Summary

The drug and the review
- Dienogest (Visabelle®) is a selective progestin, combining the pharmacological properties of 19-norprogestins with progesterone derivatives, and has a pronounced effect on endometrial tissue.
- An EU marketing authorisation application for the use of dienogest to treat endometriosis was granted by The Netherlands in December 2009.
- The aim of this review is to evaluate the data available supporting the use of dienogest for the treatment of endometriosis.

Background
- The Royal College of Obstetricians and Gynaecologists issued guidance on the treatment of endometriosis in October 2006.
- NSAIDs may be effective in treating endometriosis-associated pain but the limited evidence for their use in this condition is inconclusive, and they have significant adverse effects, including gastric ulceration and an antiovulatory effect when taken mid-cycle. There is insufficient evidence to recommend other analgesics.
- Hormonal treatment, using combined oral contraceptives, danazol, medroxyprogesterone acetate or GnRH agonists are equally effective but with differing costs and side effects (some which can limit long-term use and affect compliance) and do not always provide effective pain control. Using the levonorgestrel intrauterine system gives better symptom control. The ideal practice would be to remove endometriosis surgically, depending on the severity of the disease.
- Endometriosis is the presence of endometrial tissue outside of the uterus, most commonly the pelvic organs and peritoneum, although the bowel and lungs are occasionally affected, which results in a chronic inflammatory reaction.
- Treatments include NSAIDs and hormonal treatment, using combined oral contraceptives, danazol, medroxyprogesterone acetate or GnRH agonists.

Literature
- Medline and Embase searches were carried out and information was supplemented by that received from Bayer Plc.
- The following studies were submitted for the licence application: one pivotal Phase III study with a 52 week extension, and a comparative study with leuprorelin; all sponsored by Bayer.
- There are a number of studies comparing dienogest treatment with buserelin (double-dummy), and triptorelin (open-label), and one longer-term study. Some of these studies have been carried out in Japanese, not European, women. None of these were sponsored by Bayer.
**Efficacy studies submitted for the licence application**

- **Pivotal study**
  - The safety and efficacy of dienogest 2mg daily for 12 weeks was assessed in 198 women with endometriosis and pain above 30mm on a visual analogue scale (VAS), in a randomised, placebo-controlled study.
  - Reductions on the VAS in endometriosis-associated pelvic pain (the primary endpoint) were 27.4mm with dienogest and 15.1mm with placebo, (mean difference in core of 12.3mm; 95% CI 6.4 to 18.1, p<0.0001).
  - No difference in the amount of supportive analgesic used between the groups was seen.
  - No difference in the number of days and the number of episodes of bleeding/spotting was seen between the two groups; there was a trend towards an increase in the number of spotting-only days/episodes with dienogest treatment.
  - 168 women have continued with a further 52 weeks of dienogest treatment.

- **Long-term extension study**
  - The 52-week extension study results showed a progressive reduction in the frequency of bleeding/spotting days and episodes, decreased intensity of bleeding, shortened individual mean length of bleeding/spotting episodes and improvements in endometriosis-associated pelvic pain scores.

- **Comparison with leuprorelin**
  - Dienogest 2mg/day (n=124) was compared with leuprorelin 3.75mg/4 weeks (n=128) in a randomised 24-week study.
  - Improvements in VAS scores of endometriosis-associated pelvic pain were similar in both groups (reductions of 47.5mm with dienogest and 46.0 with leuprorelin, and showed the non-inferiority of dienogest compared with leuprorelin).
  - A similar proportion of women experienced VAS score improvements: 96.7% (dienogest) and 95.8% (leuprorelin).
  - Quality of life (both physical and mental symptoms) improved with both treatments, with a trend towards greater improvements with dienogest.

- **Other efficacy studies**
  - **Comparison with intranasal buserelin**
    - Dienogest 2mg/day (n=137) was compared with buserelin 300mcg tds (n=134) in a randomised, controlled, 24-week study.
    - The primary efficacy endpoint was the pre-to-post-treatment changes in the subjective and objective symptom scores. Clinically relevant changes for both sets of symptoms were achieved with each treatment and the differences between the treatments were not statistically significant.
    - The change in total score of the subjective symptoms was from 5.7±3.1 to 2.5±2.3 in the dienogest group and from 5.9±2.8 to 2.4±2.4 in the buserelin group (difference of mean change -0.39, 95% CI -1.11 to 0.32). In both groups the change was large enough to be clinically relevant. For the objective symptoms, the change was from 3.8±2.1 to 1.9±1.9 in the dienogest group and from 3.7±2.0 to 1.5±1.3 in the buserelin group (difference of mean change -0.35, 9% CI -0.75 to 0.05). The mean difference in the change in the combined scores of both sets of symptoms was -0.74 (95% CI -1.62 to 0.14).

  - **Comparison with triptorelin**
    - Dienogest 2mg/day (n=59) was compared with triptorelin 3.75mg/4 weeks (n=61) in an open-label 16-week study. Patients had undergone an operative laparoscopy and drug treatment was used as consolidation therapy.
    - Endometrial tissue scores did not differ between the 2 groups after 16 weeks. No reappearance of endometrial tissue was achieved in 25% of patients in each group.
    - In total 86.2% of patients treated with dienogest and 80% of patients treated with triptorelin were satisfied with treatment.
    - Fifteen patients in the dienogest group and 12 in the triptorelin group had spontaneous pregnancies in the 12 months following the end of treatment, p=0.71.

- **Long term study**
  - 52 weeks of dienogest treatment in 135 Japanese women was well tolerated and treated the subjective and objective symptoms of endometriosis in 72.5% (95/131) of patients at 24 weeks and 90.6% (106/117) at 52 weeks.
  - Mid-cycle bleeding was the main side effect, occurring in 71.9% of women; the tendency to bleed fell from 21 days at weeks 5-8 to 2 days at weeks 49-52.
Eight patients had a reduction in bone mineral density classed as an adverse drug reaction, with a mean reduction of 1.7%, which was considered mild and no significantly greater than that seen in the natural course.

Safety
- When compared with GnRH agonists, dienogest has a lower incidence of hypoestrogenic side effects (e.g. hot flushes, reduced libido) and causes significantly smaller bone mineral density reductions.
- Adverse events and adverse drug reactions that occurred during the 52-week extension study were those that would be expected from a progestin: the most frequent adverse drug reactions were breast discomfort, nausea and irritability. Weight gain, depressed mood, headache, migraine and menorrhagia were among other side effects.
- The adverse events/reactions seen did not raise any safety concerns.

Critical evaluation
- In the pivotal study, the main results showed that dienogest was significantly better than placebo in reducing the VAS score of endometriosis-associated pelvic pain, and improving patient’s ratings of pelvic pain, physical signs and total symptoms/signs to a greater extent than placebo. No major benefits with respect to bleeding or use of supportive analgesia were attained with dienogest.
- The comparative study in which dienogest was compared with leuprolelin was not rated sufficient to demonstrate the efficacy of dienogest in relieving EAPP.
- Of the studies in which dienogest was compared with other treatments, one has been carried out in Japanese women and one was not powered and poorly reported.
- Long term data is available for Japanese women and the efficacy results may not be mirrored in a European population.
- The comparative studies are limited to up to 24 weeks, because of the licences of the GnRH agonists (max 6 months treatment for endometriosis).

Potential benefits over existing technologies
- Dienogest appears to be safe and effective when taken for up to 2 years. Current treatments are limited to shorter treatment intervals.
- Dienogest is an oral therapy; GnRH agonists are given parenterally or intranasally.
- Treatment of endometriosis with dienogest is not inferior to that with GnRH agonists.
- Bone mineral density reductions are less than those seen with GnRH agonists.

Health Economics
- The price of dienogest has not yet been confirmed but it is likely to be lower than the monthly cost of a GnRH agonist (drug cost plus cost of administration). GnRH agonists should be given for a maximum of 6 months, due to concerns about loss of bone mineral density, whilst dienogest can be used longer term.

Issues for consideration
- The comparative study submitted for the licence application was not considered suitable because the efficacy of the comparator (leuprolelde) in treating endometriosis-associated pelvic pain had not been established in placebo-controlled trials.
- Longer-term treatment (up to a year) is required before a positive effect on the number and duration of days/episodes of bleeding or spotting (a reduction) can be seen.
**Background**

Dienogest is a selective progestin, combining the pharmacological properties of 19-norprogestins with progesterone derivatives, and has a pronounced effect on endometrial tissue. An EU marketing authorisation application for the use of dienogest to treat endometriosis was made in December 2009.

**Endometriosis**

The Royal College of Obstetricians and Gynaecologists issued updated guidance on the diagnosis and treatment of endometriosis in October 2006.

Endometriosis is the presence of endometrial tissue outside of the uterus, most commonly the pelvic organs and peritoneum, although the bowel and lungs are occasionally affected, which results in a chronic inflammatory reaction. The associated symptoms can impact on general physical, mental and social wellbeing. Disease severity ranges from a few small lesions to large, ovarian endometriotic cysts (endometriomas, which contain thick fluid like chocolate, hence the name 'chocolate cysts'). The ‘gold standard’ investigation is visual inspection of the pelvis by laparoscopy; serum CA125 levels may be raised but measuring this marker is not a useful diagnostic tool.

NSAIDs may be effective in treating endometriosis-associated pelvic pain (EAPP), as measured on the VAS, (0=no pain, 100=unbearable pain), from baseline to study end and by change in use of rescue medication (ibuprofen). This outcome measure was preferred above the gold standard of laparoscopic evaluation of endometriosis before and after treatment because the main clinical symptom of the disease, pelvic pain, does not necessarily correlate with the extent and volume of endometriotic lesions seen during laparoscopy. Lesions that appear similar on visual inspection may actually cause different degrees of pain; pelvic pain is an endpoint considered more relevant to the patient. Secondary outcomes include the change in the Biberoglu & Behrmann (B&B) severity profile score for symptoms and signs (see Appendix 1) and quality of life. A power calculation was carried out and the analyses were carried out on the Full Analysis Set (FAS); all patients receiving at least one dose of study drug and with at least one post-dose observation. The per protocol (PP) population were the FAS without any major protocol violations.

The majority of women had stage III or IV endometriosis (45% and 25.5% respectively). Compliance with study medication was high: 99.7% in the dienogest group and 99.1% in the placebo group, and similar proportion of patients used concomitant medication (46.1% and 46.9% respectively).

Dienogest was significantly superior to placebo in reducing EAPP in both the FAS ($p=0.00165$) and PP ($p<0.0001$) groups. The benefit was mainly due to the reduction in VAS scores, not the decrease in supportive medication.

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- FAS group: mean reductions were -27.4mm with dienogest and -15.1mm with placebo, mean difference in score from placebo of 12.3mm (p<0.0001) (see Table 1a, page 6, for more details).
- PP group: The mean difference was 13.2mm, in favour of dienogest (p<0.0001).

Rescue medication intake was modestly reduced in both groups but there was no significant difference between the two.

During treatment, there was a redistribution of patients from the ‘moderate’ or ‘severe’ categories in the B&B scale toward ‘mild’ or ‘none’, for the B&B symptoms of pelvic pain, dysmenorrhoea and dyspareunia in both groups. There was a tendency towards more frequent shifts to lower severity categories in the dienogest group. Overall severity was reduced in both groups, with a trend towards a greater reduction in the dienogest group. The main improvements in the quality of life analyses were in the bodily pain and role emotional scores, with greater improvements in the dienogest group. The mean number of days, episodes and duration of bleeding/spotting was comparable between the groups. There was a trend towards more spotting-only days and episodes in the dienogest group. More patients treated with dienogest than placebo had infrequent bleeding, though irregular bleeding and prolonged bleeding were also more common in the dienogest group.

Three patients withdrew from the study because of adverse events: two in the dienogest group (breast pain, uterine bleeding) and one in the placebo group (increased blood hCG). Drug-related adverse events included headache, breast discomfort, nausea and depression. There was one case of hot flushes and no effects on plasma lipid levels were seen.

There are no EU guidelines for the development of medicinal products for the treatment of endometriosis. An initial application based on a comparator-controlled study was withdrawn: the efficacy of the comparator was not established in placebo-controlled trials. The placebo-controlled design is a study limitation but this was considered the preferred approach for the primary endpoint of endometriosis-associated pain. The short treatment period is a limitation of this study, though it would not be justified to continue placebo treatment in patients experiencing chronic pain.

In summary, the main results of this study showed that dienogest was significantly better than placebo in reducing the VAS score of endometriosis-associated pelvic pain, and improved patient’s ratings of pelvic pain, physical signs and total symptoms/signs to a greater extent than placebo. More patients treated with dienogest had improvements in their symptoms and were most satisfied with their treatment. No major benefits with respect to bleeding or use of supportive analgesia were attained with dienogest.

Clinical evidence: Extension of pivotal study

The pivotal study was extended for another 52 weeks, resulting in maximum treatment of 64 weeks. The data have not been fully published yet and trial details have come from the clinical study synopsis. The study aim was to demonstrate safety and efficacy of dienogest 2mg/day for the treatment of endometriosis. The primary endpoint was the assessment of menstrual bleeding pattern, and the secondary endpoint was EAPP assessed by VAS every 4 weeks.

A total of 168 patients who completed the placebo controlled study were included in the one-arm follow-up extension study. Of them, 152 patients (90.5%) completed the study treatment while 16 patients (9.5%) prematurely discontinued the study treatment. The main reasons for premature study discontinuation were adverse events (AEs) in 4 patients (2.4%), withdrawal of consent by 3 patients (1.8%), protocol deviations in 3 patients (1.8%), missing information for 3 patients (1.8%), lack of efficacy in 1 patient (0.6%), and “other” (1 patient: refusal of final examination, 1 patient: polymenorrhea, and 1 patient: amenorrhea).

Bleeding patterns was analysed according to four periods of 90-day and 13 periods of 28-days. During the 90-day reference periods, the mean number of bleeding/spotting days decreased from 20.2 (period 1) to 9.7 (period 4). The mean number of bleeding/spotting episodes fell from 3.0 to 2.0 respectively. See table 1b for more results. There was a trend towards a decrease in the frequency of bleeding with heavy and normal intensity, and an increase in the frequency of no bleeding and spotting. The course of changes in the number of bleeding/spotting days and episodes analysed by 28-day reference
### Table 1a: Results of the 12 week pivotal study

<table>
<thead>
<tr>
<th></th>
<th>Dienogest (n=102)</th>
<th>Placebo (n=96)</th>
<th>Difference</th>
<th>P value [95% CI]</th>
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<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>VAS score reduction, FAS</td>
<td>-27.4mm</td>
<td>-15.1mm</td>
<td>12.3mm</td>
<td>&lt;0.0001 [6.4 – 18.1]</td>
</tr>
<tr>
<td>VAS score reduction, PP</td>
<td>Not stated</td>
<td>Not stated</td>
<td>13.2mm</td>
<td>&lt;0.0001 [7.3 – 19.2]</td>
</tr>
<tr>
<td>Use of supportive analgesia, tablets/28 days</td>
<td>-4.4 ± 6.4</td>
<td>-3.7 ± 8.2</td>
<td>0.74</td>
<td>Not significant (NS) [-1.412 – 2.895]</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
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<td></td>
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<tr>
<td>B&amp;B scale, category: “none”</td>
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<tr>
<td>Pelvic pain</td>
<td>11.8%</td>
<td>2.1%</td>
<td></td>
<td></td>
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<tr>
<td>Physical signs</td>
<td>17.6%</td>
<td>11.5%</td>
<td></td>
<td></td>
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<tr>
<td>Total symptom and sign severity</td>
<td>7.8%</td>
<td>2.1%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Quality of life improvements</strong></td>
<td></td>
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<tr>
<td>Bodily pain</td>
<td>21.8 ± 22.8%</td>
<td>10.3 ± 20.5%</td>
<td></td>
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</tr>
<tr>
<td>Emotional</td>
<td>18.4 ± 33.9%</td>
<td>9.6 ± 46.4%</td>
<td></td>
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<tr>
<td>CGI very much/much improved</td>
<td>52.9%</td>
<td>22.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI very much/much satisfied</td>
<td>43.1%</td>
<td>20.8%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Bleeding patterns (mean)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bleeding/spotting (days)</td>
<td>22.5 ± 14.7</td>
<td>22.4 ± 9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding/spotting (episodes)</td>
<td>2.6 ± 1.6</td>
<td>2.8 ± 1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of bleeding/spotting episodes (days)</td>
<td>6.1 ± 3.4</td>
<td>6.0 ± 2.1</td>
<td></td>
<td></td>
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<tr>
<td>Number of spotting-only days</td>
<td>12.0 ± 9.7</td>
<td>9.7 ± 8.7</td>
<td></td>
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<tr>
<td>Number of spotting-only episodes</td>
<td>1.2 ± 1.3</td>
<td>0.6 ± 1.2</td>
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<tr>
<td>Duration of spotting-only episodes (days)</td>
<td>3.9 ± 3.6</td>
<td>2.9 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent bleeding</td>
<td>18.4%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>19.4%</td>
<td>9.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular bleeding</td>
<td>37.8%</td>
<td>28.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>24.5%</td>
<td>5.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>1%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal bleeding</td>
<td>23.5%</td>
<td>60.9%</td>
<td></td>
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</tr>
</tbody>
</table>
periods paralleled those seen in the 90-day reference period analysis.

Endometriosis-associated pelvic pain mean VAS scores decreased from 34.08 ± 21.6 [median 31.00] at entry to the long-term extension-study to 17.69 ± 13.1 [median 16.00] after 28 weeks of treatment and to 11.52 ± 11.26 [median 9.25] after 52 weeks.

Three serious adverse events occurred; cholecystitis, depression and chronic sinusitis. Only depression was considered possibly related to dienogest treatment. Weight gain, migraine, depression and breast pain resulted in four patients discontinuing the trial. The most frequently occurring adverse drug reactions, occurring in 27 patients, were breast discomfort (4.2%), nausea (3.0%) and irritability (2.4%). Other adverse drug reactions included fatigue, weight gain, headache, migraine, depressed mood, depression, breast engorgement, breast induration, menorrhagia and ovarian cysts.

In summary: long-term use of dienogest was associated with a reduction in the frequency of bleeding/spotting days and episodes, decreased bleeding intensity and improvements in endometriosis-associated pelvic pain. The adverse drug reactions seen were those typical of progestins and no major safety concerns were raised.

Clinical evidence: comparison with GnRh agonist

The following studies show that dienogest is as effective as the GnRh agonists in treating the symptoms associated with endometriosis and in reducing the reappearance of tissue post-surgery. The advantages of dienogest over the GnRh agonist are that it is an oral formulation and is less likely to cause hypoestrogenic side effects (such as hot flushes) and reductions in bone mineral density, allowing it to be taken longer term.

Not all the studies were well designed (such as the comparison with triptorelin, which was not powered and the results have not been presented clearly) and the comparison with buserelin was in a Japanese population which may respond differently to a Western population. The two studies using intramuscular GnRH agonists were open-label; reasons for this were the need to design a placebo injection, and the characteristic side effects of GnRH agonists. Treatment was restricted to up to 24 weeks in all 3 studies because the GnRH agonists are approved for a maximum of 6 months treatment for endometriosis due to their effects on BMD.

Table 1b: results from the long-term study

<table>
<thead>
<tr>
<th>Bleeding patterns</th>
<th>Period 1</th>
<th>Period 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of bleeding/spotting days [median]</td>
<td>20.2 ± 15.2 [16.0]</td>
<td>9.7 ± 9.0 [9.0]</td>
</tr>
<tr>
<td>Mean number of bleeding/spotting episodes [median]</td>
<td>3.0 ± 1.8 [3.0]</td>
<td>2.0 ± 1.6 [2.0]</td>
</tr>
<tr>
<td>Mean length of bleeding/spotting episodes [median]</td>
<td>7.71 ± 8.19 days [4.71]</td>
<td>4.83 ± 2.52 days [4.33]</td>
</tr>
<tr>
<td>No bleeding [no. (%)]</td>
<td>9 (5.5%)</td>
<td>32 (23.5%)</td>
</tr>
<tr>
<td>Spotting [no. (%)]</td>
<td>26 (15.9%)</td>
<td>32 (23.5%)</td>
</tr>
<tr>
<td>Heaving bleeding [no. (%)]</td>
<td>16 (9.8%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Light intensity [no. (%)]</td>
<td>61 (37.2%)</td>
<td>56 (41.2%)</td>
</tr>
<tr>
<td>Normal intensity [no. (%)]</td>
<td>52 (31.7%)</td>
<td>13 (9.6%)</td>
</tr>
<tr>
<td>Spotting-only days</td>
<td>13.4 ± 11.5</td>
<td>8.8 ± 9.2</td>
</tr>
</tbody>
</table>
Comparison with leuprorelin

The efficacy and safety of dienogest 2mg orally/day (n=124) was compared with that of leuprorelin acetate, 3.75mg by im injection/4 weekly (n=128) in a 24-week, randomised, open-label European study. The primary aim was to demonstrate the non-inferiority of dienogest with leuprorelin and the primary efficacy variable was the absolute change in endometriosis-associated pelvic pain (EAPP) score from baseline to endpoint (VAS, 0=absence of pain, 100=unbearable pain). The primary analysis was based on the per protocol set (PPS), which was all randomised patients except those with major protocol deviations affecting the primary efficacy variable. There were a number of secondary endpoints, including rates of improvement in pelvic pain and responder rates. Changes in quality of life were also assessed. The incidence of hot flushes was documented using diary cards and BMD was measured in a subgroup of patients in 3 of the 17 participating centres (n=57, 26 dienogest and 32 leuprorelin).

The pre-specified non-inferiority margin was 20% points (15mm), based on the margin for response rates used in earlier products approved by the US FDA for endometriosis. A sample size of 88 evaluable patients per group was required to give the study 90% power to demonstrate non-inferiority; 252 women were randomised to treatment to allow for a 30% withdrawal rate.

The PPS comprised of 186 women (dienogest, n=90 and leuprorelin, n=96). Both treatments were associated with substantial reductions in VAS for EAPP between baseline and week 24: changes from baseline to week 24 were from 60.2mm to 12.7mm with dienogest and from 57.9 to 11.9 with leuprorelin. Absolute reductions were 47.5±28.8mm (dienogest) and 46.0±24.8mm (leuprorelin), treatment difference of 1.5mm in favour of dienogest (95% CI -9.26 to 6.25). Non-inferiority of dienogest was confirmed, based on the pre-specified non-inferiority margin of 15mm (p<0.0001).

A similar proportion of women in each group experienced improvements in VAS; 96.7% (dienogest) and 95.8% (leuprorelin), p for non-inferiority <0.0001. Pelvic symptoms and physical findings improved to a similar extent in each group. Severe symptoms were reduced from 12.3% (dienogest) and 6.3% (leuprorelin) at baseline, to none at week 24. The severity of the symptoms of pelvic pain, dysmenorrhoea, dyspareunia, pelvic tenderness and induration also decreased in both treatment groups. Quality of life improved in both groups, with a trend to greater improvements with dienogest; improvements from baseline in the SF-36 physical health summary scale were 10.2 points (dienogest) and 7.0 points (leuprorelin), whilst those in the mental health summary scale were 3.3 points and 1.9 points respectively.

Most adverse events were mild or moderate and 11 patients (6 in the dienogest group) discontinued treatment because of them; hypertension, tinnitus, ovarian cyst, nausea, depression (dienogest) and hot flushes, arthritis, depression, allergic reaction and sleep disorder (leuprorelin). Headache was the most common adverse event (12.5% dienogest, 19.5% leuprorelin). Hypoestrogenic symptoms (hot flushes, vaginal dryness, decreased libido) were more common in the leuprorelin group. Of the seven serious adverse events, only one was considered related to the study drug (severe depression in a woman treated with dienogest). Hot flushes increased in the leuprorelin group from a mean of 0.78 days with hot flushes/week at baseline to 4.70 days/week at week 24; no change was seen in the dienogest group (1.04 week 1, 0.86 week 24). Mean BMD decreased by 4% in the leuprorelin subgroup (n=29) and increased by 0.25% in the dienogest subgroup (n=21), p=0.0003 for superiority of dienogest. Regular bleeding cycles increased to a similar extent with both treatments. Both treatments resulted in a decrease in the number of both bleeding/spotting episodes and days over time, although this trend was stronger with leuprorelin. No patients withdrew prematurely from the study due to a changed bleeding pattern or adverse bleeding events. No significant changes in body weight occurred.
The following studies were not sponsored by Bayer.

**Comparison with intranasal buserelin**

Harada et al compared the efficacy and safety of dienogest 1mg orally twice daily (n=137) with buserelin 300mcg intranasally (n=134) three times a day for 24 weeks, in a randomised, controlled, double-dummy study set in Japan. Analgesics were allowed throughout the study.

The primary efficacy endpoint was the pre- to post-treatment changes in the scores of the five subjective symptoms and the two objective symptoms. The subjective symptoms were: lower abdominal pain, lumbago, defecation pain, dyspareunia and pain on internal examination. All were rated on a five level rating scale (0=none to 4=severe) and the first two were also rated on a VAS. The objective symptoms were induration in the pouch of Douglas [rectouterine pouch] and having limited uterine motility. Secondary endpoints included the change in the VAS and change in quality of life. The study was adequately powered: 125 patients in each group was calculated to be sufficient to demonstrate a clinically relevant difference of 1.5 point in the mean changes of the pre- and post-treatment total scores of five subjective symptoms.

Of the 271 patients randomised, 253 were included in the efficacy analysis (dienogest n=128 and buserelin n=125). The changes in the symptom scores from baseline to endpoint were:

- **Subjective symptoms score:** from 5.7 ± 3.1 to 2.5 ± 2.3 in the dienogest group and from 5.9 ± 2.8 to 2.4 ± 2.4 in the buserelin group. Difference of mean change -0.39, 95% CI -1.11 to 0.32. In both groups the change was large enough to be clinically relevant.
- **Objective symptoms score:** from 3.8±2.1 to 1.9±1.9 in the dienogest group and from 3.7 ± 2.0 to 1.5 ± 1.3 in the buserelin group. Difference of mean change -0.35, 95% CI -0.75 to 0.05.
- **Combined scores, mean difference in the change:** -0.74 (95% CI -1.62 to 0.14).

Mean changes in VAS for lower abdominal pain were similar (dienogest, -30.2mm and buserelin, -27.3mm) as were the mean changes in VAS for lumbago (dienogest, -15.7mm and buserelin, -17.3mm). In the quality of life scale, the largest improvements were seen for bodily pain for both treatments, the scores of which were lower than the reference value for healthy Japanese women in the same age group at baseline but were similar to the reference value at the end of treatment. The percentage reduction in chocolate cyst volume was similar in each group (47% with dienogest and 46% with buserelin).

Two treatment-related adverse events occurred: peritonitis (dienogest) and bleeding ovarian cyst (buserelin). Most frequently seen adverse reactions in both groups were uterine bleeding (mainly spotting or breakthrough bleeding, dienogest 95% vs. buserelin 67%), hot flushes (50% vs. 67%) and headache 25% vs. 34%). Bone mineral density (BMD) changes at the end of treatment were significantly higher in the buserelin group (-2.6%) compared with the dienogest group (-1.0%, p=0.003). This may be because of the higher oestradiol serum level seen in the dienogest group compared with the buserelin group.

**Comparison with triptorelin**

Cosson et al compared the efficacy and safety of dienogest 1mg orally twice daily (n=59) with triptorelin 3.75mg intramuscularly (n=61) every 4 weeks, in an open label, randomised, parallel-group 16-week European study. No hormonal therapy was allowed in the 3 month prior to randomisation. The study aim was to see if dienogest and triptorelin, used as consolidation therapy, had the same effect in patients who had undergone operative laparoscopy. The efficacy was assessed by a clinical examination and control laparoscopy. No power calculation was carried out.

After sixteen weeks of therapy, there was no statistically significant difference in the endometrial tissue scores for the two groups at the post-treatment laparoscopy (score of 2 in both groups). No reappearance of tissue was seen in at least 25% of patients in each group. The change in endometrial tissue score (worsening, stability, improvement) was not statistically significantly different between the treatments (p=0.25). In total 86.2% of patients treated with dienogest and 80% of patients treated with triptorelin were satisfied with treatment. There were 86 women who were infertile before the study began: 15 patients in the dienogest group and 12 in the triptorelin group had spontaneous pregnancies in the 12 months following the end of treatment, p=0.71.
Spotting was more frequent with dienogest (61.6% vs. 25.4%) and hot flushes more frequent with triptorelin (61.2% vs. 9.6%). Five patients withdrew from the dienogest group because of diabetes, metrorrhagia (mid-cycle breakthrough bleeding), migraine, gastric pain and patient’s choice, and one withdrew from the triptorelin group because of hot flushes and headache.

Clinical evidence: long-term study

The safety and efficacy of 52 weeks of dienogest 2mg/day treatment in 135 Japanese women was investigated by Momoeda et al in a non-randomised study. The primary endpoint was the safety evaluation of adverse drug reactions. Five subjective findings (abdominal pain, lumbago, dyschezia (difficulty with defecation), dyspareunia, pain on examination) and two objective findings (induration involving the pouch of Douglas and limited uterine motility) were regularly assessed.

Of the 18 patients who discontinued treatment, 10 were due to adverse events, of which seven were adverse drug reactions (ADR). Serious adverse events occurred in three patients: ulcerative colitis, colonic polyps and splenic injury; but none were causally related to dienogest. One case of night sweats was assessed as a severe ADR.

The primary ADR was metrorrhagia (mid-cycle bleeding), occurring in 71.9% of patients (mild in 82 cases and moderate in 15, with three patients suffering with anaemia), headaches (10.4%, mainly mild) and constipation (18.5%, mainly mild though one patient withdrew due to moderate constipation). Metrorrhagia resolved in 96/97 cases. Genital bleeding occurred in 134 patients at least once during the treatment period; the median number of days per 28 day treatment period was a maximum of 21 days at 5-8 weeks, nine days at 21-24 weeks and two days at 49-52 weeks, indicating a decrease in the tendency to bleed as treatment continued. The proportion of patients with no bleeding at the same time intervals increased from 7.4% to 24.4% to 40.5%.

Eight patients had decreased bone mineral density classified as an ADR. Follow-up was available in seven cases; five were resolving and two had not decreased further. The overall reduction in BMD was -1.7% at 52 weeks (-1.6% at 24 weeks, no cumulative decrease in BMD seen up to week 52). There were no changes in the markers of bone metabolism. The annual rate of change for spinal BMD is -0.35% in pre-menopausal Japanese women; the decrease seen in the study may be regarded as mild and is less than that seen with GnRH agonists due to the higher serum oestradiol concentrations seen with dienogest treatment.

Marked or moderate global improvement was seen in 72.5% (95/131) of patients at 24 weeks and 90.6% (116/126) at 52 weeks. The proportion of patients with marked or moderate improvements in subjective symptoms during menstruation was 65.9% at the resumed menstruation after treatment had ended. Lower abdominal pain, lumbago and bodily pain improved and shrinkage of chocolate cysts by 25% was seen in 84.7% of affected cases by week 52.

Long term use of dienogest was well tolerated, causing mainly mild ADRs and improving symptoms markedly. Increasing the treatment period resulted in a higher proportion of marked or moderate improvements in subjective and objective symptoms. Consideration should be given to the fact that study was conducted in Japan and the results may not mirror those seen in a Western population.

Impact on the NHS

Due to the variation in symptoms, women will normally have been treated with a range of medications, most likely in a primary care setting, before specialist referral. It is anticipated that dienogest will be initiated by specialists in a hospital setting as an alternative to GnRH agonists. During 2008-9, according to Hospital Episode Statistics for England, there were 487 outpatient appointments for endometriosis, but this is likely to be an underestimate because patients may be classified under other diagnoses due to the various symptoms they present with. During the same period, there were 16,278 admissions for women with a primary diagnosis of endometriosis: 7,246 were as a day case and are expected to be for surgical interventions, such as laparoscopy. [Bayer]

The price of dienogest (Visabelle®) has not yet been confirmed but it is likely to be lower than the monthly cost of a GnRH agonist (drug cost plus cost of administration). GnRH agonists should be given for a maximum of 6 months, due to concerns about loss of bone mineral density, whilst dienogest can be used longer term.
### Table 2: Current treatments and basic NHS costs

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Side effects</th>
<th>Basic NHS cost¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>Mild to moderate endometriosis, 10mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle.</td>
<td>Include: menstrual disturbances, premenstrual-like syndrome (bloating, fluid retention, breast tenderness), weight change, nausea, headache, dizziness, insomnia, drowsiness, depression, change in libido; also skin reactions, hirsutism and alopecia. Jaundice and anaphylactoid reactions have also been reported</td>
<td>90x10mg = £22.16</td>
</tr>
<tr>
<td>Danazol</td>
<td>Endometriosis, 200–800mg daily in up to 4 divided doses, adjusted to achieve amenorrhoea, usually for 3–6 months</td>
<td>Nausea, dizziness, skin reactions including rashes, photosensitivity and exfoliative dermatitis, fever, backache, nervousness, mood changes, anxiety, changes in libido, vertigo, fatigue, epigastric and pleuritic pain, headache, weight gain; menstrual disturbances, vaginal dryness and irritation, flushing and reduction in breast size; musculo-skeletal spasm, joint pain and swelling, hair loss; androgenic effects including acne, oily skin, oedema, hirsutism, voice changes and rarely clitoral hypertrophy; temporary alteration in lipoproteins and other metabolic changes, insulin resistance; thrombotic events; leucopenia, thrombocytopenia, eosinophilia, reversible erythrocytosis or polycythemia reported; headache and visual disturbances may indicate benign intracranial hypertension; rarely cholestatic jaundice, pancreatitis, peliosis hepatitis and benign hepatic adenomata.</td>
<td>28x100mg= £18.40, 60x100mg = £17.04; 56x200mg = £66.20</td>
</tr>
<tr>
<td>GNRH agonists</td>
<td>These should not be given for more than 6 months due to concerns about bone mineral density loss, and the course should not be repeated.</td>
<td>Side-effects of the gonadorelin analogues related to inhibition of oestrogen production: menopausal-like symptoms (hot flushes, increased sweating, vaginal dryness, dyspareunia and loss of libido) and a decrease in trabecular bone density. Others include headache (rarely migraine) and hypersensitivity reactions (urticaria, pruritus, rash, asthma and anaphylaxis); local injection site reactions; palpitation, hypertension, ovarian cysts (may require withdrawal), changes in breast size, musculoskeletal pain or weakness, visual disturbances, paraesthesia, changes in scalp / body hair, oedema (face, extremities), weight changes, and mood changes</td>
<td></td>
</tr>
<tr>
<td>Triptorelin</td>
<td>3mg (IM) or 3.75mg (SC/IM) every 4 weeks starting during first 5 days of menstrual cycle</td>
<td>As above plus GI disturbances.</td>
<td>Decapeptyl SR 3mg = £69.00</td>
</tr>
<tr>
<td>Buserelin</td>
<td>Intranasally, 300mcg (one 150-microgram spray in each nostril) 3 times daily (starting on days 1 or 2 of menstruation</td>
<td>As above plus: initially withdrawal bleeding and subsequently breakthrough bleeding, leucorrhoea; GI disturbances; anxiety, memory and concentration disturbances, sleep disturbances, nervousness, dizziness, drowsiness; breast tenderness, lactation; abdominal pain; fatigue; increased thirst; changes in appetite; acne, dry skin, splitting nails, dry eyes; altered blood lipids, leucopenia, thrombocytopenia; hearing disturbances; reduced glucose tolerance. Spray formulations can cause irritation of the nasal mucosa including nose bleeds.</td>
<td>2 × 100-dose pack = £87.63</td>
</tr>
<tr>
<td>Goserelin</td>
<td>3.6mg by SC injection every 28 days</td>
<td>As above plus withdrawal bleeding</td>
<td>3.6mg (Zoladex) = £84.14</td>
</tr>
<tr>
<td>Leuprorelin</td>
<td>3.75mg by SC or IM injection in first 5 days of menstrual cycle then every month</td>
<td>As above.</td>
<td>3.75-mg (Prostap SR) = £75.24</td>
</tr>
<tr>
<td>Nafarelin</td>
<td>200mcg twice daily [one spray in one nostril AM and one spray in the other nostril PM (starting on days 2–4 of menstruation</td>
<td>As above. Spray formulations can cause irritation of the nasal mucosa including nose bleeds.</td>
<td>30-dose unit = £32.28; 60-dose unit = £55.66</td>
</tr>
</tbody>
</table>
This document reflects the views of the London New Drugs Group and may not reflect those of the reviewers. Bayer have commented on this review.

Reference List


Medline: dienogest.af and ENDOMETROSIS* Embase: DIENOGEST AND ENDOMETRIOSIS IDIS: "DIENOGEST 68320033" and Disease (s): "ENDOMETRIOSIS 617."
### Appendix 1: Endometriosis severity profile scoring system based upon the Biberoglu & Behrman Scale (1981)\(^\text{12}\)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Grading</th>
</tr>
</thead>
</table>
| **Dysmenorrhoea** | Absent  
Mild  
Moderate  
Severe  
Not applicable | (0) No discomfort  
(1) Some loss of work efficiency  
(2) In bed part of one day, occasional loss of work  
(3) In bed one or more days, incapacitation  
(4) amenorrhoea |
| **Dyspareunia**   | Absent  
Mild  
Moderate  
Severe  
Not applicable | (0) No difficulty or pain  
(1) Tolerated discomfort  
(2) Intercourse painful to point of interruption of intercourse  
(3) Avoids intercourse because of pain  
(4) Not sexually active, or prefers not to answer |
| **Pelvic pain**   | Absent  
Mild  
Moderate  
Severe | (0) No discomfort  
(1) Occasional pelvic discomfort  
(2) Noticeable discomfort for most of cycle  
(3) Requires strong analgesics, persistent during cycle other than during menstruation |
| **Pelvic tenderness** | Absent  
Mild  
Moderate  
Severe | (0) No tenderness  
(1) Minimal tenderness on palpitation  
(2) Extensive tenderness on palpitation  
(3) Unable to palpate because of tenderness |
| **Induration**    | Absent  
Mild  
Moderate  
Severe | (0) No induration  
(1) Uterus freely mobile, induration in the cul-de-sac  
(2) Thickened and indurated adnexa and cul-de-sac, restricted mobility  
(3) Nodular adnexa and cul-de-sac, uterus frequently frozen |