5.22 PEGFILGRASTIM
Injection 6 mg in 0.6 mL single use pre-filled syringe, Ziextenzo®, Sandoz Pty Ltd

1 Purpose of Application

1.1 The minor submission sought a Section 100 Highly Specialised Drugs (HSD) program listing for a new biosimilar brand of pegfilgrastim (Ziextenzo®) for all indications for which the reference brand (Neulasta®) is currently PBS listed.

2 Requested listing

2.1 The submission requested the following listing for pegfilgrastim, 6 mg in 0.6 mL single use pre-filled syringe. The proposed dosage, form, strength, maximum quantity and number of repeats is the same as for the comparator.

2.2 Additions proposed by the Secretariat to the requested listing are in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PEGFILGRASTIM 6 mg/0.6 mL injection, 0.6 mL syringe	1	11	$1,175.00 (Public) $1,222.39 (Private)	Ziextenzo® Sandoz Pty Ltd

Category / Program:	Section 100 – Highly Specialised Drugs Program – Public and Private
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chemotherapy-induced neutropenia
PBS Indication:	Chemotherapy-induced neutropenia
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	Patient must be receiving chemotherapy with the intention of achieving a cure or a substantial remission, AND Patient must be at greater than 20% risk of developing febrile neutropenia; OR Patient must be at substantial risk (greater than 20%) of prolonged severe neutropenia for more than or equal to seven days.

Administrative Advice:	***Biosimilar prescribing policy*** *Prescribing of the biosimilar brand ZIEXTENZO® is encouraged for treatment naïve patients. Encouraging biosimilar prescribing for treatment naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars).*

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For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

3.1 Pegfilgrastim is currently listed on the Section 100 HSD program as an Authority Required (STREAMLINED) listing for chemotherapy-induced neutropenia.

3.2 The reference brand, Neulasta, and the other existing 'a' flagged brands of pegfilgrastim on the PBS (Ristempa® and Tezmota®) have the same Sponsor, Juno Pharmaceuticals. Ristempa and Tezmota are not biosimilar brands.

Registration status

3.3 The Ziextenzo brand of pegfilgrastim was approved by the Therapeutic Goods Administration (TGA) on 9 July 2019 and was determined to be biosimilar to the reference brand, Neulasta. It was listed on the Australian Register of Therapeutic Goods (ARTG) on 6 September 2019 with the same indication as Neulasta: 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.

3.4 The TGA Delegate concluded that the biosimilarity between Ziextenzo and Neulasta was well supported by the evidence presented.

Previous PBAC consideration

3.5 Ziextenzo has not been considered by the PBAC previously.

3.6 The PBAC recommended a different biosimilar brand of pegfilgrastim, Fulphila, sponsored by Alphapharm Pty Ltd, at its November 2018 meeting.

4 Comparator

4.1 The minor submission nominated the reference brand of pegfilgrastim, Neulasta, as the main comparator, which was appropriate.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

5.3 As a minor submission, no independent evaluation of the clinical evidence was undertaken.

5.4 The minor submission presented four studies to support its claim of biosimilarity, and equivalent efficacy and safety of Ziextenzo compared to Neulasta:

- Two bioequivalence studies undertaken in healthy subjects focused on comparing the pharmacokinetic (PK) and pharmacodynamic (PD) similarity between Ziextenzo and Neulasta medicines from the EU (Neulasta EU) and US (Neulasta US) (LA-EP06-101), and the EU only (LA-EP06-103).
- Two studies investigating efficacy and safety (LA-EP06-301 and LA-EP06-302) were also presented, comparing the PK properties of Ziextenzo and Neulasta EU in breast cancer patients undergoing TAC chemotherapy (i.e. chemotherapy regimen with docetaxel, doxorubicin and cyclophosphamide).

5.5 Details of the trials presented in the submission are provided in the table below:

Table 1: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol	Result
Direct randomised trial(s) demonstrating bioequivalence		
LA-EP06-101	Randomised, double-blind, three-arm, parallel-group, Phase 1 study, in which 279 healthy adult patients were randomised to receive either LA-EP2006 (Ziextenzo), Neulasta EU, or Neulasta US.	The AUC and Cmax were not found to be bioequivalent between LA-EP2006 and either of the Neulasta products.
LA-EP06-103	Randomised, double-blind, two-period crossover, Phase 1 study, of which 184 healthy adult patients received either LA-EP2006 or Neulasta EU on Day 1 of Periods I and II following at least a 10 hour fast.	They were found to be bioequivalent within the pre-defined limits for the ratios of the geometric means, for Cmax, and AUC.
Direct randomised trial(s) demonstrating efficacy and safety		
LA-EP06-301	Randomised, double-blind, parallel group, multi-centre study, in which 316 adult women with histologically proven breast cancer who were eligible for neo-adjuvant or adjuvant treatment with TAC chemotherapy* and had a life expectancy of more than 6 months, were to receive either LA-EP2006 or Neulasta EU on the day following TAC chemotherapy* for up to six weeks.	The results of the inferential statistics from an ANCOVA model demonstrated that LA-EP2006 is equivalent to Neulasta EU as assessed by the DSN. Adverse events and treatment-related adverse events occurred at similar rates between the two treatments.
LA-EP06-302	Randomised, double-blind, parallel group, multi-centre study, in which 308 adult women with histologically proven breast cancer who were eligible for neo-adjuvant or adjuvant treatment with TAC chemotherapy* and had a life expectancy of more than 6 months, were to receive either LA-EP2006 or Neulasta EU on the day following TAC chemotherapy* for up to six weeks.	The results of the inferential statistics from an ANCOVA model demonstrated that LA-EP2006 is equivalent to Neulasta EU as assessed by the DSN. Adverse events and treatment-related adverse events occurred at similar rates between the two treatments.

* Docetaxel, Doxorubicin and Cyclophosphamide

Source: pg 4-5 of the Submission; pg 15-16 of Attachment 3: Clinical Evaluation Report; pg 3-4 of Attachment 4: Delegates Overview; pg 9-11 of Attachment 5: Clinical Overview

Comparative effectiveness

5.6 After a first trial in a healthy population (LA-EP06-101) failed to demonstrate PK similarity, a follow up trial (LA-EP06-103) demonstrated evidence of PK/PD similarity (biosimilarity) of Ziextenzo to Neulasta EU.

5.7 The primary endpoint for LA-EP06-301 and LA-EP06-302 was the mean duration of severe neutropenia (DSN) defined as the presence of a total neutrophil count of $<0.5x10^9$ /L. The two treatments were considered equivalent as there was no more than 1 day difference in DSN for Ziextenzo and Neulasta EU.

5.8 Although the comparators used in the trials were either Neulasta EU or US or both, Neulasta EU, US and AU were determined to be indistinguishable, and therefore the Sponsor claimed the results of the studies show the biosimilarity between Ziextenzo and Neulasta AU.

5.9 The TGA found that the efficacy results were supportive of comparable therapeutic effect between Ziextenzo and Neulasta.

Comparative harms

5.10 The submission claimed that the safety endpoints were similar across treatment groups in both studies (LA-EP06-301 and LA-EP06-302).

5.11 The TGA Delegate stated that the adverse events observed were consistent with the known adverse event profile of Neulasta, and that the risk-benefit balance for Ziextenzo was positive for the proposed use.

Clinical claim

5.12 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of Ziextenzo compared with Neulasta EU.

5.13 The TGA Delegate concluded that biosimilarity between Ziextenzo and Neulasta was well supported by the chemistry, pre-clinical and clinical data evaluated which supported registration of Ziextenzo as a biosimilar product to Neulasta.

5.14 The PBAC considered that the claims of non-inferior comparative effectiveness and non-inferior comparative safety were reasonable.

Financial implications

5.15 The submission requested listing Ziextenzo on a cost-minimisation basis to the Neulasta brand of pegfilgrastim. The submission expected that Ziextenzo would meet the new lower price of pegfilgrastim at time of listing, which would result in no net cost to the Government.

5.16 The submission claimed that the listing of Ziextenzo is not expected to cause market growth of pegfilgrastim because no increase in the market occurred when other new brands of pegfilgrastim were listed. The submission stated that there was predictable

growth in the pegfilgrastim market in August 2018 related to the broadening of the restriction for pegfilgrastim recommended at the March 2018 PBAC meeting.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended the listing of the biosimilar brand of pegfilgrastim, Ziextenzo, on the basis that it should only be available under special arrangements under Section 100 (Highly Specialised Drugs program) for all indications for which the reference brand (Neulasta) is currently PBS-listed.

6.2 The PBAC recommended listing Ziextenzo on a cost-minimisation basis to the Neulasta brand of pegfilgrastim, and noted that this would result in no net cost to the Government because the listing of Ziextenzo is not expected to grow the market.

6.3 The PBAC noted the TGA Delegate conclusion that the biosimilarity between Ziextenzo and Neulasta was well supported by the chemistry, pre-clinical and clinical data evaluated, which supported registration of Ziextenzo as a biosimilar product to Neulasta.

6.4 The PBAC advised, under Section 101 (4AACD) of the *National Health Act 1953*, that the Ziextenzo, Neulasta, Ristempa, Tezmota and Fulphila brands of pegfilgrastim should be considered equivalent for the purposes of substitution (i.e. 'a' flagged).

6.5 The PBAC recalled that, at its March 2018 meeting, it had advised under Section 101(3BA) of the *National Health Act 1953*, that pegfilgrastim, lipegfilgrastim and filgrastim should be treated as interchangeable on an individual patient basis (paragraph 7.5, pegfilgrastim Public Summary Document (PSD), March 2018 PBAC meeting).

6.6 The PBAC recommended the addition of an administrative note to encourage the uptake of biosimilar prescribing for treatment-naïve patients, in accordance with the Australian Government's Biosimilar Uptake Driver policy. The PBAC recalled it recommended the Fulphila biosimilar brand with a similar note (Recommended lsiting, pegfilgrastim PSD, July 2018). Once a second biosimilar brand is listed on the PBS (whether that is Ziextenzo or Fulphila) the note should refer to both biosimilar brands.

6.7 The PBAC noted that pegfilgrastim is not included on the list of PBS medicines suitable for nurse practitioner prescribing.

6.8 The PBAC noted that the Early Supply Rule does not apply to pegfilgrastim.

6.9 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Ziextenzo® is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over Neulasta®, or not expected to address a high and urgent unmet clinical need given the presence of an

alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

6.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add new brand and add an administrative note to PBS items 6363X and 9514R:

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Administrative Advice:	**Biosimilar prescribing policy** Prescribing of the biosimilar brand ZIEXTENZO® is encouraged for treatment naïve patients. Encouraging biosimilar prescribing for treatment naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments. Further information can be found on the Biosimilar Awareness Initiative webpage (www.health.gov.au/biosimilars). Prescribers must include the proprietary name (brand) on the prescription to ensure the appropriate item is approved.

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This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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 10 Sponsor's Comment

The sponsor had no comment.