Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Pegfilgrastim

Proprietary Product Name: Ziextenzo

Sponsor: Sandoz Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations 4

I. Introduction to product submission 6

Submission details 6

Product background 7

Regulatory status 7

Product Information 7

II. Registration timeline 8

III. Submission overview and risk/benefit assessment 8

Background 8

Quality 9

Nonclinical 10

Clinical 10

Risk management plan 14

Risk-benefit analysis 14

Outcome 14

Attachment 1. Product Information 15

Common abbreviations

Abbreviation	Meaning
³	At or greater than
£	At or lesser than
<	Less than
>	Greater than
AE	Adverse event
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
CI	Confidence interval
C_{max}	Maximum plasma concentration
DSN	Duration of severe neutropaenia
EMA	European Medicines Agency (EU)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (US)
G-CSF	Granulocyte colony-stimulating factor
L	Litre
LA-EP2006	Ziextenzo (drug development code name)
mg	Milligram
mL	Millilitre
Neulasta	Pegfilgrastim
Neulasta EU	European Union-authorised Neulasta
PEG	Polyethylene glycol
PI	Product Information
PP	Per protocol

Abbreviation	Meaning
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
SAF	Safety analysis set
SC	Subcutaneous
TAC	Taxotere (docetaxel), Adriamycin (doxorubicin), and Cytoxan (cyclophosphamide) chemotherapy regimen
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
t_{max}	Time of maximum concentration
US	United States
Ziextenzo	LA-EP2006

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar
Decision:	Approved
Date of decision:	9 July 2019
Date of entry onto ARTG:	6 September 2019
ARTG number:	308367
, *Black Triangle Scheme*	No
Active ingredient:	Pegfilgrastim
Product name:	Ziextenzo
Sponsor's name and address:	Sandoz Pty Ltd 54 Waterloo Road Macquarie Park NSW 2113
Dose form:	Solution for injection
Strength:	6 mg/0.6 mL
Container:	Prefilled syringe with automatic needle guard
Pack size:	1
Approved therapeutic use:	*Ziextenzo is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifested by febrile neutropenia.*
Route of administration:	Subcutaneous
Dosage:	The recommended dosage of Ziextenzo is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle, approximately 24 hours after the administration of cytotoxic chemotherapy. For further information refer to the Product Information (PI).

Product background

This AusPAR describes the application by Sandoz Pty Ltd (the sponsor) to register Ziextenzo (pegfilgrastim) for the following indication:

> *Ziextenzo is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifested by febrile neutropenia.*

The treatment of cancer patients can involve the use of chemotherapy, which is often associated with marked neutropaenia (low level of neutrophils). Severe neutropenia is the underlying cause for chemotherapy-associated infections and contributes to cancer-associated morbidity.

Granulocyte colony-stimulating factor (G-CSF) is a lineage-specific colony-stimulating factor produced by monocytes, fibroblasts, and endothelial cells. Physiologically, G-CSF plays an important role in granulopoiesis during the inflammatory process. G-CSF regulates the production of neutrophils within the bone marrow as well as affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation. It also facilitates the migration of mature cells into the peripheral blood. This has led to the clinical use of recombinant human G-CSF (rhG-CSF) in conditions characterised by neutropenia. Over the last decades, rhG-CSF products, such as Amgen's filgrastim (Neupogen) and pegfilgrastim (Neulasta), have become an established treatment option for reducing the duration of neutropenia and hence the incidence of febrile neutropenia, in patients with malignancies treated with myelosuppressive chemotherapy regimens.

Filgrastim is a rhG-CSF. The relatively short elimination half-life of filgrastim makes a daily administration schedule necessary. Pegfilgrastim is a covalent conjugate of filgrastim, with a 20,000 dalton polyethylene glycol (PEG) covalently bound to filgrastim. Pegylation of filgrastim results in minimal renal clearance and a long half-life. Therefore, pegfilgrastim can be administered as a single subcutaneous (SC) dose after chemotherapy and does not require multiple daily administrations. Pegfilgrastim increases the absolute neutrophil count (ANC) via stimulation of the G-CSF receptor, thereby reducing the duration of severe neutropaenia in patients treated with chemotherapy.

Neulasta (pegfilgrastim) is currently licensed to Amgen in the European Union (EU), the United States (US) and Australia. The sponsor developed Ziextenzo as a biosimilar product to Neulasta. The EU-authorised Neulasta (Neulasta EU) was used as the reference product in this submission.

Regulatory status

Ziextenzo is a new biosimilar medicine for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the EU (22 November 2018) and was under consideration in the US.

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-03328-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	28 September 2018
First round evaluation completed	29 April 2019
Sponsor provides responses on questions raised in first round evaluation	3 May 2019
Second round evaluation completed	31 May 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 July 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	9 July 2019
Completion of administrative activities and registration on ARTG	6 September 2019
Number of working days from submission dossier acceptance to registration decision*	153

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

The application is to register a new chemical entity, LA-EP2006;[1] as a biosimilar product to Neulasta (Amgen), to manage neutropaenia secondary to myelosuppressive chemotherapy.

For the purposes of this document, LA-EP2006 will be referred to by the tradename Ziextenzo.

[1] LA-EP2006 is the drug development name for Ziextenzo pegfilgastrim.

Ziextenzo is a recombinant human G-CSF which is covalently bound to a PEG moiety to increase its half-life, allowing once cycle dosing.

Neulasta was registered by the TGA in 2002.

Applications to register Ziextenzo were made to the European Medicines Agency (EMA) and Food and Drug Administration (FDA) in 2015. At the time this submission was under consideration the FDA evaluation was ongoing. The initial EMA application was not approved on the basis of a lack of pharmacokinetic similarity between comparators in the submitted study (Study LA-EP06-101). However, EMA approval was granted in November 2018 following resubmission of a further pharmacokinetic study (Study LA-EP06-103).

Quality

The quality evaluator has raised no outstanding objections to the registration of Ziextenzo.

Regarding biosimilarity between Ziextenzo and the comparator, Neulasta, the sponsor has submitted a comprehensive analysis of Ziextenzo and Neulasta from both the EU and US markets. This includes bioactivity, content, di-pegylated filgrastim, dimers/high-molecular weight variants/aggregates, wrongly-pegylated filgrastim and non-pegylated filgrastim.

All tested quality attributes of Ziextenzo were within the global originator product range. Hence, the quality evaluator has concluded that the Australian product and the originator products from the EU and US are indistinguishable with respect to identity, content, potency, purity, impurities and higher order structures.

The sponsor has further provided a bridging study comparing Ziextenzo to Australian-sourced Neulasta. This demonstrates similarity in all tested attributes.

Figure 1: Bridging approach to demonstrate biosimilarity between Ziextenzo and Neulasta

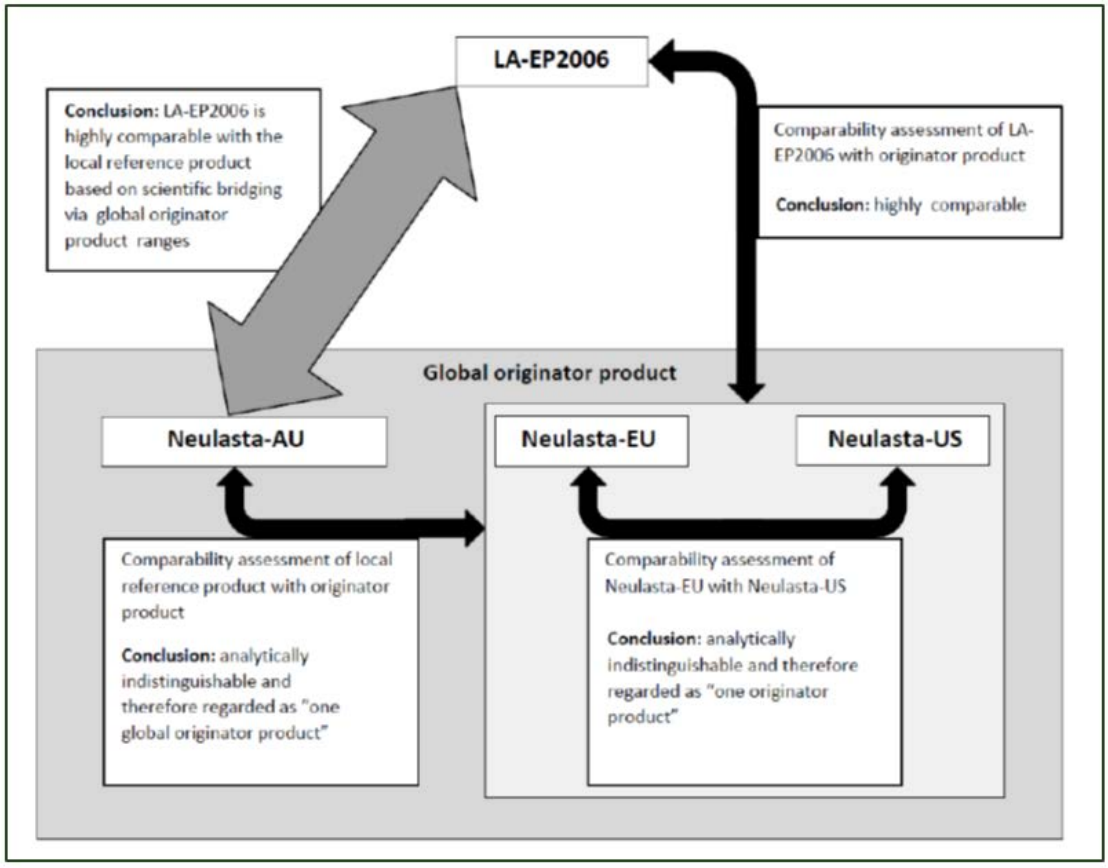

Figure 1 summarises the data comparing similarity between Ziextenzo and Neulasta. The equivalence between Ziextenzo and EU-authorised Neulasta is of significance because the pivotal clinical trials employed EU-authorised Neulasta as a comparator.

Nonclinical

The sponsor provided a nonclinical dossier which was considered acceptable by the nonclinical evaluator with the proviso that biosimilarity between Ziextenzo and Neulasta is otherwise established.

No new nonclinical issues were identified in the Ziextenzo data.

Clinical

Pharmacology

The evaluator has noted that of the two bioequivalence studies, Studies LA-EP06-101 and LA-EP06-103, the former failed to demonstrate bioequivalence between Ziextenzo and Neulasta for maximum plasma concentration (C_{max}) and area under the concentration time curve (AUC). The evaluator has noted, however, that the differences observed in these parameters are unlikely to be clinically significant and bioequivalence between both comparator products was demonstrated in Study LA-EP06-103.

The clinical evaluator noted that time of maximum concentration (t_{max}) observed in these healthy volunteers trials was lower (approximately 12 hours) than in the pivotal trials (approximately 40 hours). The sponsor has indicated that this is because the clearance of

Ziextenzo depends on binding and turnover of neutrophil receptors, which is less prevalent in patients receiving myelosuppressive therapy than in healthy subjects.

Efficacy

Two pivotal studies were submitted, Studies LA-EP06-301 and LA-EP06-302. Both were designed to compare the efficacy of Ziextenzo with EU-authorised Neulasta in women suffering from breast cancer and receiving TAC chemotherapy.[2] Patients were randomised 1:1 in each study; 316 in Study LA-EP06-301 and 308 in Study LA-EP06-302 to receive either Neulasta or Ziextenzo on Day 2 of each of six treatment cycles of the TAC regimen. The primary endpoint was the mean duration of severe neutropaenia (DSN) defined as the presence of a total neutrophil count of < 0.5 x 10^9/L.

Table 2: Duration of severe neutropaenia (DSN) from pivotal Studies LA-EP06-301 (upper panel) and LA-EP06-302 (lower panel)

	FAS set			PP set		
Summary statistics	LA-EP2006 N=159	Neulasta N=157	Total N=316	LA-EP2006 N=146	Neulasta N=149	Total N=295
n	155[1]	155[2]	310	146	149	295
Mean	0.75	0.83	0.79	0.75	0.79	0.77
Median	1.00	1.00	1.00	1.00	1.00	1.00
SD	0.878	0.898	0.887	0.875	0.872	0.872
Range	0.0-3.0	0.0-4.0	0.0-4.0	0.0-3.0	0.0-3.0	0.0-3.0

FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; PP set = per protocol set; SD = standard deviation

[1] Missing due to blind data review meeting decision (absolute neutrophil count not available): Patients [Information redacted], 4 patients

[2] Missing due to BDRM decision (ANC not available): Patients [Information redacted], 2 patients

	FAS set			PP set		
	LA-EP2006 N=155	Neulasta N=153	Total N=308	LA-EP2006 N=148	Neulasta N=144	Total N=292
n	151[a]	149[b]	300	148	144	292
Mean	1.36	1.19	1.28	1.34	1.19	1.27
Median	1.00	1.00	1.00	1.00	1.00	1.00
SD	1.133	0.984	1.063	1.141	0.991	1.071
Range	0.0-6.0	0.0-4.0	0.0-6.0	0.0-6.0	0.0-4.0	0.0-6.0

BDRM = blind data review meeting; FAS set = full analysis set; n = number of evaluable patients; N = number of patients in a treatment group or analysis set; PP set = per-protocol set; SD = standard deviation

[a] Missing due to BDRM decision (no ANC profiles available): Patients [Information redacted], 4 patients

[b] Missing due to BDRM decision (no ANC profiles available): Patients [Information redacted], 4 patients

The two treatments were considered equivalent if there was no more than 1 day difference in DSN. As the 95% confidence interval (CI) of the difference between the DSN observed in Ziextenzo and Neulasta treated patients in each trial was < 1 day (0.07 days and -0.16 days in Study LA-EP06-301 and LAEP-302, respectively);[3] and equivalence of effect was demonstrated.

[2] TAC regimen: a combination chemotherapy regimen consisting of Taxotere (docetaxel), Adriamycin (doxorubicin), and Cytoxan (cyclophosphamide).
[3] Neulasta minus Ziextenzo.

Safety

Adverse events and treatment-related adverse events which occurred in the pivotal trials at similar rates between Ziextenzo and Neulasta treated patients (see Table 3 and Table 4).

Table 3: Overview of number of patients with at least 1 adverse event (SAF set), Study LA-EP06-301

Number of patients with at least 1	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316 n (%)
TEAE	140 (88.1)	130 (82.8)	270 (85.4)
Study-drug related TEAE	19 (11.9)	23 (14.6)	42 (13.3)
Study-drug related TEAE leading to study drug discontinuation	0	0	0
TEAE leading to study drug reduction/increase/interruption	1 (0.6)	6 (3.8)	7 (2.2)
TEAE leading to death as outcome	3 (1.9)	2 (1.3)	5 (1.6)
TEAE leading to study drug discontinuation	2 (1.3)	2 (1.3)	4 (1.3)
TEAE with Grade 3 or 4	33 (20.8)	41 (26.1)	74 (23.4)
Serious TEAE	16 (10.1)	21 (13.4)	37 (11.7)
Study drug-related serious TEAE	3 (1.9)	0	3 (0.9)
Serious TEAE leading to treatment discontinuation	1 (0.6)	0	1 (0.3)
Post-TEAE	4 (2.5)	2 (1.3)	6 (1.9)
Serious post-TEAE	1 (0.6)	0	1 (0.3)

AE = adverse event; I n = number of patients with events; N = total number of patients in a treatment group or analysis set; post-TEAE = post-treatment-emergent adverse event; SAF = safety analysis set; TEAE = treatment-emergent adverse event

AEs were defined as TEAEs if the onset date of an AE was on or after the date of the first administration of chemotherapy and not later than 30 days after the last dose of chemotherapy. Post-treatment-emergent AEs (AEs occurring within the 6 month safety follow-up period) were defined as AEs with a date of onset after the time point of 30 days after the last chemotherapy administration (that is, the end time range of the TEAE period).

Table 4: Incidence of TEAEs by Preferred Term (at least 3% incidence in either treatment group) (SAF set), Study LA-EP06-301

Preferred term	LA-EP2006 N=159 n (%)	Neulasta N=157 n (%)	Total N=316 n (%)
Total number of patients with TEAEs	140 (88.1)	130 (82.8)	270 (85.4)
Alopecia	82 (51.6)	79 (50.3)	161 (50.9)
Nausea	65 (40.9)	59 (37.6)	124 (39.2)
Asthenia	63 (39.6)	56 (35.7)	119 (37.7)
Vomiting	34 (21.4)	34 (21.7)	68 (21.5)
Neutropenia	27 (17.0)	34 (21.7)	61 (19.3)
Diarrhea	23 (14.5)	31 (19.7)	54 (17.1)
Fatigue	18 (11.3)	21 (13.4)	39 (12.3)
Anemia [a]	16 (10.1)	18 (11.5)	34 (10.8)
Erythema	14 (8.8)	16 (10.2)	30 (9.5)
Leukopenia	11 (6.9)	13 (8.3)	24 (7.6)
Decreased appetite	7 (4.4)	16 (10.2)	23 (7.3)
Arthralgia	10 (6.3)	13 (8.3)	23 (7.3)
Myalgia	9 (5.7)	13 (8.3)	22 (7.0)
Thrombocytopenia	11 (6.9)	11 (7.0)	22 (7.0)
Pyrexia	10 (6.3)	12 (7.6)	22 (7.0)
Stomatitis	8 (5.0)	13 (8.3)	21 (6.6)
Febrile neutropenia	9 (5.7)	12 (7.6)	21 (6.6)
Constipation	10 (6.3)	9 (5.7)	19 (6.0)
Pain	7 (4.4)	10 (6.4)	17 (5.4)
Bone pain	7 (4.4)	8 (5.1)	15 (4.7)
Edema peripheral	10 (6.3)	5 (3.2)	15 (4.7)
Abdominal pain	8 (5.0)	7 (4.5)	15 (4.7)
Headache	5 (3.1)	9 (5.7)	14 (4.4)
Respiratory tract infection viral	3 (1.9)	9 (5.7)	12 (3.8)
Pain in extremity	6 (3.8)	6 (3.8)	12 (3.8)
Hyperglycemia	3 (1.9)	8 (5.1)	11 (3.5)
Cough	4 (2.5)	6 (3.8)	10 (3.2)
Alanine aminotransferase increased	6 (3.8)	3 (1.9)	9 (2.8)
Aspartate aminotransferase increased	6 (3.8)	2 (1.3)	8 (2.5)
Weight decreased	3 (1.9)	5 (3.2)	8 (2.5)
Gamma-glutamyltransferase increased	2 (1.3)	5 (3.2)	7 (2.2)
Respiratory tract infection	5 (3.1)	2 (1.3)	7 (2.2)
Back pain	1 (0.6)	5 (3.2)	6 (1.9)

n = number of patients with events; N = total number of patients in a treatment group or analysis set; SAF set = safety analysis set; TEAE = treatment-emergent adverse event

TEAEs by preferred terms are presented in descending order of frequency in the Safety (population) total group

[a] Patient in the Neulasta treatment group experienced a second occurrence of a serious TEAE of anemia, which had not been entered into the electronic case report form of the patient and was identified after database lock.

The adverse events observed were consistent with the known adverse events profile of Neulasta and no novel safety signal was identified.

The incidence of positive anti-drug antibodies was comparable between treatments with Ziextenzo and with Neulasta (12.6% with Ziextenzo versus 13.4% with Neulasta in Study LA- EP06-301; 8.4% versus 12.4% in Study LA-EP06-302). No neutralising antibodies were detected in Study LA-EP06-301. One patient in the Ziextenzo arm of Study LA-EP06- 302 who had a positive neutralising antibody result developed it pre-dose at Cycle 1, Day 1.

The clinical evaluator has concluded that the risk-benefit balance for Ziextenzo is positive for the proposed use.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[4]

Risk-benefit analysis

Delegate's considerations

The Delegate has concluded that biosimilarity between Ziextenzo and Neulasta is well supported by the chemistry, nonclinical and clinical data evaluated. This supports registration of Ziextenzo as a biosimilar product to Neulasta with the same indication.

Proposed action

The Delegate proposes to include Ziextenzo in the Australian Register of Therapeutic Goods (ARTG) for the indication:

> *Ziextenzo is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infections, as manifested by febrile neutropenia.*

Advisory Committee Considerations[5]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ziextenzo (pegfilgrastim) solution for injection, indicated for:

> *Ziextenzo is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifested by febrile neutropenia.*

Specific conditions of registration applying to these goods

For all injectable products the Product Information must be included with the product.

[4] The sponsor must still comply with routine product vigilance and risk minimisation requirements.
[5] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Attachment 1. Product Information

The PI for Ziextenzo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au