is for the treatment of patients with advanced cancer, the fact that pemetrexed is cytotoxic and genotoxic, and the recommended dosing schedule of once every 3 weeks, the level of (b) (4) does not represent a significant safety risk from a pharmacology/toxicology perspective.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY F WEARNE
03/31/2021 02:32:24 PM

JOHN K LEIGHTON
03/31/2021 02:34:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	214657
Supporting document/s:	003
Applicant's letter date:	July 07, 2020
CDER stamp date:	July 07, 2020
Product:	Pemetrexed Injection, 100 mg/4 mL, 500 mg/20 mL, and 1000 mg/40 mL
Indication:	Metastatic, non-squamous, non-small cell lung cancer
Applicant:	Sandoz Canada Inc. 100 College Road West Princeton, New Jersey 08540 USA
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology 2)
Reviewer:	M. Anwar Goheer, Ph.D.
Supervisor/Team Leader:	Whitney S. Helms, Ph.D.
Division Director:	John Leighton, Ph.D., D.A.B.T. (Harpreet Singh, MD)
Project Manager:	Kwadwo (Kwajo) Korsah, Pharm.D., M.S.

TABLE OF CONTENTS

Table of Tables

Table of Figures

No table of figures entries found.

1 Executive Summary

1.1 Introduction:

Sandoz has submitted NDA 214657 for Pemetrexed Injection under the 505(b)(2) pathway and is relying primarily on FDA's prior findings of safety and effectiveness for the listed drug Alimta to support the pharmacology and toxicology requirements for a new drug application. Pemetrexed Injection (25 mg/mL) is a ready-to-dilute formulation of pemetrexed with different excipients than the listed drug, Alimta. Sandoz has submitted limited pharmacokinetic and toxicology studies comparing its Pemetrexed Injection formulation to Alimta in order to help support the safety of the formulation and to qualify any novel impurities present in the Sandoz pemetrexed formulation.

1.2 Brief Discussion of Nonclinical Findings

Pemetrexed is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. The Applicant conducted a toxicology study using their proposed formulation of pemetrexed in the presence or absence of impurities potentially present in this presentation at levels above the ICHQ3B limits, though the final formulation of Pemetrexed Injection does not include any impurities that require qualification. Weekly intravenous administration of pemetrexed disodium with or without related impurities at (b) (4)% for 4 weeks followed by a 2-week recovery period did not cause any mortality, or changes in clinical signs, clinical chemistry or hematology in CD1 mice at pemetrexed doses approximately equal to the 500 mg/m^2 clinical dose of the listed drug. The major findings, regardless of impurities, were changes in the male reproductive organs including macroscopic findings of small testes and histological findings of tubular degeneration of the testes and oligospermia in the epididymides that were not reversible by the end of the recovery period. There were no macroscopic or histological changes in female animals in this study. Overall, there were no clear toxicological differences between the pemetrexed active control and pemetrexed enriched with related impurities; pemetrexed-related findings were consistent with the described nonclinical findings for the listed drug.

The Applicant's proposed formulation of pemetrexed includes excipients not included in the listed drug and present at levels higher than levels described for other products included in the inactive ingredient database, specifically high levels of sodium thiosulfate (STS) and propylene glycol. STS is approved clinically for the treatment of cyanide poisoning and there are decades of clinical experience for its use in this as well as other indications at doses higher than those delivered at the proposed dose of pemetrexed. The safety of propylene glycol at the levels included in the currently proposed pemetrexed formulation is supported by extensive toxicological reviews propylene glycol conducted by US and other international government agencies including NTP-CERHR and the Agency for Toxic Substances and Disease Registry (ATSDR). Based on these data there are no safety concerns for the levels of either STS or PG in the currently proposed formulation. The CMC team did not request further nonclinical assessment of any impurities, leachables, or extractables for the

proposed formulation and there are no outstanding issues from a nonclinical perspective that would prevent approval of Sandoz's Pemetrexed Injection.

1.3.1 Approvability

The product is approvable.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

The nonclinical recommendations to the Applicant's proposed labeling are primarily based on the listed drug, were discussed internally, and will be communicated to the Applicant.

2 Drug Information

2.1 Drug

Generic Name
Pemetrexed Injection
Code Name
None
Chemical Name
N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid
Molecular Formula/Molecular Weight
(b) (4)
Structure or Biochemical Description:

(Figure excerpted from Applicant's NDA)

Pharmacologic Class: Folate antimetabolite

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 021462 for pemetrexed disodium (Alimta®), the referenced listed drug.

2.3 Drug Formulation

Ingredient	Amount per mL (mg/mL)	Concentration (% w/w or % w/v)	Function
Pemetrexed (Pemetrexed disodium 2.5 hydrate)	25.0 mg (30.2 mg)	2.5%	Active Ingredient
Sodium thiosulfate	0.5 mg	0.05%	(b) (4)
Propylene glycol	50.0 mg	4.93%	(b) (4)
Water for Injection	q.s. for 1mL	q.s. for 1mL	
Sodium Hydroxide	as needed	as needed	pH adjuster
Hydrochloric Acid	as needed	as needed	pH adjuster

(Excerpted from Applicant's submission)

2.4 Comments on Novel Excipients

The CMC team requested input from the pharmacology/toxicology team on the acceptability of the levels of 2 excipients in the proposed formulation of pemetrexed: sodium thiosulfate and propylene glycol. Both excipients are present at levels higher than those currently listed in the inactive ingredients database.

Sodium thiosulfate (STS):

Thiosulfate is an endogenous molecule present in plasma at concentrations around 5.5 µmol/mL. Sodium thiosulfate (STS) as a drug has a long history of at least 100 years of human use, both at high intravenous (IV) doses as a drug and at low concentrations as a food additive. STS is an inorganic salt with reducing agent properties with an established role in decreasing oxidative stress in cells that is currently approved as an antidote used sequentially with sodium nitrite for acute cyanide poisoning at a dose of 12.5 g. STS has also been used to protect from cisplatin-induced ototoxicity at an IV dose of 12.8 g/m^2. Repeat-dose toxicity studies for STS are not available due to its use primarily as single dose or limited use dosing. In dogs, single intravenous doses of up to 30 g/m^2 showed no clear toxicity though doses ≥ 60 g/m^2 led to muscular twitching and profound electrolyte and hemodynamic changes, cardiovascular, and respiratory changes (including hypoxemia and metabolic acidosis) that proved fatal to 3 of 5 dogs within 24 hours of dosing. The cardiovascular and respiratory effects appeared to be secondary to a rapid rise in sodium. In addition, the 60 g/m^2 dose in dogs resulted in urinary bladder filling to overflowing within minutes of the injection, with marked diuresis in the 4/5 dogs that survived to the 3-hour time point after injection. The amount of STS in the currently proposed formulation of pemetrexed at the recommended pemetrexed dose of 500 mg/m^2 would be approximately 20 mg assuming a maximum pemetrexed dose of 1000 mg. Given the high doses used clinically and studied non-clinically, this amount does not represent a safety concern.

Propylene glycol:

To support the proposed level of propylene glycol in this pemetrexed formulation, the Applicant cites an assessment primarily based on the 2014 EMA report[1] on the safety of propylene glycol as an excipient. This report is based on an extensive literature review

[1] Background Review for the Excipient Propylene Glycol, European Medicines Agency (EMA) Report, 20 November 2014

of propylene glycol administration in multiple animal species as well as humans with heavy reliance on studies and reviews conducted by US agencies including NTP-CERHR[2] and the Agency for Toxic Substances and Disease Registry (ATSDR)[3]. Key points cited in the EMA report include that the oral bioavailability of propylene glycol is close to 100% in all tested species including humans, making oral toxicity studies relevant for the overall safety assessment of IV administration, and that the saturation of propylene glycol metabolism occurs at lower doses for humans than for rats/rabbits (0.2 g/kg vs 2 g/kg, respectively). Clinical toxicities associated with high doses of propylene glycol include confusion, hyperosmolality, lactic acidosis, acute intoxication, and acute kidney injury.

Table 1: PG Limits for Excipients in EMA Report

	neonates up to 28 days (or 44 weeks post menstrual age for pre-terms)	1month (29 days) up to 4 years	5 years up to 17 years and adults
Safety limits	1 mg/kg	50 mg/kg	500 mg/kg

(Excerpted from the 2014 EMA Report on the safety of propylene glycol as an excipient)

The maximum amount of propylene glycol assuming a maximum pemetrexed dose of 1000 mg would be 2 g (~ 20-40 mg/kg or 1.1 g/m^2) given once every three weeks. At this level, the amount of propylene glycol is below the saturation rate for metabolism in humans and well below the PDE safety limit of 500 mg/kg for people ≥ 5 years old identified in the EMA report and the PDE of 25 mg/kg as a food additive allowed by the WHO. While the PDE in humans from this report is based primarily on longer duration exposures, the proposed level in the current pemetrexed formulation is also below the 50 mg/kg level for younger children and consistent with PDEs calculated based on animal data, primarily using data from oral gavage studies. Therefore, based on the available safety data, the amount of propylene glycol in the proposed formulation is acceptable from a safety standpoint.

2.5 Comments on Impurities/Degradants/Leachables/Extractables of Concern

The CMC team did not identify any leachables or extractables at levels that required a nonclinical assessment of safety.

[2] National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) (2004). Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol. *NIH Publication No. 04-4482*.

[3] Agency for Toxic Substances and Disease Registry (1997). Toxicological profile for ethylene glycol and propylene glycol.

3 Studies Submitted

3.1 Studies Reviewed

28-Day Repeated Dose Toxicity Study of Pemetrexed and Related Impurities by Intravenous Bolus Injection to CD®-1 Mice. (b) (4) Study No. 31777.

3.2 Studies Not Reviewed

3.3 Previous Reviews Referenced

None

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title/ number:
28-Day Repeated Dose Toxicity Study of Pemetrexed and Related Impurities by Intravenous Bolus Injection to CD®-1 Mice. (b) (4) Study No. 31777.

Key Study Findings:

- Intravenous administration of pemetrexed active control and up to (b) (4)% pemetrexed related impurities once weekly for 4 weeks did not cause any mortality, body weight, hematology or clinical chemistry changes.
- The absolute and relative testis weights were reduced in test and reference animals in a dose related manner.
- Histopathological examination revealed tubular degeneration of the testes and oligospermia in the epididymides of animals treated with either pemetrexed with related impurities or pemetrexed.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Group 1-vehicle control Group 2 – 155.14 mg/kg pemetrexed active control Group 3 – (b) (4)% pemetrexed related impurity Group 4 – (b) (4)% pemetrexed related impurity
Route of administration:	Intravenous slow bolus injection into a tail vein
Frequency of Administration:	Main study - Once weekly, total 5 injections per animal Recovery animals - 2 treatment-free weeks

Formulation/Vehicle:	Isotonic saline for infusion (0.9% NaCl)
Administration volume:	24.7 mL/kg body weight (0.692 mL/28 g mouse)
Test item:	Pemetrexed LIVI impurity batch (pemetrexed with related impurities), batch # V2014141
Reference item:	Pemetrexed 1000 mg/40 mL (active control), batch # 31075319
Species/Strain:	Mouse / CD® -1 / Crl:CD1(Icr)
Number/Sex/Group:	Main study – 10/sex/group Recovery groups – 10/sex/group
Age:	Males – 33 days Females – 37 days
Body weight:	Males – 26.9 to 31.4 g Females – 21.7 to 26.3 g
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Table 2. Pemetrexed and Related Impurity Dose Levels

Compound	Pemetrexed active control (clinical Pemetrexed dose) [mg/kg b.w.]	(b) (4)% # Pemetrexed related impurities [mg/kg b.w.]	(b) (4)% # Pemetrexed related impurities [mg/kg b.w.]
Pemetrexed	155.14		
(b) (4)	n.a.		
	n.a.		
	n.a.		
	n.a.		
	n.a.		
	n.a.		
(b) (4)			(b) (4)
(b) (4)			

impurity as dose limiting reference. Pemetrexed impurity (b) (4) were observed in the test item and are expected not relevant for the impurity profile of the finished dosage form of Pemetrexed 25 mg/mL. These impurities are listed for information only.

(Excerpted from Sponsor's submission)

Table 3. Estimated Maximum Daily Dose of Pemetrexed

Species	Body weight [kg]	Estimated total dose [mg]	Dose in mg/kg b.w.	Conversion factor for different species (F1 ICHQ3C)
Human	70	905	12.9	1
Mouse	0.028	4.34	155.14	12

(Excerpted from Sponsor's submission)

Table 4. [redacted] Impurity Exposure

Species	Body weight [kg]	Estimated [redacted] exposure per dose Pemetrexed [µg]	[redacted] exposure per dose Pemetrexed [µg/kg b.w.]
Human	70	[redacted]	
Mouse	0.028		

(Excerpted from Sponsor's submission)

Table 5. [redacted] Impurity Exposure per Dose in Mice (28 g)

Species	Low dose# [redacted]% Pemetrexed related impurities [mg]	Intermediate dose: [redacted]% Pemetrexed related impurities (safety factor 10) [mg]	High dose: [redacted]% Pemetrexed related impurities (safety factor 100) [mg]
Mouse	[redacted]		

(Excerpted from Sponsor's submission)

Table 6. Observations and Results: changes from control

Parameters	Major findings
Mortality	No premature deaths
Clinical Signs	No test article changes
Body Weights	No changes in body weight or body weight gains
Ophthalmoscopy	No adverse ocular effects
Hematology	No effect on hematology parameters
Clinical Chemistry	No test or reference item-related changes
Urinalysis	No test or reference item-related findings
Gross Pathology	Group 2, pemetrexed active group – small testes in 6 of 10 animals Group 3, [redacted]% pemetrexed - small testes in 2 of 10 animals Group 4 [redacted]% pemetrexed – small testes in 5 of 10 animals

<table>
<tr><td>Organ Weights</td><td>Groups 2, 3, and 4 – Reduced testes weights

Changes in Organ Weights Compared to Control Group 1 at the End of Treatment Period (Test Day 30)
<table>
<tr><td colspan="2">Organ</td><td>Group 2
Pemetrexed active control</td><td>Group 3
(b) (4) Pemetrexed related impurities</td><td>Group 4
(b) (4) % Pemetrexed related impurities</td></tr>
<tr><td rowspan="2">Testis, left</td><td>Relative</td><td>-57**</td><td rowspan="4">(b) (4)</td></tr>
<tr><td>Absolute</td><td>-57**</td></tr>
<tr><td rowspan="2">Testis, right</td><td>Relative</td><td>-58**</td></tr>
<tr><td>Absolute</td><td>-58**</td></tr>
</table>
** - statistically significant at p≤0.01
Test item-related changes in form of reduced testes weights were still present at the end of 2-week recovery period.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>See Table 7 for details</td></tr>
<tr><td>Toxicokinetics other evaluations]</td><td>Not done</td></tr>
</table>

Table 7: Histopathology

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Number of animals	10	10	10	10	10	10	10	10
Epididymides, left, oligospermia, minimal	0	0	5	0	-	-	-	-
mild	0	8	1	5	-	-	-	-
moderate	0	0	0	2	-	-	-	-
Epididymides, right, infiltration, lymphocytic, focal, minimal	1	0	0	0	-	-	-	-
mild	1	0	0	0	-	-	-	-
Oligospermia, minimal	0	0	4	0	-	-	-	-
mild	0	8	1	4	-	-	-	-
moderate	0	0	0	2	-	-	-	-
Intestine, cecum, hyperplasia, lymphoid, mild	0	0	0	0	1	1	0	1
moderate	0	0	0	0	0	0	0	1
Larynx, infiltration, lymphocytic, focal, minimal	0	0	0	0	0	0	0	2
Lungs, inflammation, chronic, focal, minimal	0	0	0	1	0	0	0	0

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
Number of animals	10	10	10	10	10	10	10	10
Hemorrhage, focal, moderate	0	0	0	0	0	0	0	1
Testes, left, degeneration, minimal	0	0	3	0	-	-	-	-
mild	0	1	3	4	-	-	-	-
moderate	0	7	2	4	-	-	-	-
marked	0	1	1	2	-	-	-	-
Testes, right, degeneration, minimal	0	0	3	0	-	-	-	-
mild	0	2	3	4	-	-	-	-
moderate	0	6	2	4	-	-	-	-
marked	0	1	1	2	-	-	-	-
Thyroid gland, left, dilation, glandular, multifocal, mild	0	0	0	1	0	0	0	0
Urinary bladder, infiltration, lymphocytic, multifocal, minimal	0	0	0	0	0	0	0	1
Uterus, infiltration, neutrophilic, cervical, minimal	-	-	-	-	3	3	0	3
mild	-	-	-	-	0	3	0	2
moderate	-	-	-	-	0	1	0	1
Vagina, infiltration, neutrophilic, minimal	-	-	-	-	2	3	0	3
mild	-	-	-	-	0	2	0	2
moderate	-	-	-	-	0	2	0	2
Cyst, keratinized, focal, moderate	-	-	-	-	0	0	0	1

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

M A GOHEER
03/04/2021 04:42:00 PM

WHITNEY S HELMS
03/15/2021 01:06:53 PM