▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

Australian Product Information
APLIDIN (plitidepsin)

1 NAME OF THE MEDICINE
APLIDIN (plitidepsin) powder for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 2 mg of plitidepsin.
After reconstitution, each mL of reconstituted solution contains: 0.5 mg of plitidepsin, 158 mg of PEG-35 castor oil, and ethanol 0.15 mL/mL.

List of excipients
For the full list of excipients, see ***Section 6.1 List of excipients.***

3 PHARMACEUTICAL FORM
Powder for solution for infusion. The powder is a white to off-white powder or solid cake.
The solvent is a clear, slightly viscous liquid free of visible particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indication
APLIDIN, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least three prior treatment regimens, including both a proteasome inhibitor and an immunomodulator. APLIDIN may be used after two prior lines of therapy if refractory and/or intolerant to both a proteasome inhibitor and an immunomodulator.

4.2 Dose and method of administration
Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

APLIDIN is administered in combination with dexamethasone. Pre-infusion medications should be administered to reduce the risk of infusion related reactions.

The recommended dose of APLIDIN is 5 mg/m^2 according to Body Surface Area (BSA).
Infusion must be performed through a pump device over three hours (fixed rate) on Day 1 and 15 every four weeks (q4wk).

The recommended dose of dexamethasone is 40 mg orally on Day 1, 8, 15 and 22 q4wk at least one hour before plitidepsin infusion (Day 1 and 15). For additional information concerning dexamethasone, see the corresponding Product Information.

Patients should be treated until disease progression or unacceptable toxicity.

Premedication for prevention of infusion reaction
All patients must receive the following prophylactic medication 20-30 minutes before infusion of plitidepsin:

- Ondansetron 8 mg intravenously (i.v.) or equivalent (granisetron 3 mg intravenously preferred when available),
- Diphenhydramine hydrochloride 25 mg intravenously or equivalent, and
- Ranitidine 50 mg intravenously or equivalent.

Oral metoclopramide and/or extended oral ondansetron (or their equivalents) may be used at the physician's discretion.
If dexamethasone treatment is discontinued due to toxicity, dexamethasone at a lower dose (8 mg) must be given as premedication for plitidepsin treatment.

Management of infusion reaction
Prophylaxis medication is mandatory at least 30 minutes prior to each plitidepsin infusion with dexamethasone or equivalent, antiemetics (setrons) and histamine receptor antagonists (H1 and H2 receptor antagonists).

In the event of severe/life threatening reactions (NCI-CTCAE v.4 grade ≥ 3) described as cardiovascular symptoms [hypertension $\geq 160/100$ mmHg or tachycardia ≥ 120 bpm or hypotension (systolic pressure < 90 mmHg) requiring vasopressor therapy] or anaphylactic shock or respiratory symptoms (angioedema, generalised wheezing and/or respiratory distress) requiring oxygen therapy, the plitidepsin infusion must be interrupted. Immediate therapy with oxygen and bronchodilators should be considered if pulse gasometry indicates $< 92\%$ O_2 saturation at ambient air. Administer diphenhydramine 50 mg intravenously or equivalent, and hydrocortisone 100 mg up to a maximum of 300 mg intravenously, and add epinephrine (adrenaline) if clinically indicated. The infusion should not be restarted, and plitidepsin therapy must be discontinued.

In the event of mild to moderate/non-life threatening reactions (NCI-CTCAE v.4 grade ≤ 2) described as facial and/or trunk flushing, rash and/or pruritus and/or mild dyspnoea and/or coughing and/or chest discomfort, the infusion must be stopped immediately and vital signs and pulse gasometry must be continuously monitored. It should be determined if the premedication was administered appropriately and, if not, the premedication should be then properly given and the plitidepsin infusion can be re-started at least 30 minutes after.
If symptoms persist after interrupting the infusion, additional diphenhydramine at a dose of 50 mg intravenously or equivalent, and hydrocortisone 100 mg bolus intravenously or equivalent, should be administered.

Reassess symptoms and vital signs after 30 minutes, if normal or improving, then the infusion could be re-started at one third of the initial drip rate during the first hour. Signs and symptoms must be continuously monitored during infusion. Then the infusion rate could be increased according to tolerance. Any further infusions should be started at a reduced rate and should be given with prophylactic intravenous premedication, as above described. The patient should be monitored for symptoms during the first post-infusion hour. In these further infusions, dexamethasone will be administered intravenously (instead of orally). If no hypersensitivity reactions are observed, the rate of infusion to be applied could be set back to the initial one.
If there is no sign of improvement of symptoms after 30 minutes, repeat medication (H1 receptor antagonist and/or corticoids) until resolution, and plitidepsin therapy must be discontinued.

Table 1. Criteria for starting treatment with plitidepsin

Laboratory value/Component/Test	**Criteria for starting**
Absolute neutrophil count (ANC)	≥ 1.0 x 10^9/L [≥ 0.5 x 10^9/L if due to extensive and documented bone marrow (BM) disease involvement by ≥ 50% of plasma cells in BM biopsy]
Platelet count	≥ 50 x 10^9/L (≥ 25 x 10^9/L if due to extensive and documented BM disease involvement)
Haemoglobin	≥ 8.0 g/d
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤ 3.0 x the upper limit of normal (ULN)
Total bilirubin	≤ 1.0 x ULN or direct bilirubin ≤ 1.0 x ULN when total bilirubin is above ULN
Calculated creatinine clearance (CrCl)	≥ 30 mL/minute (by means of Cockcroft and Gault´s formula)
Creatine phosphokinase (CPK)	≤ 2.5 x ULN
Albumin	≥ 2.5 g/dL
Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)	above the lower limit of normal (LLN)

Method of administration

Prior to administration, APLIDIN must be reconstituted and further diluted by a healthcare professional.

Intravenous administration can be made through a peripheral venous line or a central venous line.

Infusion must be performed through a pump device over three hours (at a fixed rate).

Preparation for intravenous infusion

Appropriate aseptic techniques must be used. APLIDIN must be reconstituted and further diluted prior to administration.

Each vial of APLIDIN is reconstituted with 4 mL of APLIDIN solvent for reconstitution.

lnstructions for reconstitution

A syringe should be used to inject the 4 mL of solvent into the vial. Shake the vial until complete dissolution. The reconstituted concentrate results in a clear, colourless or slightly yellowish solution, free of visible particles.

This reconstituted concentrate contains 0.5 mg of plitidepsin per mL. lt requires further dilution and is for single-use only.

lnstructions for dilution

The reconstituted concentrate should be diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion to a total volume of 500 mL for administration via a peripheral venous line or to a total volume of 250 mL for administration via a central venous line. The required volume of reconstituted concentrate to be diluted for an individual dose should be calculated as follows:

$$\text{Volume (mL)} = \frac{\text{BSA (m}^2\text{) x individual dose (mg/m}^2\text{)}}{\text{0.5 mg/mL}}$$

BSA = Body Surface Area

Instructions for administration

APLIDIN infusion solution should be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2 µm) using an automated infusion pump.

A peripheral venous line or a central venous line for administration may be used.

APLIDIN infusion is compatible with:

- Glass and polyolefin containers (polyethylene, polypropylene and mixtures).
- PVC DEHP-free and polyolefin infusion sets (polyethylene, polypropylene and mixtures).
- Polyethersulfone and nylon in-line filters with pore sizes of 0.2 µm.
- Implantable venous access systems with titanium and plastic resin ports and with polyurethane or silicone intravenous catheters. Polyurethane intravenous catheters can be used as no adsorption has been observed under these circumstances.

The APLIDIN solution for infusion should be administered within 6 hours of reconstitution if stored at room temperature and under ambient lighting. If storage is required prior to administration then solutions should be stored refrigerated and protected from light and should be used within 24 hours of reconstitution.

APLIDIN is a cytotoxic anticancer medicinal product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Criteria for treatment continuation, dose delay or interruption

In order to receive the next planned dose of APLIDIN, patients have to meet the following criteria:

Table 2. Criteria for treatment continuation, dose delay or interruption

Laboratory value/Component/Test	**Criteria for continuing**
ANC	$\geq 1.0 \times 10^9$/L ($\geq 0.5 \times 10^9$/L if due to extensive and documented BM disease involvement by ≥ 50% of plasma cells in BM biopsy)
Platelet count	$\geq 50 \times 10^9$/L ($\geq 25 \times 10^9$/L if due to extensive and documented BM disease involvement)
Haemoglobin	≥ 8.0 g/dL
AST and ALT	≤ 5.0 x ULN
Total bilirubin	≤ 1.0 x ULN or direct bilirubin ≤ 1.0 x ULN when total bilirubin is above the ULN
Muscular toxicity (e.g., myalgia, muscular weakness, CPK increase)	≤ grade 2

If the requirements for treatment continuation are unmet on Day 1 of the following cycle, the infusion of APLIDIN will be withheld until recovery or for a maximum of 14 days. After this period, if the delay is due to toxicity assessed as related to plitidepsin, a dose decrease from 5.0 mg/m^2 to 4.0 mg/m^2 and then to 3.2 mg/m^2 is recommended. Further reductions might be performed according to clinical criteria.

If the requirements for treatment continuation are unmet on Day 15, the administration of plitidepsin will be omitted until recovery and restarted once re-treatment criteria are fulfilled. Patients requiring frequent dose omissions may have a dose reduction from 5.0 mg/m^2 to 4.0 mg/m^2 and then to 3.2 mg/m^2.

Dose reduction criteria for both medicinal products, plitidepsin and dexamethasone, are summarised in the following table:

Table 3. Dose reduction criteria

Toxicity	Worst grade	Plitidepsin	Dexamethasone
Less than 50% compliance with treatment schedule		Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Febrile neutropenia	≥ 3	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Neutropenia lasting > 7 days (except for patients with extensive BM involvement)	4	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Thrombocytopenia (except for patients with extensive BM involvement)	4	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Thrombocytopenia with grade ≥ 3 bleeding (in patients with extensive BM involvement)	4	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Any clinically relevant and/or non-haematological toxicity (except non-optimally treated nausea and vomiting, diarrhoea < 48 hours and/or asthenia/fatigue lasting < 5 days)	≥ 3	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction
Muscular toxicity (weakness, myalgia and/or CPK elevations)	≥ 3	First episode: decrease to 4 mg/m^2, then reduce dexamethasone; if toxicity recurs, reduce to 3.2 mg/m^2	First reduce plitidepsin; if this persists, decrease dexamethasone to 20 mg Days 1, 8, 15, 22 of each cycle; if toxicity recurs, first decrease plitidepsin again and, if persistent, decrease dexamethasone to 20 mg Days 1 and 15 of each cycle.
Mood disturbances/agitation	≥ 2	No reduction	First reduce to 20 mg Days 1, 8, 15, 22 of each cycle, then to 20 mg Days 1 and 15 of each cycle.
Fluid retention	≥ 3	No reduction	First reduce to 20 mg Days 1, 8, 15, 22 of each cycle, then to 20 mg Days 1 and 15 of each cycle.
Clinically documented infection	4	No reduction	First reduce to 20 mg Days 1, 8, 15, 22 of each cycle, then to 20 mg Days 1 and 15 of each cycle.
ALT/AST increase	≥ 3	Decrease to 4 mg/m^2, then to 3.2 mg/m^2	No reduction

Special populations

Paediatric population

The safety and efficacy of APLIDIN has not been studied in paediatric patients.

Elderly

No age-related dose adjustment is required for plitidepsin.

Renal impairment
No dose adjustment is necessary in patients with mild, moderate or severe renal impairment. Caution is recommended in patients with severe renal impairment (GFR 15-29 ml/min), as experience in this population is limited. Patients with end stage renal impairment (GFR < 15 mL/min) have not been included in any clinical study with plitidepsin. There is no data on the safety and efficacy of plitidepsin in patients with end stage renal impairment.

Hepatic impairment
Plitidepsin has not been formally studied in patients with impaired hepatic function. Patients with AST > 3 x ULN and/or bilirubin > ULN were not allowed to participate in most clinical studies with plitidepsin. Since most administered plitidepsin is eliminated by biliary excretion, patients with impaired hepatic function (AST > 3 x ULN and/or bilirubin > 1 × ULN) should not be treated with plitidepsin.

4.3 Contraindications

Hypersensitivity to the active substance, plitidepsin, or to the excipients PEG-35 castor oil or ethanol.

4.4 Special warnings and precautions for use

Musculoskeletal and connective tissue disorders and investigations

Musculoskeletal and connective tissue disorders and investigations
Myopathy including rhabdomyolysis: muscle weakness, myalgia and/or CPK elevation were frequently reported during treatment with plitidepsin plus dexamethasone. Isolated cases of rhabdomyolysis have also been observed. In order to minimise the risk of musculoskeletal events:

- CPK should be monitored prior to each infusion (Day 1 and Day 15) from Cycle 1 to Cycle 4.
- The treatment with plitidepsin should not be started in patients with grade > 2 myopathy or any clinical condition that causes significant and persistent elevation of CPK (i.e., > 2.5 x ULN in two different determinations performed one week apart). See section 4.2 for dose recommendations.
- If rhabdomyolysis occurs, plitidepsin treatment should be stopped. Supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established. Caution should be taken if medicinal products associated with rhabdomyolysis (e.g., statins), are administered concomitantly with plitidepsin plus dexamethasone, since the risk of rhabdomyolysis may be increased.

The clinicians are recommended to report all severe and fatal musculoskeletal events.

Injecton site reactions and hypersensitivity reactions
Infusion reactions have been reported in patients who received plitidepsin. Symptoms may include, pain, catheter site phlebitis, infusion site reaction, injection site extravasation or thrombosis in device. These reactions can occur during or immediately after the administration of plitidepsin.

Treatment-related (or with unknown relationship) hypersensitivity reactions were reported in 6.6% of patients in Arm A (plitidepsin plus DXM) and in 5.4% of patients who crossed over from Arm B to Arm A. The frequency of grade ≥ 3 hypersensitivity reactions was 1.2% in Arm A and 2.7% in the crossover patients.

Premedication must be administered prior to plitidepsin to reduce the incidence of the reactions [see ***Section 4.2 Dose and method of administration (Management of Infusion reaction)***].

Liver enzyme increase (ALT/AST)
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases according to laboratory values were reported in 66.0% and 84.9% of patients, respectively, during treatment with plitidepsin. Most of them were grade 1 or 2. Transaminase increases occurred mostly during the first 2 cycles of treatment, and they were transient and reversible. Before plitidepsin plus dexamethasone administration, the patients must have total bilirubin ≤ 1.0 x ULN (or direct bilirubin ≤ 1.0 x ULN when total bilirubin is above the ULN) and AST/ALT ≤ 3.0 x ULN. AST and ALT measurements should be performed before the administration of plitidepsin.

Cardiac effects, including QT prolonged
- Cardiac effects such as bradycardia; electrocardiogram QT prolonged; sinus tachycardia; and orthostatic hypotension have been observed in patients treated with the combination plitidepsin plus dexamethasone in the phase III study. The causal relationship has not been established yet, since most of cardiovascular events reported had confounding factors, such as cardiovascular medical history or concomitant medications known to induce such cardiovascular effects. Therefore, patients with risk factors for or existing heart disease should be closely monitored. Appropriate caution should be exercised when considering the treatment of such patients with plitidepsin plus dexamethasone, including periodic electrocardiogram monitoring.
- Patients with symptomatic arrhythmia (excluding anaemia-related sinusal tachycardia grade ≤ 2) or any arrhythmia requiring ongoing treatment, and/or prolonged QT/QTc grade ≥ 2; or presence of unstable atrial fibrillation, should not be treated with plitidepsin plus dexamethasone.
- It is recommended to monitor patients for clinical cardiac signs or symptoms. To include only patients with left ventricular ejection fraction (LVEF) by echocardiography above the lower limit of normal at baseline and to measure LVEF periodically during the treatment. LVEF assessment has to be performed every 12 weeks. If there is a decrease in LVEF, treatment should be interrupted until LVEF returns to normal values.

Other
Since APLIDIN contains *ethanol* (up to 2137.5 mg per dose), possible central nervous system and other effects might occur. Plitidepsin contains Polyoxyl 35 castor oil (Macrogolglycerol ricinoleate), which may cause severe allergic reactions.

Fertile female and male patients should use effective methods of contraception during treatment and for up to six months after treatment (see ***Section 4.6 Fertility, Pregnancy and Lactation***).

Interactions
- Co-administration with strong CY3A4 inhibitors and inducers should be avoided since they may affect the plasma concentration of plitidepsin (see section 4.5).
- Co-administration with moderate CY3A4 inhibitors and inducers should be used cautiously, since an effect on plitidepsin exposure cannot be excluded (see section 4.5).

Use in hepatic impairment
As most plitidepsin is eliminated via the liver, patients with impaired hepatic function (AST > 3 x ULN and/or bilirubin > 1 × ULN) may be at risk of increased exposure to plitidepsin (see ***Section 4.2 Dose and method of administration*** and ***Section 5 Pharmacological properties***).

Use in the elderly
No age-related dose adjustment is required for plitidepsin.

Paediatric use
The safety and efficacy of APLIDIN in the paediatric population has not been studied in MM.

Effects on laboratory tests
No effects on laboratory test have been observed.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed.

Effect of other medicinal products on APLIDIN
Interactions with CYP3A4 inhibitors
In vitro studies indicate that CYP3A4 is the main enzyme involved in the metabolism of plitidepsin. Plitidepsin should not be administered with strong CYP3A4-enzyme inhibitors (e.g. grapefruit juice, clarithromycin, itraconazole, nefazodone, telithromycin, voriconazole). Strong CYP3A4 inhibitors should be discontinued at least 1 week prior to starting treatment and while on treatment with plitidepsin.

Moderate CYP3A4-enzyme inhibitors (e.g. aprepitant, diltiazem, erythromycin, fluconazole, verapamil) should be used cautiously, since an increase of plitidepsin exposure cannot be excluded.

Interactions with CYP3A4 inducers
In order to avoid a loss of plitidepsin efficacy, plitidepsin should not be administered with strong CYP3A4-enzyme inducers such as anticonvulsants (phenytoin, phenobarbital or carbamazepine), rifampin, rifabutin and St. John's wort unless there are no therapeutic alternatives. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers has not been defined. Consideration should be given to substituting with non-enzyme inducing therapies at least 2 weeks prior to initiation and while on treatment with plitidepsin therapy.

Moderate CYP3A4-enzyme inducers (e.g. bosentan, modafinil, nafcillin) should be used cautiously, since a reduction of plitidepsin exposure cannot be excluded.

Effect of APLIDIN on other medicinal products
No relevant inhibition of key CYP isozymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) or transporters (P-glycoprotein, OATP1B1, OATP1B3, BCRP, BSEP, MRP2, OAT1, OAT3 and OCT2) was observed with plitidepsin at therapeutic concentrations *in* vitro. Accordingly, pharmacokinetic drug-drug interactions caused by plitidepsin on co-administered substances are not expected.

Oral contraceptives
Since dexamethasone is a moderate inducer of CYP3A4, efficacy of oral contraceptives may be reduced when administered concomitantly. Consequently, effective measures to avoid pregnancy must be taken.

Concomitant medication frequently used in malignancies
In multiple myeloma patients, there is experience of co-administering plitidepsin and dexamethasone with antiemetics (i.e. serotonin antagonists such as ondansetron or granisetron, and metoclopramide), antihistamines (i.e. diphenhydramine), proton pump inhibitors (i.e. ranitidine) and bisphosphonates (i.e. zoledronate). Changes in the effects of these drugs have not been reported, but drug-drug interactions between plitidepsin plus dexamethasone and these drugs have not been formally investigated.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Studies in rats and dogs have shown that the compound may affect reproductive capacity. Impairment of male and female fertility, sperm degeneration and inhibition of ovulation were observed in animals treated with plitidepsin at doses yielding systemic exposure levels (plasma AUC) below that of patients at the recommended dose.

Use in pregnancy (**Category D**)

There is no human experience with plitidepsin during pregnancy.
Administration of a single intravenous dose of plitidepsin (0.6 mg/kg) to rats during gestation caused complete embryofetal lethality in all animals. Systemic exposure (plasma AUC) in animals at this dose was below that of patients at the recommended dose.
APLIDIN should not be used during pregnancy unless the clinical benefit outweighs the potential risk to the fetus.
Women of childbearing potential must use effective contraception during and for up to 6 months after treatment.
Male patients must use effective contraception measures during and for up to 6 months after treatment if their partner is pregnant or of childbearing potential and is not using effective contraception.

Use in lactation

It is unknown whether plitidepsin and/or its metabolites are excreted in human breast milk.
A risk to newborns/infants cannot be excluded.
Breast-feeding should be discontinued during treatment with plitidepsin.

4.7 Effects on ability to drive and use machines

APLIDIN has moderate influence on the ability to drive and use machines. Fatigue/asthenia and somnolence have been reported in patients receiving plitidepsin. Furthermore, the plitidepsin formulation contains ethanol. The ability to drive and use machines may be affected. Therefore, patients who experience such events during therapy should not drive or operate machinery.

4.8 Adverse effects (Undesirable effects)

A total of 250 of 255 patients randomised in the ADMYRE study were treated (n=167 in P+DXM arm and n=83 in the DXM arm).

The most common adverse reactions were gastrointestinal disorders (nausea, 37.1% of patients; vomiting, 16.8%; diarrhoea, 14.4%); general disorders (fatigue, 36.5%; oedema peripheral, 12.0%); metabolism and nutrition disorders (decreased appetite, 12.6%); and musculoskeletal disorders (myalgia, 14.4%; muscular weakness, 9.6%). The most common grade ≥ 3 adverse reactions were fatigue (10.8%), myalgia (5.4%), muscular weakness (3.6%) and nausea (3.6%).

Table 4. Adverse Events Reported frequency ≥ 5% regardless of relationship; APL-C-001-09 (ADMYRE trial).

		Arm A (P+DXM) N=167		Arm B (DXM) N=83	
		Any grade	Grade >=3	Any grade	Grade >=3
System Organ Class	Preferred term	n(%)	n(%)	n(%)	n(%)
Blood and lymphatic system disorders	Anaemia	74 (44.3%)	59 (35.3%)	36 (43.4%)	35 (42.2%)
	Neutropenia	13 (7.8%)	13 (7.8%)	2 (2.4%)	1 (1.2%)
	Thrombocytopenia	18 (10.8%)	17 (10.2%)	8 (9.6%)	8 (9.6%)
Cardiac disorders	Atrial fibrillation	9 (5.4%)	3 (1.8%)	1 (1.2%)	1 (1.2%)
Gastrointestinal disorders	Abdominal pain	10 (6.0%)	1 (0.6%)	4 (4.8%)	0 (0%)
	Abdominal pain upper	16 (9.6%)	1 (0.6%)	1 (1.2%)	0 (0%)
	Constipation	23 (13.8%)	0 (0%)	6 (7.2%)	0 (0%)
	Diarrhoea	60 (35.9%)	5 (3.0%)	8 (9.6%)	0 (0%)
	Dyspepsia	9 (5.4%)	1 (0.6%)	4 (4.8%)	0 (0%)
	Nausea	82 (49.1%)	7 (4.2%)	19 (22.9%)	1 (1.2%)
	Vomiting	44 (26.3%)	4 (2.4%)	4 (4.8%)	1 (1.2%)
General disorders and administration site conditions	Chest pain	9 (5.4%)	1 (0.6%)	2 (2.4%)	0 (0%)
	Fatigue	90 (53.9%)	20 (12.0%)	31 (37.3%)	9 (10.8%)
	Oedema peripheral	34 (20.4%)	2 (1.2%)	7 (8.4%)	0 (0%)
	Pain	13 (7.8%)	4 (2.4%)	1 (1.2%)	1 (1.2%)
	Pyrexia	37 (22.2%)	1 (0.6%)	12 (14.5%)	0 (0%)
Infections and infestations	Infection	9 (5.4%)	2 (1.2%)	0 (0%)	0 (0%)
	Nasopharyngitis	7 (4.2%)	0 (0%)	5 (6.0%)	1 (1.2%)
	Pneumonia	16 (9.6%)	10 (6.0%)	4 (4.8%)	3 (3.6%)
	Sepsis	9 (5.4%)	9 (5.4%)	2 (2.4%)	2 (2.4%)
	Upper respiratory tract infection	15 (9.0%)	2 (1.2%)	6 (7.2%)	0 (0%)
	Urinary tract infection	14 (8.4%)	3 (1.8%)	3 (3.6%)	1 (1.2%)
	Viral infection	9 (5.4%)	0 (0%)	1 (1.2%)	0 (0%)
Investigations	Alanine aminotransferase increased	27 (16.2%)	17 (10.2%)	0 (0%)	0 (0%)
	Aspartate aminotransferase increased	15 (9.0%)	10 (6.0%)	0 (0%)	0 (0%)

		Arm A (P+DXM) N=167		Arm B (DXM) N=83	
		Any grade	Grade >=3	Any grade	Grade >=3
System Organ Class	Preferred term	n(%)	n(%)	n(%)	n(%)
	Blood creatine phosphokinase increased	29 (17.4%)	26 (15.6%)	0 (0%)	0 (0%)
	Electrocardiogram QT prolonged	16 (9.6%)	4 (2.4%)	3 (3.6%)	0 (0%)
	Platelet count decreased	7 (4.2%)	6 (3.6%)	5 (6.0%)	5 (6.0%)
	Weight decreased	13 (7.8%)	0 (0%)	1 (1.2%)	0 (0%)
Metabolism and nutrition disorders	Decreased appetite	36 (21.6%)	2 (1.2%)	6 (7.2%)	0 (0%)
	Hypercalcaemia	12 (7.2%)	7 (4.2%)	9 (10.8%)	4 (4.8%)
	Hyperglycaemia	12 (7.2%)	4 (2.4%)	3 (3.6%)	0 (0%)
	Hypokalaemia	20 (12.0%)	7 (4.2%)	6 (7.2%)	1 (1.2%)
	Hypomagnesaemia	10 (6.0%)	1 (0.6%)	1 (1.2%)	0 (0%)
Musculoskeletal and connective tissue disorders	Arthralgia	10 (6.0%)	2 (1.2%)	7 (8.4%)	1 (1.2%)
	Back pain	23 (13.8%)	4 (2.4%)	17 (20.5%)	6 (7.2%)
	Bone pain	16 (9.6%)	3 (1.8%)	23 (27.7%)	3 (3.6%)
	Muscular weakness	21 (12.6%)	7 (4.2%)	4 (4.8%)	1 (1.2%)
	Musculoskeletal pain	15 (9.0%)	4 (2.4%)	1 (1.2%)	0 (0%)
	Myalgia	30 (18.0%)	9 (5.4%)	4 (4.8%)	0 (0%)
	Pain in extremity	10 (6.0%)	2 (1.2%)	4 (4.8%)	2 (2.4%)
Nervous system disorders	Headache	21 (12.6%)	1 (0.6%)	5 (6.0%)	0 (0%)
	Neuropathy peripheral	17 (10.2%)	0 (0%)	1 (1.2%)	0 (0%)
	Peripheral sensory neuropathy	4 (2.4%)	1 (0.6%)	6 (7.2%)	0 (0%)
	Polyneuropathy	3 (1.8%)	1 (0.6%)	5 (6.0%)	0 (0%)
Psychiatric disorders	Insomnia	19 (11.4%)	1 (0.6%)	12 (14.5%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Cough	33 (19.8%)	0 (0%)	12 (14.5%)	0 (0%)
	Dyspnoea	24 (14.4%)	5 (3.0%)	3 (3.6%)	1 (1.2%)
	Epistaxis	10 (6.0%)	2 (1.2%)	9 (10.8%)	3 (3.6%)
Vascular disorders	Hypertension	17 (10.2%)	0 (0%)	5 (6.0%)	0 (0%)
	Hypotension	17 (10.2%)	5 (3.0%)	2 (2.4%)	0 (0%)

*Multiple occurrences of the same event from a patient were counted only once (under the worst grade) within each preferred term.

Tabulated List of Adverse Reactions

The adverse reactions observed in patients with MM treated with plitidepsin are listed in the table below, sorted by MedDRA System Organ Class (SOC), that fall below 1% frequency.

Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing frequencies. Frequencies are defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); and uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and unknown (cannot be estimated from available data).

Table 5: Adverse Drug Reactions (treatment-related or unknown causality) < 1% frequency* (APL-C-001-09 [ADMYRE trial])

		Arm A (P+DXM) N=167
System Organ Class	**Preferred term**	**CIOMs category**
Blood and lymphatic system disorders	Coagulopathy, Disseminated intravascular coagulation, Febrile neutropenia, Pancytopenia	Uncommon
Cardiac disorders	Angina pectoris, Atrial tachycardia, Cardiac arrest, Cardiac failure chronic, Cardiac failure congestive, Left ventricular failure, Mitral valve incompetence, Myocardial infarction, Palpitations, Supraventricular tachycardia, Systolic dysfunction	Uncommon
Endocrine disorders	Cushingoid	Uncommon
Eye disorders	Diplopia, Dry eye, Eye pain, Eyelid oedema, Visual impairment	Uncommon
Gastrointestinal disorders	Abdominal distension, Dry mouth	Uncommon
	Abdominal discomfort, Gastrooesophageal reflux disease, Oesophageal pain, Stomatitis, Duodenitis, Dysphagia, Epigastric discomfort	Uncommon
General disorders and administration site conditions	Catheter site pain, Infusion site reaction, Injection site extravasation, Malaise, Thrombosis in device	Uncommon
Hepatobiliary disorders	Hepatocellular injury, Cholestasis, Hepatomegaly, Portal vein thrombosis	Uncommon
Immune system disorders	Drug hypersensitivity, Anaphylactic Shock	Uncommon
Infections and infestations	Herpes simplex	Uncommon

		Arm A (P+DXM) N=167
System Organ Class	**Preferred term**	**CIOMs category**
	Atypical pneumonia, Bacteraemia, Catheter site cellulitis, Cystitis, Enterocolitis infectious, Escherichia sepsis, Febrile infection, Herpes virus infection, Influenza, Localised infection, Neutropenic sepsis, Oesophageal candidiasis, Septic shock, Wound infection	Uncommon
Injury, poisoning and procedural complications	Fall, Procedural nausea, Transfusion reaction	Uncommon
Investigations	Activated partial thromboplastin time prolonged, Amylase, Bilirubin conjugated increased, Blood creatine phosphokinase[#], Blood creatine phosphokinase MB increased, C-reactive protein increased, Ejection fraction abnormal, Electrocardiogram T wave inversion, Electrocardiogram abnormal, Hepatic enzyme increased, International normalised ratio increased, N-terminal prohormone brain natriuretic peptide increased, Troponin T increased, Troponin increased	Uncommon
Metabolism and nutrition disorders	Hyperuricaemia, Hypokalaemia[#]	Uncommon
	Hypernatraemia[#], Hyponatraemia[#]	Uncommon
Musculoskeletal and connective tissue disorders	Bone pain, Muscle contracture, Myopathy toxic, Myositis	Uncommon
Nervous system disorders	Dizziness	Uncommon
	Hypoaesthesia, Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy, Somnolence, Syncope	Uncommon
Psychiatric disorders	Psychotic disorder	Uncommon
	Depressed mood, Depression, Delirium, Anxiety, Dysthymic disorder, Restlessness	Uncommon
Renal and urinary disorders	Pollakiuria	Uncommon
Respiratory, thoracic and mediastinal disorders	Haemothorax, Apnoea, Hypoxia, Pleural effusion, Productive cough	Uncommon
Skin and subcutaneous tissue disorders	Erythema	Uncommon
	Eczema, Night sweats, Onychomadesis, Pruritus, Rash popular, Skin hyperpigmentation, Urticaria	Uncommon
Vascular disorders	Hot flush	Uncommon
	Circulatory collapse, Deep vein thrombosis, Flushing, Orthostatic hypotension, Thrombophlebitis, Venous thrombosis	Uncommon

*Multiple occurrences of the same event from a patient were counted only once (under the worst grade) within each preferred term.

[#] Laboratory abnormalities, assessed by sponsor (company) as treatment-related

The safety population includes all subjects that took at least one dose of study treatment.

Description of selected adverse reactions

Musculoskeletal and connective tissue disorders and investigations

The most common musculoskeletal disorders reported as adverse reactions were myalgia (14.4% of patients) and muscular weakness (9.6%). CPK increase regardless of grade was reported in 44.5% of patients; this parameter was the most common grade 3/4 biochemical abnormality, reported in 20.0% of patients. The median onset of grade 3/4 CPK increase (day from first dose) was 48 days; the median number of cycles during which the patients experienced grade 3/4 CPK increase was 1 cycle, and the median time to recovery was 14.5 days. The treatment was withdrawn only in 0.5% of patients who experienced grade 3/4 CPK increase, while dose delay, dose reduction, dose omission and dose interruption occurred in 8.8%, 11.3%, 5.9% and 0.5%, respectively. The vast majority of patients (83.9%) who experienced CPK increase recovered. Adverse drug reactions of grade 3/4 rhabdomyolysis were reported in 1.2% of patients. Refer to ***Section 4.4 Special warnings and precautions for use*** for the management of myopathy occurring during treatment with plitidepsin.

Immune system and skin and subcutaneous tissue disorders

Treatment-related (or with unknown relationship) hypersensitivity reactions were reported in 6.6% in Arm A (plitidepsin plus DXM), 5.4% in patients who crossed over from Arm B to Arm A. The frequency of grade ≥ 3 hypersensitivity reactions was 1.2% in Arm A and 2.7% in the crossover patients. Severe hypersensitivity reactions included an anaphylactic shock with grade 4 cardiac arrest, a grade 3 infusion-related reaction with hypoxia that led to treatment discontinuation, and a grade 3 rash requiring dose reduction. The majority of hypersensitivity reactions occurred in the first two cycles and, no change in severity was observed over time. Hypersensitivity reactions usually occurred on the day of plitidepsin plus dexamethasone infusion (median was the infusion day, range: 0-13 days); they were rapidly reversible (lasting one or two cycles); symptomatic treatment (corticosteroids, antihistamines and local treatment) was common, and no fatal outcome was reported.

Gastrointestinal disorders

Nausea, vomiting and diarrhoea were very common reactions with the combination plitidepsin plus dexamethasone, occurring in 36.5%, 16.8% and 14.4% of patients, respectively. Few events were severe: grade ≥ 3 nausea was found in 3.6% of patients, grade ≥ 3 vomiting in 1.8% and grade ≥ 3 diarrhoea in 1.2%. The majority of these events were grade 1 or 2 and were reversible after symptomatic treatment. In case of diarrhoea, the clinicians are recommended to follow local guidelines on the symptomatic management of diarrhoea in patients administered chemotherapy.

Cardiac effects, including QT prolonged

Cardiac effects such as bradycardia; electrocardiogram QT prolonged; sinus tachycardia; and orthostatic hypotension have been observed in patients treated with the combination plitidepsin plus dexamethasone in the phase III study. The causal relationship has not been established yet, since most of cardiovascular events reported had confounding factors, such as cardiovascular medical history or concomitant medications known to induce such cardiovascular effects. Most of these events were non-serious and mild in severity and they mainly occurred between cycle 1 and 3.

Liver enzyme increase (ALT/AST)

During the treatment with the combination plitidepsin plus dexamethasone, 84.9% and 66% of patients respectively reported ALT and AST increase. Grade 3/4 ALT and AST increase was

respectively reported in 14.5% and 9.0% of patients who received plitidepsin plus dexamethasone. Grade 3/4 ALT increase occurred on Day 14 (range, 1-35 days) after dosing, with a median duration of 6 days (range, 1-16 days). Grade 3/4 AST appeared on Day 18 (range, 1-35 days) after dosing with a median duration of 6.5 days (range, 1-28 days). Grade 3/4 AST or ALT were more frequent in the first treatment cycle than in subsequent cycles. The median values for peak counts of ALT or AST from all patients, over 32 cycles, showed no evidence of cumulative toxicity.

Elderly population
Myalgia, muscular weakness and hyperglycaemia were the most reported adverse drug reactions in patients aged ≥ 65 years treated with plitidepsin plus dexamethasone. Among patients who experienced hyperglycaemia, 80% had a previous medical history of diabetes mellitus. Myalgia and hyperglycaemia were reported as serious adverse drug reactions in 1.3% and 5.1% of elderly patients, respectively. No serious adverse drug reaction of muscular weakness was observed. None of these events led to treatment discontinuation or death.

Post-marketing experience
Not applicable.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems and to drugsafety-sta@stbiopharma.com.

4.9 Overdose

In clinical trials there are no cases of accidental overdose. There is currently insufficient information to draw conclusions about the safety of doses higher than those evaluated in clinical studies. Grade 3/4 CPK increase and other muscular events are expected. There is no known antidote to plitidepsin.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Plitidepsin interacts with eukaryotic Elongation Factor 1A2 (eEF1A2), a protein that forms part of the cell's translation machinery and described to have oncogenic properties. eEF1A2 is overexpressed in various tumour cells, including some multiple myeloma cells. It is also expressed in brain, heart, pancreatic acinar and islet cells, endocrine cells of the gut, and skeletal muscle. Plitidepsin triggers the generation of early oxidative stress, which induces the sustained activation of MAPK signalling cascades that finally lead to apoptosis.

Pharmacodynamic effects
Plitidepsin has been shown to exert in vitro antiproliferative effects against a range of human tumour cell lines (particularly against multiple myeloma (MM), leukaemia, lymphoma, pancreas, non-small cell lung cancer [NSCLC] and breast), as well as in vivo activity against experimental MM tumours. Enhanced antitumour activity was found for plitidepsin when combined with other agents, such as melphalan, dexamethasone, lenalidomide or bortezomib.

Clinical trials

The efficacy of plitidepsin in combination with dexamethasone (P+DXM) was evaluated in a phase III multicentre, open-label, two-arm, randomised clinical trial, APL-C-001-09 (ADMYRE) that compared the efficacy of P+DXM versus dexamethasone (DXM) alone. Eligible subjects were patients with relapsed/refractory MM after at least three but not more than six prior therapeutic regimens for this disease (median of 4 prior lines of systemic therapy (range of 2 – 6 in the P+DXM)). The most common previous agents that patients received prior to entering the study were: bortezomib (98.4%), lenalidomide (97.6%), dexamethasone (97.6%), melphalan (87.8%), cyclophosphamide (74.5%), thalidomide (65.1%), doxorubicin (47.1%), vincristine (32.5%), and prednisone (23.9%). Other more novel anti-MM agents previously administered included: pomalidomide (13.3%), carfilzomib (3.9%), vorinostat (2.7%), elotuzumab (2.0%), and panobinostat (1.2%).

A total of 255 patients were enrolled in the study: 171 in Arm A (P+DXM) and 84 in Arm B (DXM). The median age of the whole population was 65 years (36-85 years). There were 51.8% of males enrolled and 48.2% of females.

Patients in the control arm (DXM alone, Arm B) with documented disease progression after a minimum of eight weeks from randomisation were offered crossover to the combination arm (P+DXM, Arm A). A total of 44% of patients crossed over from DXM to P+DXM arm.

Patients in the P+DXM arm (Arm A) received DXM 40 mg orally on Day 1, 8, 15 and 22 q4wk, at least one hour before plitidepsin infusion, plus plitidepsin 5 mg/m2 intravenously over three hours on Day 1 and 15 q4wk. Patients in Arm B received DXM 40 mg orally on Day 1, 8, 15 and 22 q4wk.

The primary efficacy objective was the progression-free survival (PFS) calculated according to the 2008 International Myeloma Working Group (IMWG) criteria. Secondary efficacy endpoints included overall response rate (ORR) and overall survival (OS).

Progression-free survival

In the primary efficacy analyses of all randomised patients, P+DXM showed statistically significant longer PFS compared to DXM in patients with relapsed/refractory MM, in both the blinded Independent Review Committee (IRC) assessment and the Investigator assessment.

The median PFS analysis from the blinded Independent Review Committee (IRC) was 2.6 months (95% CI, 1.9-3.0 months) in P+DXM arm and 1.7 months (95% CI, 1.1-2.0 months) in DXM arm (log-rank p=0.0054)

An updated analysis of PFS with confirmation of PD by IA at the censoring rate of 38.6% and 40.5% of patients in P+DXM and DXM arms, respectively, showed the following results: median PFS=3.8 months (95% CI, 2.9-5.6 months) in P+DXM arm, and median PFS=1.9 months (95% CI, 1.1-2.7 months) in DXM arm (log-rank p=0.0040) (HR=0.611; p=0.004).

A pre-planned sensitivity analysis of PFS requiring confirmation of PD was performed. There was a statistically significantly longer PFS with P+DXM (5 months) compared to DXM alone (2 months) (log-rank p=0.0005) and the relative risk of progression or death was reduced by 48.3% (HR=0.517; 95%CI: 0.354 – 0.756, p=0.0007). All other pre-planned supportive sensitivity analyses of PFS showed results consistent with the primary analysis with HRs ranging between 0.466 and 0.739.

Overall Survival

The study was not powered for the evaluation of the secondary end-point of OS. Final OS data was conducted with 195 events (76.5% of all the recruited patients). Median OS was 11.6 months in the P+DXM arm and 8.9 months in the DXM arm following the intention to treat principle (HR=0.797, 95% CI, 0.596-1.067). 37 (44%) of the patients in the control arm (Arm B) crossed over to the combination arm (Arm A); when crossover effect is mitigated, a statistically significant difference in favour of the combination arm (Arm A) was observed with a HR of 0.667 (log rank test p-value=0.0065), and median OS values of 11.6 months in the P+DXM arm and 6.7 months in the DXM arm.

Table 6. Overall survival in all randomised patients (APL-C-001-09, ADMYRE).

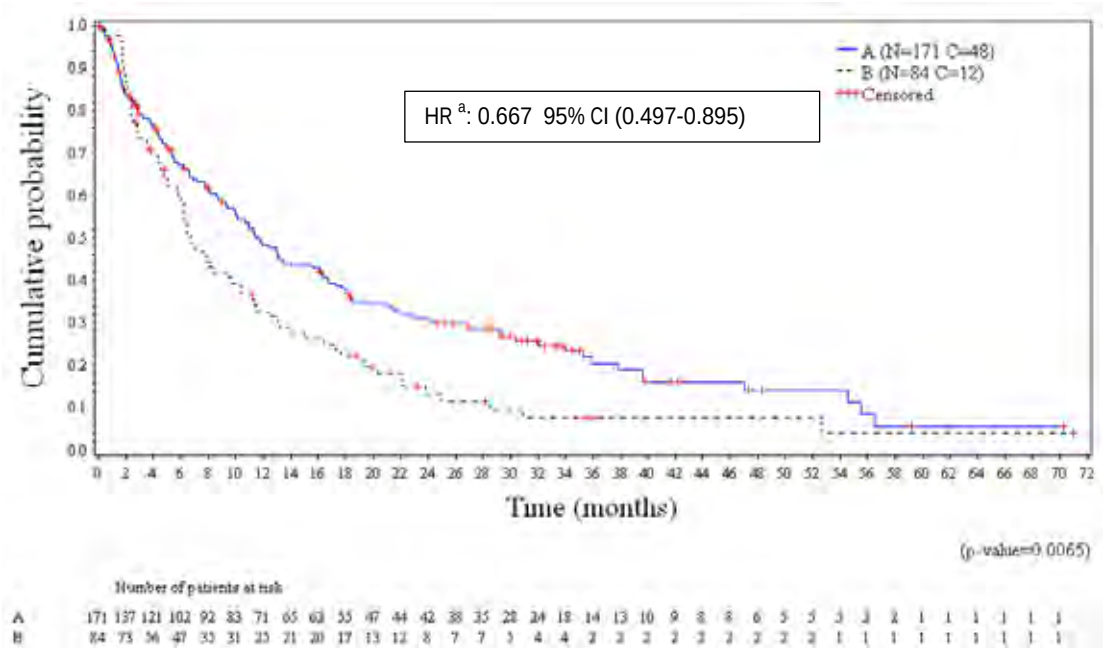
Overall survival (Final analysis)		**Arm A (P+DXM)**	**Arm B (DXM)**	**Parameter**	**p-value**
ITT – No adjustment for crossover	**n**	171	84	.	.
	Events	123 (71.9%)	72 (85.7%)	Log-rank: 2.339	LR: 0.1261
	Median	11.6	8.9	HR [a]: 0.797	HR [a]: 0.1273
	(95% CI)	(9.2-16.1)	(6.0-15.4)	95% CI (0.596-1.067)	
	OS at 12 months	48.3%	42.1%	Diff: 6.2%	0.3625
	(95% CI)	(40.4-56.2%)	(31.3-52.9%)		
	OS at 24 months	30.8%	21.0%	Diff: 9.8%	0.1037
	(95% CI)	(23.3-38.3%)	(12.0-30.1%)		
After crossover adjustment (two-stage method)	**n**	171	84		
	Events	123 (71.9%)	72 (85.7%)	Log-rank: 7.402	LR: 0.0065
	Median	11.6	6.7	HR [a]: 0.667	HR [a]: 0.0069
	(95% CI)	(9.2-16.1)	(5.7-9.7)	95% CI (0.497-0.895)	
	OS at 12 months	48.3%	32.9%	Diff: 15.4%	0.0203
	(95% CI)	(40.4-56.2%)	(22.5-43.2%)		
	OS at 24 months	30.8%	13.4%	Diff: 17.4%	0.0017
	(95% CI)	(23.3-38.3%)	(5.5-21.3%)		

Median in months. Median follow-up for survival was 33.4 months in Arm A and 36.3 months in Arm B.

[a] HR: Arm A compared to Arm B. HR and p-value as determined by Cox regression.

CI, confidence interval; Diff, difference between Arm A and Arm B; DXM, dexamethasone; HR, hazard ratio; LR, unstratified log-rank; P, plitidepsin.

Figure 1: Overall survival: After crossover adjustment by the two-stage method



Response rate

Overall response rate was higher in the P+DXM arm (9.9%) than in the DXM arm (1.2%) (p=0.0085). Very good partial response (VGPR) were only observed in the combination arm.

In Arm A (P+DXM), median duration of response by the IRC in patients with response (VGPR, n=2; partial response [PR], n=15) was 12.0 months (95% CI, 2.8-23.2 months). In Arm B (DXM), only one patient had PR (duration of response was 1.8 months) (p=0.1015). Median duration of response as determined by investigator's assessment in responding patients was 5.1 months in P+DXM arm versus 0.9 months in DXM arm (p=0.0001). This includes patients with minor response (MR), partial response (PR) and VGPR.

5.2 Pharmacokinetic properties

A population pharmacokinetic analysis was carried out in 303 patients with cancer, including 182 patients with relapsed/refractory MM. These patients received plitidepsin at doses of 2.0 to 5.0 mg/m² weekly or every two weeks.

Absorption

Plitidepsin is dosed via an intravenous route and therefore is immediately and completely bioavailable.

Distribution

The pharmacokinetics of plitidepsin is characterised by a 3-compartment model. Plitidepsin is distributed largely outside the blood volume, with a total volume of distribution in plasma of approximately 600 L. Blood cells are an important distribution compartment of plitidepsin. Partitioning equilibrium between blood cells and plasma is mostly reached during the infusion and the extent of partitioning can be considered linear up to the mean maximal concentration of the compound. In the blood, approximately 20% is present in plasma, and 80% in blood cells. In plasma,

approximately 98% is bound to proteins, independent of concentration over the range of 100 to 500 ng/mL. Binding is mostly to albumin, with a lesser contribution by α_1–acid glycoprotein.

Metabolism

In vitro studies indicate that plitidepsin undergoes metabolism in the liver and also the plasma. Experiments performed with human liver microsomes (both sexes) and recombinant CYP isoforms pointed to CYP3A4 as the main isoform involved in the phase I metabolism of plitidepsin, with smaller contributions by CYP2A6, CYP2E1 and CYP4A11. The contribution of phase II-mediated metabolism is negligible.

Plitidepsin experiences a moderate clearance in plasma from humans, suggesting the involvement of plasma esterases as an additional route of its metabolism. Owing to its distribution in blood cells, unchanged plitidepsin was the major circulating component (95% of radioactivity in the systemic circulation) *in vivo* in patients with cancer who received a single dose of [^{14}C]-plitidepsin (2.2 mg). In plasma, the radioactivity measured was less explained by the parent compound as time after dosing increases, resulting in 30% of the administered dose, thus suggesting a gradual formation of metabolites. None of them was present at a relevant concentration relative to unchanged plitidepsin or total radioactivity in plasma.

Excretion

Plitidepsin has a population estimated for plasma clearance of 5.4 L/h (coefficient of variation [CV] 46%), and a long terminal half-life of approximately 6 days. No significant accumulation of plitidepsin is observed on biweekly administration.

Plitidepsin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown, although preclinical *in vitro* studies indicate that plitidepsin is transported by P-glycoprotein (Pgp).

Linearity/non-linearity

Studies in patients have demonstrated linear pharmacokinetics in the dose range of 2.0 to 5.0 mg/m^2.

Characteristics in specific groups

Elderly

Population pharmacokinetic analyses included patients with ages ranging from 19 to 86 years old and indicate that age does not influence plitidepsin clearance (exposure in plasma).

Renal impairment

A small fraction of the plitidepsin dose is excreted in the urine, mostly as unchanged substance, thus indicating minimal effect of renal impairment on the excretion of plitidepsin. In addition, the plasma exposure of plitidepsin is not dependent on the GFR of patients with mild (GFR of 60-89 mL/min), moderate (GFR of 30-59 mL/min) or severe (15-29 mL/min) renal impairment. Therefore, adjustments to the starting dose in patients with mild or moderate renal impairment are not required. However, the number of patients with severe renal impairment is too limited (n=5) to reach a firm conclusion. The pharmacokinetics of plitidepsin in patients with end stage renal disease (GFR of < 15 mL/min) has not been studied, so there is no data on the safety and efficacy of plitidepsin in this subgroup of patients.

Hepatic impairment

A formal clinical study to evaluate the impact of hepatic impairment on the pharmacokinetics of plitidepsin was not performed.

Most plitidepsin is eliminated via the liver; patients with cancer who received a single dose of [^{14}C]-plitidepsin (2.2 mg) showed that 70% of total radioactivity was recuperated in faeces.

Based on the population PK analysis, patients with alterations at baseline in markers of hepatic function (ALT, AST, bilirubin and serum albumin) treated with the compound did not present differences in plasma CL or volume of distribution.
In addition, the clearance of plitidepsin is not different in patients with and without liver metastasis. Despite the results from the population analysis, plitidepsin should not be used in patients with impaired hepatic function.

Other intrinsic factors
Population pharmacokinetic analyses indicate that body weight (44-137 kg) and gender do not have a clinically relevant effect on plitidepsin clearance in adult patients. No differences were found in plitidepsin pharmacokinetics between patients of European and Asian descent.

5.3 Preclinical safety data

Genotoxicity
Genotoxicity was observed with plitidepsin *in vitro* in the mouse lymphoma tk assay, occurring in conjunction with marked cytotoxicity. Plitidepsin was not mutagenic in the bacterial reverse mutation assay (Ames test).

Carcinogenicity
Carcinogenicity studies have not been performed with plitidepsin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Mannitol

Solvent:
PEG-35 castor oil, Ethanol, Water for injections

6.2 Incompatibilities

Refer to ***Section 4.5 Interactions with other medicines and other forms of interactions.***

6.3 Shelf life

Unopened vial and ampoule
4 years when stored at 2ºC-8ºC.

Stability after reconstitution and dilution
After reconstitution
After reconstitution of the plitidepsin 2 mg vial with 4 mL of solvent, the solution should be immediately diluted in the infusion fluids described in the ***Section 4.2 Dose and method of administration (Instructions for dilution)***.

Chemical, physical and microbiological in-use stability of the reconstituted concentrate has been demonstrated for 24 hours at refrigerated conditions (2ºC-8ºC) and for 6 hours at room temperature (up to 25°C) when stored in the original vial and protected from direct sunlight. However, as the product has no added preservatives, and from a microbiological point of view, the reconstituted concentrated solution should be used immediately.

After dilution

Aplidin solution for infusion should be administered within 6 hours of reconstitution if stored at room

temperature and under ambient lighting. If storage is required prior to administration then solutions should be stored refrigerated and protected from light and should be used within 24 hours of reconstitution.

6.4 Special precautions for storage

Store between 2ºC and 8ºC. Refrigerate - do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Vial: 10 mL Type I clear glass vial with a 20 mm grey butyl rubber stopper covered by a flip-off aluminium capsule.

Each vial contains 2 mg of plitidepsin.

Ampoule: Colourless and hydrolytic class I glass ampoule (nominal volume 5mL).

After reconstitution, each mL of concentrate contains 0.5 mg of plitidepsin.

Each carton contains 1 vial and 1 ampoule.

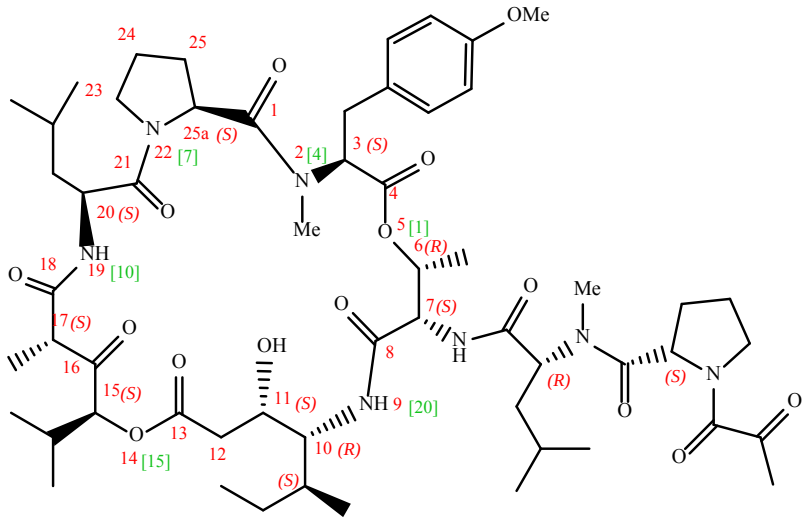
6.6 Special precautions for disposal

APLIDIN is a cytotoxic anticancer medicinal product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure
Chemical Name: (-)-(3*S*,6*R*,7*S*,10*R*,11*S*,15*S*,17*S*,20*S*,25a*S*)-11-hydroxy- 3-(4-methoxybenzyl)-2,6,17-trimethyl-15-(1-methylethyl)- 7-[[(2*R*)-4-methyl-2-[methyl[[(2*S*)-1-(2-oxopropanoyl)pyrrolidin- 2-yl]carbonyl]amino]pentanoyl]amino]-10-[(1*S*)-1-methylpropyl]- 20-(2-methylpropyl)tetradecahydro-15*H*-pyrrolo[2,1-f]-[1,15,4,7,10,20]dioxatetrazacyclotricosine-1,4,8,13,16,18,21(17*H*)-heptone

Molecular Weight: 1110.34
Molecular Formula: $C_{57}H_{87}N_7O_{15}$



CAS number
137219-37-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Specialised Therapeutics Pharma Pty Ltd
Level 2, 17 Cotham Road, Kew, Victoria 3101

Ph: 1300 798 820
Fax: 1800 798 829
www.stbiopharma.com

9 DATE OF FIRST APPROVAL

10 December 2018

10 DATE OF REVISION

Summary table of changes

Section Changed	Summary of new information
9	Date of TGA Approval