

Memo (for local adaptation) - shortage of supply

To:
From:
Date:

Re: Evorel hormone replacement therapy (HRT) patch range

Description of products affected

Evorel is an oestrogen-only HRT patch (25, 50, 75 and 100 micrograms estradiol released over 24 hours) applied to the skin twice weekly. For women with an intact uterus, progestogen should normally be added to Evorel for the prevention of adverse endometrial effects and should be added for at least 12-14 days every month/28 day cycle. The regimen may be either cyclic or continuous sequential.¹

Evorel Conti is a continuous combined HRT preparation that contains 3.2 mg of estradiol hemihydrate corresponding to a nominal release of 50 micrograms of estradiol per 24 hours and 11.2 mg of norethisterone acetate corresponding to a nominal release of 170 micrograms per 24 hour. Patches are applied to the skin twice weekly.²

Evorel Sequi is a transdermal therapy comprising 4 Evorel 50 patches, and 4 Evorel Conti patches. Evorel Sequi is a continuous sequential HRT preparation. Patches are applied to the skin twice weekly. A treatment cycle is 28 days. During the first 14 days, one estradiol-only (Evorel 50) patch should be worn at all times, without interruption. During days 15-28, one estradiol + norethisterone (Evorel Conti) patch should be worn at all times, without interruption.³

Background

Evorel Conti and Evorel Sequi patches are due to go out of stock from mid-September. The estradiol only patches (Evorel 25, 50, 75 and 100) are due to go out of stock from the beginning of October. Janssen is unable to provide resupply dates at present. Product availability has been impacted by increased demand in some countries including the UK, combined with issues in bulk supply, resulting in an accelerated depletion of current stock. This is due in part to the lack of availability of alternative HRT products not produced by Janssen, and subsequently challenges in adjusting and maintaining supply to meet this increase in demand.⁴

Alternative agents and management options

NICE HRT guidance recommends transdermal rather than oral HRT for menopausal women who are at increased risk of venous thromboembolism (VTE), including those with a BMI over 30 kg/m². It also notes that taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke though the baseline population risk of stroke in women aged under 60 years is very low.⁵

Unopposed oestrogen

For women on unopposed oestrogen (if uterus is intact an adjunctive progestogen must be used) in the form of a patch, there are several other transdermal products available, as well gel formulations. Oral oestrogen is also an option for those women considered suitable for oral therapy:⁶

TABLE OF CURRENTLY AVAILABLE OESTROGEN PREPARATION

Patches (estradiol)	Gels (estradiol)	Tablets (estradiol)	Tablets (conjugated oestrogens)
Elleste Solo MX (40mcg, 80mcg) Estraderm MX (25mcg, 50mcg, 75mcg, 100mcg) Estradot (25mcg, 37.5mcg, 50mcg, 75mcg, 100mcg) Progynova TS (50mcg, 100mcg) Femseven Mono (50mcg, 75mcg, 100mcg)	Oestrogel (0.06%) Sandrena (500mcg, 1mg)	Bedol (2mg)✘ Elleste Solo (1mg, 2mg) Progynova (1mg, 2mg) Zumenon (1mg, 2mg)	Premarin (300mcg, 625mcg, 1.25mg)

✘ currently out of stock

Combination HRT transdermal patches

For women using **Evorel Conti and Sequi patches**, the only other combination transdermal patches on the market are **FemSeven Conti and Sequi** containing estradiol and a different progestogen, levonorgestrel.⁷ However these products are also out of stock as the FemSeven product range was divested by Teva to Theramex in mid-2018. Theramex have confirmed that whilst new manufacturing arrangements are being established, FemSeven Conti and Sequi will be out of stock until second quarter of 2020. This supply issue does not affect supplies of FemSeven Mono.⁷

Other brands of estradiol patches are available but there are no progestogen patches. Therefore, one of alternative treatment options is to switching to a combined oral HRT product for those women who are suitable for oral oestrogen therapy.

Continuous combined oral therapy

The following products are alternatives to **Evorel Conti** in women *for whom oral therapy is suitable* include:⁶

- Elleste Duet Conti (estradiol 2mg, norethisterone 1mg)
- Femoston Conti (estradiol [500mcg, 1mg], dydrogesterone [2.5mg, 5mg])
- Indivina (estradiol [1mg, 2mg], medroxyprogesterone [2.5mg, 5mg])
- Kliofem (estradiol 2mg, norethisterone 1mg)
- Kliovance (estradiol 1mg, norethisterone 500mcg)
- Premique (low dose conjugated oestrogen 300mcg, medroxyprogesterone 1.5mg)

Sequential combined oral therapy

The following products are alternatives to **Evorel Sequi** in women *for whom oral therapy is suitable* include:⁶

- Elleste Duet (estradiol [1mg, 2mg], norethisterone 1mg)
- Femoston (estradiol [1mg, 2mg], dydrogesterone 10mg)
- Novofem (estradiol 1mg, norethisterone 1mg)
- Tridestra (estradiol 2mg, medroxyprogesterone 20mg)
- Trisequens (estradiol [2mg, 2mg, 1mg], norethisterone 1mg)

Two other products, Clinorette (estradiol [2mg, 2mg], norethisterone 1mg) and Cyclo-progynova (estradiol 2mg, norgestrel 500mcg) are currently out of stock.

Women who require transdermal oestrogen as part of combination HRT

Although transdermal oestrogen products are available, there are no transdermal progestogen products. The only way to provide the progestogen component of combined HRT is to use an estradiol patch or gel product with an oral progestogen licensed for adjunctive use as HRT, and administered as a sequential combined or continuous combined regimen. Currently there are two licensed oral progestogen products but only Utrogestan capsules (micronised progesterone 100mg) are available⁸; Climanor tablets (medroxyprogesterone 5mg) has been out of stock long term.⁹ Another other option is the Mirena IUS (levonorgestrel 20mcg/24hrs) which is licenced for protection from endometrial hyperplasia during oestrogen replacement therapy¹⁰, but it would not suit all women and needs to be fitted, with likely delay depending on length of waiting list.

Advice on switching

There is a wide range of alternative treatment options, subject to availability. The British Menopause Society advises that prescribers consider equivalent preparations that provide a similar dose to what their patient is using. If an exact match is not possible, prescribers can seek guidance available on the practical prescribing chart on its website and Menopause Matters website, to clarify equivalent doses.¹¹

For some more complex cases, advice may need to be sought from specialists. If there is insufficient transdermal estradiol products to meet demand then prioritising their use for women at increased risk of VTE may have to be considered.

References

1. Janssen-Cilag Ltd. Evorel 50 Patches. SPC, date of revision of the text, 26 June 2017: <https://www.medicines.org.uk/emc/product/7635/smpc>
2. Janssen-Cilag Ltd. Evorel Conti. SPC, date of revision of the text, 14 June 2016: <https://www.medicines.org.uk/emc/product/5591/smpc>
3. Janssen-Cilag Ltd. Evorel Sequi. SPC, date of revision of text, 15 June 2016: <https://www.medicines.org.uk/emc/product/5590/smpc>
4. Janssen-Cilag Ltd. Notification of interruption of supply of Evorel range of transdermal patch, 15th August 2019
5. NICE. Menopause: diagnosis and management; Guideline [NG23], November 2015: <https://www.nice.org.uk/guidance/ng23/chapter/Recommendations#long-term-benefits-and-risks-of-hormone-replacement-therapy>
6. MIMS: Hormone Replacement Therapy (HRT) Table, accessed online, 05 August, 2019: <https://www.mims.co.uk/table-hormone-replacement-therapy-hrt/womens-health/article/1415738> (access for subscribers only)
7. FemSeven SPCs (Theramex Ireland Limited) accessed via MHRA 21 Aug 2019: <http://www.mhra.gov.uk/spc-pil/index.htm?subsName=ESTRADIOL%20HEMIHYDRATE&pageID=SecondLevel>
8. Besins Healthcare (UK) Ltd. Utrogestan 100mg Capsules. SPC, date of revision of the text, 4 April 2019: <https://www.medicines.org.uk/emc/product/352/smpc>
9. Resource Medical Limited. Climanor SPC, date of revision of the text, 06 April 2009: <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1362976047465.pdf>
10. Bayer plc. Mirena. SPC, date of revision of the text, 15 February 2019: <https://www.medicines.org.uk/emc/product/1132>
11. British Menopause Society. Update on HRT supply shortages, 9 August 2019: <https://thebms.org.uk/2019/08/british-menopause-society-update-on-hrt-supply-shortages/>

Acknowledgements

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