Public Summary Document

Product: Levonorgestrel, intrauterine system, 13.5 mg, Jaydess®,
Sponsor: Bayer Australia Limited
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought a Restricted benefit listing for contraception for up to three years.

2. Background

Intrauterine levonorgestrel contraceptive system (releasing approximately 12 micrograms per 24 hours) (LCS12) had not previously been considered by the PBAC.

3. Registration Status

The PBAC noted that both the clinical evaluation report and the TGA Delegates overview were available at the time of the consideration by the PBAC in July 2013.

LCS12 was registered by the TGA on 18 September 2013 for the following indication:

- Contraception for up to 3 years

4. Listing Requested and PBAC's View

Restricted benefit
Contraception for up to 3 years

The PBAC noted and agreed with the Secretariat suggested amendment to remove the duration of contraception

5. Clinical Place for the Proposed Therapy

The submission stated that more than 70% of Australian women currently use contraception. However, unplanned pregnancy occurs in up to 50% of women which can be both a clinical and economic burden.

The clinical management algorithm is based on the currently available contraception options listed on the PBS and concurs with the management algorithm of the main comparator, Mirena. The intended use of LCS12 is for women who require progesterone only, long acting reversible contraception (LARC).

6. Comparator

The submission nominated Mirena and Implanon as the main comparators. Mirena is a levonorgestrel releasing intrauterine system but has a larger frame (32 x 32 mm), compared to LCS12 (28 x 28 mm) and releases more levonorgestrel per 24 hours (20 µg/day) than LCS12. Implanon is a single rod sub-dermal implant containing 68 mg of etonogestrel, which is a pharmacological analogue of levonorgestrel. The release rate for Implanon is 35-40 µg/day.

The PBAC considered that Mirena is the most appropriate comparator due to the similarity in devices. The populations using injection or sub-dermal implant are likely to differ in terms of their preferences, from those using an intra-uterine contraceptive device. In addition, given

that Mirena is already available on the PBS, the PBAC agreed that any substitution from Implanon to an intrauterine system has likely already occurred.

7. Clinical Trials

In comparing LCS12 to Mirena, the submission presented one head-to-head randomised phase II trial (LCS12 Phase 2 study) and one supplementary randomised phase III clinical trial (Phase 3 Study; Protocol 310442-91665) comparing LCS12 and LCS16.

In comparing LCS12 to Implanon, the submission presented an indirect comparison of one RCT comparing LCS12 with Mirena, one RCT comparing Mirena with Norplant/Norplant-2 (another sub-dermal progestogen releasing contraceptive) and eight randomised controlled trials comparing Norplant/Norplant-2 with Implanon. Three meta-analyses were also included in the submission, comparing Mirena to other forms of contraception

None of these studies had been published at the time of submission.

8. Results of Trials

The results of primary (number of pregnancies) and secondary outcomes (bleeding patterns) were presented. For the comparison with Mirena, the PBAC noted that non-inferiority was largely inferred by overlapping confidence intervals and that the number of pregnancies was very low using either method of contraception. However, the PBAC further noted the TGA Delegate's observation that the observed efficacy of LCS12 in the registration studies was consistent with the adopted guidelines (EMA CHMP guidelines for Pearl Index criteria) and comparable but nevertheless lower than Mirena, which may be an issue at individual user level.

The PBAC considered that the data to support the comparison with Implanon were difficult to interpret but overall the event rates showed that both products are effective methods for contraception.

While the submission provided a comparison of bleeding outcomes associated with use of each product, these studies were difficult to interpret in the Australian setting, as acceptability of bleeding is influenced by cultural considerations and there may have been considerable reporting bias. There was little data to support any meaningful differences between products.

With regard to comparative harms, the PBAC noted that no formal indirect comparisons were done for the safety outcomes for either Mirena or Implanon. The clinical claim of non-inferiority of comparative safety was based on comparing descriptive analyses of adverse events.

9. Clinical Claim

The submission described LCS12 as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over Mirena.

The submission further described LCS12 as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over Implanon.
The PBAC was yet to accept these claims, as the PBAC noted the following:

- Numerically higher rates of unintended pregnancy for LCS12 compared to Mirena

- The LCS Phase 2 Study was not powered to test inferiority and an absence of any formal statistical analysis; the reliance on a two step indirect comparison of LC12 to Implanon in terms of bleeding outcomes, amenorrhoea, frequent bleeding and prolonged bleeding. There are exchangeability issues between the different trials including different inclusion and exclusion criteria, and the disparate healthcare systems (e.g. Indonesia versus Australia) and regions where the trials were conducted.
- The TGA Delegate's observations of comparable but lower efficacy of LCS12 compared to Mirena, and, higher relative risk of ectopic pregnancy with LCS12 compared to Mirena; and
- The absence of a recommendation by the TGA Delegate

10. Economic Analysis

A cost-minimisation analysis was presented based on cost-equivalence of LCS12 with Mirena and Implanon, including all health care costs to both the PBS and the MBS. The total costs included the cost of the implant, health care costs and insertion and removal costs. The total costs and the average annual cost for each implant was estimated, with the average annual cost for each implant based on the in-situ times presented in the submission.

The PBAC noted an error in the cost analysis arising from the submission's use of Mirena's published price which incorporated a weighting for another subsidised indication (menorrhagia). The cost-minimisation analysis was redone during the evaluation.

Based on a weighting of Mirena and Implanon derived from market research, the submission's proposed price was estimated and a revised price was calculated during the evaluation for the contraception indication only. The proportion of patients on Mirena or Implanon from the submission's market research was converted to units replaced on the PBS according to the differing in-situ times for the products.

The PBAC noted that the cost-minimisation analysis was most sensitive to the substitution weightings, the basis of which were not accepted by the PBAC at this stage because the PBAC considered that the market research was poorly substantiated. The PBAC noted that the greater the weighting that is placed on Mirena, the lower the proposed cost of the LCS12 would need to be to maintain cost-minimisation

11. Estimated PBS Usage and Financial Implications

The PBAC considered that the substitution for Implanon was overestimated and more substitution would be from Mirena.

The submission's estimated total net cost to the PBS was between $100,000-$200,000 over the first 5 years, with estimated cost savings in the first 2 years of listing and again in year 5. With the revised price for LCS12, this net cost to the PBS over the first 5 years was revised to be greater than $200,000. The financial implications are yet to be verified.

Overall, the total cost per year to the Government was estimated in the submission to be less than $10 million over the first five years of listing.

The PBAC considered that the assumptions used to determine the financial costs were likely to overestimate reductions in cost. The PBAC noted that if Mirena is the only comparator and substituted at 100%, overall, over the 5 years, the total cost to Government, was estimated by

a sensitivity analysis conducted during the evaluation in the range of $10 million to $30 million.

12. Recommendation and Reasons

The PBAC deferred the submission in the absence of a positive TGA Delegate's recommendation to register LCS12, at the time of consideration by the PBAC. The PBAC noted the concern in the TGA Delegates overview that while the ectopic pregnancy rate for LCS12 is low, lack of comparison with Mirena in the pivotal study raises concern that there may be an undetected clinically significant difference in risk of pregnancy, and specifically ectopic pregnancy.

The PBAC indicated that it would reconsider the submission as it currently stands once a positive Advisory Committee on Prescription Medicines (ACPM) outcome is received. The PBAC did not request that the Sponsor provide any additional information prior to reconsideration, apart from updating the status of the TGA application

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

Bayer does not agree with Committee's current view regarding comparator weighting nor the stated financial impact estimates and will bring forward a further submission addressing these points. In addition, Bayer will also bring forward the positive ACPM outcome within the re-submission. Bayer is committed to continue working with the PBAC to facilitate access of an additional long acting reversible contraceptive (LARC) option for Australian women.