MMOLL
Análisis Físico-Químicos Microbiológicos

BOLETIN DE ANALISIS

ASP00049-19.002

Producto **ALKERAN COMPRIMIDOS RECUBIERTOS 2mg**		Presentación **25 COMPRIMIDOS RECUBIERTOS**
Procedencia **ASPEN CHILE SA**		Cód. producto **GR80549CL1**
Lote: **914797-1**	N° Registro **F-1420/03**	Guía de Despacho **287322 / 295303**
Fecha de fabricación **05/2019**	Fecha de expiración **05/2021**	Periodo de eficacia **24 MESES**
País de fabricación **ALEMANIA**	Fabricante **EXCELLA GMBH & CO.KG,**	Proc. de muestreo **NOVOFARMA NFS-120177**
Fecha de recepción **13-dic-2019**	Unidades recibidas **02 UND + 1UND**	Unidades totales **1000 UND**
Condiciones de Almacenamiento **CONSERVAR ENTRE 2 y 8 °C**	Especificación Vigente **EPT 17/AGO/2005**	

ENSAYOS	ESPECIFICACION	RESULTADOS
ASPECTO	COMPRIMIDO RECUBIERTO DE PELÍCULA, BLANCO A BLANCUZCO, BICONVEXO, CON UNA "A" GRABADA POR UN LADO Y "GX EH3" POR EL OTRO.	COMPRIMIDO RECUBIERTO DE PELÍCULA, BLANCO A BLANCUZCO, BICONVEXO, CON UNA "A" GRABADA POR UN LADO Y "GX EH3" POR EL OTRO.
PESO PROMEDIO	100mg (ONTROL EN PROCESO) 96.5 - 103.5mg	105.9 mg (*)
DUREZA	8kP (CONTROL EN PROCESO) LÍMITES: 5 - 11kP	10 KP
IDENTIDAD - MELFALAN	POSITIVA (HPLC)	POSITIVA (HPLC)
IDENTIDAD - MELFALAN	POSITIVA UV	POSITIVA UV
VALORACIÓN - MELFALAN	2.0mg LÍMITES: 1.8 - 2.1mg/ COMPRIMIDO 90.5 - 105.0% DEL CONTENIDO DECLARADO EN LA ETIQUETA. (HPLC)	1.9 mg/COMPRIMIDO (95.1%)
DISOLUCIÓN	CUMPLE CON LA USP VIGENTE Q = 80% A LOS 30 MINUTOS (APARATO II // HCl 0.1 N // 50rpm // 37°C)	CUMPLE CRITERIO S1 DISOLUCIÓN: PROMEDIO=92% (MIN=86% - MAX=97%)
UNIFORMIDAD DE CONTENIDO	CUMPLE CON LA FARMACOPEA EUROPEA.	CUMPLE L1 / AV=3.6 (91% - 101%)
ENVASE	COMPRIMIDOS RECUBIERTOS ENVASADOS EN FRASCO DE VIDRIO TOPACIO TIPO II, CON TAPA A PRUEBA DE NIÑOS, EN ESTUCHE DE CARTULINA IMPRESO.	COMPRIMIDOS RECUBIERTOS ENVASADOS EN FRASCO DE VIDRIO TOPACIO TIPO II, CON TAPA A PRUEBA DE NIÑOS, EN ESTUCHE DE CARTULINA IMPRESO.

Observaciones:
(*) Peso promedio Fuera de Especificaciones (Control en proceso), cumple con el fabricante

Metodología de análisis **ASP-011**	Según los ensayos: **APROBADO** **Resultados válidos sólo para la muestra analizada**	Fecha de inicio del análisis **03-feb-2020** Fecha de término del análisis **09-mar-2020**

Analistas: CLAUDIA VARAS GONZALEZ [006-016/006-020 al 006-016/006-020]; LISMARY GUERRERO ANGULO [015-045 al 015-046];

Este boletín ha sido autorizado por CLAUDIA VARAS GONZALEZ Jefe de Laboratorio	Signal electronic security	Este boletín ha sido aprobado por NATALIA MAGDALENA GOMEZ GALAZ Firmado digitalmente por NATALIA MAGDALENA GOMEZ GALAZ Nombre de reconocimiento (DN): c=CL, title=PERSONA NATURAL, cn=NATALIA MAGDALENA GOMEZ GALAZ, email=direccióntecnica@analisismmoll.cl, serialNumber=12258053-9 Fecha: 2020.03.10 18:07:03 -03'00' Q. F. NATALIA GOMEZ Director Técnico

Dirección : José Ananías 152 - Macul Santiago Chile Fono : 56 2 28168570 email : laboratorio@analisismmoll.cl www.analisismmoll.cl

FAREVA

EXCELLA PHARMA SOURCE

Batch Certificate for Medicinal Products

acc.to EMEA/MRA/23/01 and Annex 16 to EU GMP Guide

Excella GmbH & Co. KG
Nürnberger Str. 12
D-90537 Feucht

Manufact. Licence n°: DE_BY_05_MIA_2018_0038
GMP-Certificate n° : DE_BY_05_GMP_2018_0064

Prüfplan No.: **1870915**
Certificate No.: **81051**
Material No.: **1493000**

Customer:	Aspen Global Incorporated
Product:	ALKERAN 2MG TBL(25)FL ASPEN(RCH)
Batch-No. Customer:	914797
Batch-No. Excella:	1914797
Package type:	☐ blisters ☒ bottles ☐ bulk
Marketing Authorization n°:	F-1420/18

☐ Australia ☐ Japan
☐ Canada ☐ New Zealand
☐ Israel ☐ Switzerland
☐ EU / EEA ☒ Others
Country: Chile

☒ Finished product — Master Batch record: 1493000-06-13

Mat.-No. Customer:	1002570
Site of secondary packaging/labelling:	Excella GmbH & Co. KG
Quality Control Site:	Excella GmbH & Co. KG

☒ Primary Packaged product — Master Batch record: 6484000-04-13
(only applicable if prim. packaging is an independent production step)

Batch-No. Customer:	1908862	Batch-No. Excella:	1908862
Site of primary packaging:	Excella GmbH & Co. KG		
Quality Control Site:	Excella GmbH & Co. KG		

☒ Bulk product — Master Batch record: 6475600-07-10

Batch-No. Customer:		Batch-No. Excella:	1906066
Manufacturing Site:	Excella GmbH & Co. KG	Date of manufacture:	06-May-2019
Quality Control Site:	Excella GmbH & Co. KG		

Active Pharmaceutical Ingredient:	Batch-No. Excella:	Manufacturer:
MELPHALAN	1813138	AMPAC Fine Chemicals, California, USA
MELPHALAN	1900697	AMPAC Fine Chemicals, California, USA

I hereby certify that all manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the EU and [when within the EU] with the requirements of the Marketing Authorization(s) of the destination country/countries.
All deviations that may influence the release of the batch have been reviewed and approved in accordance with an established deviation procedure. The following deviations have been registered:

☒ None ☐

Additional Information:

NOV 15 2019

Printing date : 15-Nov-2019

Date/ Signature of Qualified Person

☒ Dr. B. Hoffmann ☐ Dr. K. Kupsch ☐ Dr. M. Höhn ☐ Dr. J. Utz
☐ S. Lehmann

Attachment(s): Certificate(s) of Analysis

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 1 of 6

Customer batch no. : 914797

Lot size : 2000.000 ST

Customer item no. : 1002570

Manufacturing date : 06-May-2019

Expiry date: 31-May-2021

Monograph:

Characteristics : white to off-white film-coated tablets, unscored, engraved with GX EH3 (upper side) and A (lower side), round, biconvex, diameter: 6.5 mm

Remarks :

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 2 of 6

Mat. no.	Description	Batch	Testprotocol
6475600	ALKERAN 2MG FILM-COATED TABLETS Specification : PQK400/088/03/13	1906066	1862958

Parameter	Analyt.Procedure	Limit	Result	Lab.
Characteristics				
Characteristics (Release and Stability)	43000/251/99/6	conforms	Complies	Excella
Characteristic values				
Average mass (film-coated tablet)	43000/214/00/0		105.1 mg/ftbl.	Excella
Mass (minimum)	43000/214/00/0		104 mg	Excella
Mass (maximum)	43000/214/00/0		107 mg	Excella
Uniformity				
Uniformity of mass (film-coated tablet)	43000/214/00/0	conforms	Complies	Excella
Identity				
Identity Melphalan (LC)	PQK410/015/02/4	conforms	Complies	Excella
Identity Melphalan (UV)	PQK410/013/02/3	conforms	Complies	Excella
Identity Melphalan (UV) (JP)	PQK410/015/02/4	conforms	Complies	Excella
Characteristic values				
Hardness (50 - 107 N) (IPC)	43000/212/00/6	conforms	Complies	Excella
Hardness	43000/212/00/6		106 N	Excella
Disintegration time (IPC)	43000/213/00/3	Max. 10 min	3 min	Excella
Friability (IPC)	43000/230/00/2	Max. 0.5 %	0.2 %	Excella
Related compounds LC				
Monohydroxymelphalan	PQK410/015/02/4	Max. 3.0 %	0.5 %	Excella
Melphalan dimer	PQK410/015/02/4	Max. 1.0 %	0.5 %	Excella
Melphalan methyl ester	PQK410/015/02/4	Max. 0.4 %	0.1 %	Excella
Melphalan methyl ester (China)	PQK410/015/02/4	Max. 0.2 %	0.1 %	Excella
Dihydroxymelphalan (NL)	PQK410/015/02/4	Max. 0.5 %	<0.1 %	Excella
Impurity RRT 0.36-0.39 (NL)	PQK410/015/02/4	Max. 0.5 %	<0.1 %	Excella
Impurity RRT 0.78-0.82 (NL)	PQK410/015/02/4	Max. 0.5 %	0.1 %	Excella
Impurity RRT 1.02-1.03 (NL)	PQK410/015/02/4	Max. 0.5 %	<0.1 %	Excella
Impurity RRT 1.04-1.08/Chloroethoxymelphalan (NL)	PQK410/015/02/4	Max. 0.5 %	0.1 %	Excella
Impurity RRT 1.08-1.11 (NL)	PQK410/015/02/4	Max. 0.5 %	<0.1 %	Excella
Impurity RRT 1.49-1.50 (NL)	PQK410/015/02/4	Max. 0.5 %	<0.1 %	Excella
impurity, unknown single (NL)	PQK410/015/02/4	Max. 0.2 %	0.1 %	Excella
Impurity unknown single (ROW/Japan)	PQK410/015/02/4	Max. 0.4 %	0.1 %	Excella
Impurity second unknown (ROW)	PQK410/015/02/4		0.1 %	Excella
Impurity total unknown (ROW)	PQK410/015/02/4		0.2 %	Excella

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 3 of 6

Mat. no.	Description	Batch	Testprotocol
6475600	ALKERAN 2MG FILM-COATED TABLETS Specification : PQK400/088/03/13	1906066	1862958

Parameter	Analyt.Procedure	Limit	Result	Lab.
impurity, unknown single (China)	PQK410/015/02/4	Max. 0.2 %	0.1 %	Excella
Impurities total (with synthesis impurity)	PQK410/015/02/4	Max. 5.0 %	1.3 %	Excella
Assay				
Assay Melphalan	PQK410/015/02/4	1.91 ... 2.10 mg/tbl.	2.01 mg/tbl.	Excella
Assay Melphalan	PQK410/015/02/4	95.5 ... 105.0 % L.S.	100.4 % L.S.	Excella
Uniformity				
Uniformity of dosage units (Ph.Eur. / USP / JP)	PQK410/013/02/3		99.4 %	Excella
Uniformity of dosage units (min)	PQK410/013/02/3		97.5 %	Excella
Uniformity of dosage units (max)	PQK410/013/02/3		100.5 %	Excella
Uniformity of dosage units (rsd)	PQK410/013/02/3		1.0 %	Excella
Uniformity of dosage units, acceptance value (AV)	PQK410/013/02/3	Max. 15.0 %	2.4 %	Excella
Uniformity of dosage units (USA)	PQK410/013/02/3		97.3 %	Excella
Uniformity of dosage units (min) (USA)	PQK410/013/02/3		95.3 %	Excella
Uniformity of dosage units (max) (USA)	PQK410/013/02/3		98.3 %	Excella
Uniformity of dosage units (rsd) (USA)	PQK410/013/02/3		1.0 %	Excella
Dissolution				
Dissolution within 30 min (Q)	PQK410/005/04/4		93 %	Excella
Dissolution within 30 min (minimum)	PQK410/005/04/4		91 %	Excella
Dissolution within 30 min (maximum)	PQK410/005/04/4		103 %	Excella
Dissolution assessment (Q = 80%)	PQK410/005/04/4	Acceptable : Complies on stage 1, Complies on stage 2, Complies on stage 3	Complies on stage 1	Excella
Dissolution within 60 min (JP)	PQK410/006/04/3	Min. 70 %	86 %	Excella
Dissolution within 60 min (minimum) (JP)	PQK410/006/04/3		78 %	Excella
Dissolution within 60 min (maximum) (JP)	PQK410/006/04/3		97 %	Excella

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 4 of 6

Mat. no.	Description	Batch	Testprotocol
6484000	ALKERAN 2 MG F.C.T. PRIMVERP(25)BT AMPAC Specification : 6484000/01/4	1908862	1865572

Parameter	Analyt.Procedure	Limit	Result	Lab.
Characteristics				
Packaging	PQK0S/007/16/0	Packaging	Complies	Excella
Identity				
Comparison with reference sample	PQK0S/007/16/0	Comparison with reference sample complies	Complies	Excella

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 5 of 6

Mat. no.	Description	Batch	Testprotocol
1493000	ALKERAN 2MG TBL(25)BT ASPEN(RCH) Specification : M090007/01/4	1914797	1870915

Parameter	Analyt.Procedure	Limit	Result	Lab.
Comparison with reference sample	PQK0S/007/16/0	Comparison with reference sample complies	Complies	Excella
Characteristics				
Packaging	PQK0S/007/16/0	Packaging	Complies	Excella
Organisation				
time out-of-cold storage (packaging)		Max. 28 days	11 days	Excella

CERTIFICATE OF ANALYSIS

Material : ALKERAN 2MG TBL(25)BT ASPEN(RCH)	Certificate no. : 81051 Material no.: 1493000 Date of issuance : 15-Nov-2019
Batch no.: **1914797**	Page 6 of 6

The material was tested under current GMP requirements.
The material was tested according to the current test procedures.

Batch 1914797 complies with the specification.

Conditions / comment :

Disposition Status :	released by:	Release date :
Released	Dr. Hoffmann, Bernhard Director Quality Control Pharma & Qualified Person	14-Nov-2019

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 54417 Material no.: 3860300 Date of issuance : 02-Oct-2019
Batch no.: **1813138**	Page 1 of 4

Supplier : ASPEN GLOBAL INCORP.

Supplierlotno. : 18-385-090

Manufacturer : AMPAC Fine Chemicals, California, USA

Packaging : Kunststoffbehälter (WE)

Retest date : 27-Jul-2019

Expiry date: 27-Jul-2019

Specification : PQK00/699/09/3

Monograph:

Ph.Eur.	Melphalan	8.0
BP	Melphalan	2016

Characteristics : white to almost white hygroscopic powder

Remarks :

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 54417 Material no.: 3860300 Date of issuance : 02-Oct-2019
Batch no.: **1813138**	Page 2 of 4

Mat. no.	Description	Batch	Testprotocol
3860300	MELPHALAN Specification : PQK00/699/09/3	1813138	1853185

Parameter	Limit	Result	Lab.
Organisation			
Content for production		96.5 %	Supplier
Characteristics			
Colour	Complies	Complies	Excella
Identity			
IR spectrum	Complies	Complies	Excella
Identity HPLC	Complies	Complies	Supplier
Chloride (JP)	Chloride (JP)	Complies	Excella
Characteristic values			
Specific rotation	-36.0 ... -30.0 °	-34.2 °	Supplier
Purity			
Water (KF)	Max. 5.0 %	2.2 %	Supplier
Total volatiles	Max. 7.0 %	2.7 %	Supplier
Chloride (in 0,1 M AgNO3)	Max. 1.0 ml	0.1 ml	Supplier
Sulphated ash	Max. 0.1 %	0.0 %	Supplier
Heavy metals (JP)	Max. 20 ppm	< 20 ppm	Supplier
Arsenic (JP)	Max. 2 ppm	< 2 ppm	Supplier
Loss on drying (JP)	Max. 7.0 %	1.7 %	Supplier
Related compounds LC			
Dihydroxymelphalan	Max. 0.10 %	< 0.10 %	Supplier
Morpholino derivative	Max. 0.3 %	< 0.3 %	Supplier
Mono-(2-chloroethyl)aminomelphalan	Max. 0.10 %	< 0.10 %	Supplier
Monohydroxymelphalan	Max. 3.0 %	0.4 %	Supplier
2-Methoxyethylmelphalan	Max. 0.2 %	< 0.2 %	Supplier
Chloroethoxymelphalan	Max. 0.5 %	0.1 %	Supplier
3-Chloromelphalan	Max. 0.10 %	0.01 %	Supplier
Melphalan dimer	Max. 1.0 %	0.3 %	Supplier
Melphalan methyl ester	Max. 0.5 %	< 0.5 %	Supplier
unknown single	Max. 0.10 %	< 0.10 %	Supplier
total	Max. 5.5 %	0.9 %	Supplier
Residual solvents			
Methanol	Max. 2.5 %	0.4 %	Supplier
Diethylamine	Max. 0.5 %	0.1 %	Supplier
Benzene	Max. 1 ppm	< 1 ppm	Supplier
Particle size			
Sieve residue 250 µm	Max. 10 %	< 10 %	Supplier

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 54417 Material no.: 3860300 Date of issuance : 02-Oct-2019
Batch no.: **1813138**	Page 3 of 4

Mat. no.	Description	Batch	Testprotocol
3860300	MELPHALAN Specification : PQK00/699/09/3	1813138	1853185

Parameter	Limit	Result	Lab.
particle size d(10)	Max. 4 µm	3 µm	Supplier
particle size d(50)	5 ... 40 µm	11 µm	Supplier
particle size d(90)	Max. 100 µm	40 µm	Supplier
Assay			
HPLC	95.0 ... 100.5 %	99.1 %	Supplier
Purity			
Palladium	Max. 10 ppm	< 1 ppm	Supplier

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 54417 Material no.: 3860300 Date of issuance : 02-Oct-2019
Batch no.: **1813138**	Page 4 of 4

The material was tested under current GMP requirements.
The material was tested according to the current test procedures.

Batch 1813138 complies with the specification.

Conditions / comment :

Disposition Status :	released by:	Release date :
Released	Eichhorn, Udo Manager Quality Control Pharma	06-Nov-2018

AMPAC FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-090

Manufacture Date 27 July 2018
Retest Date 27 July 2019
Batch Net Weight 4.15 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Appearance	White or almost white hygroscopic powder	White Hygroscopic Powder
Identification by FTIR	Concordant with IR Reference Standard	Conforms
Identification by HPLC	Concordant with HPLC Reference Solution	Conforms
Identification – Chloride (JP)	Positive Qualitative Tests for Chloride	Conforms
Ionisable Chlorine (JP)	NMT 1.0 mL of 0.1M $AgNO_3$ per 0.5g	0.1 mL
Heavy Metals (JP)	NMT 20 ppm	< 20 ppm
Arsenic (JP)	NMT 2 ppm	< 2 ppm
Optical Rotation	-36.0 ° to -30.0 °	-34.2°
Water Content by Karl Fischer	NMT 5.0%	2.2%
Loss on Drying (JP)	NMT 7.0 % w/w	1.7%
Sulfated Ash	NMT 0.1% w/w	0.0%
Non Aqueous Solvents Methanol Impurity K (Diethylamine) Benzene	 NMT 2.5% w/w NMT 0.5% w/w NMT 1 ppm	 0.4% 0.1% Not Detected

AMPAC FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-090

Manufacture Date	27 July 2018
Retest Date	27 July 2019
Batch Net Weight	4.15 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Total Volatiles including water	NMT 7.0% w/w	2.7%
Particle Size Sieve through 250 µm	NLT 90% w/w	100%
Particle Size by Laser Sizer		
Particle Size at x 10%	NMT 4µm	3 µm
Particle Size at x 50%	5 to 40 µm	11 µm
Particle Size at x 90%	NMT 100µm	40 µm
Related Substances		
Impurity A (Dihydroxymelphalan)	NMT 0.10%	Not Detected
Impurity B (Morpholino derivative)	NMT 0.3%	Not Detected
Impurity C (Mono-(2-chloroethyl)-aminomelphalan)	NMT 0.10%	Not Detected
Impurity D (Monohydroxymelphalan)	NMT 3.0%	0.38%
Impurity F (3-Chloromelphalan)	NMT 0.10%	0.01%
Impurity G (Melphalan dimer)	NMT 1.0%	0.32%
Impurity H (Melphalan methyl ester)	NMT 0.5%	Not Detected
Impurity I (2-Methoxyethylmelphalan)	NMT 0.2%	0.01%
Impurity J (Chloroethoxymelphalan)	NMT 0.5%	0.06%
Unknown Impurity	NMT 0.10%	RRT 0.64, 0.01% RRT 0.71, 0.01% RRT 0.77, 0.01% RRT 0.88, 0.01% RRT 1.07, 0.01% RRT 1.14, 0.01% RRT 1.87, 0.01%
Total Impurities	NMT 5.5%	0.85%

AMPAC FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-090

Manufacture Date	27 July 2018
Retest Date	27 July 2019
Batch Net Weight	4.15 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Assay		
Melphalan Volatiles Free	95.0 - 100.5% w/w	99.1%*
Assay As Is	Report Results	96.5%
Parts per 100 Parts Melphalan	Report Results	104 parts per 100 parts Melphalan
Palladium Content by ICP-OES	NMT 10 ppm	< 1 ppm

* The result for Melphalan Volatiles Free Assay is an average of values which include one value which is higher than the specified range. All values (range of 98.06% - 100.63%) from investigation INV-180007 were included in the calculation of the average, which is within the specified range.

It is hereby certified that the above product is acceptable under the requirements of the applicable product specification.

Samuel Kluck — Quality Control Laboratory

08/16/18 — Date

This is to certify that the above product meets the requirements of the Purchase Order. The Product was manufactured in conformance to applicable AFC procedures and the requirements for good manufacturing practices as recommended by the United States Food & Drug Administration. This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7). This lot is approved and released for distribution.

Quality Assurance

8/16/18 — Date

AMPAC Fine Chemicals
Hwy 50 and Hazel Ave • Rancho Cordova, California 95670
Tel +1 (888) 330-2232 • Fax +1 (916) 353-3523
www.ampacfinechemicals.com

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 61279 Material no.: 3860300 Date of issuance : 13-Feb-2019
Batch no.: **1900697**	Page 1 of 4

Supplier : ASPEN GLOBAL INCORP.

Supplierlotno. : 18-385-088

Manufacturer : AMPAC Fine Chemicals, California, USA

Packaging : Kunststoffbehälter (WE)

Retest date : 24-Jul-2019

Expiry date: 24-Jul-2019

Specification : PQK00/699/09/3

Monograph:

Ph.Eur.	Melphalan	8.0
BP	Melphalan	2016

Characteristics : white to almost white hygroscopic powder

Remarks :

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 61279 Material no.: 3860300 Date of issuance : 13-Feb-2019
Batch no.: **1900697**	Page 2 of 4

Mat. no.	Description	Batch	Testprotocol
3860300	MELPHALAN Specification : PQK00/699/09/3	1900697	1858152

Parameter	Limit	Result	Lab.
Organisation			
Content for production		96.5 %	Supplier
Characteristics			
Colour	Complies	Complies	Excella
Identity			
IR spectrum	Complies	Complies	Excella
Identity HPLC	Complies	Complies	Supplier
Chloride (JP)	Chloride (JP)	Complies	Excella
Characteristic values			
Specific rotation	-36.0 ... -30.0 °	-33.7 °	Supplier
Purity			
Water (KF)	Max. 5.0 %	1.8 %	Supplier
Total volatiles	Max. 7.0 %	2.7 %	Supplier
Chloride (in 0,1 M AgNO3)	Max. 1.0 ml	0.2 ml	Supplier
Sulphated ash	Max. 0.1 %	0.0 %	Supplier
Heavy metals (JP)	Max. 20 ppm	< 20 ppm	Supplier
Arsenic (JP)	Max. 2 ppm	< 2 ppm	Supplier
Loss on drying (JP)	Max. 7.0 %	2.3 %	Supplier
Related compounds LC			
Dihydroxymelphalan	Max. 0.10 %	< 0.10 %	Supplier
Morpholino derivative	Max. 0.3 %	< 0.3 %	Supplier
Mono-(2-chloroethyl)aminomelphalan	Max. 0.10 %	< 0.10 %	Supplier
Monohydroxymelphalan	Max. 3.0 %	0.4 %	Supplier
2-Methoxyethylmelphalan	Max. 0.2 %	< 0.2 %	Supplier
Chloroethoxymelphalan	Max. 0.5 %	0.1 %	Supplier
3-Chloromelphalan	Max. 0.10 %	< 0.10 %	Supplier
Melphalan dimer	Max. 1.0 %	0.3 %	Supplier
Melphalan methyl ester	Max. 0.5 %	< 0.5 %	Supplier
unknown single	Max. 0.10 %	< 0.10 %	Supplier
total	Max. 5.5 %	0.8 %	Supplier
Residual solvents			
Methanol	Max. 2.5 %	0.7 %	Supplier
Diethylamine	Max. 0.5 %	0.2 %	Supplier
Benzene	Max. 1 ppm	< 1 ppm	Supplier

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 61279 Material no.: 3860300 Date of issuance : 13-Feb-2019
Batch no.: **1900697**	Page 3 of 4

Mat. no.	Description	Batch	Testprotocol
3860300	MELPHALAN Specification : PQK00/699/09/3	1900697	1858152

Parameter	Limit	Result	Lab.
Particle size			
Sieve residue 250 µm	Max. 10 %	0 %	Supplier
particle size d(10)	Max. 4 µm	3 µm	Supplier
particle size d(50)	5 ... 40 µm	10 µm	Supplier
particle size d(90)	Max. 100 µm	28 µm	Supplier
Assay			
HPLC	95.0 ... 100.5 %	99.3 %	Supplier
Purity			
Palladium	Max. 10 ppm	< 1 ppm	Supplier

CERTIFICATE OF ANALYSIS

EXCELLA PHARMA SOURCE

Material : MELPHALAN	Certificate no. : 61279 Material no.: 3860300 Date of issuance : 13-Feb-2019
Batch no.: **1900697**	Page 4 of 4

The material was tested under current GMP requirements.
The material was tested according to the current test procedures.

Batch 1900697 complies with the specification.

Conditions / comment :

Disposition Status :	released by:	Release date :
Released	Eichhorn, Udo Manager Quality Control Pharma	13-Feb-2019

AMPAC™
FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-088

Manufacture Date	24 July 2018
Retest Date	24 July 2019
Batch Net Weight	4.295 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Appearance	White or almost white hygroscopic powder	White Hygroscopic Powder
Identification by FTIR	Concordant with IR Reference Standard	Conforms
Identification by HPLC	Concordant with HPLC Reference Solution	Conforms
Identification – Chloride (JP)	Positive Qualitative Tests for Chloride	Conforms
Ionisable Chlorine (JP)	NMT 1.0 mL of 0.1M $AgNO_3$ per 0.5g	0.2 mL
Heavy Metals (JP)	NMT 20 ppm	< 20 ppm
Arsenic (JP)	NMT 2 ppm	< 2 ppm
Optical Rotation	-36.0 ° to -30.0 °	-33.7°
Water Content by Karl Fischer	NMT 5.0%	1.8%
Loss on Drying (JP)	NMT 7.0 % w/w	2.3%
Sulfated Ash	NMT 0.1% w/w	0.0%
Non Aqueous Solvents Methanol Impurity K (Diethylamine) Benzene	 NMT 2.5% w/w NMT 0.5% w/w NMT 1 ppm	 0.7% 0.2% Not Detected

AMPAC™
FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-088

Manufacture Date 24 July 2018
Retest Date 24 July 2019
Batch Net Weight 4.295 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Total Volatiles including water	NMT 7.0% w/w	2.7%
Particle Size Sieve through 250 µm	NLT 90% w/w	100%
Particle Size by Laser Sizer		
Particle Size at x 10%	NMT 4µm	3 µm
Particle Size at x 50%	5 to 40 µm	10 µm
Particle Size at x 90%	NMT 100µm	28 µm
Related Substances		
Impurity A (Dihydroxymelphalan)	NMT 0.10%	Not Detected
Impurity B (Morpholino derivative)	NMT 0.3%	Not Detected
Impurity C (Mono-(2-chloroethyl)-aminomelphalan)	NMT 0.10%	Not Detected
Impurity D (Monohydroxymelphalan)	NMT 3.0%	0.43%
Impurity F (3-Chloromelphalan)	NMT 0.10%	Not Detected
Impurity G (Melphalan dimer)	NMT 1.0%	0.28%
Impurity H (Melphalan methyl ester)	NMT 0.5%	Not Detected
Impurity I (2-Methoxyethylmelphalan)	NMT 0.2%	Not Detected
Impurity J (Chloroethoxymelphalan)	NMT 0.5%	0.08%
Unknown Impurity	NMT 0.10%	Not Detected
Total Impurities	NMT 5.5%	0.80%

AMPAC™
FINE CHEMICALS

Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-088

Manufacture Date	24 July 2018
Retest Date	24 July 2019
Batch Net Weight	4.295 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Assay		
Melphalan Volatiles Free	95.0 - 100.5% w/w	99.3%
Assay As Is	Report Results	96.5%
Parts per 100 Parts Melphalan	Report Results	104 parts per 100 parts Melphalan
Palladium Content by ICP-OES	NMT 10 ppm	< 1 ppm

It is hereby certified that the above product is acceptable under the requirements of the applicable product specification.

Quality Control Laboratory — Date: 08/14/18

This is to certify that the above product meets the requirements of the Purchase Order. The Product was manufactured in conformance to applicable AFC procedures and the requirements for good manufacturing practices as recommended by the United States Food & Drug Administration. This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7). This lot is approved and released for distribution.

Quality Assurance — Date: 08/14/18

AMPAC Fine Chemicals
Hwy 50 and Hazel Ave • Rancho Cordova, California 95670
Tel +1 (888) 330-2232 • Fax +1 (916) 353-3523
www.ampacfinechemicals.com

Supplemental Certificate of Analysis / Compliance

Melphalan Milled

4-[Bis-(2-chloroethyl)amino]-L-phenylalanine

Lot Number 18-385-088

Manufacture Date	24 July 2018
Retest Date	24 July 2019
Batch Net Weight	4.295 kg

AGI Material Code: GA20040
Aspen Global Inc. P.O. # 91000869

Test	Specifications	Results
Appearance of Solution (For Injectable Formulation Only)	The solution is clear (2.2.1) and colourless (2.2.2, Method II)	Conforms
Ethylene Oxide (If Tested)	NMT 10 ppm	N/A

It is hereby certified that the above product is acceptable under the requirements of the applicable product specification.

Quality Control Laboratory — Date: 09/14/18

This is to certify that the above product meets the requirements of the Purchase Order. The Product was manufactured in conformance to applicable AFC procedures and the requirements for good manufacturing practices as recommended by the United States Food & Drug Administration. This batch has been manufactured, packaged and tested in accordance with EU GMP Guideline Volume 4 Part II (ICHQ7). This lot is approved and released for distribution.

Quality Assurance — Date: 08/17/18

AMPAC Fine Chemicals
Hwy 50 and Hazel Ave • Rancho Cordova, California 95670
Tel +1 (888) 330-2232 • Fax +1 (916) 353-3523
www.ampacfinechemicals.com

N° Ref: AU1288846/19

Resolución Exenta N° 29814
Santiago, 10 de diciembre de 2019

AUTORIZACIÓN DE USO Y DISPOSICIÓN

VISTO ESTOS ANTECEDENTES: La solicitud de **ASPEN CHILE S.A.** para el Uso y Disposición de las mercancías señaladas en la presentación adjunta, correspondiente a la Declaración de Ingreso ante Aduana de fecha, 9 de diciembre de 2019 que acompaña el Certificado de Destinación Aduanera **N° 97826/2019** del Instituto de Salud Pública de Chile.

CONSIDERANDO: que da cumplimiento al Artículo N°3 de la Ley 18.164 del Ministerio de Hacienda; y

TENIENDO PRESENTE: Lo dispuesto en el artículo 96° del Código Sanitario, el Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo Nº 3 de 2010, del Ministerio de Salud; el artículo 59º letra b) Nº3 del DFL Nº 1 de 2005, el artículo 28º del D.S. Nº 1222 de 1996 del Ministerio de Salud, que aprueba el Reglamento del Instituto de Salud Pública de Chile; la Ley Nº 18.164 de 1982, del Ministerio de Hacienda, y en uso de las facultades que me otorga la resolución exenta N° 56 de 11 de enero de 2019 del Instituto de Salud Pública de Chile, dicto lo siguiente:

R E S O L U C I Ó N

1.- AUTORÍZASE a **ASPEN CHILE S.A.** e infórmese favorablemente el Uso y Disposición de la mercancía detallada en el anexo foliado adjunto, que forma parte de la presente resolución, ingresada por la(s) factura(s) 90015632 // 2019 que acompaña el Certificado de Destinación Aduanera **Nº 97826/2019** autorizada por la DIN Nº3480310326 de la Aduana METROPOLITANA del Servicio Nacional de Aduana.

2.- El titular, importador o distribuidor en su caso, deberá dar cumplimiento a lo establecido en el Titulo VII “Del Control de Calidad”, del Decreto Supremo Nº3 de 2010; antes de su uso y distribución, debiendo presentar el protocolo de análisis realizado en el país, por cada partida o serie autorizada por la presente resolución, cuando éste sea requerido por el Instituto de Salud Pública de Chile.

3.-DÉJASE ESTABLECIDO que la presente autorización no interfiere ni invalida otra acción de carácter sanitario establecida en el Código Sanitario y sus Reglamentos que regulan la tenencia, uso, venta, cesión o disposición de la mercancía certificada.

Por delegación del Director del Instituto de Salud Pública de Chile.

ANÓTESE Y COMUNÍQUESE

Q.F. Isabel Elena Sánchez Cerezzo
SUBDEPARTAMENTO CONTROL COMERCIO EXTERIOR, ESTUPEFACIENTES Y PSICOTRÓPICO
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

N° Ref: AU1288846/19

Resolución Exenta N° 29814
Santiago, 10 de diciembre de 2019

AUTORIZACIÓN DE USO Y DISPOSICIÓN

"ANEXO DE PROVEEDOR Y PRODUCTOS"

Proveedor	**País**	**Factura/año**
ASPEN GLOBAL INCORPORATED	MAURICIO	90015632 // 2019

Sección II. Productos importados que disponen de registro sanitario.

Titular: ASPEN CHILE S.A.

1.- ALKERAN COMPRIMIDOS 2 mg

N° registro sanitario:	F-1420/18
Control Legal:	NO
País Producción:	ALEMANIA
País Procedente:	ALEMANIA
Régimen:	IMPORTADO TERMINADO CON REACONDICIONAMIENTO LOCAL
Cantidad:	1000
Unidad de medida:	COMPRIMIDO
Lotes:	914797