PUBLIC SUMMARY DOCUMENT
Product: Poly-L-lactic acid, powder for intradermal injection, 150 mg, Sculptra®
Sponsor: Sanofi-Aventis Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application
The submission sought an Authority required listing for the treatment of facial lipoatrophy caused by antiretroviral therapy in HIV positive patients.

2. Background
This product had not previously been considered by the PBAC. It is included on the Australian Register of Therapeutic Goods (ARTG) as a medical device. The submission stated that there was a precedent on the PBS for devices and provided the ocular lubricants and glucose indicator strips as examples.

3. Registration Status
Sculptra was included as a Medical Device by TGA on the ARTG on 28 April 2008. The functional description of the device on the register was for soft tissue augmentation via intradermal or subcutaneous injection of polylactic acid. The product requires hydration and suspension prior to use. It provides a physical filling effect.

4. Listing Requested and PBAC's View
Authority Required
For the treatment of facial lipoatrophy caused by antiretroviral therapy in HIV positive patients. Treatment should be only by an accredited medical practitioner.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Facial lipoatrophy is one of the adverse effects of highly active antiretroviral therapy that is of most concern to patients with HIV. Treatment with Sculptra reverses the visible effects of facial lipoatrophy and improves the quality of life for HIV patients.

6. Comparator
The submission nominated placebo as the main comparator. Data against secondary comparators, autologous fat transfer and polyacrylamide hydrogel filler, were also presented. The PBAC considered comparison to placebo to be appropriate.

7. Clinical Trials
Two direct randomised unblinded trials comparing poly-L-lactic acid (PLLA) injections and no treatment (Carey 2007, Moyle 2004). A supplementary trial (Guaraldi 2005) compared autologous fat transfer, polyacrylamide hydrogel, and poly-L-lactic acid treatment. A supplementary meta-analysis of five non-randomised studies was also included. The clinical trials and associated reports published at the time of the submission were:

Trial ID	Publication title	Publication citation
Direct randomised trials		
Carey 2007	A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy.	Journal of Acquired Immune Deficiency Syndromes 2007;46(5): 581-589.
Moyle 2004 (Chelsea and Westminster Study)	A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection.	HIV Medicine 2004;5(2): 82-7.
	Moyle 2006 Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV-related facial lipoatrophy.	HIV medicine 2006; 7(3): 181-5. *(Follow up study)*
Supplementary randomised trial		
Guaraldi 2005	Comparison of three different interventions for the correction of HIV-associated facial lipoatrophy: A prospective study.	Antivir Ther 2005;10(6): 753-759.

8. Results of Trials

There were statistically significant changes in the dermal thickness of treated compared with untreated patients in both of the key randomised trials, but their clinical importance was unknown. The submission argued that facial lipoatrophy had a profound effect on quality of life for HIV patients, and treatment with PLLA reverses its visible effects, thus improving quality of life. Carey 2007 showed improved outcomes in quality of life measures (SF-36 and Multidimensional Body Self Relations Questionnaire) at 24 weeks.

In Moyle 2004 the mean differences between the groups were not statistically significant (though this may be due to the lack of power of the trial). At 12 weeks the "no treatment" group in Moyle 2004 was given PLLA treatment. At the two year follow up, 14 patients over both groups had additional PLLA treatment.

Within group improvement in anxiety scores was not sustained over two years in either group, and only the delayed treatment group showed a significant difference from baseline in depression scores. The submission also presented a review of non-randomised trials of poly-L-lactic acid treatment. While quality of life measures showed some improvement in the first six months after treatment, gains over longer periods have not been convincingly demonstrated. No reliable data were presented in the submission for the persistence of early quality of life gains (approx. 6 months) with re-treatment beyond two years.

PLLA was generally well tolerated, the main adverse effect being the occurrence of subcutaneous papules or nodules.

9. Clinical Claim

The submission described PLLA as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over no treatment.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The steps of the model are summarised in the table below.

Step	Description
Step 1	Evaluation based on presented trials, for initial treatment (dermal thickness)
Step 2	Incorporation of maintenance phase (dermal thickness)
Step 3	Extension to 10 year time frame; inclusion of utilities (dermal thickness; QALYs)
Step 4	Inclusion of Australian pattern of resource use and response rates (responder; QALYs)

The model had an initial treatment phase, at the end of which a patient was judged to be either a responder or non-responder. A responder's quality of life (utility) was assumed to increase from baseline to a peak at 6 months and then declined until maintenance therapy was assumed to be given. Maintenance therapy was assumed to give the same maximum utility as was achieved with the initial treatment phase. This utility was equivalent to the utility of a person with HIV and no facial lipoatrophy. Non-responders were assumed to cease treatment after the initial treatment phase. The costs included were the costs of poly-L-lactic acid and the cost of administration by a specialist. Untreated patients were assumed to have no treatment costs and have a constant utility of a person with HIV and facial lipoatrophy (the baseline utility for treated patients).

The incremental cost per QALY gained was in the range of $15,000 - $45,000. The results of the sensitivity analyses indicated that the model was most sensitive to the extent of utility gained with treatment, the number of re-treatments and the time horizon of the model.

For PBAC's view see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions/packs dispensed per year was estimated to be in the range of 10,000 – 50,000 vials at a financial cost to the PBS of < $10 million in Year 3.

12. Recommendation and Reasons

The PBAC agreed that it was appropriate to consider this product for inclusion on the PBS, given that is has a biological action additional to its mechanical effect.

The PBAC acknowledged the substantial impact that facial lipoatrophy had on the quality of life of HIV patients and recognised the clinical need for treatment options for patients experiencing this unfortunate side effect of anti-retroviral treatment. The Committee also took note of the consumer input received relating to treatment with poly-L-lactic acid and individuals' reports on the related effect on their quality of life.

The PBAC considered a comparison with placebo to be the appropriate analysis. The Committee considered the monitoring of medical practitioners' accreditation to inject poly-L-lactic acid by Medicare Australia proposed in the restriction to be inappropriate considering that accreditation was administered by the sponsor following completion of a training course. The PBAC considered that the sponsor should be required to continue to manage the accreditation program, associated administrative records and the distribution of drug to company approved providers in the event of a positive recommendation for poly-L-lactic acid.

The submission presented two direct randomised unblinded trials comparing poly-L-lactic acid injections and no treatment (Carey 2007, Moyle 2004). Comparative effectiveness was based on the results of objective measures (dermal thickness) and subjective quality of life measures. The PBAC noted that there were statistically significant increases in dermal thickness reported in both of the key trials, however the effect of this on quality of life outcomes was uncertain. In Carey 2007 there was a statistically significant improvement in the SF-36 General Health Questionnaire Sub-Scale (SF-36) and the Multidimentional Body-Self Relations Questionnaire – Appearance Scales (MBSRQ) at 24 weeks. However, in Moyle 2004 the mean difference at 12 weeks in the Hospital Anxiety and Depression Scale was not statistically significant compared to no treatment. At 12 weeks the "no treatment" group in Moyle 2004 were given poly-L-lactic acid treatment and at the two year follow up, 14 patients over both groups had additional poly-L-lactic acid treatment. Within group improvement in anxiety scores was not sustained over two years in either group, and only the delayed treatment group showed a significant difference from baseline in depression scores.

The PBAC hence considered that poly-L-lactic acid appeared to be effective in treating facial lipoatrophy in HIV patients on antiretroviral treatment, and that some studies showed quality of life gains after the initial treatment course. However, there was a lack of demonstrable improvement in quality of life outcomes in the long term. The Committee considered there was also some uncertainty with the applicability of the trial population to the proposed PBS population considering the Moyle 2004 and Carey 2007 trials included patients with moderate to severe facial lipoatrophy only, whereas the proposed PBS-restriction does not limit treatment to more severe lipoatrophy.

The PBAC noted that poly-L-lactic acid was generally well tolerated in the trials with the main adverse effects being the occurrence of subcutaneous papules or nodules, and whilst not equivalent in terms of safety to no treatment, adverse events were minor and generally self-limiting.

The PBAC also noted there were a number of sources of considerable uncertainty in the economic model. The Committee noted the utility gain applied in the model for treatment with poly-L-lactic acid was a utility equivalent to a person with HIV and no facial lipoatrophy. The Committee considered this assumption likely to overestimate the utility gain from treatment with poly-L-lactic acid and that it was subject to potential confounding. There may be other sources of disutility between the two populations and it was assumed that all differences in utility were due to the presence or absence of facial lipoatrophy (and that resolution of facial lipoatrophy was the same as never having had the condition). In addition, treatment with poly-L-lactic acid also did not result in total resolution of the lipoatrophy.

Additionally, maintenance therapy was assumed to give the same utility as achieved with the initial treatment phase. The PBAC considered there was uncertainty associated with a number of derivations used in the model. Further, the model used the results of the sponsor's survey of seven specialists. There was considerable uncertainty associated with the survey and the sponsor's analysis of the survey results, and as the survey results were extrapolated to the ICER gain, the ICER was consequently highly uncertain.. The model also assumed that non-responders cease treatment and that all grades of severity of facial lipoatrophy had the same magnitude of utility gain from treatment. The ten year time horizon of the model with multiple maintenance phases was also inadequately supported by the evidence presented in the submission.

The Committee questioned the reason for using the modelled economic evaluation literature based utility estimates rather than the quality of life data from Carey 2007 trial which measured SF-36. The PBAC considered the data from Carey 2007 would have provided more directly applicable patient based estimates and/ or provided appropriate data for sensitivity analysis.

The PBAC concluded that there were a number of poorly supported assumptions in the economic model, which resulted in highly uncertain cost effectiveness, and the submission was rejected on this basis. The Committee indicated its willingness to work with the sponsor towards reducing this uncertainty sufficiently to allow a listing recommendation.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

As part of sanofi-aventis' strong commitment to the HIV community, we welcome the opportunity to continue to work with the PBAC by addressing its questions and concerns surrounding the listing of Sculptra on the PBS.

Sculptra is TGA registered as a class III device containing a Schedule 4 medicine. It provides a physical filling effect in addition to an inflammatory response with increased deposition of fibroblasts and collagen fibres that leads to a gradual and progressive increase in the volume in the treated area.