Providers: ***(Surrey & Sussex NHS Foundations Trust, Royal Surrey County NHS Foundation Trust, Epsom & St Helier University Hospital NHS Trust, Kingston Hospital NHS Foundation Trust, Ashford & St Peter NHS Foundation Trust)*** **Commissioners** ***(East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG)***

Evidence review for consideration

This template should be completed when applying to either:

- Add a treatment onto a provider formulary OR
- Request consideration by the Prescribing Clinical Network for use where the treatment could potentially impact on primary and secondary care

Please ensure that all fields are completed and use the guidance notes within the template to formulate your review.

Please be aware that this consolidated review template is to ensure that any evidence review can be discussed at provider and commissioner level. This will ensure that there are minimal delays in any potential implementation.

Please ensure that you follow your organisations individual standard operating procedure for ensuring this evidence review is discussed at local level

Intervention details	
Name, brand name	Dienogest (Zalkya)
Manufacturer	Stragen UK Ltd. Distributed by Kent Pharma
Proposed indication	Management of endometriosis and associated pain symptoms
Licensed status?	Please indicate: Licensed
Requested by	If request from secondary care. What should PCN consider? E.g. specific indication / place in therapy Ashford and St Peters NHS Trust- Initiation recommended by secondary care and continuation by primary care

SUMMARY

Clinical Effectiveness

Summarise results from trials, or evidence reviews, or if available include summary of evidence review from Trusted source where it exists.
How much improvement in quality and/or length of life is the intervention likely to produce? i.e. what are the improvements in patient orientated outcomes
How likely is it that the improvement will happen? Include ARR and number needed to treat (NNT) if possible
What is the strength of the evidence? Use NICE / SIGN levels of evidence grading criteria to describe level of evidence and SORT criteria to describe strength of evidence
SORT criteria – see http://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf
(Note GRADE criteria is preferred, but more complex than SORT)

Dienogest has been demonstrated to be effective at preventing recurrence of disease and or symptoms following surgery for endometriosis, and reducing endometriosis-associated pain[11-20]. A number of prospective, observational real-world studies of long term dienogest treatment in women with endometriosis have been conducted including VIPOS and ENVISIOeN[21, 22]. Findings from these large studies have demonstrated real world safety in the long term use of dienogest and improvement in health related quality of life scores. Pain improvement of up to 82.2% has been described[12].
The efficacy of dienogest in effectively treating the symptoms of pelvic pain related to endometriosis and also preventing the recurrence of endometriosis related symptoms after surgery has been confirmed in recent meta-analysis[23, 24].

Safety

Summarise safety issues.
What are the safety issues, how serious are they?
What is the risk of harm from the intervention? Include ARI and number needed to harm (NNH) if possible
Are there any other risk considerations?

Endogenous oestrogen levels are moderately suppressed during treatment with Zalkya. Currently, long-term

data on bone mineral density (BMD) and risk of fractures in users of Zalkya are not available. It has been shown to have a less adverse effect on bone health when compared to alternative current treatments such as GnRHa[24]. There is emerging data that long-term use of dienogest (>3 years) may be associated with significant reduction in bone mineral density and that this should be considered so that preventative treatment can be considered when used long term[25].

Safety in adolescents: The safety of Zalkya with respect to BMD was investigated in an uncontrolled clinical trial over 12 months in 111 adolescent women (12 to<18 years) with clinically suspected or confirmed endometriosis. The mean relative change in BMD of the lumbar spine (L2-L4) from baseline in the 103 patients with BMD measurement was -1.2 %. In a subset of the patients with decreased BMD a follow-up measurement was performed 6 months after end of treatment and showed an increase in BMD to -0.6% [1]

Patient impact

PRIMARY CARE	*Will it be easy for the people who need this intervention to actually use it? To what extent does this intervention reflect the wishes or preferences of the public, the people at whom it is aimed or other stakeholders? Are there any commissioning or service implications to enable the intervention to be given to patients?* Easy to take tablet. No need for HCP to administer as in Depot Provera, Mirena, Gonadorelin
SECONDARY CARE	The use of dienogest has been highlighted as one of the key recommendations by the All Party Parliamentary Group report into Endometriosis which was developed by Clinicians, Charities and patients which received over 10,000 responses and included testimony from 75 patients who gave an account of their symptoms and treatment[10]

Cost implications

PRIMARY CARE	Is there any cost-effectiveness data? What is the overall budgetary impact? How much does the intervention cost, what are the costs of comparative treatments? What is population cost per 100,000 population? Are there additional health costs related to use of the intervention? Are there any savings from using the intervention? Limit of follow-up visits related to endometriosis may provide a cost saving. Cheaper in short term (6 months) compared to GnRH agonist although can be used for longer. No need for HCP to administer No additional cost to cover “add back” therapy (as sometimes needed with GnRH agonist) Preventative treatment for reduction in BMD may be needed when used long term Cost for 7 new patients per year (at ASPH) = 7 x £297.84=£2084.88
SECONDARY CARE	

Relevant guidance / reviews

Summarise relevant recommendations or conclusions from NICE, MTRAC, SMC, AWMSG, LMEN
Differentiate between guidance from NICE accredited guideline producers and other sources of guidelines.
Are there any local guidelines that are relevant? Include relevant PCN policy statements

The use of dienogest has been highlighted as one of the key recommendations by the All Party Parliamentary Group report into Endometriosis which was developed by Clinicians, Charities and patients which received over 10,000 responses and included testimony from 75 patients who gave an account of their symptoms and treatment.[10]

Dienogest under the brand name Visanne is widely used in Europe, Australia and the US

Likely place in therapy relative to current treatments and suggested protocol for use (Primary & Secondary Care)

Describe likely place in therapy and which patient’s it should be used in.
Where does the intervention potentially fit in the context of national or local guidance
Is the intervention likely to be used more widely than intended?
Indicate potential prescribing status

If the intervention is for an unlicensed use is there a licensed equivalent and if so why is this not being considered for use?
Is the intervention likely to be suitable for shared care?
Include advantages and disadvantages?
Any capacity issues for the service if this intervention is added to formulary at provider level and has there been any dialogue with commissioners already?

It is considered that Dienogest would be used as an alternative treatment method for women with endometriosis associated pelvic pain where either routine analgesics or first line hormonal contraceptive methods have failed (such as POP, COCP, Mirena coil). In line with NICE guidance, patients with endometriosis symptoms would continue to be offered surgical treatment (Laparoscopy) if there is a poor response to analgesics and hormonal contraceptives. Dienogest would be used where there is need to continue suppression of endometriosis after surgical excision and where conventional progesterone treatments have been ineffective. Alternatively, it may also be used in women who have surgically proven endometriosis who have a recurrence of symptoms but where there is thought to be little benefit or unacceptable risk of further surgery. This decision would be made by clinicians experienced in Endometriosis who are working as part of a tertiary level BSGE (British Society of Gynaecological Endoscopy) approved Endometriosis centre.

It is anticipated that treatment would be initiated and under the supervision of the Endometriosis centre but continued in the community by primary care. Secondary care teams would review the need for long-term therapy based on an individualised risk assessment and based on patient's response.

No capacity issues are anticipated. It is hoped that Dienogest will prove to be a more effective therapy than what is currently available and this may have a beneficial effect on secondary care pelvic pain clinic capacity.

Recommendation to Prescribing Clinical Network/Drugs & Therapeutics Committee/ New Drugs & Interface Groups

Considered proposed formulary status at provider?
If this intervention is to be considered by PCN make a recommendations (or options) to PCN for them to consider using traffic light status
If BLACK status is recommended, what would that mean for patients already on this treatment, should treatment be stopped OR reviewed with a view to switching?

Amber * or Blue

Colour classification guidelines

What action is needed to implement?

Equality Impact Assessment

Consider impact of the recommendations being made on the 9 protected characteristics (Equality Act 2010)

Protected Characteristic	No impact? (mark X against each characteristic that applies)	Positive impact? (mark X against each characteristic that applies)	Adverse (negative) impact? (mark X against each characteristic that applies)	If adverse (negative) impact, how can this be mitigated? (please add comments below)
Age	x			
Disability	x			
Gender reassignment	x			
Marriage & civil partnership	x			
Pregnancy & maternity			**Not recommended/ appropriate**	
Race	x			
Religion & belief	x			
Sex	x			
Sexual orientation	x			

Impact to primary care

Consider availability/supply
Likelihood of requirement to prescribe/monitor in primary care
Change in prescribing / activity required as a consequence

Primary care to prescribe after initiation by secondary care, no need for HCP to administer, No issue with supply-available from usual wholesalers. May continue for a number of months,

Impact to secondary care

Consider availability/supply
Likelihood of need prescribing/monitoring in secondary care
Are local Trusts commissioned to provide this service?
Consider if non-drug related activity is required i.e. additional resource / clinic capacities.
Any saving on drug costs / non-drug activity anticipated
Can we be sure that the intervention will be delivered to the right people, at the right time, in the right place, by the right personnel? i.e. are there any service delivery or commissioning considerations

ASPH- CEMIG service (Centre for Endometriosis and Minimally Invasive Gynaecology) already in place

Impact to CCGs

Consider if non-drug related activity is required i.e. further commissioning needs
Any saving on drug costs / non-drug activity anticipated

Drug is cheaper for 6 month but can be given longer than this
There is a possibility that the use of dienogest will limit the need for potentially complex pelvic surgery or follow-up visits related to endometriosis and may therefore provide a cost saving.
No HCP need to administer

Intervention details

Name and brand name	Dienogest (Zalkya)
Licensed indication, formulation and usual dosage	Treatment of endometriosis. 2mg oral tablet 2mg daily
Summary of mechanism of action, and relevant pharmacokinetics	Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect in vivo. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity in vivo Dienogest acts on endometriosis by reducing the endogenous production of oestradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions Absorption: Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47ng/ml are reached at about 1.5 hours after single ingestion. Bioavailability is about 91%. Distribution: Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10 % of the total serum drug concentration is present as free steroid, 90 % is non-specifically bound to albumin. Biotransformation: Dienogest is completely metabolized by the known pathways of steroid metabolism mainly by the enzyme CYP3A4, with the formation of endocrinologically mostly inactive metabolites, which are excreted very quickly so that in plasma unchanged dienogest is the dominating fraction. Elimination: Dienogest serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 9-10 hours. Dienogest is excreted in form of metabolites which are excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary metabolites excretion is 14 hours. Following oral administration approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 h, mostly with the urine [1]
Therapeutic risk	There is a significant risk of patient harm if the intervention is not used as

	intended.
Important drug interactions	Due to metabolism by cytochrome CYP3A4 enzyme, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism. This could lead to reduce therapeutic effect (inducers) or increased exposure leading to undesirable effects (inhibitors) Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction), e.g.: phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort When co-administered with sex hormones, many combinations of HIV protease inhibitors and non- nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of the progestin. The net effect of these changes may be clinically relevant in some cases Substances decreasing the clearance of sex hormones (enzyme inhibitors). The clinical relevance of potential interactions with enzyme inhibitors remains unknown [1]
Side effects	**Common (>1/100 to <1/10)** Weight increase, depressed mood, sleep disorder, nervousness, loss of libido, altered mood, headache, migraine, nausea, abdominal pain, flatulence, abdominal distension, vomiting, acne, alopecia, back pain, breast discomfort, ovarian cyst, hot flushes, uterine / vaginal bleeding including spotting, asthenic conditions, irritability. **Uncommon (≥1/1000 to <1/100)** anaemia, weight decrease, increased appetite, anxiety, depression, mood swings, autonomic nervous system imbalance, disturbance in attention, dry eye, tinnitus, unspecific circulatory system disorder, palpitations, hypotension, dyspnoea, diarrhoea, constipation, abdominal discomfort, gastrointestinal inflammation, gingivitis, dry skin, hyperhidrosis, pruritus, hirsutism onychoclasis, dandruff, dermatitis, abnormal hair growth, photosensitivity reaction pigmentation disorder, bone pain, muscle spasms, pain in extremity, heaviness in extremities, urinary tract infection, vaginal candidiasis, vulvovaginal dryness, genital discharge, pelvic pain, atrophic vulvovaginitis, breast mass, fibrocystic breast disease, breast induration, oedema[1]

Precautions	Any hormonal contraception needs to be stopped prior to initiation of Zalkya. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method). As Zalkya is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of progestogen-only preparations are also valid for the use of Zalkya although not all of the warnings and precautions are based on respective findings in the clinical studies with Zalkya. If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before treatment with Zalkya can be started or continued. • Serious uterine bleeding: Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of Zalkya. If bleeding is heavy and continuous over time, this may lead to anemia (severe in some cases). In the event of anemia, discontinuation of Zalkya should be considered • Changes in bleeding pattern: The majority of patients treated with Zalkya experience changes in their menstrual bleeding pattern • Circulatory disorders: From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. Rather, the risk of cardiovascular and cerebral events is related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations. Although not statistically significant, some studies indicate that there may be a slightly increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilization, major surgery or major trauma. In case of long-term immobilization it is advisable to discontinue the use of Zalkya (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilization. The increased risk of thromboembolism in the puerperium must be considered. Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof. • Tumours: A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR =1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined OC (COC) use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in users of progestogen-only preparations is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in users of OCs tend to be less advanced clinically than the cancers diagnosed in those who have never used OCs. In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Zalkya. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Zalkya. • Osteoporosis: Changes in bone mineral density (BMD) The use of Zalkya in adolescents (12 to <18 years) over a treatment period of 12 months was

	associated with a decrease in bone mineral density (BMD) in the lumbar spine (L2-L4). The mean relative change in BMD from baseline to the end of treatment (EOT) was - 1.2% with a range between -6% and 5% (IC 95%: -1.70% and -0.78%, n=103. Repeated measurement at 6 months after the EOT in a subgroup with decreased BMD values showed a trend towards recovery. (Mean relative change from baseline: –2.3% at EOT and 0.6% at 6 months after EOT with a range between -9% and 6% (IC 95%: -1.20% and 0.06% (n=60) Loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life. In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Zalkya because endogenous estrogen levels are moderately decreased during treatment with Zalkya . Adequate intake of calcium and Vitamin D, whether from the diet or from supplements, is important for bone health in women of all ages. • Other conditions Patients who have a history of depression should be carefully observed and the drug should be discontinued if the depression recurs to a serious degree. Dienogest generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of Zalkya, it is advisable to withdraw Zalkya and treat the hypertension. Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of Zalkya. Dienogest may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking Zalkya. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Zalkya. Pregnancies that occur among users of progestogen-only preparations used for contraception are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. Therefore, in women with a history of extrauterine pregnancy or an impairment of tube function, the use of Zalkya should be decided on only after carefully weighing the benefits against the risks. Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of Zalkya. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain [1]

Contraindications	Zalkya should not be used in the presence of any of the conditions listed below, which are partially derived from information on other progestogen-only preparations. Should any of the conditions appear during the use of Zalkya, treatment must be discontinued immediately. active venous thromboembolic disorder • arterial and cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease) • diabetes mellitus with vascular involvement • presence or history of severe hepatic disease as long as liver function values have not returned to normal • presence or history of liver tumours (benign or malignant) • known or suspected sex hormone-dependent malignancies • undiagnosed vaginal bleeding • hypersensitivity to the active substance or to any of the excipients [1]
Pregnancy & Lactation	Zalkya must not be administered to pregnant women because there is no need to treat endometriosis during pregnancy Treatment with Zalkya during lactation is not recommended. It is unknown whether dienogest is excreted in human milk. Data in animals have shown excretion of dienogest in rat milk. A decision must be made whether to discontinue breast-feeding or to abstain from Zalkya therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman [1]
Monitoring requirements	Include any relevant information on monitoring requirements either for efficacy or toxicity
Prescribing considerations	• Likely traffic light status (see attached guidelines) **Amber* or Blue** Colour classification guidelines
Other considerations	*How does this treatment link to documents already on the prescribing advisory database? Will there need to be other documents reviewed and if so how do they need to be updated? Consider timescales (within 3 months, 6 months etc.?)Does the intervention need to be available in the out of hours period?* No need for intervention out of hours Taken with or without food. Take continuously without regard to vaginal bleeding. No interruption between packs. Start on any day of menstrual cycle. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).

Potential patient group (if appropriate to include)	
Brief description of disease	*Include disease severity, morbidity and mortality, prognosis* Endometriosis is a chronic condition of unknown cause that affects up to 10% of women between the ages of puberty and menopause that causes symptoms of pelvic pain, painful periods, painful intercourse and sub fertility that may be debilitating. A recent All Party Parliamentary Group enquiry (APPG) has shown that 95% of women with endometriosis report that the disease has negatively impacted on their well being and have called for the use of Dienogest to be supported by the NHS [10]

	Current treatment methods include simple analgesics, neuropathic analgesics, hormonal treatments and surgery. No curative treatment has been identified. It is recognised that treatment needs to be long term and focused on symptom relief. There is sufficient evidence that progestogens are effective in producing analgesic effects for women with endometriosis. Dienogest is a 4th generation progestin that has been approved for use within the European Union since 2009. It has been accepted by the MHRA for use in the United Kingdom in 2019 and has been approved for use under the name Zalkya since 2020. Dienogest is a nortesterone derivative that has an antiandrogenic effect. It binds to endometriotic lesions and reduces endogenous production of oestradiol thereby reducing the trophic effects of oestradiol on the endometriotic lesions. When used continuously, it leads to a hypoestrogenic environment resulting in atrophy of endometriotic tissue. In clinical studies it has been shown to have a significant improvement in physical, mental, social, emotional, and general health parameters. It has been shown to be beneficial in women who have undergone surgical treatment for either Deep Endometriosis or Ovarian Endometriomas by reducing the risks of recurrence and minimising symptom recurrence. There may also be some additional benefit for women with Ovarian Endometriomas who choose not to have a surgical treatment, by reducing the size of the endometriomas.
Potential patient numbers per 100,000	*Describe number of patients affected and potential number of patients likely to receive the treatment* CEMIG at ASPH is one of the largest Endometriosis centres in the UK and performs upwards of 300 surgeries each year related to Endometriosis. Of these, between 30-70 will be for highly complex endometriosis surgery as defined by the BSGE. It is anticipated that initially, Dienogest would be considered for use in <10% of the patient group and only in those who do not respond to currently available medication and therapy. Initiation would be by an Endometriosis Consultant.
Patient outcomes required	Describe desired treatment benefits, and what outcomes/benefits, and size of effect are considered clinically significant Reduction in pain associated with endometriosis

Summary of current treatment pathway

Include treatment options, relevant national or local guidance, and place in care pathway

Endometriosis is sensitive to your natural fertility hormones:
- It grows in response to the hormone oestrogen.
- The hormone progesterone prevents it from growing.

Treatments for endometriosis works by changing the balance of hormones in your body:
- **Hormone treatments:** these suppress your natural fertility hormones, replacing them with a small amount of man-made hormones and preventing the growth of endometriosis. I.e. Combined contraceptive. Progesterone contraceptive, Depot Provera, progesterone implant, Mirena IUS
- **Hormone blocking treatments:** stopping the production of oestrogen and preventing the growth of endometriosis i.e. GnRH (Gonadorelin/Leuprorelin)
- **Surgery**

Evidence review

If there is an up to date summary of the evidence from a Trusted source e.g. NICE evidence summary new medicines (ESNM), MTRAC, SMC, AWMSG, London Medicines Evaluation Network attach the summary, it is unnecessary to do an evidence review
If an up to date summary of the evidence is not available – summarise the clinical evidence supporting the application for both efficacy and safety.
Outline and summarise the clinical literature reviewed. Include a brief explanation of the trials included and the rationale for focusing on specific studies (for example, active comparator RCTs only may be considered, or a recent meta-analysis). For included studies summarise key characteristics; for RCTs, for example:

- *The trial design including the population*
- *The number of subjects and the allocation process*
- *The primary efficacy endpoint*
- *The key results and their statistical / clinical significance*

Follow this with a summary of the strengths and limitations of the efficacy data, and key safety data identified in the studies.
Further tips are included in the SOP for writing evidence reviews

Superiority of Zalkya over placebo was demonstrated in a 3-months study including 198 patients with endometriosis. Endometriosis-associated pelvic pain was measured on a Visual Analog Scale (0-100 mm). After 3 months of treatment with Zalkya a statistically significant difference compared to placebo (Δ = 12.3 mm; 95%CI: 6.4 – 18.1; p<0.0001) The open-label extension to this placebo-controlled study suggested a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months
Three studies including a total of 252 patients who received a daily dose of 2 mg dienogest demonstrated a substantial reduction of endometriotic lesions after 6 months of treatment compared to a GnRH agonist[1]

Strowitzki reported that Dienogest 2 mg/day orally demonstrated equivalent efficacy to depot Leuprorelin at standard dose in relieving the pain associated with endometriosis, although offering advantages in safety and tolerability[2]

McCormack reviewed the use of dienogest and concluded that in randomized clinical trials, oral dienogest was significantly more effective than placebo in reducing pelvic pain in patients with confirmed endometriosis and was non-inferior to leuprorelin [3]

Momoeda investigated the safety and efficacy of 52weeks treatment and concluded the long-term effect of dienogest on bone mineral density was slight, whereas the efficacy increased cumulatively. [4]

Quality of life assessments in the dienogest studies indicated that improvements in both physical and mental indices were attained within 12-week and 24-week treatment durations, and that these benefits were sustained in studies of up to one year [8]

Dienogest 2mg maybe offer a long-term choice as it doesn't have the same effect on BMD as a GnRH [8]

Muzii et al showed 2mg Dienogest significantly reduced endometrioma diameter and associated pain but preserved the ovarian reserve [6]

Ouchi reviewed 167 patients following laproscopic surgery. Patients received gonadotrophin-releasing hormone agonist, oral contraceptive pills (OCP), dienogest or no medication. There was no recurrence 5 years after surgery in medicated group where as no medication resulted in up to 50% recurrence rate [6]

Long term studies showed dienogest was effective against symptoms of endometriosis-associated pelvic pain (EAPP) include dysmenorrhoea (menstrual cramps), deep dyspareunia (pain during sexual intercourse), non-cyclic pelvic pain, cyclic bowel pain, and cyclic urinary pain) [2,9]

Römer found that long-term (60-month) treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced EAPP and avoided pain recurrence post-surgery [17]

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs	Include decisions from neighbouring APCs or DTCs if known St Helier's NHS Trust SWL joint formulary application
Recommendations from national / regional decision making groups	Include conclusions or recommendations from NICE, SMC, AWMSG, MTRAC etc Not included
Stakeholder views	*Use the enclosed proforma to obtain views from clinicians* *Summarise who has been consulted e.g. secondary care consultants, what their views are and any declared conflict of interest* *Have views of patient groups been sought?*
CCG priorities	*Does this treatment fit with existing national, regional or local priorities, policies or activity?*

Health economic considerations	
Cost per year per patient	Include annual cost per patient, and population cost per 100,000 people £24.82 (incl. VAT at 20% for 1 month) £297.84 per patient per year How many patients? Anticipate 7 patients per year
Alternative treatments cost per patient per year	Include comparable costs of alternative treatments at patient and per 100,000 population if relevant GnRH agonist (Gonadorelin Zoladex implant 3.6 mg every 28 days maximum duration of treatment 6 months (do not repeat) £84 x 6= £504 incl. VAT at 20%
Other financial considerations (if relevant)	Include additional costs such as monitoring costs, and any potential off-set costs No HCP cost to administer No additional cost to cover "add back" therapy (as sometimes needed with GnRH agonist)
Health economic data (if available)	*Include information from relevant health economic analysis, indicate the level of robustness of the analysis*

References

Include references written in Vancouver style

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VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1		*M.Errity/D.Hopper*		*Out for consultation*
v.2				

Comments on Evidence review

Intervention and proposed indication	
Comments by	Name, designation and organisation
Comments on evidence review	
Additional evidence and references for consideration	Include any additional evidence and references you would like to submit for inclusion in the evidence review
Specific clinical questions	Specific questions arising from review
Other colleagues who should be contacted	Include name, designation and contact details of any other colleagues who should be consulted about this evidence