7.06 PLITIDEPSIN, Powder for I.V. infusion 2 mg with 4 mL solvent, Aplidin®, Specialised Therapeutics Pharma Pty Ltd

1 Purpose of submission

1.1 The resubmission requested a Section 100 - Efficient Funding of Chemotherapy, Authority Required (telephone) listing for plitidepsin for the treatment of relapsed/refractory multiple myeloma (RRMM) in patients who are refractory (experienced treatment failure/contraindicated) to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD; third-line setting) or in patients who have received at least three prior treatment regimens including both a PI and an IMiD (fourth-line setting). The treatment setting remains unchanged from the July 2019 submission.

1.2 The resubmission presented an indirect comparison against pomalidomide in the third-line setting and a direct comparison against dexamethasone (Dxm) in the fourth-line setting. Separate economic evaluations were presented in each setting. The submission presented a cost-minimisation analysis (CMA) compared to pomalidomide (third-line setting) and a cost-utility analysis (CUA) compared to Dxm (fourth-line setting). The key components of the clinical issue presented in the resubmission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Patients with RRMM who have received at least three prior treatment regimens, including both a PI and an IMiD, or failure of two prior treatments if contraindicated or intolerant to a PI and an IMiD.
Intervention	Plitidepsin in combination with Dxm
Comparator	3rd line treatment setting: Pomalidomide in combination with Dxm. 4th line treatment setting: Dxm
Outcomes	PFS, OS, RR, DoR, TEAEs
Clinical claim	3rd line treatment setting: In patients with RRMM who have received at least two prior treatment regimens, including both a PI and an IMiD, plitidepsin + Dxm is no worse than pomalidomide + Dxm at improving PFS and OS, with a different safety profile. 4th line treatment setting: In patients with RRMM who have received at least three prior treatment regimens, including both a PI and IMiD, plitidepsin + Dxm is superior in terms of effectiveness and inferior in terms of safety compared with Dxm monotherapy[a].

Source: Table 9, p31 of the March 2020 resubmission.

DoR = duration of response; Dxm = dexamethasone; IMiD = immunomodulatory agent; OS = overall survival; PFS = progression free survival; PI = proteasome inhibitor; RR = response rate; RRMM = relapsed/refractory multiple myeloma; TEAE = treatment-emergent adverse event.

[a] July 2019 submission claimed non-inferior safety for plitidepsin + Dxm compared to Dxm monotherapy.

2 Background

Registration status

2.1 Plitidepsin was TGA registered on 10 December 2018 for use in combination with Dxm, for the treatment of patients with RRMM who have received at least three prior treatment regimens, including both a PI and an IMiD. Plitidepsin may be used after two prior lines of therapy if refractory and/or intolerant to both a PI and an IMiD.

2.2 During the TGA review process, registration of plitidepsin was recommended in the Clinical Evaluation Report; however, the first assigned TGA Delegate noted an intention to reject the application on the basis of an unfavourable balance of benefits to harms. The registration was subsequently approved following a meeting with the sponsor, the appointment of a second delegate and lodgement of a Section S31 request.

2.3 Plitidepsin was rejected by the European Medicines Agency (EMA) in December 2017. The Sponsor requested a re-examination of the initial opinion, and after re-examination the Committee for Medicinal Products for Human Use (CHMP) confirmed the refusal of the marketing authorisation in March 2018.[1] The EMA stated that plitidepsin + Dxm demonstrated only a modest increase in progression free survival (PFS) of approximately one month compared to Dxm monotherapy, improvement in overall survival (OS) was not adequately demonstrated, and that severe side effects were reported. The EMA considered that the benefits of plitidepsin did not outweigh its risks.

2.4 Plitidepsin has not been considered by the Food and Drug Administration (FDA) in the USA.

Previous PBAC consideration

2.5 Plitidepsin in combination with Dxm was previously considered by the PBAC for this indication in July 2019. It was not recommended. A summary of the matters of concern raised by the PBAC in respect to the July 2019 submission, and how they have been addressed in the March 2020 resubmission is provided in Table 2.

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/aplidin

Table 2: Summary of key matters of concern

Matter of concerns identified by PBAC in July 2019 meeting	How the resubmission addressed it
PBS restriction issues	
Authority Required (telephone) restriction level was inappropriate (para 2.3, July 2019 PSD).	Not addressed.
The maximum amount was sufficient for a BSA of 1.8 m^2. At a BSA of 2.2 m^2, a maximum amount of 22 mg would be required. This had minor implications for the estimated financial impact (para 2.5, July 2019 PSD).	Not addressed.
Clinical issues	
The PBAC considered that, for the comparison of plitidepsin + Dxm versus Dxm alone, the magnitude of the clinical benefit in terms of PFS (median increase of 0.9 months) was marginal (para 7.1, July 2019 PSD).	The resubmission argued that the most relevant PFS outcome was IRC assessed PFS with PD confirmation based on the IMWG guidelines. There was a 3 month increase in median PFS with PD confirmation in ADMYRE trial; however, the ESC considered that PFS with PD confirmation was not a reliable estimate of PFS with plitidepsin + Dxm as it was a preplanned sensitivity analysis to test the consistency of the primary PFS outcome, PFS without PD confirmation, and as over half the patients were censored in the analysis.
Patients treated with plitidepsin experienced a significant increase in AEs in the ADMYRE trial (para 7.2, July 2019 PSD).	Resubmission claimed inferior safety of plitidepsin against Dxm monotherapy. This was supported by the evidence presented.
The PBAC considered that for the comparison with pomalidomide + Dxm, the claim of non-inferior efficacy was uncertain, and the claim of non-inferior safety was not adequately supported (para 7.1, July 2019 PSD).	No new data were presented. The resubmission's claim of non-inferiority with respect to effectiveness remained unsupported. The claim of a different safety profile might be reasonable based on a naïve comparison of AEs with RRMM treatments.
Economic issues – CMA	
The submission used only the AEs rates from the ADMYRE trial under the assumption that the toxicity profile of pomalidomide + Dxm was not different to that of Dxm monotherapy. The evidence provided in Section 2 of the submission does not support this assumption' (para 6.38, July 2019 PSD).	The resubmission used the ITC as the primary method for determining the relative toxicity of plitidepsin and pomalidomide.
Economic issues – CUA	
The KM data should have been applied until the median follow-up, with the extrapolated data applied thereafter (para 6.41, July 2019 PSD).	The base case model used KM estimates with extrapolation after median follow-up for PFS (33-36 months) and TTF (17-20 months) and before median follow-up for OS (17-20 months).
The method used to estimate utility weights derived an average utility value rather than a health state specific utility value (para 6.42, July 2019 PSD).	The resubmission incorrectly stated that it used the utility values that were recalculated in the July 2019 plitidepsin commentary and instead used utility values from the carfilzomib PBAC submission in its base case.
Time horizon of 7 years was inappropriate (para 7.10, July 2019 PSD).	Reduced to 5 years.
Source of TTF could not be verified (para 7.10, July 2019 PSD)	Unaddressed. The resubmission stated that TTF was a mathematical construct derived from PFS.
It was not possible to estimate the interim steps used to calculate the crossover adjusted OS data for the Dxm monotherapy arm (para 7.10, July 2019 PSD).	OS data unadjusted for crossover were provided in the economic model.

Matter of concerns identified by PBAC in July 2019 meeting	How the resubmission addressed it
Any future analysis should account for the issues raised and the resulting ICER would need to be < $40,000/QALY to account for the substantial toxicity and minor additional benefit of plitidepsin para 7.13, July 2019 PSD).	Model base case ICER: $[redacted]. Resubmission argued ICER of $45,000/QALY – $75,000/QALY was reasonable based on previous PBAC's considerations for pomalidomide and carfilzomib.
Financial issues	
Uptake rates likely overestimated due to the toxicity of plitidepsin and clinically meaningful effect on small undefinable subgroup of patients (para 7.12, July 2019 PSD).	Uptake rates unchanged.
Costs for prophylactic agents were underestimated (para 6.63, July 2019 PSD).	Estimated increased use of promethazine and prochlorperazine.

Source: Table 1, pp2-6 of the resubmission, July 2019 Plitidepsin Public Summary Document.
AE = adverse events; BSA = body surface area; CMA = cost-minimisation analysis; CUA = cost-utility analysis; Dxm: dexamethasone; ICER = incremental cost-effectiveness ratio; IMWG = international myeloma working group; IRC = independent review committee; ITC = indirect treatment comparison; OS = overall survival; para = paragraph; PBS = pharmaceutical benefit; scheme; PD = progressive disease; PFS = progression-free survival; PSD = public summary document; QALY = quality-adjusted life years; RCT = randomized control trial; RRMM = relapsed refractory multiple myeloma; TTF= time to treatment failure.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max Amt	№. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer	
Plitidepsin Vial, 2 mg injection	~~20 mg~~ *11 mg*	~~0~~ *1*	$[redacted]	Aplidin	Specialised Therapeutics Pharma

Category/Program:	Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital code)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Restriction level/Method:	☐ Unrestricted benefit ☐ Restricted benefit ☒ *Authority Required – In Writing* ☒ ~~Authority Required – Telephone/Electronic/Emergency~~ ☐ Authority Required - Streamlined
Indication:	Multiple myeloma
Treatment phase:	Initial treatment *of relapsed and refractory multiple myeloma*

Clinical criteria:	The treatment must be in combination with dexamethasone ~~AND~~ ~~Patient must have undergone or be ineligible for a primary stem cell transplant~~ AND Patient must have ~~received~~ *progressive disease after* at least three prior treatment regimens including both a proteasome inhibitor and an immunomodulatory agent; OR Patients must have experienced treatment failure with ~~a proteasome inhibitor~~ or be intolerant to or be contraindicated according to the TGA approved product information *to at least two prior treatment regimens that include a proteasome inhibitor and an immunomodulatory agent* ~~AND~~ ~~Patients must have experienced treatment failure with an immunomodulatory agent or be intolerant to or be contraindicated according to the TGA approved product information~~ AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, pomalidomide, bortezomib or carfilzomib
Prescribing instructions:	Proteasome inhibitor or immunomodulatory agent treatment failure is the absence of achieving at least a partial response or as progressive disease during treatment or within 6 months of discontinuing treatment with these drugs. If treatment with either a proteasome inhibitor or immunomodulatory agent is contraindicated according to the relevant TGA-approved Product Information, the application must provide details of the contraindication. If intolerance to either proteasome inhibitor or immunomodulatory agent treatment develops during the relevant period of use which is of a severity to necessitate withdrawal of the treatment, the application must provide details of the nature and severity of this intolerance. *For the purposes of this restriction, a proteasome inhibitor refers to bortezomib or carfilzomib. An immunomodulatory agent refers to lenalidomide, pomalidomide or thalidomide.* Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein. *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed Multiple Myeloma plitidepsin Authority Application Supporting Information form that includes details of:* *(i) past treatment failures;* *(ii) any intolerance or contraindication to a proteasome inhibitor and immunomodulatory agent;*

Administrative advice:	~~Authority applications may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001* *Special Pricing Arrangements apply.*

Category/Program:	Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital code)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Restriction level/Method:	☐ Unrestricted benefit ☐ Restricted benefit ☒ ~~Authority Required – In Writing~~ ☒ *Authority Required – Telephone/Electronic/Emergency* ☐ Authority Required - Streamlined
Indication:	Multiple myeloma
Treatment phase:	Continuing treatment *of relapsed and refractory multiple myeloma*
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug AND ~~Patient must not have progressive disease~~ *Patient must not have progressive disease while receiving treatment with this drug* AND The treatment must be in combination with dexamethasone AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, pomalidomide, bortezomib or carfilzomib *(specify in alphabetical order)*
Prescribing instructions:	Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). ~~Patients receiving this drug under the PBS listing must be registered in the i-access risk management program.~~

Administrative advice:	Authority applications may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). *Special Pricing Arrangements apply.*

PBS = pharmaceutical benefits scheme; Rpts = repeats; TGA = therapeutic goods administration.

3.2 The proposed restriction was unchanged from July 2019. The PBAC noted that the changes suggested by the Secretariat and the PBAC in July 2019 were not addressed in the resubmission.

3.3 The resubmission did not propose a Special Pricing Arrangement (SPA) for plitidepsin but acknowledged that one may be required given that pomalidomide (the comparator in the third-line setting) is listed under a SPA.

3.4 The March 2020 resubmission proposed a published dispensed price for maximum amount (DPMA) of $[redacted] per 20 mg dose, which was a reduction of approximately [redacted]% from the previous price of $[redacted] per 20 mg dose in the July 2019 submission. The proposed price of plitidepsin was weighted across the third (DPMA = $[redacted], 53%) and fourth-line settings (DPMA = $[redacted], 47%). The weighting differed slightly from the estimated proportions of patients using third (56%) and fourth-line (44%) plitidepsin in the financial estimates (excluding grandfathered patients). Using the weightings applied in the financial estimates resulted in a price of $[redacted].

3.5 The PBAC again considered that an Authority Required (telephone) restriction level was inappropriate and that the restriction level for initial treatment with plitidepsin should be consistent with that of pomalidomide, which was Authority Required (written).

3.6 The proposed restriction was consistent with the use of plitidepsin in the ADMYRE trial (the main source of the evidence comparing plitidepsin + Dxm with Dxm monotherapy) and the TGA approved Product Information. The proposed maximum amount of 20 mg assumed a body surface area (BSA) of 2.0m^2 (dose of 5 mg/m^2 allows for two administrations per cycle at 10 mg per dose). At a BSA of 2.2 m^2, a maximum amount of 22 mg would have been required. While this calculation may not have altered the proposed price (on a cost-minimisation basis), it has minor implications for the estimated financial impact. These could not be tested given the structure of the financial estimate workbook provided.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple myeloma (MM) arises due to malignant clonal plasma cell proliferation in the bone marrow microenvironment. The overall median survival is currently five to six years from diagnosis of MM; however, outcomes vary largely by the influence of

biological characteristics, such as cytogenetics and age. In the RRMM setting, MM becomes typically more aggressive with successive relapses.

5 Comparator

5.1 Unchanged from the previous submission, the resubmission nominated two comparators for plitidepsin: pomalidomide with Dxm (for patients with refractory/intolerant MM in the third-line setting) and Dxm monotherapy (for patients with relapsed/refractory MM in the fourth-line setting). The nominated comparators were considered appropriate by the PBAC at the July 2019 meeting. The PBAC considered that plitidepsin was likely to displace, rather than replace, pomalidomide. For this reason, the PBAC considered that the comparison against Dxm alone was the most relevant to determining the cost effectiveness of plitidepsin, while noting that the comparison with pomalidomide provided a useful reference point (paragraph 7.3, plitidepsin Public Summary Document (PSD), July 2019 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (49), health care professionals (2) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from the individuals described the desire for another treatment option to become available on the PBS and concerns regarding toxicity and side effects.

6.3 The comments from the health care professionals were supportive of providing PBS-subsidised access to treatment for patients, describing their experience with plitidepsin and how patients have benefitted from treatment.

6.4 The PBAC noted the advice from Myeloma Australia describing the benefit of plitidepsin for some patients. The PBAC considered the advice from the Leukaemia Foundation, the South East Myeloma Support Group and Rare Cancers Australia provided little additional insight into the need for plitidepsin.

Clinical trials

6.5 No new data were presented in the resubmission. As per the previous submission, the resubmission presented:

- A direct comparison between plitidepsin + Dxm and Dxm monotherapy in the fourth-line setting (ADMYRE, N = 255); and

- An indirect comparison between plitidepsin + Dxm and pomalidomide + Dxm in the third-line setting (ADMYRE versus NIMBUS, N = 455).

Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission*

Trial	Protocol title/ Publication title	Publication citation
ADMYRE (NCT01102426)	Pharma Mar S.A. ADMYRE: Aplidin – Dexamethasone in Relapsed/Refractory MYeloma) Randomized, multicenter, open-label, phase III study of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma.	CSR, APL-C-001-09, 2016.
	Pharma Mar S.A. ADMYRE: Aplidin – Dexamethasone in Relapsed/Refractory MYeloma) Randomized, multicenter, open-label, phase III study of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma.	CSR, APL-C-001-09, Addendum, 2017.
	Spicka I, Ocio EM, *et al.* Randomized phase III study (ADMYRE) of plitidepsin in combination with dexamethasone vs. dexamethasone alone in patients with relapsed/refractory multiple myeloma.	*Annals of Hematology* 2019; 98 (9): 2139-2150.
	Gomez J, Extremera S, *et al.* Overall Survival Results Of Randomized Phase III Study (ADMYRE Trial) Of Plitidepsin And Dexamethasone (Dxm) Vs.Dxm Alone In Patients With Relapsed/Refractory Multiple Myeloma: Evaluation Of The Crossover Impact. Poster presented at: ASCO (Chicago, USA).	*Journal of Clinical Oncology* 2018; 36 (15):8018.
	National Institute For Health And Care Excellence. Single Technology Appraisal Final scope for the single technology appraisal of pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib.	NICE. Committee papers [ID985], 2016.
NIMBUS (NCT01311687)	European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report Pomalidomide. Procedure No. EMEA/H/C/002682	EMA. Report, 2013.
	San Miguel J; Weisel K; *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized, open-label, phase 3 trial.	*Lancet Oncology* 2013, 14(11):1055-1066.
	Dimopoulos MA, Weisel KC, *et al.* Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone.	*Haematologica* 2015; 100(10):1327-1333.
	Richardson PG, Dimopoulos MA, *et al.* Efficacy and Safety Of Pomalidomide Plus Low-Dose Dexamethasone In Advanced Multiple Myeloma: Results Of Randomized Phase 2 and 3 Trials (MM-002/MM-003).	*Blood* 2013; 122 (21) 3185.
	Moreau P, Weisel KC, *et al.* Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS).	*Leukemia & Lymphoma* 2016; 57(12): 2839-2847.
	Morgan G, Palumbo A, *et al*. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone.	*British Journal of Haematology* 2015; 168(6): 820-823.
	San Miguel JF, Weisel KC, *et al.* Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma.	*Haematologica* 2015; 100 (10): 1334-1339.

Trial	Protocol title/ Publication title	Publication citation
	Siegel DS, Weisel KC, *et al.* Pomalidomide plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma and moderate renal impairment: a pooled analysis of three clinical trials.	*Leukemia & Lymphoma* 2016; 57(12):2833-2838.
	Song KW, Dimopoulos MA, *et al.* Health-related quality of life from the MM-003 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed and/or refractory multiple myeloma.	*Hematologica* 2015; 100(2):e63-e67.
	Weisel K, Dimopoulos M, *et al.* Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial.	*Clinical Lymphoma Myeloma and Leukemia* 2015; 15(9):519-530.
	Weisel K, Dimopoulos M, *et al*. Pomalidomide and Low-Dose Dexamethasone Improves Health-Related Quality of Life and Prolongs Time to Worsening in Relapsed/Refractory Patients With Multiple Myeloma Enrolled in the MM-003 Randomized Phase III Trial.	*Clinical Lymphoma, Myeloma and Leukemia* 2015; 15(9):610.
	Weisel KC, Dimopoulos MA, *et al*. Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in refractory or relapsed and refractory multiple myeloma.	*Haematologica* 2016; 101(7):872-878.

Source: Table 22, pp66-69 of the March 2020 resubmission.

* For conference abstract citations see July 2019 Public Summary Document for plitidepsin

6.6 The key features of the randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence (unchanged from previous submission)

Trial	N	Design/median follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Plitidepsin + Dxm vs. Dxm monotherapy						
ADMYRE	225	R, OL, MC Plitidepsin arm: PFS: 17.1 months[a]; OS: 33.4 months[b]; Dxm arm: PFS: 20.7 months[a]; OS: 36.3 months[b]	Low	RRMM patients who received prior bortezomib and lenalidomide (or thalidomide)	PFS, PFS with PD confirmation, OS, Safety	PFS with PD confirmation, OS, TTF
Pomalidomide + Dxm vs. HI-Dxm						
NIMBUS	455	R, OL, MC IRC:10 months[c]	Low	RRMM patients who failed prior bortezomib and lenalidomide	PFS with PD confirmation, OS, Safety	Not used

Source: pp iii-viii, 7-24, 61-196 in the resubmission.

Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; IRC = independent review committee; MC = multi-centre; N = total patients in each arm; OL = open label; OS = overall survival; PD = progressed disease; PFS = progression-free survival; R = randomised; RRMM = relapse or refractory multiple myeloma; TTF = time to treatment failure; TTFST = time to subsequent first treatment; vs = versus.

[a] PFS cut-off November 2015

[b] OS cut-off May 2017

[c] Cut-off 1 March 2013

6.7 The ADMYRE trial was a Phase III trial that compared plitidepsin (5 mg/m^2 IV; Day 1 and 15 every four weeks) in combination with Dxm (40 mg orally; Day 1, 8, 15 and 22 every four weeks) to Dxm monotherapy (40 mg orally; Day 1, 8, 15 and 22 every four weeks). The NIMBUS trial was a Phase III trial comparing pomalidomide (4 mg/day orally; Day 1-21 every four weeks) + Dxm (40 mg orally; Day 1, 8, 15 and 22 every four weeks) to high-dose Dxm (HI-Dxm, 40 mg orally; Day 1-4, 9-12 and 17-20 every four weeks). The different Dxm regimens used in the common comparator arms of the

ADMYRE and NIMBUS trials affected the interpretation of the indirect comparison (refer to Comparative Effectiveness section below).

6.8 The primary outcome of the ADMYRE trial was PFS without confirmation of progressive disease (PD). The resubmission considered the most relevant PFS outcome was PFS with PD confirmation and this outcome was used in the indirect comparison with pomalidomide and the base case of the cost-utility analysis. The resubmission's rationale was that:

- The variability in the M-protein used to assess disease progression necessitated a second measurement for confirmation of progression;
- The International Myeloma Working Group (IMWG) guidelines from 2006, 2011, and 2014 recommend confirmation of PD, however the 2008 guidelines did not explicitly require PD confirmation;
- The NIMBUS trial used PFS with PD confirmation as their PFS outcome. Implicitly, this would improve the transitivity of the outcomes in the indirect comparison; and
- PFS without PD confirmation was not used in recent trials for RRMM and is no longer considered clinically meaningful.

6.9 The ESC considered that IRC assessed PFS with PD confirmation was not a reliable estimate of PFS with plitidepsin + Dxm in the context of the ADMYRE trial as this outcome was one of a number of preplanned sensitivity analysis to test the consistency of the PFS primary outcome. In addition, it was noted that:

- Over half the patients were censored in the IRC assessed PFS with PD confirmation analysis (52%) compared with 25% in the PFS without PD confirmation analysis. The effect of censoring on the reliability of the reported result was unknown;
- It was unclear when patients without a second PD confirmation were censored in the IRC assessed PFS with PD confirmation analysis. More patients were at risk of a progression event in the analysis requiring confirmation of PD; and
- The median time from the first observation of PD to confirmation of PD by the IRC was 28 days in both treatment arms. However, confirmation of PD resulted in a substantial change in median PFS in the plitidepsin + Dxm arm only (2.6 months to 5.0 months in the plitidepsin + Dxm arm compared to 1.7 months to 2.0 months in the Dxm arm). This may suggest that there was an underlying difference between plitidepsin + Dxm patients with/without PD confirmation.

6.10 The Pre-Sub-Committee Response (PSCR) stated that of the 191 patients who had experienced PD without confirmation, 68 patients were reclassified as censored in the PFS with PD confirmation analysis. Patients already censored (41 in the plitidepsin + Dex arm and 23 in the Dxm arm) remained censored (see Table 5). The ESC were concerned about the high number of patients censored in the PFS with PD confirmation analysis. The pre-PBAC response clarified that all patients who had not

progressed or died at the data-cut were considered to have been censored. Therefore, patients who were censored were not restricted to those who had missing data or who had discontinued.

6.11 The PSCR stated that for 30 of the 68 reclassified patients who experienced PD without confirmation and 22 of the patients who experienced PD with confirmation, the time-at-risk was increased as they were returned to the cohort for up to an additional 5.7 months and 8.3 months, respectively. The ESC were concerned that this may have artificially increased the PFS duration in the PD confirmation analysis.

Table 5: PFS with and without PD confirmation

	Plitidepsin + Dxm	Dxm	Total
N	171	84	255
PFS without PD confirmation			
Number of events	130 (76.0%)	61 (72.6%)	191
Censored	41 (24.0%)	23 (27.4%)	64
PFS with PD confirmation			
Number of events	80 (46.8%)	43 (51.2%)	123
Censored	91 (53.2%)	41 (48.8%)	132
Difference			
Number of events/censored	50	18	68

Dxm = dexamethasone; PD = progressive disease; PFS = progression free disease
Source: Table 3, p5 of the PSCR

Comparative effectiveness

Plitidepsin + Dxm versus Dxm: the ADMYRE trial

6.12 The results of the key PFS outcomes comparing plitidepsin + Dxm and Dxm monotherapy are presented in Table 6. The Kaplan-Meier plots for PFS are presented in Figure 1. The PBAC previously considered use of the IRC analysis to be the most appropriate (paragraph 7.4, plitidepsin PSD, July 2019 PBAC meeting).

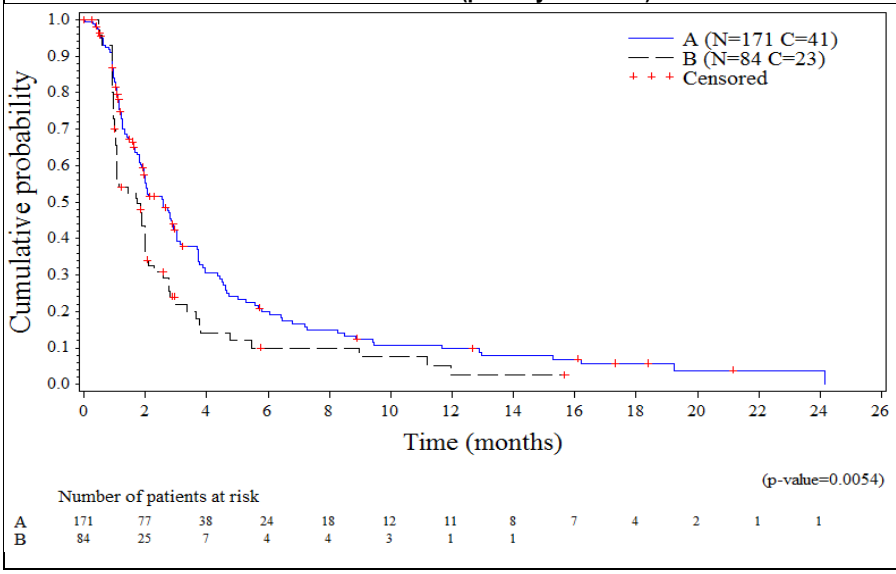
Table 6: Key IRC assessed PFS outcomes for plitidepsin + Dxm versus Dxm monotherapy

	Plitidepsin + Dxm	Dxm	Absolute difference (months)	HR (95% CI)
Progression-free survival (IRC without PD confirmation) – primary outcome				
Progressed, n/N (%)	130/171 (76.0%)	61/84 (72.6%)	-	**0.65 (0.48, 0.89)** p-value = 0.0062
Censored, n/N (%)	41/171 (24.0%)	23/84 (27.4%)	-	
Median PFS, months (95% CI)	2.6 (1.9, 3.0)	1.7 (1.1, 2.0)	0.9	
% not progressed at 6 months (95% CI)	20.0% (13.1, 26.9)	10.0% (2.0, 18.0)	-	
Progression-free survival (IRC with PD confirmation)				
Progressed, n/N (%)	80/171 (46.8%)	43/84 (51.2%)	-	**0.52 (0.35, 0.76)** p-value = 0.0005
Censored, n/N (%)	91/171 (53.2%)	41/84 (48.8%)	-	
Median PFS, months (95% CI)	5.0 (3.0, 6.4)	2.0 (1.7, 3.0)	3.0	
% not progressed at 6 months (95% CI)	42.6% (32.6, 52.6)	19.7% (7.2, 32.2)	-	

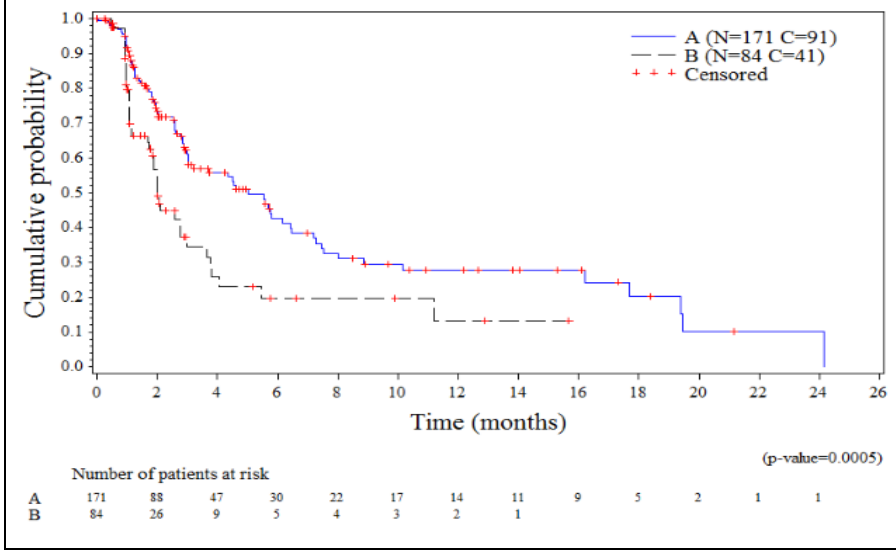
Source: Table 39, p118; Table 41, p121 of the resubmission.
CI = confidence interval; Dxm = dexamethasone; IRC = independent review committee; HR = hazard ratio; ITT = intention to treat; PD = progressed disease; PFS = progression-free survival; **bold** = statistically significant.

Figure 1: Kaplan-Meier curves of IRC assessed PFS, the ADMYRE trial

IRC assessed PFS without PD confirmation (primary outcome)



IRC assessed PFS with PD confirmation



Source: Figure 32, p118, Figure 34, p122 of the resubmission.
A = plitidepsin + dexamethasone treatment arm; B = dexamethasone monotherapy treatment arm; C = censored patients in each arm; ITT = intention to treat; IRC = independent review committee; N = total patients in each arm; PD = progressive disease; PFS = progression-free survival.

6.13 Unchanged from the previous submission, patients in the plitidepsin + Dxm arm had a statistically significant improvement in PFS (IRC assessed without PD confirmation, primary outcome) (hazard ratio (HR) = 0.65; 95% CI: 0.48, 0.86; median difference 0.9 months). At six-months, 20% of patients in the plitidepsin + Dxm arm were progression-free, compared with 10% in the Dxm arm. In July 2019 the PBAC considered that for the comparison of plitidepsin + Dxm versus Dxm alone, the magnitude of the clinical benefit in terms of PFS (median increase of 0.9 months) was marginal (paragraph 7.1, plitidepsin PSD, July 2019 PBAC meeting).

6.14 In the IRC assessed PFS with PD confirmation analysis, patients treated with plitidepsin + Dxm demonstrated a statistically significant improvement in PFS compared to patients treated with Dxm monotherapy (HR = 0.52; 95% CI: 0.35, 0.76; median difference 3.0 months). In addition, 42.6% of patients in the plitidepsin + Dxm arm were progression-free at six months, compared with 19.7% in the Dxm arm. The IRC assessed PFS with PD confirmation analysis resulted in an increase in the difference in median PFS (from 0.9 months to 3 months), a reduction in the hazard ratio (from 0.65 to 0.52), and an increase in the absolute proportion of plitidepsin + Dxm patients' progression-free at six months (from 20% to 42.6%), all in favour of plitidepsin.

6.15 As PFS with PD confirmation was a preplanned sensitivity analysis and due to the censoring concerns, the ESC considered that the most reliable estimate of PFS from the ADMYRE trial was the primary outcome, IRC assessed PFS without PD confirmation. The ESC considered that this outcome should have been used in the indirect comparison with pomalidomide + Dxm and in the cost-utility analysis.

6.16 Table 7 presents the key OS results from the ADMYRE trial. Figure 2 presents the Kaplan-Meier plots for OS. The OS results were unchanged from the previous submission. In July 2019 the PBAC considered that the OS gain was uncertain given it was statistically significant only when adjusted for crossover (paragraph 7.1, plitidepsin PSD, July 2019 PBAC meeting).

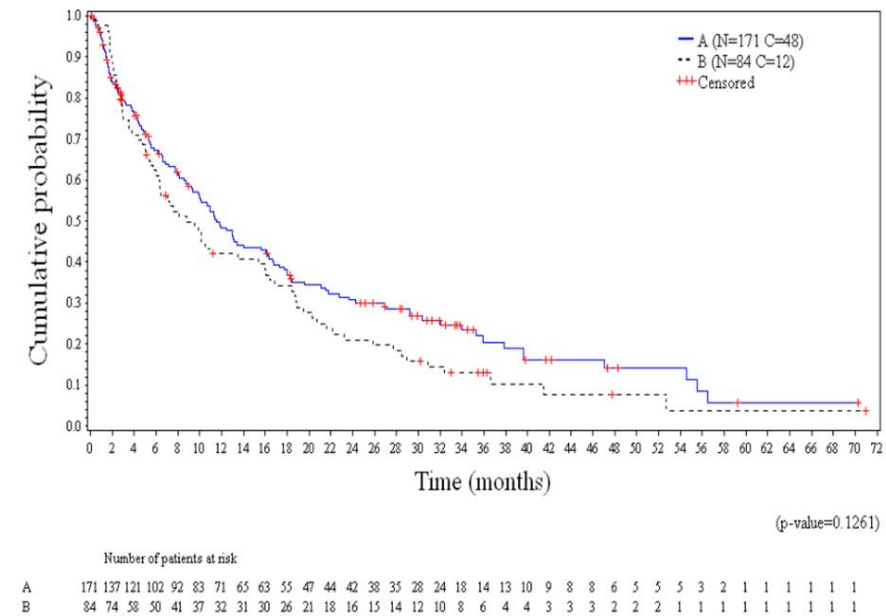
Table 7: Summary of OS outcomes, the ADMYRE trial

	Plitidepsin + Dxm	Dxm	Absolute difference (months)	HR (95% CI)
Overall survival (ITT)				
Deaths, n/N (%)	123/171 (71.9%)	72/84 (85.7%)	-	0.80 (0.60, 1.07) p-value = 0.1273
Median OS, months (95% CI)	11.6 (9.2, 16.1)	8.9 (6.0, 15.4)	2.7	
% alive at 12 months (95% CI)	48.3% (40.4, 56.2)	42.1% (31.3, 52.9)	6.2%	
% alive at 24 months (95% CI)	30.8% (23.3, 38.3)	21.0% (12.0, 30.1)	9.8%	
Overall survival (two-stage adjustment for crossover)				
Deaths, n/N (%)	123/171 (71.9%)	72/84 (85.7%)	-	**0.67 (0.50, 0.90) p-value = 0.0069**
Median OS, months (95% CI)	11.6 (9.2, 16.1)	6.7 (5.7, 9.7)	4.9	
% alive at 12 months (95% CI)	48.3% (40.4, 56.2)	32.9% (22.5,43.2)	15.4%	
% alive at 24 months (95% CI)	30.8% (23.3, 38.3)	13.4% (5.5, 21.3)	17.4%	

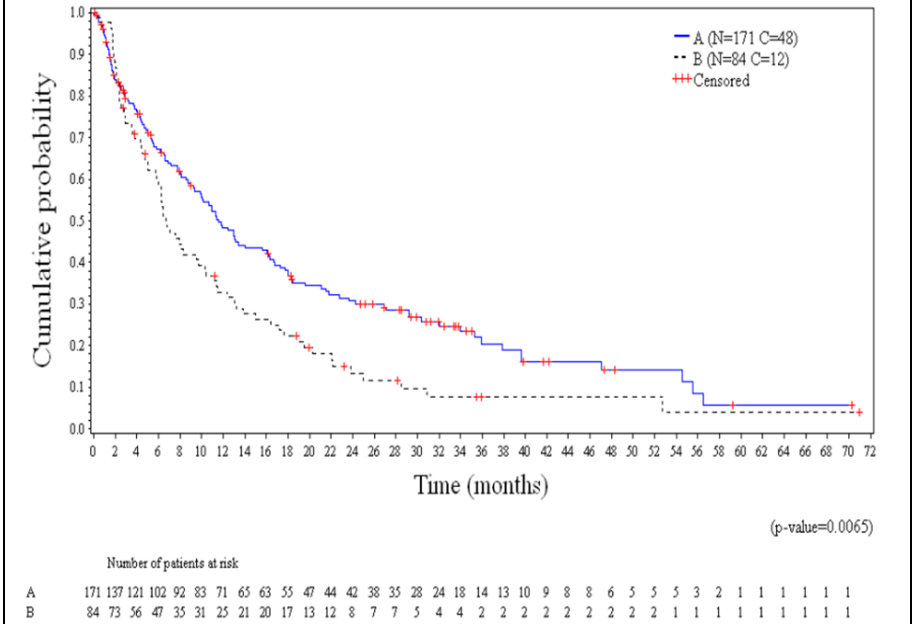
Source: Table 30, p105; Table 34, p112; Table 68, p175 of the resubmission; Table 8, p75 of ADMYRE CSR addendum.
CI = confidence interval; Dxm = dexamethasone; HR = hazard ratio; ITT = intention to treat; OS = overall survival; **bold** = statistically significant.

Figure 2: Kaplan-Meier curves of OS, the ADMYRE trial

OS (ITT population)



OS (two-stage adjustment for crossover)



Source: Figure 25, p105; Figure 29, p112 of the resubmission

A = plitidepsin + dexamethasone treatment arm; B = dexamethasone monotherapy treatment arm; C = censored patients in each arm; ITT = intention to treat; N = total patients in each arm; OS = overall survival

6.17 The resubmission highlighted that at 24 months and when applying the two-stage analysis, patients in the plitidepsin + Dxm arm were more than twice as likely to be alive compared to patients in the Dxm monotherapy arm (30.8% versus 13.4%). The resubmission considered that this difference was maintained at 36 months when 8.2%

of plitidepsin patients and 4.8% of dexamethasone patients remained alive. The Kaplan-Meier curve for plitidepsin + Dxm at 36 months was likely to be highly unstable due to substantial censoring between 24 and 36 months.

Pomalidomide + Dxm versus HI-Dxm: the NIMBUS trial

6.18 The key clinical effectiveness results for the NIMBUS trial are presented in Table 8. These results were unchanged from the previous submission. The PBAC previously favoured the use of the two-stage method for crossover adjustment in the NIMBUS trial (paragraph 7.7, pomalidomide PSD, July 2014 PBAC meeting).

Table 8: Summary of key survival outcomes in the NIMBUS trial

	Pomalidomide + Dxm		HI-Dxm		Difference in median (months)	HR (95% CI)
	n/N (%)	Median PFS, months (95% CI)	n/N (%)	Median PFS, months (95% CI)		
PFS, with confirmation of PD						
IRC (ITT)	234/302 (77.5%)	3.7 (3.0, 4.5)	130/153 (85.0%)	1.9 (1.6, 2.2)	1.8	**0.49 (0.39, 0.61) p-value <0.001**
OS						
IRC (ITT)	147/302 (48.7%)	12.7 (10.4,15.5)[a]	86/153 (56.2%)	8.1 (6.9, 10.8)	4.6	**0.74 (0.56, 0.97)[b] p-value = 0.0285**
IRC (Two-stage method crossover adjustment)	147/302 (48.7%)	12.7 (10.4,15.5)	NR	5.7 (4.2, 7.5)	7.0	**0.52 (0.39, 0.68)** p-value NR

Source: Table 42, p123; Table 31, p106; Table 35, p113 of the resubmission. Tables 22-23, pp72-73 of NICE_committee-paper [ID985]; pp1059-60 of San Miguel *et al* (2013).

CI = confidence interval; Dxm = dexamethasone; IRC = independent review committee; HI-Dxm = high-dose dexamethasone; HR = hazard ratio; IRC = independent review committee; ITT = intention to treat; OS = overall survival; NICE = National Institute for Health and Care Excellence; NR = not reported; PD = progressive disease; PFS = progression-free survival; **bold** = statistical significance.

[a] In the NICE committee evaluation papers (Fayter *et al.* 2016) Table 4.9 and in Morgan *et al*. (2015) Table 1 overall survival is reported as 12.7 months. In the NICE committee evaluation papers (Fayter *et al.* 2016) Table 23 it is reported as 12.5 months.

[b] In the NICE committee evaluation papers (Fayter *et al*. 2016) Table 4.9 HR is reported as 0.74. In the NICE committee evaluation papers (Fayter *et al*. 2016) Table 23 it is reported as 0.70 (95% CI: 0.54 to 0.92).

6.19 In the ITT analysis, the median OS increased by 4.6 months with pomalidomide compared to the control arm (data cut-off 1 September 2013). The analysis was potentially confounded due to the extent of crossover of patients from HI-Dxm (with and without progression of disease) to pomalidomide. After adjustment for crossover using the two-stage method, the difference in median overall survival time was seven months. The ESC noted that both OS analyses resulted in a statistically significant improvement.

Plitidepsin + Dxm versus pomalidomide + Dxm: indirect treatment comparison (ITC)

6.20 Unchanged from the previous submission, the resubmission presented an ITC between plitidepsin + Dxm and pomalidomide + Dxm using Dxm/HI-Dxm as the common reference arm (Table 9). The PBAC previously considered that the claim of non-inferior efficacy of plitidepsin + Dxm and pomalidomide + Dxm was uncertain (paragraph 7.1, plitidepsin PSD, July 2019 PBAC meeting).

Table 9: Summary of results of the indirect comparison for effectiveness

	Experimental median, months (95% CI)	Common reference median, months (95% CI)	HR (95% CI)
PFS with confirmation of PD: IRC			
Plitidepsin + Dxm vs. Dxm [ADMYRE]	5.0 (3.0, 6.4)	2.0 (1.7, 3.0)	**0.52 (0.35, 0.76)**
Pomalidomide + Dxm vs. HI-Dxm [NIMBUS]	3.7 (3.0, 4.5)	1.9 (1.6, 2.2)	**0.49 (0.39, 0.61)**
Indirect estimate of effect adjusted for the common reference	–	–	1.06 (0.68, 1.64)
PFS without confirmation of PD: IRC			
Plitidepsin + Dxm vs. Dxm [ADMYRE]	2.6 (1.9, 3.0)	1.7 (1.1, 2.0)	**0.65 (0.48, 0.89)**
Pomalidomide + Dxm vs. HI-Dxm [NIMBUS]	3.7 (3.0, 4.5)	1.9 (1.6, 2.2)	**0.49 (0.39, 0.61)**
Indirect estimate of effect adjusted for the common reference	-	-	1.33 (0.87, 2.02)
Overall survival (ITT)			
Plitidepsin + Dxm vs. Dxm [ADMYRE]	11.6 (9.2, 16.1)	8.9 (6.0, 15.4)	0.80 (0.60, 1.07)
Pomalidomide + Dxm vs. HI-Dxm [NIMBUS]	13.1 (11.0, 15.4)	8.1 (6.9, 9.2)	**0.72 (0.56, 0.92)**
Indirect estimate of effect adjusted for the common reference	–	–	1.11 (0.76, 1.62)
Overall survival (two-stage method)			
Plitidepsin + Dxm vs. Dxm [ADMYRE]	11.6 (9.2, 16.1)	6.7 (5.7, 9.7)	**0.67 (0.50, 0.90)**
Pomalidomide + Dxm vs. HI-Dxm [NIMBUS]	12.7 (10.4,15.5)	5.7 (4.2, 7.5)	**0.52 (0.39, 0.68)**
Indirect estimate of effect adjusted for the common reference	–	–	1.28 (0.86, 1.92)

Source: Table 62, p158, Table 63, p159 of the resubmission; Table 22, p72; Table 23, p151, NICE committee-papers [ID985]
CI = confidence interval; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone; HR = hazard ratio; IRC = independent review committee; ITT = intention to treat; PD = progressed disease; PFS = progression-free survival; vs = versus; **bold** = statistical significance.

6.21 The ESC considered that the most relevant ITC comparison for PFS would be a comparison which used PFS without PD confirmation for plitidepsin + Dxm. The ESC noted that this resulted in a hazard ratio of 1.33 (95% CI: 0.87, 2.02).

6.22 The ESC noted that the HR point estimates for each of the PFS and OS analyses in the ITC were greater than one, which favoured pomalidomide, and that the resubmission did not nominate non-inferiority margins for PFS or OS. In the July 2019 PBAC consideration of pomalidomide, the PBAC noted that the upper limits of the 95% confidence intervals were in the region of 1.6, which may exceed a reasonable non-inferiority margin [for PFS and OS] (paragraph 7.9, pomalidomide, PSD, July 2019 PBAC meeting). The ESC considered that as the upper limits of the 95% confidence intervals for PFS, when using plitidepsin without PD confirmation in the ITC, exceeded 2.0 and for OS exceeded 1.6, that the claim in the resubmission that plitidepsin + Dxm has non-inferior effectiveness compared with pomalidomide + Dxm may not be supported.

6.23 Transitivity issues noted in the resubmission and during the previous PBAC consideration included:

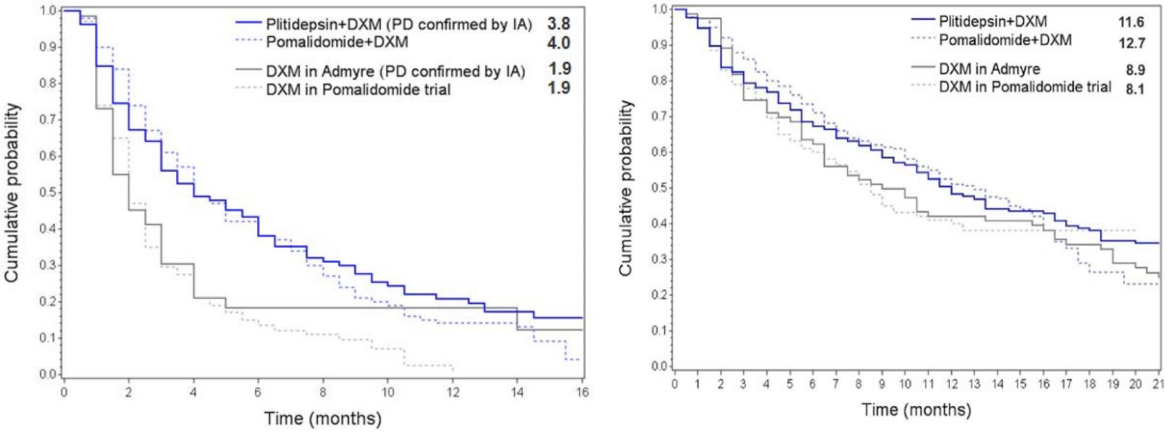
- Differences in the comparator arm Dxm regimens utilised in the trials. The comparator arm of ADMYRE utilised a low-dose Dxm regimen (40 mg Dxm on Day 1, 8, 15, 22 of a 28-day cycle) while the NIMBUS trial utilised a high-dose Dxm

regimen (HI-Dxm: 40 mg Dxm (20 mg if over 75 years) on Day 1-4, 9-12, and 17-20 of a 28-day cycle); and

- The populations in the two trials may not be comparable with respect to prior disease status as the definitions of RRMM at baseline were unclear and highly variable. The proportion of patients whose MM was refractory to prior therapy in the ADMYRE trial was approximately 30% compared to 82.2% in the NIMBUS trial (paragraph 6.19, plitidepsin PSD, July 2019 PBAC meeting).

6.24 The PSCR noted that there were differences between the ADMYRE and NIMBUS trial populations and with the Dxm doses used in the common reference arm. However, the PSCR claimed that there was no difference between plitidepsin + Dxm and pomalidomide + Dxm in terms of PFS and OS and provided additional Kaplan-Meier plots from the ADMYRE and NIMBUS trials (Figure 3). The ESC acknowledged that there was little difference in terms of efficacy between the Dxm regimens used, but considered that the issues regarding the results for the comparison between plitidepsin + Dxm and pomalidomide + Dxm remained.

Figure 3: Kaplan-Meier plots of PFS (left, PD confirmed) and OS (right) in the ADMYRE and NIMBUS studies



DXM = dexamethasone; IA = investigator's assessment; OS = overall survival; PD = progressed disease; PFS = progression free survival
Source: PSCR p3. Cross reference: Figure 41 of submission.

Plitidepsin Early Access Program data

6.25 The resubmission presented additional data from 116 patients in its Australian Early Access Program. This consisted of patients who accessed plitidepsin using the TGA's Special Access Scheme (SAS) before TGA registration and patients from the sponsor's Product Familiarisation Program. In brief, patients in the access program appeared broadly similar to the ADMYRE trial population in term of Eastern Cooperative Oncology Group (ECOG) performance status and number of prior MM treatments. The resubmission presented data on the number of plitidepsin cycles received by patients in the access program (Table 10). The mean number of plitidepsin cycles received by patients in the access program was lower than the ADMYRE trial. The PBAC, like the ESC, were unsure whether the Early Access Program data better represented the likely use of plitidepsin in the PBS population as the trial patients were healthier than

patients in the Australian community, or whether the trial data better represented likely use as patients who access compassionate schemes have usually received all available treatments.

6.26 In addition, the resubmission highlighted that four of seven patients with an ECOG performance of 2 or 3 used two or more cycles of plitidepsin, suggesting that plitidepsin was well tolerated by patients with poor performance status.

Table 10: Comparison plitidepsin cycles used in plitidepsin access program and the ADMYRE trial

Plitidepsin cycles used	Access program, n/N (%)	ADMYRE trial, n/N (%)
1	≈ 26/94 (27.1%)[a]	35/167 (21.0%)
2	≈ 29/94 (30.2%)[a]	41/167 (24.6%)
3	≈ 12/94 (12.5%)[a]	22/167 (13.2%)
4	≈ 12/94 (12.5)[a]	14/167 (8.4%)
5	≈ 4/94 (4.2%)[a]	6/167 (3.6%)
6	≈ 2/94 (2.1)[a]	49/167 (29.3%)
≥ 7	≈ 3/94 (3.1)[a]	
Mean	2.8[b]	5.04[c]

Source: Section biii, pp17-24 of the resubmission; Table 43, pp114-15 of plitidepsin CSR.
[a] Estimated from graph
[b] Calculated during the evaluation from Figure 12, p22 of the resubmission based on 66 patients who had used three or more lines of treatment.
[c] Calculated during the evaluation based on 842 total plitidepsin cycles divided by 167 patients.

Comparative harms

Plitidepsin + Dxm versus Dxm: the ADMYRE trial

6.27 The resubmission made a clinical claim of inferior safety for plitidepsin + Dxm compared with Dxm. The July 2019 submission made a claim of non-inferior safety compared with Dxm. A summary of key adverse events (AEs) from the ADMYRE trial are presented in Table 11.

Table 11: Summary of key AEs and Grade 3/4 AEs in the ADMYRE trial

	Plitidepsin + Dxm, n/N (%)	Dxm, n/N (%)	RR (95% CI)
Any TEAEs	144/167 (86.2%)	38/83 (45.8%)	**1.88 (1.48, 2.40)**
Serious AEs	47/167 (28.1%)	6/83 (7.2%)	**3.90 (1.74, 8.73)**
Grade ≥ 3 TEAEs	86/167 (51.5%)	9/83 (10.8%)	**4.75 (2.52, 8.96)**
Treatment discontinuation due to AEs	15/167 (9.0%)	8/83 (9.6%)	0.93 (0.41, 2.11)
TEAEs that occurred in ≥ 10% of patients of any grade			
Diarrhoea	24/167 (14.4%)	2/83 (2.4%)	**5.96 (1.44, 24.63)**
Nausea	62/167 (37.1%)	9/83 (10.8%)	**3.42 (1.79, 6.54)**
Vomiting	28/167 (16.8%)	2/83 (2.4%)	**6.96 (1.70, 28.51)**
Fatigue	61/167 (36.5%)	7/83 (8.4%)	**4.33 (2.07, 9.05)**
Myalgia	24/167 (14.4%)	2/83 (2.4%)	**5.96 (1.44, 24.63)**
Decreased appetite	21/167 (12.6%)	2/83 (2.4%)	**5.22 (1.25, 21.73)**
Grade 3/4 fatigue	18/167 (10.8%)	1/83 (1.2%)	**8.95 (1.22, 65.87)**

Source: Table 57, p138; Table 12.2.2.3 of 12 CSR Safety Analysis (25AUG16) tables in CSR; Listing 12.2.2.13, of CSR Safety Analysis (25AUG16) tables; Section 12.3.1.2, p136 of ADMYRE CSR.
AE = adverse event; CI = confidence interval; Dxm = dexamethasone; RR = relative risk; SAE = serious adverse events; TEAEs = treatment related adverse events; **bold** = statistical significance

6.28 More patients in the plitidepsin arm experienced treatment emergent adverse events (TEAEs), serious AEs or Grade 3 or higher TEAEs. The ESC considered that the claim of inferior safety was supported by the ADMYRE trial. The pre-PBAC response stated that many of the AEs were of short duration and reversible.

Plitidepsin + Dxm versus pomalidomide + Dxm: indirect comparison of safety

6.29 The results of the indirect comparison of safety for AEs are presented in Table 12. Unchanged from the previous submission, the resubmission considered the interpretation of the indirect comparison of AEs to be difficult due to the differences in the Dxm regimen used in the comparator arm and due to likely differences in the trial populations.

Table 12: Key results of the indirect comparison for adverse events

	Plitidepsin + Dxm/ Pomalidomide + Dxm, n/N (%)	Dxm/HI-Dxm, n/N (%)	RR (95% CI)
Diarrhoea			
ADMYRE	24/167 (14.4%)	2/83 (2.4%)	**5.96 (1.44, 24.63)**
NIMBUS	66/300 (22.0%)	28/150 (18.7%)	1.18 (0.79, 1.75)
Indirect comparison: ADMYRE vs. NIMBUS			**5.05 (1.16, 22.06)**
Nausea			
ADMYRE	62/167 (37.1%)	9/83 (10.8%)	**3.42 (1.79, 6.54)**
NIMBUS	45/300 (15.0%)	16/150 (10.7%)	1.41 (0.82, 2.40)
Indirect comparison: ADMYRE vs. NIMBUS			**2.43 (1.05, 5.63)**
Fatigue			
ADMYRE	61/167 (36.5%)	7/83 (8.4%)	**4.33 (2.07, 9.05)**
NIMBUS	101/300 (33.7%)	41/150 (27.3%)	1.23 (0.91, 1.67)
Indirect comparison: ADMYRE vs. NIMBUS			**3.52 (1.59, 7.82)**
Muscular weakness			
ADMYRE	16/167 (9.6%)	2/83 (2.4%)	3.98 (0.94, 16.89)
NIMBUS	9/300 (3.0%)	19/150 (12.7%)	**0.24 (0.11, 0.51)**
Indirect comparison: ADMYRE vs. NIMBUS			**16.58 (3.23, 85.09)**

Source: Table 66, pp164-168 of the resubmission.
CI = confidence interval; Dxm = dexamethasone; HI-Dxm = high-dose dexamethasone;; RR = relative risk; vs. = versus; **bold** = statistical significance.

6.30 The ESC noted that high dose Dxm, as used in the NIMBUS trial, was associated with more adverse events than low dose Dxm, as used in the ADMYRE trial. The indirect comparison of AEs found a significant increase in the rates of diarrhoea, nausea, fatigue and muscular weakness with plitidepsin + Dxm compared with pomalidomide + HI-Dxm. Accordingly, the ESC considered that the claim of non-inferior safety compared to pomalidomide + Dxm could not be supported.

Plitidepsin versus other RRMM treatments

6.31 The resubmission presented an additional naïve comparison of AEs associated with plitidepsin and other RRMM treatments including pomalidomide, carfilzomib and daratumumab (Table 13) to support its claim that the frequency and severity of AEs resulting from plitidepsin + Dxm treatment were no worse than the toxicity associated with other treatments for RRMM. The resubmission highlighted that plitidepsin + Dxm

treatment resulted in less haematological and neurological toxicity compared with other RRMM treatments, which was considered to be important in heavily pre-treated patients who may have cumulative toxicity.

Table 13: Grade 3 or 4 toxicity in common therapies in relapsed/refractory MM compared with plitidepsin

	Plitidepsin plus Dxm	Pomalidomide plus Dxm	Carfilzomib	Daratumumab + Bortezomib
Source	Plitidepsin PI	NIMBUS	FOCUS[a]	CASTOR
Common > 10%	Anaemia: 35.3% CPK increased: 15.6% Fatigue; 12.0% Thrombocytopenia: 10.2% ALT increased: 10.2%	Neutropenia: 48.3% Infection: 34.0% Anaemia: 32.7% Thrombocytopenia: 22.0% Pneumonia: 12.7%	Thrombocytopenia: 24.2% Anaemia: 25.5%	-
Occasional 5-10%	Neutropenia: 7.8% AST increased: 6.0% Pneumonia: 6.0% Myalgia; 5.4%	Febrile neutropenia: 9.3% Leukopenia: 9.0% General physical health deterioration: 8.0% Bone pain: 7.3% Back pain: 5.0% Dyspnoea: 5.0% Fatigue: 5.3%	Neutropenia: 7.6% Pneumonia: 6.4% Acute renal failure: 7.6% Renal failure: 5.1%	-
Treatment discontinuation due to AEs	Treatment related: 15/167 (9.0%) Unrelated to treatment: 9/167 (5.4%)	Treatment related: 11/300 (3.7%) Unrelated to treatment: 13/300 (4.3 %)	23/157 (14.6%)	9.1%
Treatment-related deaths	1/167 (0.6%)	11/300 (3.7%)	16/157 (10.2%)	5.8%[b]

Source: Table 4, p15 of the resubmission; Miguel *et al.* (2013); Table 5, carfilzomib November 2016 PBAC Public Summary Document; Table 9, daratumumab PBAC Public Summary Document, March 2019

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; MM = multiple myeloma; PI = product information

[a] Not previously considered by PBAC. The trial participants had received at least three prior treatments for MM, including bortezomib, lenalidomide or thalidomide, an alkylating agent, corticosteroids and anthracycline.

[b] Deaths within 30 days of last dose

6.32 Based on the naïve comparison presented by resubmission, the ESC considered that the adverse event profile of plitidepsin appeared to differ from pomalidomide and carfilzomib.

Benefits/harms

6.33 A summary of the comparative benefits and harms for plitidepsin + Dxm versus Dxm monotherapy is presented in Table 14.

Table 14: Summary of comparative benefits and harms for plitidepsin + Dxm and Dxm

Benefits				
Event	**Plitidepsin + Dxm**	**Dxm**	**Absolute difference**	**HR (95% CI)**
PFS (IRC assessed, disease progression not confirmed, primary outcome)[a]				
Progressed, n/N (%)	130/171 (76.0%)	61/84 (72.6%)		**0.65 (0.48, 0.89) p-value = 0.0062**
Median PFS, months (95% CI)	2.6 (1.9, 3.0)	1.7 (1.1, 2.0)	0.9	
% not progressed at 6 months (95% CI)	20.0% (13.1, 26.9)	10.0% (2.0, 18.0)	10%	
PFS (IRC assessed, disease progression confirmed)[a]				
Progressed, n/N (%)	80/171 (46.8%)	43/84 (51.2%)		**0.52 (0.35, 0.76) p-value = 0.0005**
Median PFS, months (95% CI)	5.0 (3.0, 6.4)	2.0 (1.7, 3.0)	3.0	
% not progressed at 6 months (95% CI)	42.6% (32.6, 52.6)	19.7% (7.2, 32.2)	22.9%	
OS, two-stage method crossover adjustment [a]				
Deaths, n/N (%)	123/171 (71.9%)	72/84 (85.7%)		**0.67 (0.50, 0.90) p-value = 0.0069**
Median OS, months (95% CI)	11.6 (9.2, 16.1)	6.7 (5.7, 9.7)	4.9	
% alive at 6 months (95% CI)	48.3% (40.4, 56.2)	32.9% (22.5, 43.2)	15.4%	
% alive at 12 months (95% CI)	30.8% (23.3, 38.3)	13.4% (5.5, 21.3)	17.4%	

Harms						
	Plitidepsin + Dxm, n/N (%)	**Dxm, n/N (%)**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Plitidepsin + Dxm	**Dxm**	
Any Grade						
Nausea	62/167	9/83	**3.42 (1.79, 6.54)**	37.1	10.8	**0.26 (0.15, 0.37)**
Fatigue	61/167	7/83	**4.33 (2.07, 9.05)**	36.5	8.4	**0.28 (0.17, 0.39)**
Vomiting	28/167	2/83	**6.96 (1.70, 28.51)**	16.8	2.4	**0.14 (0.07, 0.22)**
Diarrhoea	24/167	2/83	**5.96 (1.44, 24.63)**	14.4	2.4	**0.12 (0.05, 0.20)**
Myalgia	24/167	2/83	**5.96 (1.44, 24.63)**	14.4	2.4	**0.12 (0.05, 0.20)**
Decreased appetite	21/167	2/83	**5.22 (1.25, 21.73)**	12.5	2.4	**0.10 (0.03, 0.17)**
Oedema peripheral	20/167	2/83	**4.97 (1.19, 20.76)**	12.0	2.4	**0.09 (0.03, 0.17)**
Grade 3/4 AE						
Myalgia	18/167	1/83	**8.95 (1.22, 65.87)**	10.8	1.2	**0.10 (0.03, 0.16)**

Source: Table 34, p112; Table 39, p118; Table 41, p41 of the resubmission; Table 8, p75 of ADMYRE CSR addendum; and calculated during evaluation.

AE = adverse events; CI = confidence interval; Dxm = dexamethasone; HR = hazard ratio; IRC = independent review committee; ITT = intention to treatOS = overall survival; PFS = progression free survival; RR = relative risk; RD = risk difference; **bold** = statistically significant.

[a] In ADMYRE trial, PFS - median duration of follow-up: 17.1 months (Plitidepsin + Dxm) and 20.7 months (Dxm); OS - median duration of follow up: 33.4 months (Plitidepsin + Dxm) and 36.3 months (Dxm).

6.34 On the basis of direct evidence presented in the pivotal ADMYRE trial, for every 100 patients treated with plitidepsin + Dxm in comparison to Dxm monotherapy and over a median duration of follow-up of 17.1 months (plitidepsin + Dxm arm) and 20.7 months (Dxm monotherapy arm):

- Approximately 10 additional patients remained progression-free at 6 months.
- After adjustment for crossover, approximately 15 more patients remained alive at 6 months and 17 more patients at 12 months
- Approximately 26 more patients would experience nausea.
- Approximately 28 more patients would experience fatigue.
- Approximately 14 more patients would have vomiting.

- Approximately 12 more patients would have diarrhoea.
- Approximately 12 more patients would experience myalgia (muscle pain) of which 10 patients would experience grade 3/4 (more severe) myalgia.
- Approximately 10 more patients would have decreased appetite.
- Approximately 9 more patients would have peripheral oedema (swelling of the legs/arms).

6.35 A summary of the comparative benefits and harms is not presented for the comparison of plitidepsin with pomalidomide given the non-inferiority claim.

Clinical claim

Plitidepsin + Dxm compared with Dxm (fourth-line setting)

6.36 The resubmission described plitidepsin + Dxm as superior in terms of effectiveness compared with Dxm monotherapy (fourth-line setting). This was unchanged from the July 2019 submission. The PBAC previously considered that the claim of superior comparative effectiveness compared to Dxm in the fourth-line setting was reasonable for PFS, with a marginal increase in clinical benefit (increase in median PFS of 0.9 months) (paragraph 6.32, plitidepsin PSD, July 2019 PBAC meeting). Overall, the PBAC considered that plitidepsin resulted in an incremental benefit versus Dxm in a small subset of patients who experienced a prolonged response, but that there was no way to target treatment to those patients who were most likely to respond (paragraph 7.6, plitidepsin PSD, July 2019 PBAC meeting). The ESC considered that the interpretation of clinical evidence remained unchanged from the July 2019 submission. The ESC noted that the increase in OS was only statistically significant when adjusted for crossover.

6.37 The PBAC considered that the clinical benefit from PFS with PD confirmation (HR = 0.52; 95% CI: 0.35, 0.76), with an increase in median PFS of 3.0 months, was not reliable as the analysis was a preplanned sensitivity analysis conducted to test the consistency of the primary PFS outcome, PFS without PD confirmation. The PBAC considered that based on the primary outcome of the trial, PFS without PD confirmation, plitidepsin + Dxm resulted in a marginal increase in clinical benefit over Dxm monotherapy (HR = 0.65; 95% CI 0.48, 0.89; increase in median PFS = 0.9 months).

6.38 The resubmission provided an updated safety claim, describing plitidepsin + Dxm as inferior compared with Dxm monotherapy. The PBAC agreed with the ESC and considered that the claim of inferior safety was supported by the evidence presented from the ADMYRE trial.

Plitidepsin + Dxm versus pomalidomide + Dxm (third-line setting)

6.39 The resubmission again claimed that plitidepsin + Dxm was non-inferior compared to pomalidomide + Dxm in terms of improving PFS and OS. The ESC considered that the resubmission's claim with respect to effectiveness could not be supported, particularly

as the most relevant indirect comparison for PFS, which utilised plitidepsin without PD confirmation, resulted in a point estimate of 1.33 and an upper 95% confidence interval of the hazard ratio (2.02), indicating that the hazard of progression with plitidepsin could be up to twice that of with pomalidomide. Noting that no new data were presented, the PBAC again considered that the claim of non-inferior efficacy was uncertain and not adequately supported by the data as a non-inferiority margin was not proposed, the point estimates of the hazard ratios from the indirect comparison favoured pomalidomide, and the 95% confidence intervals were wide.

6.40 The resubmission claimed that plitidepsin + Dxm was non-inferior in terms of safety to pomalidomide + Dxm. The ESC considered that the claim that plitidepsin + Dxm was non-inferior to pomalidomide + Dxm was not supported and remained concerned about an apparent increase in diarrhoea, nausea, fatigue and muscle weakness with plitidepsin compared with pomalidomide that may have a significant impact on quality of life. As per July 2019, the PBAC considered that the claim of non-inferior comparative safety compared to pomalidomide + Dex was not adequately supported by the data.

Economic analysis

Cost-minimisation analysis (third-line setting)

6.41 The resubmission presented a revised CMA based on the indirect comparison between plitidepsin + Dxm and pomalidomide + Dxm.

6.42 The ESC considered that the appropriateness of a CMA was not adequately supported as no new evidence was presented in the resubmission and the claim of non-inferior efficacy and safety between plitidepsin + Dxm and pomalidomide + Dxm remained uncertain.

6.43 The following were unchanged from the previous submission:

- The equi-effective doses were 5 mg/m^2 IV of plitidepsin on Day 1 and 15 of a 28-day cycle and 4 mg oral of pomalidomide on Days 1-21 of 28-day cycle. Both regimens were used combination with 40 mg of Dxm orally on Day 1, 8, 15 and 22 of a 28-day cycle. The equi-effective doses were from the ADMYRE and the NIMBUS trials. Actual dose exposure was assumed to be equivalent to the recommended dose for plitidepsin + Dxm and pomalidomide + Dxm. It was previously considered this approach was reasonable (paragraph 6.34, plitidepsin PSD, July 2019 PBAC meeting);
- A median of three cycles of pomalidomide were used. It was previously noted that the application of three treatment cycles for pomalidomide was conservative and considered that this was appropriate (paragraph 6.35, plitidepsin PSD, July 2019 PBAC meeting);
- The approach assumed that differences in AEs only resulted in a cost difference and not a relevant quality of life difference. This may not be reasonable,

particularly given the potential for some AEs to impact on quality of life (such as fatigue, peripheral oedema and febrile neutropenia); and

- The private hospital DMPQ for 4 mg pomalidomide ($10,547.29) was used for the pomalidomide cost per cycle. Results using the approved ex-manufacturer price (AEMP) are presented in Table 15.

6.44 The resubmission used the indirect comparison to calculate the cost of AEs in the CMA, which was presented as a sensitivity analysis in the July 2019 submission. The previous sensitivity analysis only considered the differences in the costs of managing diarrhoea and peripheral oedema. The resubmission also included the costs of treating neutropenia and several other AEs. This increased the cost of managing pomalidomide AEs from $11.99 in July 2019 to $517.06 in the resubmission and plitidepsin AEs from less than $10 million to less than $10 million. The increase in pomalidomide AE costs were primarily due to the inclusion of the costs associated with managing neutropenia.

6.45 The resubmission stated it also included the costs of managing myalgia and vomiting. However, the costs of managing these AEs were not included in the base case. This was calculated during the evaluation. The ESC and PBAC considered that this was appropriate.

6.46 The resubmission did not explicitly state the assumed plitidepsin dose in the CMA. Unlike pomalidomide, which has a flat dosing regimen irrespective of patient size, the dose of plitidepsin depends on a patient's body surface area (BSA). The CMA results were based on the assumption that plitidepsin and pomalidomide would require the same number of cycles (thus, the cost-minimising price was calculated on the basis of one cycle only). As the resubmission did not explicitly state the plitidepsin dose used in the CMA, the quantity of plitidepsin corresponding to the cost minimised price was unclear. It appeared that the cost minimisation analysis referenced a dose of 20 mg per cycle (distributed across two injections two weeks apart). This was sufficient for a patient with a BSA up to 2.0 m^2. For larger patients, the implicit CMA claim that the overall cost of plitidepsin treatment is the same as the cost of therapy with pomalidomide, may not hold.

6.47 Table 15 presents the results of the CMA. The CMA in the resubmission was based on the published DPMQ of pomalidomide. The calculations provided in Table 15 use the AEMP.

Table 15: Results of the cost-minimisation analysis (based on the published AEMP of pomalidomide)

Component	Plitidepsin + Dxm	Pomalidomide + Dxm
Treatment costs	-	-
Plitidepsin dose (mg/m^2)	5	-
Plitidepsin dosing frequency per 28 day cycle	2	-
Cost of plitidepsin per cycle (AEMP)	$[redacted]	-
Pomalidomide dose (mg)	-	4
Pomalidomide dosing frequency per 28 day cycle	-	21
Cost of pomalidomide per cycle (AEMP)	-	$10,500.00
Dxm dose [mg] (patients ≤ 75 years of age)	40	40
Dxm dosing frequency per cycle (patients ≤ 75 years of age)	4	4
Dxm dose [mg] (patients >75 years of age)	40	20
Dxm dosing frequency per cycle (patients > 75 years of age)	4	4
Cost of Dxm per cycle	$22	$21
Cost of prophylaxis medications	-	-
Ondansetron 8 mg intravenous	$1	-
Promethazine hydrochloride	$8	-
Prochlorperazine mesylate	$4	-
Aspirin	-	$4.56
Administration costs	-	-
Intravenous administration	$[redacted]	-
Treatment of Adverse events	-	-
Cost of AEs	$[redacted]	$517.06
Total cost of therapy (AEMP pricing)	**$11,042.78**	**$11,042.78**
Total cost of therapy (Corrected AE costs, AEMP pricing)[a]	**$11,130.35**	**$11,130.35**
Total cost of therapy DPMQ pricing	**$11,090.07**	**$11,090.07**
Total cost of therapy (July 2019 submission, DPMQ pricing)[b]	**$10,585**	**$10,585**

Source: Table 85, p210 of the resubmission, Excel Worksheet 'Aplidin_EconomicModel_November2019_PRIMARY.xlsm', sheet AEs of the resubmission and calculated during the evaluation.

AEs = adverse events; AEMP = approved ex-manufacturer price; Dxm = dexamethasone.

[a] Included cost of treating vomiting and myalgia increasing plitidepsin AE costs to $[redacted] and pomalidomide AE costs to $517.65. Cost of plitidepsin decreased to $[redacted] (AEMP).

[b] As presented in the July 2019 PSD which used corrected AE costs of $[redacted] for plitidepsin and $11.99 for pomalidomide.

6.48 Based on the CMA, the AEMP for a cycle of plitidepsin was $[redacted], which was more than the requested PBS price based on a maximum dose of 20 mg per cycle of $[redacted].

<u>Cost-utility analysis (fourth-line setting)</u>

6.49 The resubmission presented a revised cost utility analysis that compared plitidepsin + Dxm with Dxm monotherapy as a fourth-line treatment. The structure of the model was unchanged from the previous submission. Table 16 presents an overview of the economic model presented in the resubmission compared to that presented in July 2019.

Table 16: Key differences between submissions in the economic model

Component	July 2019 submission		Current resubmission	
Treatments	Plitidepsin + Dxm vs. Dxm monotherapy			
Time horizon	7 years (modelled) 5.9 years (trial based)		5 years (modelled) 5.9 years (trial based)	
Cycle length	1 week			
Outcomes	QALYs and LYs			
Method used to generate results	Partitioned survival model			
Allocation to health states	Pre-progression on-treatment: TTF KM plot Pre-progression off-treatment: PFS KM plot - TTF KM plot Post-progression: OS KM - PFS KM Death: OS KM (two-stage method adjustment for crossover)			
PFS data used	IRC assessed PFS with PD confirmation		IRC assessed PFS with PD confirmation	
Survival extrapolation	KM analysis with extrapolation applied over the entire time horizon		KM analysis with extrapolation applied after median follow-up[a]	
Cost of plitidepsin (DPMQ)	$		$ [b]	
Cost of subsequent therapy	Plitidepsin + Dxm: $; Dxm: $		Plitidepsin + Dxm: $; Dxm: $	
Utility	Plitidepsin + Dxm arm: Pre-progression 0.718 Post-progression 0.681 Dxm arm: Pre-progression 0.679 Post-progression 0.642		Plitidepsin + Dxm and Dxm arms: Pre-progression 0.750[c] Post-progression 0.645[c]	
Disutility for AEs	0.010[d]	0.0002[d]	0.011[d]	0.001[d]

Source: Table 1, pp2-6 of the resubmission.

AE = adverse event; CUA = cost-utility analysis; DPMA = Dispensed Price for Maximum Quantity; Dxm = dexamethasone; IRC = independent review committee; IMWG = international myeloma working group; Lys = life years; KM = Kaplan-Meier; OS = overall survival; QALY = quality-adjusted life years; PD = progressive disease; PFS = progression-free survival; TTF = time to treatment failure

[a] Extrapolation was applied at time points that differed from median follow-up. Referred to as extrapolation from median follow-up for brevity.

[b] Proposed fourth-line price

[c] Actual values used in the economic model. The resubmission stated that it used utility values recalculated in the July 2019 commentary.

[d] Annualised as: weekly disutility × 365.25/7

6.50 Table 17 presents the key drivers of economic model.

Table 17: Key drivers of the model

Component	Summary	Impact
Post-progression costs	Plitidepsin + Dxm arm: $; Dxm monotherapy arm: $, including post-progression plitidepsin use.	High. Favoured plitidepsin
OS data	OS data was adjusted for crossover.	High, Favoured plitidepsin
PFS data	IRC assessed PFS with PD confirmation used rather than primary outcome (IRC assessed PFS without PD confirmation)	Moderate. Favoured plitidepsin
Utilities	Pre-progression: 0.750 Post progression: 0.645	Moderate. Favoured plitidepsin
Operational errors	Operational validity errors resulting implausible proportions of patients in health states and the proportion of patients across health states exceeding 100%.	Low. Favoured plitidepsin

Dxm = dexamethasone; IRC = independent review committee; OS = overall survival; PD = progressive disease; PFS = progression free survival.

Source: Excel spreadsheet 'Aplidin_EconomicModel_November2019_PRIMARY'.

6.51 The resubmission assumed patients in the Dxm monotherapy arm would incur post-progression treatment costs of less than $10 million per patient, which included the cost of post-progression plitidepsin use. This was inconsistent with the use of OS adjusted for the effect of crossover to plitidepsin using the two-stage method. Post-

progression costs for the plitidepsin + Dxm arm were less than $10 million per patient. The large difference in post-progression treatment costs was the key driver of the ICER. The PSCR stated that post-progression treatment costs were based on the actual treatments patients received in each treatment arm of the ADMYRE trial. The PSCR also stated that the July 2019 submission applied similar post-treatment costs to both arms of the analysis, but this was amended in the resubmission as a result of feedback from the evaluators. The ESC noted that the post-progression costs were substantially higher in the Dxm arm, favouring plitidepsin.

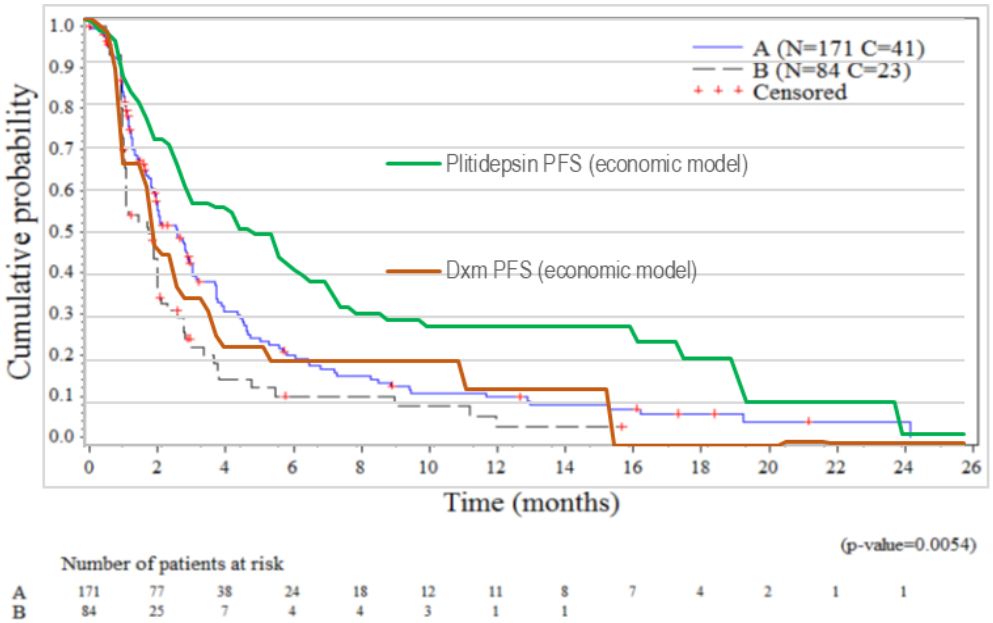
6.52 In addition, the resubmission applied post-progression treatment costs to all patients exiting the pre-progression on-treatment health state. The ESC noted that this was inconsistent with the results of the ADMYRE trial, in which 39.5% and 48.2% of patients in the plitidepsin and Dxm arms, respectively, received subsequent therapies. Data from the Australian Myeloma and Related Diseases Registry reported 43% (20/46) of patients who received a fourth-line therapy went on to receive a fifth-line therapy (Zhao 2019[2]).

6.53 Unchanged from the previous submission, IRC assessed PFS with PD confirmation was the PFS outcome used in the base case. The ESC considered that this was not appropriate as this outcome was a preplanned sensitivity analysis. The ESC considered that the model should have utilised the primary outcome from the trial, PFS without PD confirmation.

6.54 Figure 4 presents a comparison of PFS in the model (based on IRC assessed PFS with PD confirmation) and the primary outcome the ADMYRE trial, IRC assessed PFS without PD confirmation. The ESC noted that the incremental benefit of plitidepsin + Dxm in term of PFS was higher in the IRC assessed PFS with PD confirmation analysis. Results using the IRC assessed PFS without PD confirmation are presented in the sensitivity analysis.

[2] Zhao J et al 2019. Real-world treatment patterns in relapsed/refractory multiple myeloma in Australia: results from the Myeloma and Related Diseases Registry. Abstract accepted for oral presentation at Blood 2019 on 21/10/2019, Perth Convention & Exhibition Centre, 20 - 23 October 2019.

Figure 4: Comparison of IRC PFS with PD confirmation in the economic model (green and red lines) with IRC PFS without PD confirmation (primary outcome) in the ADMYRE trial (blue and grey lines).



Source: Constructed during the evaluation using the Section 3 spreadsheet and Figure 34, p122 of the resubmission.
A = plitidepsin + dexamethasone treatment arm; B = dexamethasone monotherapy treatment arm; C = censored patients in each arm; Dxm = dexamethasone; ITT = intention to treat; IRC = independent review committee; N = total patients in each arm; PFS = progression-free survival; PD = disease progression.

6.55 In the previous submission, modelled extrapolations were used for the entire time horizon. The ESC previously noted that the available KM data should have been applied for the period in the model up to the time when there is uncertainty due to small number of patients remaining event-free (typically the median duration of follow-up), with the extrapolated data applied thereafter (paragraph 6.41, plitidepsin PSD, July 2019 PBAC meeting). In response, the resubmission presented base case results with extrapolation applied from the trial median follow-up at the 20 November 2015 data cut (17.1 months for the plitidepsin arm and 20.7 months for the Dxm arm) for TTF and OS. For PFS extrapolation was applied from the median follow-up at the 19 May 2017 data cut, 33.4 months for the plitidepsin arm and from 36.3 months for the Dxm arm. The extrapolation point for PFS (and for the Dxm arm of TTF) appeared to be an error, as extrapolation commenced after the end of the digitised Kaplan-Meier data, resulting in the proportion of patients in these states equal to zero for a period of time. Correcting the base case modestly decreased the ICER. The changes to correct the base case included:

- extrapolation of PFS and TTF from 6.0 months for the plitidepsin arms and 3.46 months for the Dxm arms. Extrapolating from later follow-up points resulted in validity errors (inappropriate negative patient numbers in the pre-progression off treatment state in the plitidepsin and Dxm arms);
- extrapolation of OS from the median follow-up reported at the 19 May 2017 data cut (33.4 months for plitidepsin and 36.3 months for the Dxm).

6.56 The July 2019 submission calculated utility values using a regression equation from the 2015 pomalidomide submission to NICE. The aim of applying the method was to estimate a utility value for each of the relevant health states, e.g. time without progression. However, the submission included the proportions of patients who have progressive disease as an input for calculating the utility for pre-progression health states, and vice versa. The July 2019 commentary recalculated utility values assuming the health states were mutually exclusive. The resubmission and PSCR stated it used the recalculated utility values from the July 2019 commentary; however, the base case used utility values from the July 2017 carfilzomib PSD. A comparison of the utility values used in the July 2019 submission, the recalculated values from the July 2019 commentary and those actually used in the March 2020 resubmission are presented in Table 18. The ESC considered that it would have been more appropriate for the resubmission to have used the utilities values that were recalculated in the July 2019 commentary, as the utility values from the July 2017 carfilzomib PSD were for an earlier line of treatment. These values are tested in the sensitivity analysis.

Table 18: Comparison of utility values used in the previous submission and the resubmission

Health state	July 2019 values used		July 2019 values recalculated in the Commentary		March 2020 values used	
	Value	Source	Value	Source	Value	Source
Plitidepsin + Dxm						
Pre-progression	0.718	NICE pomalidomide regression with ADMYRE trial values	0.7051	Recalculation of NICE pomalidomide regression	0.750	Carfilzomib PBAC PSD, July 2017
Post-progression	0.681		0.6241		0.645	
AEs	0.010[a]	Nord (1997)	0.011[a]	Nord (1997)	0.011[a]	Nord (1997)
Dxm monotherapy						
Pre-progression	0.679	NICE pomalidomide regression with ADMYRE trial values	0.7051	Recalculation of NICE pomalidomide regression	0.750	Carfilzomib PBAC PSD, July 2017
Post-progression	0.642		0.6238		0.645	
AEs	0.002[a]	Nord (1997)	0.001[a]	Nord (1997)	0.001[a]	Nord (1997)

Source: Tables 99-101, pp232-234 of the resubmission; Section 3 spreadsheet.
AE = adverse events; Dxm = dexamethasone; NICE = National Institute for Health and Care Excellence.
[a] Annualised as: weekly disutility × 365.25/7.

6.57 The ESC noted that the time horizon in the resubmission was reduced from seven to five years which was consistent with the time horizon accepted by the PBAC as reasonable for pomalidomide (paragraph 6.45, plitidepsin PSD, July 2019 PBAC meeting).

6.58 Unchanged from the previous submission, the resubmission did not present the underlying TTF data. The PBAC previously noted that the data underlying the TTF could not be verified as it was not an outcome of the ADMYRE trial and may have underestimated treatment exposure (paragraph 7.10, plitidepsin PSD, July 2019 PBAC meeting). The resubmission stated that TTF was a mathematical construct derived from the PFS data and the proportion of patients on treatment at each time point.

6.59 The base case results of the economic model are provided in Table 19. The price of plitidepsin used in the CUA model was based on the CMA presented above, which relied on the published price of pomalidomide.

Table 19: Results of the economic analysis

	Plitidepsin + Dxm	Dxm	Increment
Trial-based cost utility analysis			
Total cost ($)	$ [redacted]	$ [redacted]	$ [redacted]
LYs	1.589	1.060	0.529
QALYs	1.069	0.723	0.346
Incremental cost per QALY gained			**$** [redacted]
Modelled[a] cost utility analysis (base case)			
Total cost ($)	$ [redacted]	$ [redacted]	$ [redacted]
LYs	1.560	1.043	0.517
QALYs	1.060	0.718	0.341
Incremental cost per QALY gained			**$** [redacted]
Corrected cost-utility analysis[b]			
Total cost ($)	$ [redacted]	$ [redacted]	$ [redacted]
LYs	1.558	1.003	0.555
QALYs	1.056	0.700	0.356
Incremental cost per QALY gained			**$** [redacted]
July 2019 submission (modelled base case)			
Total cost ($)	$ [redacted] ($ [redacted])[c]	$ [redacted] ($ [redacted])[c]	$ [redacted] ($ [redacted])[c]
LYs	1.669	1.044	0.625
QALYs	1.138	0.690	0.449
Incremental cost per QALY gained			$ [redacted] ($ [redacted])[b]

Source: Table 114, p246 of the resubmission; and Table 3B.8.1, p123 July 2019 plitidepsin commentary.

AE = adverse event; Dxm = dexamethasone; LYs = life years; OS = overall survival; QALY = quality adjusted life years; TTF = time to treatment failure.

[a] Extrapolated from 33.4 months (plitidepsin) and 36.3 months (Dxm) for PFS; 17.1 months (plitidepsin) and 20.7 months (Dxm) for TTF and OS.

[b] Plitidepsin TTF and PFS extrapolated from 6 months. Dxm TTF and PFS extrapolated from 3.46 months. Plitidepsin OS extrapolated from 33.4 months. Dxm OS extrapolated from 36.3 months. 'PF PLIT' cells O13 and Q13 where changed to zero.

[c] Recalculated during in the July 2019 commentary when the errors for entering AEs proportions were corrected.

6.60 In July 2019, the PBAC considered that any future analysis should result in an ICER of less than $40,000 per QALY to account for the substantial toxicity and minor additional benefit of plitidepsin. The PBAC further considered that the benefit observed in the ADMYRE trial may be reduced due to the poorer prognosis and reduced tolerability of plitidepsin in the PBS population (paragraph 7.13, plitidepsin PSD, July 2019 PBAC meeting). The resubmission argued that the PBAC's request for the ICER to be less than $40,000 per QALY was inconsistent with previous recommendations for RRMM. The resubmission highlighted that in the July 2017 consideration of daratumumab, the PBAC recalled that it recommended Cd [carfilzomib + Dxm] in July 2017 based on superior efficacy compared to Bd [bortezomib + Dxm] with an ICER in the range of $45,000 per QALY to $75,000 per QALY. The PBAC considered an ICER within this range would be appropriate for DBd [daratumumab + bortezomib + Dxm] (paragraph 6.53, daratumumab PSD, March 2019 PBAC meeting). The ESC noted that daratumumab and carfilzomib were considered as second-line treatments. Additionally, the resubmission highlighted that pomalidomide (November 2014 PBAC meeting), required price reductions to achieve an ICER of $45,000 to $75,000 per QALY for the same line of therapy as plitidepsin.

6.61 The ICER for the corrected base case cost-utility analysis was $45,000 – $75,000 per QALY. The ESC considered that the ICER was likely underestimated as:

- the post-progression treatment costs in the Dxm arm were substantially higher than the plitidepsin arm (less than $10 million for plitidepsin versus less than $10 million for Dxm, favouring plitidepsin). Additionally, post-progression costs were applied to all patients exiting the pre-progression on-treatment health state, which was likely higher than the 43% of Australian fourth-line RRMM patients who received fifth-line therapy (Zhao 2019);
- the PFS outcome used, IRC assessed PFS with PD confirmation, which was a preplanned sensitivity analysis, not the primary outcome of the trial, and which estimated a substantially higher PFS for plitidepsin than the primary outcome of the ADMYRE trial, IRC assessed PFS without PD confirmation; and
- the use of utilities from the carfilzomib July 2017 PSD was inappropriate as they represented an earlier line of treatment. The utilities recalculated in the July 2019 commentary would have been more appropriate.

6.62 The results of key sensitivity analyses are presented in Table 20. The ICER was sensitive to the use of lower post-progression treatment costs for the Dxm arm and the use of the ITT OS analysis (not adjusted for treatment crossover). The ICER also increased modestly using the primary outcome of the ADMYRE trial (IRC assessed PFS without PD confirmation) and the recalculated utility values from the July 2019 commentary.

Table 20: Results of sensitivity analysis

Analyses	Incremental cost	Incremental QALY	ICER
Modelled Base case	**$**	**0.341**	**$**
Modelled Base case (corrected)	**$**	**0.356**	**$**
Sensitivity analyses (using corrected base case)			
IRC PFS without disease confirmation (base case: IRC PFS with PD confirmation)	$	0.339	$
July 2019 Commentary utilities: 0.705 pre-progression, 0.624 post-progression (base case: 0.750, 0.645)	$	0.338	$
Lower post-progression treatment costs for Dxm arm: $ (base case: $ Dxm)	$	0.356	$
ITT OS (not adjusted for crossover)	$	0.129	$
Multivariate sensitivity analysis (using corrected base case)			
IRC PFS without PD confirmation + July 2019 commentary utilities + lower post-progression treatment costs	$	0.325	$

Source: Table 115, p249 in the resubmission.

Dxm = dexamethasone; ICER = incremental cost-effectiveness ratio; IRC= Independent Review Committee; KM= Kaplan-Meier; NICE = National Institute for Health and Care Excellence; OS = overall survival; PBAC = Pharmaceutical Benefit Advisory Committee; PFS = progression-free survival; QALY = quality-adjusted life years; TTF = time to treatment failure.

The redacted table shows ICERs in the range of $45,000 – $105,000/QALY.

6.63 The ESC considered that the ICER resulting from the multivariate sensitivity analysis which incorporated IRC assessed PFS without PD confirmation, the July 2019

commentary utilities and lower post-progression treatment costs in the Dxm arm (ICER = $75,000 - $105,000) was a more appropriate base case, although likely still underestimated due to the application of OS adjusted for crossover.

Drug cost/patient/treatment

6.64 The cost per patient per course is presented in Table 21. The proposed DPMA of plitidepsin ($[redacted]) was weighted across the third (DPMA = $[redacted], 53%) and fourth-line (DPMA = $[redacted], 47%) settings. Using the trial-based costs and the weighted plitidepsin DPMA resulted in a higher cost per patient per course for plitidepsin ($[redacted], mean 5 treatment cycles) compared with the CUA ($[redacted], mean 4.93 treatment cycles).

Table 21: Drug cost per patient for proposed and comparator drugs

	Plitidepsin				Pomalidomide		
	Trial dose and duration	**CMA**	**CUA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Equi-effective dose (recommended)	5 mg/m^2	5 mg/m^2	5 mg/m^2	5 mg/m^2	4 mg/day	4 mg/day	4 mg/day
Frequency/28-day cycle	2	2	2	2	21	21	21
Median treatment cycles	Mean: 5.0 cycles[a]	3 cycles	Mean: 4.93 cycles	3 cycles	3 cycles	3 cycles	3 cycles
BSA	1.81	NR	1.81	NR	NA	NA	NA
Vials per dose	4.6[b]	NR	4.6[b]	5	NA	NA	NA
Cost/patient/ cycle	$[redacted][c]	$[redacted][d]	$[redacted][e]	$[redacted][f]	$10,547.29 (private) $10,500.00 (public)	$10,547.29	$10,547.29 (private) $10,500.00 (public)
Cost/patient/ course	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$31,571[g]	$31,642	$31,571[g]

Source: March 2020 resubmission.

AE = adverse event; CMA = cost minimisation analysis; CSR = clinical study report; CUA = cost utility analysis; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; NA = not applicable; NR = not reported

[a] 842 cycles/167 patients, Table 43 ADMYRE CSR.

[b] Based on a BSA of 1.8 m^2, 19.8%, 7.8% and 1.2% of patients having one, two, or three dose reductions, respectively based on the ADMYRE trial

[c] Cost of plitidepsin accounting for dose interruptions and reductions using weighted DPMA (Drug acquisition costs E48 = $[redacted]). Excludes co-administered medicines.

[d] Cost-minimised plitidepsin price presented in resubmission using DPMQ. Calculated in the submission as cost of total cost of pomalidomide therapy including treatment of AEs ($11,090.07) minus the cost of administration and AE costs of plitidepsin ($[redacted]).

[e] Cost of plitidepsin accounting for dose interruptions and reductions excluding co-administered medicines.

[f] Weighted DPMQ ($[redacted]) × 3 doses

[g] Average of public and private prices × 3 cycles, without accounting for co-payment.

Estimated PBS usage & financial implications

6.65 This resubmission was not considered by DUSC.

6.66 The resubmission presented an epidemiological approach to estimate the financial implications of plitidepsin on the PBS. A market-share approach was also presented to validate the results. The ESC noted that the key input parameters for the financial estimates were unchanged from the July 2019 submission (Table 22).

Table 22: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident population (unchanged from July 2019 submission)		
MM incidence	7.62 – 8.08 per 100,000 (AIHW ACIM 2013)	The source was appropriate.
Previously received IMiD and bortezomib	38.2% based on 2017 DUSC report (regimens used over 2-3 years from initiation)	Overestimated population eligible in year of MM diagnosis. Only 2.3% used pomalidomide after IMiD and bortezomib.
Patients using further treatment	28 - 29% based on 2017 DUSC report. Estimated uptake of pomalidomide from eligible population + 5% market growth.	Market growth not supported by effectiveness and safety of plitidepsin (para 6.8, plitidepsin Public Summary Document, Jul 2019 PBAC meeting)
Prevalent population (unchanged from July 2019 submission)		
IMID + PI (3rd and 4th line eligible)	18.8% and 16.2 % based on the PBS 10% sample analysis.	Likely overestimated.
Refractory or intolerant of IMiD + PI	42% (assumption, source not stated).	Unclear whether estimate appropriate. Many MM patients will experience treatment failure (disease progression on or 6 months after treatment).
Uptake (3rd and 4th line)	81.9% and 45% based on PBS 10% sample analysis.	Inappropriate and overestimated. Based on use of any third-line treatment (bortezomib, carfilzomib, lenalidomide and thalidomide) not just pomalidomide.
Grandfathered patients	22 in Year 1 based on the Aplidin Access Program.	Previously 20.
Uptake (incident and prevalent patients)		
Uptake rate	Yr 1: 22% to Yr 6: 45%. Calculated based on the difference in forecast versus actual patients using therapy with pomalidomide (DUSC 2017).	Uptake uncertain and overestimated due to plitidepsin toxicity and clinically meaningful effect observed in only a small and undefinable subgroup of patients (para 7.12, plitidepsin Public Summary Document, Jul 2019 PBAC meeting).
Changes in use of other medicines		
Scripts changed	Increase: Dxm, ondansetron, promethazine, and prochlorperazine. Decrease: pomalidomide and aspirin.	This was appropriate.

Source: pp252-269 in the resubmission.

ACIM = Australia Cancer Incidence and Mortality; AIHW = Australian Institute of Health and Welfare; Dxm = dexamethasone; DUSC = drug utilisation sub-committee; IMiD = immunomodulator; MBS = Medicare Benefit Schedule; MM = multiple myeloma; PBS = Pharmaceutical Benefits Scheme; PI = proteasome inhibitor; Yr = year.

6.67 The methodology, data sources and key assumptions were unchanged from the previous submission. Therefore, the following issues remain:

- Plitidepsin uptake and market growth was likely overestimated due to the additional toxicity and relatively small clinical benefit. This applied to:
  - the plitidepsin uptake rates (22% in Year 1, increasing to 45% in Year 6);
  - the assumption that 44.4% of pomalidomide patients would receive subsequent therapy with plitidepsin, and,
  - the assumption of 5% market growth due to the PBS listing of plitidepsin;
- The eligible third-line patient population was calculated based on all patients currently receiving any third-line therapy (including pomalidomide, bortezomib, carfilzomib, lenalidomide and thalidomide) rather than patients only receiving

pomalidomide. This approach likely underestimated the extent of substitution (assumed to be pomalidomide only) relative to the estimated number of patients (all third line treatment);

- Estimated plitidepsin utilisation was substantially higher than the supplementary market-share approach, which was based on the prescription volumes of pomalidomide (unchanged from the previous submission). These estimates could be considered as a separate validation of the epidemiological approach, but were not used as such by the resubmission; and
- The financial estimates added the estimated incidence and prevalent patients, likely overestimating the eligible population.

6.68 The resubmission used the proposed weighted DMPA of $[redacted] ($[redacted] in the previous submission) and assumed increased use of promethazine and prochlorperazine (rather than decreased use). This was appropriate as promethazine and prochlorperazine are administered with plitidepsin but not with pomalidomide.

6.69 The net financial implications to PBS/RPBS of listing plitidepsin on PBS are presented in Table 23.

Table 23: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible population						
Incident	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grandfathered	[redacted][a]	-	-	-	-	-
Estimated extent of use						
Number of patients treated	[redacted][b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed	[redacted][c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market-share approach[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of plitidepsin						
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications of other medicines[e]						
Cost to PBS/RPBS less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
3rd line[f]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
4th line[f]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission (Net cost to PBS/RPBS)						
3rd line	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
4th line	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 125, p262; and Section 4 spreadsheet of the resubmission.

IMiD = immunomodulatory agent; MBS = Medicare Benefit Schedule; PBS = Pharmaceutical Benefits Scheme; PI = proteasome inhibitor; RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] Changed from 20 in the previous submission

[b] Changed from 287 in the previous submission

[c] Changed from 860 in the previous submission

[d] Based on plitidepsin capturing 22% to 45% of the pomalidomide market and 44.4% of patients using plitidepsin after pomalidomide. Not used to estimate financial implications in the resubmission.

[e] Displaced medicine included pomalidomide, dexamethasone, ondansetron, promethazine, prochlorperazine and aspirin.

[f] Disaggregated during evaluation using the model from the resubmission, for 3rd-line treatment, the % of patients who have received both PI and IMiD (3+) and % of patients electing to receive 4th-line treatment was assumed to be 0%. The 22 grandfathered patients were included in this treatment setting. For 4th-line treatment, the % of patients who have received both PI and IMiD (2 only) and % of patients electing to receive 3rd-line treatment were assumed to be 0%. Sheet 3b. Impact - PUB cell G73 = $9,811.87.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.70 The resubmission estimated net cost to PBS/RPBS for listing plitidepsin was less than $10 million in Year 1 increasing to $10 – $20 million in Year 6. As the financial estimates were broadly similar to July 2019 submission, the ESC considered that they remained overestimated.

6.71 The supplementary market-share approach presented in the resubmission estimated lower utilisation and may provide a better estimate of plitidepsin utilisation.

Quality Use of Medicines

6.72 The resubmission did not identify any new quality use of medicines issues. The resubmission provided the summary of safety concerns and planned pharmacovigilance actions for plitidepsin as presented in the July 2019 submission.

Financial Management – Risk Sharing Arrangements

6.73 Unchanged from the previous submission, no Risk Sharing Arrangement (RSA) was proposed in the resubmission. An RSA with subsidisation caps is currently in place for pomalidomide.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of plitidepsin in patients who are refractory to a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) (third-line setting) or in patients who have received at least three prior treatment regimens including both a PI and an IMiD (fourth-line setting). The PBAC considered that, for the comparison of plitidepsin + dexamethasone (Dxm) versus Dxm monotherapy (fourth-line setting), the magnitude of the clinical benefit in terms of progression free survival (PFS) without progressive disease (PD) confirmation (median increase of 0.9 months) was marginal, and the magnitude of the clinical benefit in terms of PFS with PD confirmation (median increase of 3.0 months) was not reliable. The PBAC considered that the overall survival (OS) gain was uncertain given it was statistically significant only when adjusted for cross-over. The PBAC considered that the incremental cost-effectiveness ratio (ICER) for plitidepsin versus Dxm remained high and underestimated. The PBAC considered that for the comparison against pomalidomide + Dxm (third-line setting), the claim of non-inferior efficacy was uncertain and the claim of non-inferior safety was unable to be assessed. Therefore the PBAC considered that the cost-minimisation analysis (CMA) for this comparison was not adequately supported.

7.2 The PBAC noted the large number of consumer comments describing the desire for another treatment option in this setting.

7.3 The PBAC noted that, although registered by the TGA, plitidepsin was rejected by the European Medicines Agency (EMA) in December 2017 as the EMA considered that the benefits of plitidepsin did not outweigh its risks. Plitidepsin is yet to be considered by the Food and Drug Administration (FDA) in the USA.

7.4 Unchanged from the July 2019 submission, pomalidomide + Dxm was nominated as the third-line comparator and Dxm monotherapy was nominated as the fourth-line comparator. The PBAC again considered that both comparators were appropriate.

7.5 For the comparison between plitidepsin + Dxm and Dxm monotherapy, the PBAC

noted that no new clinical data were presented in the resubmission. The resubmission did present a preplanned sensitivity analysis from the ADMYRE trial that reported PFS with PD confirmation. The PBAC considered that the clinical benefit from PFS with PD confirmation (HR = 0.52; 95% CI: 0.35, 0.76), with an increase in median PFS of 3.0 months, was not reliable as the analysis was a preplanned sensitivity analysis conducted to test the consistency of the primary PFS outcome, PFS without PD confirmation. The PBAC considered that based on the primary outcome of the trial, PFS without PD confirmation, plitidepsin + Dxm resulted in a marginal increase in clinical benefit over Dxm monotherapy (HR = 0.65; 95% CI 0.48, 0.89; increase in median PFS = 0.9 months). The PBAC again noted that the OS benefit was only statistically significant when adjusted for crossover (HR = 0.67; 95% CI 0.50, 0.90).

7.6 Overall, the PBAC maintained its view from July 2019 and considered that plitidepsin resulted in an incremental benefit versus Dxm in a small subset of patients who experienced a prolonged response. The PBAC noted that there was no way to target treatment with plitidepsin to those patients who are most likely to respond.

7.7 In terms of safety, the PBAC noted that the resubmission had updated its claim and stated that plitidepsin + Dxm was inferior compared to Dxm monotherapy. The PBAC considered that this was appropriate, noting that plitidepsin + Dxm resulted in statistically significant increases in any treatment emergent adverse events (TEAEs), serious adverse events (AEs) and Grade 3 or higher TEAEs compared to Dxm monotherapy.

7.8 Unchanged from the July 2019 submission, the resubmission presented an indirect comparison of plitidepsin + Dxm and pomalidomide + Dxm based on the results of the ADMYRE and NIMBUS trials. The PBAC again considered the claim that plitidepsin + Dxm was non-inferior in terms of efficacy compared to pomalidomide + Dxm in the third-line setting was uncertain as:

- a non-inferiority margin was not proposed;
- the point estimates of the hazard ratios favoured pomalidomide + Dxm over plitidepsin + Dxm; and
- the 95% confidence intervals were wide, with the upper limits exceeding 2.0 for PFS without PD confirmation, and 1.6 for OS.

7.9 The PBAC again noted that the higher toxicity profile of HI-Dxm (NIMBUS trial) compared to Dxm (ADMYRE trial) made it difficult to assess the comparability of the common comparator arms in the indirect comparison in terms of safety. The PBAC reiterated that the claim that plitidepsin + Dxm was non-inferior in terms of safety compared to pomalidomide + Dxm could not be adequately assessed.

7.10 The PBAC noted that the resubmission presented a revised CMA, which appropriately included updated AE costs, that were based on the indirect comparison of plitidepsin + Dxm and pomalidomide + Dxm in the third-line setting. The PBAC noted that uncertainty remained relating to the dose of plitidepsin used in the CMA. As the claim

of non-inferior safety was highly uncertain and the claim of non-inferior safety could not be assessed, the PBAC considered that the basis of the CMA was not adequately supported.

7.11 The PBAC noted the submission did not nominate an effective price for plitidepsin, instead relying on the price determined in the CMA.

7.12 The resubmission presented a revised cost-utility analysis (CUA) comparing plitidepsin + Dxm with Dxm monotherapy in the fourth-line setting. The PBAC noted that the resubmission appropriately reduced the time horizon from seven to five years; however, noted that there were errors in the extrapolation of PFS, time to treatment failure (TTF) and OS and the utility values applied, and that TTF remained unable to be verified.

7.13 The PBAC considered that the base case ICER of $45,000 – $75,000 per quality adjusted life year (QALY), using the published price and corrected for the extrapolation errors, was underestimated as:

- PFS with PD confirmation overestimated PFS for plitidepsin compared to the ADMYRE trial's primary outcome, PFS without PD confirmation;
- the post-progression treatment costs were substantially higher in the Dxm arm (less than $10 million for plitidepsin versus less than $10 million for Dxm) and applied to all patients who progressed; and
- the resubmission mistakenly applied utility values sourced from the carfilzomib PSD (July 2017), which were for second-line therapy.

7.14 The PBAC also considered that the ICER was uncertain as the model applied OS data adjusted for crossover effects.

7.15 The PBAC considered that the clinical uncertainties were magnified in the economic evaluation and, as such, a substantially more conservative economic evaluation with respect to both the incremental efficacy and implication of the additional toxicity would be appropriate. The PBAC reiterated that an appropriate ICER would be less than $40,000 per QALY to account for the substantial toxicity and minor additional benefit of plitidepsin.

7.16 The PBAC noted that as the majority of the issues with the usage and financial implication estimates identified in July 2019 were not addressed in the resubmission, the results remained overestimated. The identified issues included plitidepsin uptake rates, market growth, the eligible third-line patient population, and the eligible overall patient population.

7.17 The PBAC noted that the restriction changes suggested in July 2019 were not addressed in the resubmission. The PBAC considered that the restriction level for initial treatment with plitidepsin should be Authority Required (written).

7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.