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APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: February 23, 2016

To: File for NDA 207155

From: Brenda J Gehrke, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

Through: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

Subject: NDA Resubmission
NDA: 207155
Drug: Evomela (melphalan hydrochloride) for Injection
Indication: High-dose conditioning treatment prior to hematopoietic progenitor cell transplantation in patients with multiple myeloma and palliative treatment of patients with multiple myeloma
Applicant: Spectrum Pharmaceuticals Inc.

The current submission, Supporting Document 20 for NDA 207155, is a Class 2 Resubmission. NDA 207155 was submitted in December 2014 as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug. The FDA issued a complete response letter to the Applicant in October 2015 based on deficiencies related to product quality. The primary pharmacology/toxicology review of the NDA was completed and filed on August 24, 2015. There were no pharmacology/toxicology concerns with the application and the recommended regulatory action from pharmacology/toxicology was approval. This resubmission contains no new pharmacology/toxicology information.

Recommendation:

Recommending approval. There are no pharmacology/toxicology issues for NDA 207155 to preclude approval of the drug for the proposed indications.

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/s/

BRENDA J GEHRKE
02/24/2016

CHRISTOPHER M SHETH
02/24/2016

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207155
Supporting document/s:	1
Applicant's letter date:	December 23, 2014
CDER stamp date:	December 23, 2014
Product:	Evomela™ (Captisol®-enabled melphalan HCl) for Injection
Indication:	High-dose conditioning treatment prior to hematopoietic progenitor cell transplantation in patients with multiple myeloma and palliative treatment of patients with multiple myeloma
Applicant:	Spectrum Pharmaceuticals Inc.
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Brenda J Gehrke, PhD
Acting Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Rachel S McMullen, MPH, MHA

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207155 are owned by Spectrum Pharmaceuticals Inc. or are data for which Spectrum Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 207155 that Spectrum Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207155.

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1 Executive Summary

1.1 Introduction

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin is a phenylalanine derivative of nitrogen mustard and an alkylating agent. The current melphalan product, Alkeran® (melphalan hydrochloride) for Injection, is approved for the palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. Evomela™ (Captisol®-enabled melphalan hydrochloride) for Injection is a new melphalan hydrochloride product that contains Captisol as an excipient instead of propylene glycol. NDA 207155 has been submitted as a 505(b)(2) application for Evomela with Alkeran (melphalan hydrochloride) for Injection as the listed drug. With the submission of NDA 207155, Spectrum Pharmaceuticals Inc. is pursuing two indications for Evomela, the current palliative treatment indication for Alkeran and a new indication of high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma. To support the proposed indications, the Applicant has submitted literature of the nonclinical studies conducted with melphalan, an in vitro hemolytic study of the vehicle, and a bridging pharmacokinetic study comparing Evomela to Alkeran in rats. Additionally, the Applicant is relying on the FDA's previous finding of safety and efficacy for Alkeran.

1.2 Brief Discussion of Nonclinical Findings

An in vitro hemolytic study of rodent and human red blood cells from fasted subjects was conducted to determine the hemolytic potential of the melphalan vehicle containing Captisol and the Alkeran vehicle in rodent and human blood. The vehicle containing Captisol produced no hemolysis and the Alkeran vehicle produced minor hemolysis in rat and human red blood cells.

A pharmacokinetic study containing data following intravenous administration of melphalan in the presence or absence of Captisol in the delivery vehicle to male Sprague Dawley rats was submitted as a bridging pharmacokinetic study comparing Evomela to Alkeran. Commercial Alkeran vials were used for both formulations. The Captisol-free formulation was prepared as per the product insert for the commercial Alkeran injectable formulation using the sterile diluent that is provided with the Alkeran product, while in the Captisol formulation, Alkeran was reconstituted with a Captisol solution resulting in a final formulation with (b) (4)% (w/v) Captisol. No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following a single intravenous administration of melphalan in the (b) (4)% (w/v) Captisol or Captisol-free formulations.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. The nonclinical studies submitted to this NDA and the previous findings of safety and efficacy for the listed drug Alkeran provide sufficient

information to support the use of Evomela (Captisol®-enabled melphalan hydrochloride) for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

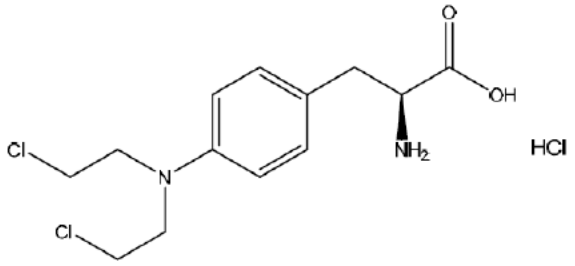
None

1.3.3 Labeling

The proposed labeling is consistent with the label for the intravenous Alkeran Injection product. No new pharmacology or toxicology information was added to the proposed label. Changes were made to the pregnancy related sections of the prescribing information in order for the label to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

2 Drug Information

2.1 Drug

CAS Registry Number	3223-07-2; 148-82-3 (melphalan free base)
Generic Name	Melphalan hydrochloride
Code Names	CDX-353
Chemical Name	(b) (4)
Molecular Formula/ Molecular Weight	$C_{13}H_{18}Cl_2N_2O_2 \cdot HCl$/ (b) (4) g/mol
Structure or Biochemical Description	
Pharmacologic class	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 104925, NDA 20207 (NDA for listed drug, Alkeran)

2.3 Drug Formulation

Captisol-enabled melphalan hydrochloride for Injection is a lyophilized powder containing (b) (4) mg of melphalan hydrochloride (HCl) equivalent to (b) (4) mg of melphalan free base. The composition is provided in the table below. The product is supplied in a 20 mL Type 1 clear glass vial closed with a (b) (4) rubber stopper and capped with an aluminum 'flip-off' seal. The product is reconstituted in 8.6 mL of 0.9% sodium chloride injection, USP. Prior to administration, (b) (4) reconstituted melphalan (5 mg/mL) is admixed with (b) (4) 0.9% sodium chloride injection, USP.

Table 1: Composition of the Captisol-enabled melphalan HCl for Injection, 50 mg (free base)/vial

(excerpted from Applicant's submission)

Ingredients	Composition		Function	Reference to Standard
	Quantity per vial	Percent (%)		
Melphalan HCl	(b) (4) mg, equivalent to (b) (4) mg Melphalan free base	(b) (4)	Active Pharmaceutical Ingredient	In-house
Captisol[a] (Betadex Sulfobutyl Ether Sodium)			(b) (4)	NF
			(b) (4)	USP
				NF[b]
				NF[c]
				NF

2.4 Comments on Novel Excipients

At the proposed dose of 100 mg/m^2/day melphalan for the high-dose conditioning treatment, the daily exposure to Captisol is approximately (b) (4) for a 70 kg human. The daily exposure to Captisol for the proposed melphalan product is similar to the daily exposures with other approved products (Nexterone, 100 and 150 mg/kg; Noxafil, (b) (4) mg/kg; VFend I.V., (b) (4) mg/kg), therefore, there are no safety concerns with the amount of Captisol in the Captisol-enabled melphalan product.

2.5 Comments on Impurities/Degradants of Concern

There are 3 impurities in the drug product that are above the ICH Q3B qualification threshold: (b) (4) . According to the Alkeran label, melphalan is eliminated from plasma primarily by (b) (4) therefore, both of these impurities are metabolites observed in humans. Degradation products that are also significant metabolites present in animal or human studies are qualified based on ICH Q3B. The levels of the (b) (4) present in Captisol-enabled melphalan HCl are lower than those observed in the listed drug Alkeran (see levels in the tables below), and therefore, qualified. The first table below contains the proposed limits for the impurities and the levels observed from testing for single vials of Captisol-enabled melphalan HCl and the listed drug Alkeran. The second table below contains a side-by-side stability comparison of Captisol-enabled melphalan HCl and the listed drug Alkeran by comparing impurities in admixtures prepared from products at the end of their use-period.

Table 2: Impurity levels for Captisol-enabled melphalan HCl and Alkeran
(excerpted from Applicant's submission)

Description / Test		Proposed Limits	CE-Melphalan HCl	Alkeran (FDA RLD)	Melphalan HCl for Injection (Generic Drug)		
Manufacturer		---	Spectrum	(b) (4)	Mylan		
Lot #		---	*	S311	N1300513	N1300665	N1400128
Product Expiry Date		---	*	Dec 2015	Apr 2015	May 2015	Dec 2015
Date Tested		---	*	Sep 2014	Sep 2014	Sep 2014	Sep 2014
Remaining Shelf Life		---	0-36 mo	(b) (4)			(b) (4)
Test	Assay	90.0% – 110.0%	(b) (4)				
	(b) (4)	NMT (b) (4)%					
		NMT %					
		NMT %					
	Largest Ind. Unid.	NMT %					
	Total Impurities	NMT %					

* Spectrum product results are maximum values (or ranges in the case of Assay) reported from all long-term stability results.

ND = Not Detected

Table 3: Assay and impurities in "in use" normal saline admixtures: Alkeran versus for Captisol-enabled melphalan HCl
(excerpted from Applicant's submission)

Product		Alkeran	CE-Melphalan HCl
Lot		S311	A97139
Recon Hold Time			(b) (4)
Admix Hold			
Admix Replicate			
Assay	mg/mL		
	%[a]		
(b) (4)			
RRT (b) (4) %			
RRT %			
Total Chromatographic Impurities, %			
			(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

There are two proposed indications for Evomela (Captisol-enabled melphalan hydrochloride):

- The palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate. The recommended dose for palliative treatment is 16 mg/m^2 administered as a single infusion over 15-20 minutes at 2-week intervals for 4 doses, then, after adequate recovery from toxicity, at 4-week intervals.

- Use as a high dose conditioning treatment prior to hematopoietic progenitor cell transplantation in patients with multiple myeloma. The proposed recommended dose for conditioning treatment is 100 mg/m^2/day administered over 30 minutes by intravenous infusion for 2 consecutive days (Day -3 and Day -2) prior to autologous stem cell transplantation on Day 0.

2.7 Regulatory Background

Melphalan hydrochloride is currently available as Alkeran for Injection. Ligand Pharmaceuticals Incorporated developed a new melphalan hydrochloride drug product containing Captisol as an excipient, currently named Evomela. In March 2013, Spectrum Pharmaceuticals Inc. acquired the rights from Ligand for the global development and commercialization of Evomela. Melphalan hydrochloride was granted Orphan Drug designation (08-2700) on November 24, 2008 for high-dose conditioning treatment prior to hematopoietic progenitor cell transplantation. A pre-IND meeting for IND 104925 was held with the FDA on May 27, 2009 with (b) (4) as the sponsor, and the IND has been active since July 23, 2009. The FDA provided preliminary meeting comments regarding the adequacy of the bridging pharmacokinetic and/or toxicology studies to support a 505 (b)(2) NDA for Evomela on January 3, 2014. Additional meetings held with the FDA included a CMC only pre-NDA meeting (Type C) on April 16, 2014 and a pre-NDA meeting on June 23, 2014. NDA 207155 was submitted on December 23, 2014.

3 Studies Submitted

3.1 Studies Reviewed

Study#	Title	Module
09N-Z02-RP	In vitro hemolytic potential evaluation of CDX-353 vehicle	4.2.1.3.
(b) (4)-08-001	Effect of Captisol® on the pharmacokinetics of miconazole, chlorpromazine and melphalan following IV administration to male Sprague Dawley rats	4.2.2.2.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 104925 Nonclinical Review by Haw-Jyh Chiu, Ph.D., DARRTS date: July 23, 2009

4 Pharmacology

4.3 Safety Pharmacology

Study title: In vitro hemolytic potential evaluation of CDX-353 vehicle

Study no.:	09N-Z02-RP
Study report location:	eCTD 4.2.1.3.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Study conducted May 21, 2009
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	CDX-353 vehicle (Captisol) and Alkeran vehicle, lot # not provided

Key Study Findings

- CDX-353 vehicle (Captisol) produced no hemolysis and Alkeran vehicle produced minor hemolysis in rat and human red blood cells in vitro.

To determine the hemolytic potential of the CDX-353 vehicle containing Captisol and the Alkeran vehicle in rodent and human blood, an in vitro study was conducted to spectrometrically evaluate rodent and human red blood cells from fasted subjects. Approximately 12 mL of heparinized blood was collected from 2-3 overnight fasted rats (Sprague Dawley or Han Wistar) after euthanasia and approximately 12 mL of heparinized human blood was collected from a fasted ($\geq$8 hours) donor. The contents of the vehicles and the controls are listed in the table below. The following dilutions of the vehicles with saline were tested: 0, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, and 1:128.

Table 4: Contents of vehicles and controls

Identification	Contents	Material Type
Normal saline	0.9% sodium chloride	Negative control and blank
Triton X-100	1% Triton X-100 in phosphate buffered saline	Positive control
CDX-353 vehicle	(b) (4) g Captisol Q.S. (b) (4) mL with normal saline	Test article
Alkeran vehicle	(b) (4) mg Povidone (b) (4) (b) (4) mg sodium citrate (b) (4)) propylene glycol (b) (4)) ethanol (b) (4) water Q.S. (b) (4) mL with normal saline	Reference article

Results

- No hemolysis was found at any dilution for the CDX-353 vehicle.
- Minor hemolysis was found at 100% (0) and the 1:2 dilution for the Alkeran vehicle in rat blood and at 100% in human blood.

Table 5: Results of in vitro hemolysis study of CDX-353 and Alkeran vehicles in rat and human red blood cells

(excerpted from Applicant's submission)

CDX-353 Vehicle Rat Red Blood Cell			CDX-353 Vehicle Human Red Blood Cell		
	Abs.	%Hemolysis		Abs.	%Hemolysis
Neg Control	0.12192		Neg Control	0.01691	
Pos Control	2.96010		Pos Control	2.89670	
0	0.10951	0	0	0.02141	0
1:2	0.11421	0	1:2	0.02147	0
1:4	0.10959	0	1:4	0.02194	0
1:8	0.11673	0	1:8	0.01895	0
1:16	0.11577	0	1:16	0.01730	0
1:32	0.11760	0	1:32	0.01648	0
1:64	0.11908	0	1:64	0.01726	0
1:128	0.11841	0	1:128	0.02519	0

Alkeran Vehicle Rat Red Blood Cell			Alkeran Vehicle Human Red Blood Cell		
	Abs.	%Hemolysis		Abs.	%Hemolysis
Neg Control	0.12657		Neg Control	0.02046	
Pos Control	2.86630		Pos Control	2.91930	
0	0.17809	2	0	0.03711	1
1:2	0.15459	1	1:2	0.03116	0
1:4	0.14085	1	1:4	0.03302	0
1:8	0.12836	0	1:8	0.02025	0
1:16	0.12540	0	1:16	0.02535	0
1:32	0.12112	0	1:32	0.02165	0
1:64	0.12277	0	1:64	0.02667	0
1:128	0.12389	0	1:128	0.02676	0

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Effect of Captisol® on the pharmacokinetics of miconazole, chlorpromazine and melphalan following IV administration to male Sprague Dawley rats

Study no.:	(b) (4)-08-001
Study report location:	eCTD 4.2.2.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not provided
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Commercial Alkeran, D075 and D789 Captisol® (cyclodextrin), CY-04A-05010

Study was initially reviewed under IND 104925 by Dr. Haw-Jyh Chiu, in the Division of Biologic Oncology Products. The review was modified to fit this review.

This study was designed to investigate the potential for Captisol to perturb the in vivo pharmacokinetics of compounds having different association constants for the Captisol-ligand complexes. Miconazole was selected as the compound with a high binding affinity for Captisol (K_a=4.2 x 10^5 M^{-1}), chlorpromazine was the compound with an intermediate binding affinity for Captisol (K_a=1 x 10^4 M^{-1}), and melphalan was the compound with a low binding affinity for Captisol (K_a=3 x 10^2 M^{-1}). Pharmacokinetic parameters were determined for miconazole, chlorpromazine, and melphalan following intravenous administration to male Sprague Dawley rats in the presence or absence of Captisol in the delivery vehicle. Since this study was submitted as a bridging pharmacokinetic study comparing Captisol-enabled melphalan to Alkeran in rats, the methods and results for the melphalan portion of the study are the focus of the review below.

Key Study Findings

- No significant differences in pharmacokinetic parameters or urinary excretion of melphalan were observed following a single intravenous administration of melphalan in the (b) (4)% (w/v) Captisol or Captisol-free (Alkeran) formulations.

Methods

Doses:	2 mg/kg melphalan
Frequency of dosing:	Single administration
Route of administration:	Intravenous infusion via jugular vein, 10 minute infusion
Dose volume:	1.0 mL
Formulation/Vehicle:	(b) (4)% (w/v) Captisol or Captisol-free
Species/Strain:	Crl:CD (SD) Sprague Dawley rat
Number/Sex/Group:	4-5 males/group
Age:	Not reported
Weight:	Not reported
Unique study design:	Rats were fasted overnight prior to drug administration

Melphalan formulations

- The Captisol-free formulation was prepared as per the product insert for the commercial Alkeran injectable formulation using 10 mL of the sterile diluent that is provided with the Alkeran product (containing (b) (4) sodium citrate, (b) (4) propylene glycol, (b) (4) ethanol ((b) (4)%) and water) to reconstitute the Alkeran. The solution was then diluted with 0.9% normal saline (2 mL in 10 mL saline). The concentration of melphalan in the formulation was (b) (4) mg/mL (as free base).
- For the Captisol formulation, Alkeran was reconstituted with 10 mL of a (b) (4)% (w/v) Captisol solution that was prepared by (b) (4). This solution was then diluted with 0.9% normal saline (2 mL in 10 mL saline). The formulation administered to rats contained (b) (4)% (w/v) Captisol and the measured concentration of melphalan was (b) (4) mg/mL (as free base).

Observation and Times

Pharmacokinetics:

- Blood/plasma sampling times: Pre-dose, 5, 10 (end-of-infusion), 15, 25, 40, 55, 70, 100, 130, 190, 250, 370, and 490 min-post-dose
- Urine sampling intervals: 0-70 min, 70-130 min, 130-190 min, 190-250 min, 250-310 min, 310-370 min, 370-430 min, 430-490 min, and 490-1450 min

Results

Clinical signs

No significant test-article-related clinical signs were observed in either group.

Pharmacokinetics

- No significant differences in pharmacokinetic parameters were observed following a single intravenous administration of melphalan in a (b) (4)% (w/v) Captisol or Captisol-free formulations.
- No apparent difference in the urinary excretion of melphalan when administered in either formulation was observed.

Table 6: Pharmacokinetic parameters for melphalan (2 mg/kg) in whole blood and plasma following intravenous administration in Captisol and Captisol-free formulations in male Sprague Dawley rats
(excerpted from Applicant's submission)

(b) (4)% (w/v) Captisol® formulation							
Parameter		Rat 110608F	Rat 110608G	Rat 110608H	Rat 240608A	Mean	SD
Measured dose (mg/kg)		2.14	1.99	1.91	2.00	2.01	0.10
Whole Blood	Apparent $t_{1/2}$ (h)	0.7	0.9	1.0	0.7	0.8	0.1
	Blood CL_{total} (mL/min/kg)	11.6	9.3	13.4	9.2	10.9	2.0
	V_z (L/kg)	0.7	0.7	1.1	0.6	0.8	0.2
	$AUC_{0\text{-}tlast}$/D (μM*min*kg/μmol)	86.4	107.5	74.4	108.2	94.1	16.6
	$AUC_{0\text{-}inf}$/D (μM*min*kg/μmol)	86.4	107.6	74.5	108.4	94.2	16.6
Plasma	Apparent $t_{1/2}$ (h)	0.7	0.9	0.8	0.7	0.8	0.1
	Plasma CL_{total} (mL/min/kg)	7.9	7.2	9.6	7.6	8.1	1.1
	V_z (L/kg)	0.5	0.6	0.7	0.5	0.6	0.1
	$AUC_{0\text{-}tlast}$/D (μM*min*kg/μmol)	126.8	138.2	104.0	132.0	125.3	14.9
	$AUC_{0\text{-}inf}$/D (μM*min*kg/μmol)	126.8	138.4	104.1	132.3	125.4	15.0
% Dose in urine [a]		0.7	1.0	5.0	2.4	2.3	2.0

CD-free formulation								
Parameter		Rat 110608A	Rat 110608B	Rat 110608C	Rat 110608D	Rat 110608E	Mean	SD
Measured dose (mg/kg)		1.92	1.92	1.85	1.87	1.81	1.87	0.05
Whole Blood	Apparent $t_{1/2}$ (h)	1.0	0.9	0.9	0.8	1.0	0.9	0.1
	Blood CL_{total} (mL/min/kg)	11.2	13.7	11.7	10.8	13.4	12.2	1.3
	V_z (L/kg)	1.0	1.1	0.9	0.7	1.1	1.0	0.2
	$AUC_{0\text{-}tlast}$/D (μM*min*kg/μmol)	88.9	72.8	85.3	92.1	74.2	81.1	9.3
	$AUC_{0\text{-}inf}$/D (μM*min*kg/μmol)	89.1	72.8	85.5	92.4	74.4	82.8	8.8
Plasma	Apparent $t_{1/2}$ (h)	1.0	0.8	0.7	0.8	0.9	0.9	0.1
	Plasma CL_{total} (mL/min/kg)	11.4	10.0	8.5	7.7	8.8	9.3	1.4
	V_z (L/kg)	1.0	0.7	0.5	0.6	0.7	0.7	0.2
	$AUC_{0\text{-}tlast}$/D (μM*min*kg/μmol)	87.4	99.9	117.4	129.4	113.3	109.5	16.2
	$AUC_{0\text{-}inf}$/D (μM*min*kg/μmol)	87.7	100.0	117.5	129.4	113.5	109.6	16.1
% Dose in urine [a]		No sample [b]	4.7	3.5	1.2	1.4	2.7	1.7

[a] Unchanged melphalan present in pooled urine (collected up to 24 hours post-dose)
[b] No sample was available as Rat 110608A died overnight between 8-24 hour sample.

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/s/

BRENDA J GEHRKE
08/21/2015

CHRISTOPHER M SHETH
08/24/2015