Module 1.3.1.1 PROFESSIONAL INFORMATION

Line	PROPOSED PROFESSIONAL INFORMATION
1	**SCHEDULING STATUS S4**
2	
3	**1. NAME OF THE MEDICINE**
4	**DETENER,** concentrate for solution for infusion
5	
6	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
7	Each 1 ml of concentrate contains 6 mg of busulfan (60 mg in 10 ml).
8	After dilution: Each 1 ml of solution contains 0,5 mg of busulfan.
9	Sugar free.
10	For the full list of excipients see section 6.1.
11	**3. PHARMACEUTICAL FORM**
12	Concentrate for solution for infusion (sterile concentrate).
13	Clear, colourless solution free from visible particles.
14	
15	**4. CLINICAL PARTICULARS**
16	**4.1 Therapeutic indications**
17	Conditioning treatment prior to haematopoeietic progenitor cell
18	transplantation (HPCT) in adults when the combination of busulfan and
19	cyclophosphamide (Bu/Cy2) is considered the best available option.
20	
21	**4.2 Posology and method of administration**
22	**DETENER** should be administered under the supervision of a qualified
23	medical practitioner who is experienced in conditioning treatment prior to
24	HPCT in the use of cancer chemotherapeutic medicines and in the
25	management of patients with severe pancytopenia.

Line	PROPOSED PROFESSIONAL INFORMATION
26	
27	**Posology**
28	It is recommended to use actual body weight for dosing. The
29	recommended dosage and regimen is 0,8 mg/kg body weight of
30	**DETENER** as a two hour infusion every 6 hours over 4 consecutive days,
31	for a total of 16 doses prior to haematopoietic progenitor cell
32	transplantation.
33	
34	**Special populations**
35	*Obese patients:*
36	For obese or severely obese patients, dosing based on adjusted ideal
37	body weight could be considered. Ideal body weight (IBW) should be
38	calculated as follows (height in cm and weight in kg):
39	IBW (kg; men) = 50 + 0,91 X (height - 152); IBW (kg; women) = 45 + 0,91
40	X (height-152).
41	Adjusted ideal body weight (AIBW) should be calculated as follows:
42	AIBW = IBW + 0,25 X (actual body weight - IBW)
43	
44	**Method of administration:**
45	**DETENER** should be administered by IV infusion via central venous
46	catheter.
47	**DETENER** should not be given by rapid IV injection or bolus.
48	All patients should be premedicated with anticonvulsant medicines to
49	prevent seizures reported with the use of high dose busulfan.
50	Antiemetics should be administered prior to the first dose and continued on
51	a fixed schedule through its administration.

Line	PROPOSED PROFESSIONAL INFORMATION
52	*Precautions to be taken before handling or administering the medicinal*
53	*product.*
54	**DETENER** must be diluted before administration.
55	A final concentration of approximately 0,5mg/ml busulfan should be
56	achieved.
57	For instructions on dilution of the medicinal product before administration,
58	see section 6.6.
59	**DETENER** should be administered by IV infusion via central venous
60	catheter.
61	
62	**4.3 Contraindications**
63	Hypersensitivity to busulfan or to any of the excipients listed in section 6.1.
64	Pregnancy and lactation (see section 4.6).
65	The safety and efficacy in children have not been established.
66	Hepatic insufficiency.
67	
68	**4.4 Special warnings and precautions for use**
69	The consequence of treatment with **DETENER** at the recommended dose
70	and schedule is profound myelosuppression, occurring in all patients.
71	Severe granulocytopenia, thrombocytopenia, anaemia, or any combination
72	thereof may develop. Frequent complete blood counts, including
73	differential white blood cell counts, and platelet counts should be
74	monitored during the treatment and until recovery is achieved.
75	
76	Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should
77	be considered for the prevention and management of infections during the

Line	PROPOSED PROFESSIONAL INFORMATION
78	neutropenic period. Platelet and red blood cell support, as well as the use
79	of growth factors such as granulocyte colony stimulating factor (G-CSF),
80	should be employed as medically indicated.
81	
82	In adults, absolute neutrophil counts < $0,5x10^{9/}$ L at a median of 4 days
83	post transplant occurred in 100% of patients and recovered at median day
84	10 and 13 days following autologous and allogeneic transplant respectively
85	(median neutropenic period of 6 and 9 days respectively).
86	Thrombocytopenia (< $25x10^{9/}$ /L or requiring platelet transfusion) occurred
87	at a median of 5-6 days in 98% of patients. Anaemia (haemoglobin< 8.0
88	g/dL) occurred in 69% of patients.
89	
90	There is limited clinical experience of the use of busulfan as a component
91	of a conditioning regimen prior to HSCT in children with Fanconi's
92	anaemia. Therefore **DETENER** should be used with caution in this type of
93	patients.
95	
96	*Hepatic impairment*
97	**DETENER** as well as busulfan has not been studied in patients with
98	hepatic impairment. Since busulfan is mainly metabolised through the liver,
99	exposure to busulfan is expected to increase if liver function is impaired
100	and the use of **DETENER** in hepatic impaired populations is contra-
101	indicated.
102	It is recommended when treating these patients that serum transaminase,
103	alkaline phosphatase, and bilirubin should be monitored regularly 28 days
104	following transplant for early detection of hepatotoxicity.

Line	PROPOSED PROFESSIONAL INFORMATION
105	Hepatic veno-occlusive disease is a major complication that can occur
106	during treatment with **DETENER**. Patients who have received prior
107	radiation therapy, greater than or equal to three cycles of chemotherapy,
108	or prior progenitor cell transplant may be at an increased risk.
109	
110	Caution should be exercised when using paracetamol prior to (less than 72
111	hours) or concurrently with **DETENER** due to a possible decrease in the
112	metabolism of busulfan (see section 4.5).
113	
114	Cardiac function should be monitored regularly in patients receiving
115	**DETENER.**
116	
117	Occurrence of acute respiratory distress syndrome with subsequent
118	respiratory failure associated with interstitial pulmonary fibrosis was
119	reported in busulfan studies in one patient who died, although, no clear
120	aetiology was identified.
121	In addition, busulfan might induce pulmonary toxicity that may be additive
122	to the effects produced by other cytotoxic medicines. Therefore, attention
123	should be paid to this pulmonary issue in patients with prior history of
124	mediastinal or pulmonary radiation.
125	
126	Periodic monitoring of renal function should be considered during therapy
127	with **DETENER.**
128	
129	Seizures have been reported with high dose busulfan treatment. Special
130	caution should be exercised when administering the recommended dose

Line	PROPOSED PROFESSIONAL INFORMATION
131	of **DETENER** to patients with a history of seizures, head trauma or
132	receiving other potentially epileptogenic medicines. Patients should
133	receive adequate anticonvulsant prophylaxis.
134	
135	*Fertility*
136	Busulfan can impair fertility. Therefore, men treated with **DETENER** are
137	advised not to father a child during and up to 6 months after treatment and
138	to seek advice on cryo-conservation of sperm prior to treatment because
139	of the possibility of irreversible infertility due to therapy with **DETENER**.
140	Ovarian suppression and amenorrhoea with menopausal symptoms
141	commonly occur in pre-menopausal patients. Busulfan treatment in a pre-
142	adolescent girl prevented the onset of puberty due to ovarian failure.
143	Impotence, sterility, azoospermia, and testicular atrophy have been
144	reported in male patients.
145	
146	**4.5 Interactions with other medicines and other forms of interaction**
147	Administration of itraconazole to patients receiving high-dose busulfan
148	may result in reduced busulfan clearance. Patients should be monitored
149	for signs of busulfan toxicity when itraconazole is used as an antifungal
150	prophylaxis with busulfan.
151	Ketobemidone may be associated with high levels of busulfan. Special
152	care is recommended when combining these two medicines. For the
153	BuCy2 regimen it has been reported that the time interval between the last
154	oral busulfan administration and the first cyclophosphamide administration
155	may influence the development of toxicities. A reduced incidence of HVOD
156	and other regimen-related toxicity have been observed in patients when

Line	PROPOSED PROFESSIONAL INFORMATION
157	the lag time between the last dose of oral busulfan and the first dose of
158	cyclophosphamide is > 24 hours.
159	Paracetamol is described to decrease glutathione levels in blood and
160	tissues and may therefore decrease busulfan clearance when used in
161	combination.
162	The concomitant systemic administration of phenytoin to patients receiving
163	high-dose busulfan has been reported to increase busulfan clearance, due
164	to induction of glutathion-S-transferase. However, no evidence of this
165	effect has been seen in the IV data.
166	No interaction has been reported when benzodiazepines such as
167	diazepam, clonazepam or lorazepam have been used to prevent seizures
168	with high-dose busulfan.
169	No interaction was observed when busulfan was combined with
170	fluconazole or 5-HT3 antiemetics such as ondansetron or granisetron.
171	
172	**4.6 Fertility, pregnancy and lactation**
173	**Women of childbearing potential/contraception in males and females**
174	Women of childbearing potential must use effective contraception during
175	and up to 6 months after treatment.
176	
177	**Pregnancy**
178	HPCT is contraindicated in pregnant women; therefore, **DETENER** is
179	contraindicated during pregnancy.
180	There are no or limited amount of data from the use of busulfan or
181	dimethylacetamide (DMA) in pregnant women. A few cases of congenital
182	abnormalities have been reported with low-dose oral busulfan, not

Line	PROPOSED PROFESSIONAL INFORMATION
183	necessarily attributable to the active substance, and third trimester
184	exposure may be associated with impaired intrauterine growth.
185	
186	**Breast-feeding**
187	It is unknown whether busulfan and DMA are excreted in human milk.
188	Because of the potential for tumorigenicity shown for busulfan in human
189	and animal studies, breast-feeding should be discontinued during
190	treatment with busulfan.
191	
192	**Fertility**
193	Busulfan and DMA can impair fertility in man or woman. Therefore, it is
194	advised not to father child during the treatment and up to 6 months after
195	treatment and to seek advice on cryo-conservation of sperm prior to
196	treatment because of the possibility of irreversible infertility (see section
197	4.4).
198	
199	**4.7 Effects on ability to drive and use machines**
200	Not relevant
201	
202	**4.8 Undesirable effects**
203	***a. Summary of the safety profile***
204	Most patients were considered high-risk for transplant, having at least one
205	of the following risk factors such as previous transplant, active disease,
206	refractory and/or relapsed disease and co-morbid factors such as age over
207	45 year.
208	

Line	PROPOSED PROFESSIONAL INFORMATION

- The most frequent, serious, toxic effect of busulfan is myelosuppression resulting in leukopenia, thrombocytopenia and anaemia in all patients.
- Serious adverse events involved liver toxicity.

b. Tabulated summary of adverse reactions

System organ class	Frequency	Side-effect
Blood and lymphatic system disorders	*Frequent*	Neutropenia Thrombocytopenia Anaemia Pancytopenia Febrile neutropenia
Immune system disorders	*Frequent*	Allergic reaction
Nervous system disorders	*Frequent*	Dizziness
	Less frequent	Encephalopathy Cerebral haemorrhage Seizure
Psychiatric disorders	*Frequent*	Insomnia Anxiety Depression Confusion
	Less frequent	Delirium Nervousness Hallucination

Line	PROPOSED PROFESSIONAL INFORMATION		
235			Agitation
236	Metabolism and	*Frequent*	Hyperglycaemia
237	nutrition disorders		Hypomagnesaemia
238			Hypokalaemia
239			Hypocalcaemia
240			Hypophosphataemia
241			Hyponatraemia
242	Cardiac disorders	*Frequent*	Tachycardia
243			Arrhythmia
244			Atrial fibrillation
245			Cardiomegaly
246			Pericardial effusion
247			Pericarditis
248		*Less*	Ventricular extrasystoles
249		*frequent*	Bradycardia
250			
251	Vascular disorders	*Frequent*	Hypertension
252			Hypotension
253			Vasodilation
254			Thrombosis
256		*Less*	Femoral artery thrombosis
257		*frequent*	Capillary leak syndrome
258	Respiratory thoracic	*Frequent*	Dyspnoea
259	and mediastinal		Cough
260	disorders		Hiccup
261			Epistaxis

Line	PROPOSED PROFESSIONAL INFORMATION		
262			Hyperventilation
263			Respiratory failure
264			Alveolar haemorrhages
265			Asthma
266			Atelectasis
267			Pleural effusion
268		*Less*	Hypoxia
269		*frequent*	Acute respiratory distress
270			syndrome
271	Infections and	*Frequent*	Rhinitis
272	infestations		Pharyngitis
273		*Less*	Pneumonia
274		*frequent*	Graft versus host disease
275			One or more episodes of
276			infection (mostly mild to
277			moderate)
278	Gastrointestinal	*Frequent*	Nausea
279	disorders		Stomatitis
280			Vomiting
281			Anorexia
282			Diarrhoea
283			Constipation
284			Dyspepsia
285			Anus discomfort
286			Oesophagitis
287			Ileus

Line	PROPOSED PROFESSIONAL INFORMATION		
288			Haematemesis
289 290		*Less frequent*	Gastrointestinal haemorrhage
291 292 293 294 295 296	Hepato-biliary disorders	*Frequent*	Hyperbilirubinaemia Jaundice Increased hepatic enzymes Blood alkaline phosphatase increased Hepatomegaly
297 298 299		*Less frequent*	Hepatic veno-occlusive disease (HVOD) Severe AST elevations
300 301 302	Skin and subcutaneous tissue disorders	*Frequent*	Rash Pruritis Alopecia
303 304 305	Musculoskeletal and connective tissue disorders	*Frequent*	Back pain Myalgia Arthralgia
306 307 308 309	Renal and urinary disorders	*Frequent*	Dysuria Oligurea Haematuria Moderate renal insufficiency
310 311 312 313	General disorders and administration site conditions	*Frequent*	Fever Headache Abdominal pain Asthenia

Line	PROPOSED PROFESSIONAL INFORMATION

		Chills
		Pain
		Oedema
		Oedema general
		Pain or inflammation at the injection site
		Chest pain
Investigations	*Frequent*	Decreased ejection fraction
		Creatinine elevated
		BUN increase
		Weight increase
		Abnormal breath sounds

c. Description of selected adverse reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The principal toxic effect is profound myeloablation and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may also be affected.

Line	PROPOSED PROFESSIONAL INFORMATION
340	There is no known antidote to **DETENER** other than haematopoietic
341	progenitor cell transplantation. In the absence of
342	haematopoietic progenitor cell transplantation, the recommended dose of
343	**DETENER** would constitute an overdose of busulfan. The haematologic
344	status should be closely monitored and vigorous supportive measures
345	instituted as medically indicated.
346	Dialysis should be considered in the case of an overdose.
347	Since, busulfan is metabolised through conjugation with glutathione,
348	administration of glutathione might be considered.
349	It must be considered that overdose of **DETENER** will also increase
350	exposure to DMA. No specific antidote for DMA overdose is known. In
351	case of overdose, management would include general
352	supportive care.
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361	**5. PHARMACOLOGICAL PROPERTIES**
362	**5.1 Pharmacodynamic properties**
363	Pharmacotherapeutic group: Alkyl sulfonates, ATC code: L01AB01.
364	Category and class: A 26 Cytostatics
365	

Line	PROPOSED PROFESSIONAL INFORMATION
366	**Mechanism of action**
367	Busulfan is a cytotoxic medicine and a bifunctional alkylating medicine. In
368	aqueous media, release of the methanesulphonate groups produces
369	carbonium ions which can alkylate DNA, thought to be an important
370	biological mechanism for its cytotoxic effect.
371	
372	**5.2 Pharmacokinetic properties**
373	The information presented on biotransformation and elimination is based
374	on oral busulfan.
375	**Pharmacokinetics in adults**
376	**Absorption**
377	Immediate and complete availability of the dose is obtained after
378	intravenous infusion of busulfan.
379	
380	**Distribution**
381	Terminal volume of distribution Vz ranged between 0,62 and 0,85 L/kg.
382	Busulfan concentrations in the cerebrospinal fluid are comparable to those
383	in plasma although these concentrations are probably insufficient for anti-
384	neoplastic activity. Reversible binding to plasma proteins was around 7%
385	while irreversible binding, primarily to albumin, was about 32%.
386	
387	**Biotransformation**
388	Busulfan is metabolised mainly through conjugation with glutathione
389	(spontaneous and glutathione-S-transferase mediated). The glutathione
390	conjugate is then further metabolised in the liver by oxidation. None of the
391	

Line	PROPOSED PROFESSIONAL INFORMATION
392	metabolites is thought to contribute significantly to either efficacy or
393	toxicity.
394	
395	**Elimination**
396	Total clearance in plasma ranged 2.25 - 2.74 mL /minute/kg. The terminal
397	half-life ranged from 2,8 to 3,9 hours. Approximately 30% of the
398	administered dose is excreted into the urine over 48 hours with 1% as
399	unchanged busulfan. Elimination in faeces is negligible. Irreversible protein
400	binding may explain the incomplete recovery. Contribution of long lasting
401	metabolites is not excluded.
402	
403	**6 PHARMACEUTICAL PARTICULARS**
404	**6.1 List of excipients**
405	Citric acid anhydrous
406	Macrogol 400
407	Purified N, N-Dimethyl Acetamide
408	
409	**6.2 Incompatibilities**
410	In the absence of compatibility studies, this medicinal product must not be
411	mixed with other medicinal products except those mentioned in section
412	6.6.
413	Do not use polycarbonate syringes with **DETENER.**
414	
415	**6.3 Shelf life**
416	Vials: 2 years
417	

Line	PROPOSED PROFESSIONAL INFORMATION
418	Diluted solution: Chemical and physical in-use stability after dilution has
419	been demonstrated for:
420	8 hours (including infusion time) after dilution in glucose 5% or sodium
421	chloride 9 mg/ml (0,9%) solution for injection when stored at 20 °C ± 5 °C.
422	
423	6 hours after dilution in sodium chloride 9 mg/ml (0,9%) solution for
424	injection when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5
425	°C (including infusion time).
426	From a microbiological point of view, unless the method of dilution
427	precludes the risk of microbial contamination, the product should be used
428	immediately. If not used immediately, in-use storage times and conditions
429	are the responsibility of the user.
430	
431	**6.4 Special precautions for storage**
432	Store in a refrigerator (2°C – 8°C). Excursions not permitted.
433	Do not freeze.
434	For storage conditions after dilution of the medicinal product see section
435	6.3.
436	KEEP OUT OF REACH OF CHILDREN.
437	
438	**6.5 Nature and contents of container**
439	Busulfan 6mg/ml concentrate for solution for infusion is packed in 11 ml
440	clear tubular Lyo Type I glass vial with a 20mm purple flip off aluminium
441	seal and a 20mm rubber stopper. The vials are packaged into folded
442	cardboard cartons with a leaflet enclosed.
443	

Line	PROPOSED PROFESSIONAL INFORMATION
444	Busulfan is packed in a single pack of 1 vial and 8 single cartons are
445	packed in a shrink sleeve.
446	
447	**6.6 Special precautions for disposal and other handling**
448	Preparation of dilution:
449	Procedures for proper handling and disposal of anticancer drugs should be
450	followed. Caution should be exercised in handling and preparing the
451	solution. The use of gloves is recommended as skin reactions may occur
452	with accidental exposure. If this occurs, wash the skin or mucosa
453	immediately and thoroughly with water.
454	**DETENER must** be diluted with 0,9 % sodium chloride or 5 % glucose
455	solution for injection. The quantity of the diluent must be 10 times the
456	volume of **DETENER** to ensure the final concentration of busulfan remains
457	at approximately 0,5 mg/ml.
458	
459	For example, for a 70 kg (actual body weight) patient, the amount of drug
460	to be administered will be calculated as follows:
461	(70 kg patient) X (0,8 mg/kg)/ 6 mg/ml) = 9,3 ml **DETENER** (56 mg total
462	dose).
463	To prepare the final solution for infusion, add 9,3 ml of **DETENER** to 93 ml
464	of diluent 0,9 % sodium chloride or 5 % dextrose solution for injection) as
465	calculated below:
466	(9,3 ml **DETENER**) X (10) = 93 ml of either diluent plus the 9,3 ml
467	**DETENER** to yield a final concentration of busulfan of 0,5 mg/ml (9,3 ml X
468	6 mg/ml/ 102,3 ml = 0,5 mg/ml)
469	Diluted **DETENER** should be used within 8 hours if stored at 20 °C ± 5 °C.

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470	All transfer procedures require strict adherence to aseptic techniques,
471	preferably employing a vertical laminar flow safety hood while wearing
472	gloves and protective clothing.
473	Using a syringe fitted with a needle remove the calculated volume of
474	**DETENER** from the vial and dispense the content of the syringe into an
475	intravenous bag (or syringe) which already contains the calculated amount
476	of diluent, making sure that the drug flows into and through the solution.
477	Do not put **DETENER into** an IV bag that does not contain diluent. Always
478	add **DETENER to** the diluent, not the diluent to **DETENER**. Mix thoroughly
479	by inverting several times.
480	Do not use polycarbonate syringes with **DETENER.**
481	The entire prescribed dose should be administered over two hours. Prior to
482	and following each infusion, flush the catheter line with approximately 5 ml
483	of the diluent. Do not flush residual drug in the administration tubing as
484	rapid infusion of **DETENER** is not recommended.
485	Do not infuse concomitantly with another IV solution.
486	
487	
488	
489	**7. HOLDER OF CERTIFICATE OF REGISTRATION**
490	Emcure Pharmaceuticals SA (Pty) Ltd.
491	Arizona House, First floor, South Wing, Aspen Business Park
492	1 Madison Avenue, Aspen Lakes, Extension 13
493	Johannesburg South,
494	2190
495	

Line	PROPOSED PROFESSIONAL INFORMATION
496	
497	**8. REGISTRATION NUMBER(S)**
498	56/26/0353
499	
500	**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE**
501	**AUTHORISATION**
502	24 January 2023