

## **5.14 TERIPARATIDE, Injection 250 micrograms per mL, 2.4 mL in multi-dose pre-filled pen, Teriparatide Lupin, Generic Health Pty Ltd**

### **1 Purpose of Submission**

- 1.1 The Category 4 submission requested a General Schedule, Authority Required (STREAMLINED) listing of the Teriparatide Lupin brand of teriparatide injection 250 micrograms per mL, 2.4 mL in multi dose pre-filled pen (PFP) (hereafter referred to as 'Lupin PFP') under the same circumstances as the listed teriparatide injection 250 micrograms per mL, 2.4 mL in multi dose pre-filled cartridge (PFC) (Terrosa®) (hereafter referred to as 'Terrosa PFC') with an 'a'-flag to the existing listing.
- 1.2 The submission refers to Lupin PFP as a pre-filled cartridge, however, Lupin PFP presents as a pack containing a cartridge pre-assembled into a pen device and will for the remainder of the minutes be referred to as a PFP. 'PFC' in these minutes will refer to a pack containing a cartridge and pen device separately where the cartridge must be assembled into the pen device by the user.

### **2 Background**

- 2.1 Teriparatide, is a form of parathyroid hormone consisting of the first (N-terminus) 34 amino acids, which is the bioactive portion of the hormone. Forteo®, the reference brand and innovator, is a biological product in which the active ingredient is produced by recombinant deoxyribonucleic acid (rDNA) technology in Escherichia coli. Lupin PFP is of synthetic origin (i.e. not a biological product).
- 2.2 Forteo, a teriparatide injection 250 micrograms per mL, 2.4 mL in multi dose PFP device, was first registered on the Australian Register of Therapeutic Goods (ARTG) on 22 May 2003.

#### ***Registration status***

- 2.3 Lupin PFP was registered on the ARTG on 5 April 2023 for:
  - the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures.
  - the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

- 2.4 The Therapeutic Goods Administration (TGA) considered Lupin PFP to be bioequivalent to Forteo PFP.
- 2.5 The TGA had previously determined that Terrosa PFC was biosimilar to Forteo PFP.
- 2.6 The TGA, in its Australian Public Assessment Report (hereafter referred to as ‘the AusPAR’) of Lupin PFP stated that it had been developed as a generic of Forteo PFP. It noted that the active ingredient and product formulation were the same as for the reference product, and the proposed indication, patient groups and dosing regimen were identical to that of the reference product.
- 2.7 The AusPAR stated that Lupin PFP did not fulfill the requirements for consideration as a biosimilar or a generic medicine and the TGA considered it as a new chemical entity. A biosimilar is a product determined to have similar physicochemical, biological, immunological, efficacy and safety characteristics as the reference product. While Lupin PFP is bioequivalent to Forteo PFP, that is, it has the same amount of active ingredient absorbed by the body over the same period of time for the same dose of the reference product, it is of synthetic origin and therefore does not have similar biological characteristics to Forteo PFP. Furthermore, a generic is a product with an identical active ingredient (chemical that is biologically active in the body). While the active ingredient of Lupin PFP is the same as Forteo PFP and they are bioequivalent, because they are of different origin (synthetic versus biological respectively), it cannot be considered as a generic product.
- 2.8 The AusPAR referred to guidance from the United States Food & Drug Administration (FDA) that states that given the current state of technology for peptide synthesis and characterisation, the FDA believes it is now possible for an applicant to demonstrate that the active ingredient in a proposed generic synthetic peptide drug product is the ‘same’ as the active ingredient in a previously approved peptide of rDNA origin. The similarity depends largely on its impurity profile as compared to the impurity profile for the peptide of rDNA origin. Differences in impurities, particularly peptide-related impurities, may affect the safety or effectiveness of a peptide drug product as compared to the reference listed drug.
- 2.9 The AusPAR specified that the only and most important difference between the Forteo PFP and Lupin PFP was the manufacturing process of the active substance. While the Forteo PFP contains recombinantly produced teriparatide, the active substance in the Lupin PFP is of synthetic origin. The report highlighted that the overseas evaluator nonclinical assessment noted that the pharmacodynamic, pharmacokinetic and toxicological properties of teriparatide are well known. It stated that as teriparatide is a widely used, well known active substance, the applicant did not provide additional studies and further studies were not required. An overview based on literature review was, thus, appropriate and the TGA nonclinical evaluator concurred. The TGA nonclinical and clinical evaluators did not identify any new safety concerns and considered the summary of safety concerns identical to those of recombinant teriparatide products and therefore acceptable.

- 2.10 The AusPAR stated that Lupin PFP must be included in the Black Triangle Scheme and the Australian Product Information (PI) and Consumer Medicine Information documents must include the black triangle symbol and mandatory accompanying text for five years starting from the date that the sponsor notified the TGA of supply of the product. This was because all new prescription medicines must be included in the scheme when they are registered with the exception of biosimilars and generic versions of already-approved prescription medicines not included in the Black Triangle Scheme. As Lupin PFP was considered as a new entity by the TGA and was neither a biosimilar nor a generic of Forteo PFP, it must be on the Black Triangle Scheme despite the TGA evaluators not having any new safety concerns.

### ***Previous PBAC consideration***

- 2.11 On 1 May 2009, Forteo PFP was listed on the PBS in the form of teriparatide 250 microgram/mL injection, 2.4 mL pen device.
- 2.12 At its March 2021 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended Terrosa PFC and Forteo PFP be 'a'-flagged, that is, deemed equivalent for the purposes of substitution.
- 2.13 Terrosa PFC became the only form of teriparatide listed on the PBS following the delist of Forteo PFP from the PBS in June 2022.
- 2.14 Terrosa PFC is currently listed on the PBS as a General Schedule, Authority Required (STREAMLINED) listing for severe established osteoporosis (initial and continuing treatment) with a maximum quantity of 1 and a maximum of 5 repeats (PBS code – 12670W).
- 2.15 Lupin PFP has not been considered by the PBAC previously.
- 2.16 The PBAC at this meeting considered and recommended a PFP presentation of Terrosa on a cost-minimisation basis to Terrosa PFC.

## **3 Requested listing**

- 3.1 The submission requested the addition of Lupin PFP listing with no changes to the existing restrictions. A shortened version of the requested listing is presented below. Proposed changes are in italics and deletions in strikethrough:

Public Summary Document – November 2023 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TERIPARATIDE						
Teriparatide 250 microgram/mL injection, 2.4 mL cartridge		12670W MP	1	1	5	Terrosa
Teriparatide 250 microgram/mL injection, 2.4 mL pen device		NEW MP	1	1	5	Teriparatide Lupin
<b>Restriction Summary / Treatment of Concept:</b>						
		<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
		<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
Prescribing rule level		<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised				
		<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
		<b>Administrative Advice</b> <i>Pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL cartridge (Terrosa) and the pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL pen device (Teriparatide Lupin) are equivalent for the purposes of substitution.</i>				
		<b>Severity:</b> Severe				
		<b>Condition:</b> Established osteoporosis				
		<b>Indication:</b> Severe established osteoporosis				
		<b>Treatment Phase:</b> Initial treatment				
<b>Restriction Summary 12270 / Treatment of Concept: 12270</b>						
		<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
		<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
		<b>Indication:</b> Severe established osteoporosis				
		<b>Treatment Phase:</b> Continuing treatment				

- 3.2 The submission requested for Lupin PFP to be treated as equivalent to Terrosa PFC for the purposes of substitution (i.e. ‘a’-flagged in the schedule) on the basis that Terrosa PFC was treated as equivalent to Forteo PFP prior to its delisting in June 2022 and Lupin PFP is bioequivalent to Forteo PFP. The submission did not provide any pharmacokinetic studies directly comparing Lupin PFP to Terrosa PFC.
- 3.3 The submission requested that the biosimilar policy note not be included in the restriction. Given the reference brand has delisted and Lupin PFP is not a biosimilar to Forteo, it would not be necessary to include the biosimilar policy note on either listing.
- 3.4 As stated in their respective approved PI’s, there is a difference between the devices for Teriparatide Lupin, Forteo and the two forms of Terrosa. While Lupin PFP, Forteo PFP, and Terrosa PFP are a pre-filled cartridge pre-assembled into a pen, Terrosa PFC is a pre-filled cartridge with a reusable pen that the user has to assemble the cartridge into. As such, Lupin PFP, Forteo PFP and Terrosa PFP are referred to as a pen device in

their Australian Medicines Terminology form name, whereas Terrosa PFC is referred to as a cartridge. Despite the difference in presentation, the PBAC considered Terrosa PFC equivalent to Forteo PFP for the purposes of substitution prior to the delisting of Forteo PFP from the PBS.

## **4 Comparator**

- 4.1 The submission nominated Terrosa PFC as the main comparator. This was appropriate. Terrosa PFP would also be a relevant comparator.
- 4.2 Like Terrosa PFC, the approved PI for Lupin PFP states that one pen of 2.4 mL contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL) with each dose of 80 microlitres containing 20 micrograms of teriparatide (corresponding to 28 doses). Similarly, there was no difference in the recommended dose and method of administration in the approved PI of Lupin PFP compared to Terrosa PFC, which states that 20 micrograms should be administered once daily by subcutaneous injection in the thigh or abdomen.

## **5 Consideration of the evidence**

### ***Sponsor hearing***

- 5.1 There was no sponsor hearing.

### ***Consumer comments***

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

### ***Clinical claim***

- 5.3 The submission claimed non-inferior comparative effectiveness and safety of Lupin PFP compared to Terrosa PFC.
- 5.4 The submission stated that there were no data to suggest significant differences in clinical effectiveness or safety between Lupin PFP and Terrosa PFC noting that the TGA approved PI for both products list identical indications, contraindications, special warnings, precautions, and interactions with other medicines.
- 5.5 The submission did not provide a switching study between Terrosa PFC and Lupin PFP as there was no specific study available to determine the safety of switching between both brands. The submission noted that the PBAC has previously approved 'a'-flagging across various biosimilar brands of pegfilgrastim without the need of specific switching studies. Switching studies were not considered to be as relevant for pegfilgrastim in comparison to other biosimilars noting that the PBAC had previously considered that there were no major safety concerns for switching between various brands of pegfilgrastim due to factors such as the short duration of use, smaller molecule size, and the nature of its use (discrete cycles during neutropenia where switching within treatment cycles is unlikely) (paragraph 5.7, pegfilgrastim Public Summary Document,

July 2018). It is unclear why the submission used pegfilgrastim as a precedent. Presumably it was because it is an injectable biosimilar, however, the treatment course is less than one month where, similar to Terrosa PFC, the approved PI for Lupin PFP states that treatment with Lupin PFP is recommended for a lifetime duration of 24 months. The submission did not comment on differences in the molecule size between Terrosa PFC and Lupin PFP.

- 5.6 The PBAC considered that the claim of non-inferior comparative effectiveness and safety to Terrosa PFC was adequately supported.

### ***Economic analysis***

- 5.7 The submission presented a cost-minimisation analysis of Lupin PFP compared with Terrosa PFC. The submission stated the equi-effective doses were 250 microgram/mL of Lupin PFP to 250 microgram/mL of Terrosa PFC.
- 5.8 The submission requested the same approved ex-manufacturer price and dispensed price for maximum quantity for Lupin PFP as that of Terrosa PFC.
- 5.9 The submission stated that the proposed listing would result in no additional prescribing or administration costs and that there was no cost associated with the management of adverse events anticipated.
- 5.10 As a Category 4 submission, the economic analysis has not been independently evaluated.

### ***Estimated PBS usage and financial implications***

- 5.11 The submission adopted a market share approach to estimate the utilisation and financial impact of listing Lupin PFP. The submission assumed that Lupin PFP would substitute the existing use of Terrosa PFC on a 1:1 basis. As such, the submission estimated the requested listing of Lupin PFP to be cost neutral to the PBS/RPBS.
- 5.12 Table 1 showed the market growth rate of teriparatide from 2017 to 2022. The submission suggested that the significant decrease in total utilisation observed in 2022 may have resulted from decreased access to teriparatide following the delisting of Forteo PFP in June 2022. The submission claims that the listing of Lupin PFP on the PBS would provide further access to the medicine, thereby stabilising the market growth to its pre-2022 level. This does not address the market size decline in 2020 and 2021; and implies that listing Lupin PFP may grow the teriparatide market. It is unclear whether a stable market growth trajectory will be realised.

**Table 1: Market growth of Teriparatide from 2017-2022**

Year	Total Utilisation	Market Growth
2016	8,403	-
2017	9,123	8%
2018	10,845	16%
2019	10,939	1%
2020	10,593	-3%
2021	9,358	-13%
<b>2022</b>	<b>5,942</b>	<b>-57%</b>
<b>Average market growth rate (2016-2021)</b>		<b>1.6%</b>

Source: Table 4-2 provided in the submission main body.

5.13 Table 2 presents the estimated net financial implications of listing teriparatide to the PBS/RPBS at a 100% substitution rate.

5.14 The submission stated that the estimated net financial impact to the PBS/RPBS over six years for the listing of Lupin PFP is nil.

**Table 2: Estimated net financial implications for Lupin PFP**

	2024	2025	2026	2027	2028	2029
<b>PBS</b>						
New listing	1	1	1	1	1	1
Changed listing	2	2	2	2	2	2
Net cost to PBS	1	1	1	1	1	1
<b>RPBS</b>						
New listing	1	1	1	1	1	1
Changed listing	2	2	2	2	2	2
Net cost to RPBS	1	1	1	1	1	1
<b>Net cost PBS/RPBS</b>	1	1	1	1	1	1

Source: Submission's financial model spreadsheet.

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

<sup>2</sup> net cost saving

## 6 PBAC Outcome

6.1 The PBAC recommended the listing of Lupin PFP under the same circumstances as Terrosa PFC for the initial and continuing treatment of severe established osteoporosis on a cost-minimisation basis.

6.2 The PBAC noted that while the TGA has not established a direct bioequivalence between Lupin PFP and Terrosa PFC, both brands have been considered bioequivalent to the reference brand Forteo PFP.

6.3 The PBAC considered that the submission's claim that Lupin PFP had non-inferior comparative effectiveness and safety compared with Terrosa PFC was appropriate.

6.4 The PBAC considered that the equi-effective doses were 250 microgram/mL of Lupin PFP to 250 microgram/mL of Terrosa PFC.

6.5 The PBAC advised, under section 101(4AACD) of the Act, that Lupin PFP, Terrosa PFP, and Terrosa PFC should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule). The PBAC considered that this was appropriate given the

TGA assessment of the clinical effectiveness of safety of Lupin PFP compared to Forteo PFP, to which Terrosa PFC was 'a'-flagged.

- 6.6 The PBAC noted that Terrosa PFC and Lupin PFP do not share the same form and that they would be listed under different PBS item codes and different pharmaceutical items on the Schedule. As such, the PBAC advised that an administrative note be added to the PBS listing of Lupin PFP to allow cross-prescribing and to state that the cartridge form is equivalent to the pen device form for the purpose of substitution.
- 6.7 The PBAC considered that Lupin PFP will likely substitute for the existing use of Terrosa PFC and therefore not increase overall market utilisation, resulting in no net financial implication to the PBS/RPBS.
- 6.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Lupin PFP is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Terrosa PFC, 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 2022* for Pricing Pathway A were not met.
- 6.9 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

**Outcome:**

Recommended

## **7 Recommended listing**

- 7.1 Add new medicinal product pack as follows: As per the existing listing of Terrosa PFC

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TERIPARATIDE					
Teriparatide 250 microgram/mL injection, 2.4 mL cartridge	12670W MP	1	1	5	Terrosa
Teriparatide 250 microgram/mL injection, 2.4 mL pen device	NEW MP	1	1	5	Teriparatide Lupin
<b>Restriction Summary / Treatment of Concept:</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice</b> Pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL cartridge and the pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL pen device are equivalent for the purposes of substitution.					
<b>Severity:</b> Severe					
<b>Condition:</b> Established osteoporosis					
<b>Indication:</b> Severe established osteoporosis					
<b>Treatment Phase:</b> Initial treatment					
<b>Restriction Summary / Treatment of Concept:</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction Type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]					
<b>Indication:</b> Severe established osteoporosis					
<b>Treatment Phase:</b> Continuing treatment					

7.2 Flow on changes will apply to the listing of Terrosa PFC to include the following administrative advice:

Pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL cartridge and the pharmaceutical benefits that have the form teriparatide 250 microgram/mL injection, 2.4 mL pen device are equivalent for the purposes of substitution.

***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 Sponsor's Comment**

The sponsor had no comment.