

Supply Issues – Hormone Replacement Therapy (HRT)

Including the Elleste, Evorel, FemSeven and Indivina HRT Product Ranges

Updated: 24th December 2019

Description of products affected

Elleste HRT Range

- Mylan, the sole supplier have been experiencing ongoing manufacturing issues at their contract manufacturing site since the beginning of 2019.
- Mylan have now advised that the Elleste range will be unavailable from the middle of December 2019 until mid-2020.

Evorel HRT Range

- **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 hours. 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
- On the 24th of October Janssen-Cilag divested the Evorel HRT transdermal patch range (Evorel; Evorel Conti; Evorel Sequi) to Theramex UK Ltd.
 - All preparations are now out of stock.
 - Currently, Theramex have advised a resupply date of February 2020.

FemSeven HRT Range⁷

- **FemSeven Conti** is a continuous combined HRT preparation in which each patch contains 1.5 mg of estradiol hemihydrate and 0.525 mg levonorgestrel in a patch size of 15 cm², releasing 50 micrograms of estradiol and 7 micrograms of levonorgestrel per 24 hours. Patches are applied to the skin once weekly.
- **FemSeven Sequi** is a transdermal therapy comprising of 2 phases and is a continuous sequential HRT preparation. Each phase 1 patch (1st and 2nd week of the patient's cycle) contains 1.5 mg of estradiol hemihydrate, in a patch size of 15 cm², releasing 50 micrograms of estradiol per 24 hours. Each phase 2 patch (3rd and 4th week of patient's cycle) contain 1.5 mg of estradiol hemihydrate and 1.5mg levonorgestrel, in a patch size of 15 cm², releasing 50 micrograms of estradiol and 10 micrograms of levonorgestrel per 24 hours. Patches are applied to the skin once weekly. A treatment cycle is 28 days.
- These products are currently 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 the second quarter of 2020.

Indivina HRT Range

- Orion, the sole manufacturer of the Indivina range HRT tablets are out of stock of both strengths until January 2020 due to manufacturing issues.
- Unlicensed imports are available; lead times vary.

Background

- The Department of Health and Social Care (DHSC) are aware of the ongoing manufacturing issues that have affected the supply of some hormone replacement therapy (HRT) products throughout 2019.
- Please see appendix 1, which provides the latest update on the availability of all HRT products marketed in the UK and the known resupply date for products that are currently experiencing supply issues.
- This table also provides an update of all HRT preparations that remain available. Clinicians may be required to switch patients to alternative HRT products that contain the same active ingredients for a temporary period.
- **netFormulary, our online formulary platform, is updated regularly to reflect the current stock situation of formulary choices of HRT.**
- The DHSC will continue to provide updates on HRT availability in the monthly supply report, which is uploaded to the Specialist Pharmacist Services website. All registered user can access this update via this following link: <https://www.sps.nhs.uk/articles/department-of-health-and-pharmaceutical-market-strategy-group-pmsg-supply-updates/>

MHRA Drug Safety Update August 2019

[Hormone replacement therapy \(HRT\): further information on the known increased risk of breast cancer with HRT and its persistence after stopping](#)

New data have confirmed that the risk of breast cancer is increased during use of all types of HRT, except vaginal estrogens, and have also shown that an excess risk of breast cancer persists for longer after stopping HRT than previously thought. Prescribers of HRT should discuss the updated total risk with women using HRT at their next routine appointment.

Advice for healthcare professionals:

- A new meta-analysis of more than 100,000 women with breast cancer has shown that some excess risk of breast cancer with systemic HRT persists for more than 10 years after stopping; the total increased risk of breast cancer associated with HRT is therefore higher than previous estimates (see link above).
- Prescribers of HRT should inform women who use or are considering starting HRT of the new information about breast cancer risk at their next routine appointment (see [resources](#) provided).
- Only prescribe HRT to relieve post-menopausal symptoms that are adversely affecting quality of life and regularly review patients using HRT to ensure it is used for the shortest time and at the lowest dose.
- Remind current and past HRT users to be vigilant for signs of breast cancer and encourage them to attend for breast screening when invited

Alternative agents and management options

- In line with the MHRA Drug Safety Update above, it is important to regularly review patients using HRT for continued need to ensure it is used for the shortest time and at the lowest dose. For more information please see [NICE Guidance NG23 - Long-term benefits and risks of hormone replacement therapy](#).
- Prescribing information regarding HRT equivalence to support local decision making is available through various sources such as the British National Formulary, Summary of Product Characteristics (SPC), The Monthly Index of Medical Specialities (MIMS), and other sources including local Medicines Information Centres.
- The British Menopause Society has produced an 'HRT preparations and equivalent alternatives' document to support whilst there are supply difficulties. Available at: <https://thebms.org.uk/wp-content/uploads/2019/11/HRT-alternatives-04.11.2019.pdf>
- Clinicians are advised to work closely with community pharmacies to understand local availability of HRT products and use the table below and netFormulary, our online formulary platform, to help make the decision about appropriate HRT products for patients who are affected by the supply issues.
- 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 other transdermal products available, as well as gel formulations. Oral oestrogen is also an option for those women considered suitable for oral therapy:⁶

Table 1 – Currently available formulary choice of oestrogen preparations in Cambridgeshire and Peterborough suitable for prescribing in Primary Care

<u>Patches (estradiol)</u>	<u>Gels (estradiol)</u>	<u>Tablets (estradiol)</u>	<u>Tablets (conjugated oestrogens)</u>
<ul style="list-style-type: none">• Estradot (25mcg, 37.5mcg, 50mcg, 75mcg, 100mcg)	<ul style="list-style-type: none">• Sandrena (1mg)	<ul style="list-style-type: none">• Elleste Solo (1mg, 2mg)• Progynova (1mg, 2mg)	<ul style="list-style-type: none">• Premarin (300mcg, 625mcg, 1.25mg)

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 mid-2020.⁷

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

Continuous combined oral therapy

Indivina (estradiol [1mg, 2mg], medroxyprogesterone [2.5mg, 5mg]) is currently NON-FORMULARY in Cambridgeshire and Peterborough as it has not yet been considered by the Cambridgeshire and Peterborough Joint Prescribing Group.

The following products are formulary choices in Cambridgeshire and Peterborough and are also alternatives to **Evorel Conti** in women *for whom oral therapy is suitable*:⁶

- Femoston Conti (estradiol [500mcg, 1mg], dydrogesterone [2.5mg, 5mg])
- Kliofem (estradiol 2mg, norethisterone 1mg)
- Kliovance (estradiol 1mg, norethisterone 500mcg)

Sequential combined oral therapy

The following products are formulary choices in Cambridgeshire and Peterborough and alternatives to **Evorel Sequi** in women *for whom oral therapy is suitable*:⁶

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

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 Utrogestran capsules (micronised progesterone 100mg) are available⁸ (please note these are NON-FORMULARY however these could be considered for prescribing in primary care where no other clinically suitable option is available); Climanor tablets (medroxyprogesterone 5mg) has been out of stock long term.⁹ Another 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

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Appendix 1. HRT Availability (Updated 23/12/2019)

		Oestrogen Only			
Ingredient (s)	Manufacturer	Brand	Strength	Current Availability	Anticipated resupply date
		Oral preparations			
Estradiol hemihydrate	Mylan	Elleste Solo*	1mg	In stock until late December	Mid-2020
			2mg	In stock until late January	
	Mylan	Zumenon*	1mg	In stock	
			2mg	In stock	
Estradiol valerate	Bayer	Progynova	1mg	In stock	
			2mg	In stock	
Conjugated oestrogens	Pfizer	Premarin	300mcg	In stock	
			625mcg	In stock	
			1.25mg	In stock	
Transdermal patches					
Estradiol	Janssen-Cilag	Evorel **	25 mcg	OOS	February 2020. Unlicensed imports available, lead times vary.
			50mcg	OOS	
			75mcg	OOS	
			100mcg	OOS	
Estradiol hemihydrate	Novartis	Estradot	25 mcg	In stock	
			37.5mcg	In stock	
			50mcg	In stock	
			75mcg	In stock	
			100mcg	In stock	
Topical (Transdermal gels/creams/other delivery systems)					
Estradiol	Besins Healthcare (UK) Ltd	Oestrogel	0.06%	In stock	
Estradiol hemihydrate	Orion	Sandrena	0.5mg	OOS	Mid-January 2020
			1mg (28)	In stock	
			1mg (91)	In stock	End of October 2019
	Pfizer	Estring vaginal delivery system	7.5mcg/24hours	In stock	
	Novo Nordisk	Vagifem vaginal tablets	10mcg	In stock	
	Marlborough Pharma	Estriol cream (generic)	0.01%	In stock	
Aspen	Ovestin cream	1mg	In stock		
Progestogen only					
Levonorgestrel	Bayer	Mirena Intrauterine device	20mcg/24hrs	In stock	

Progesterone	Besins Healthcare UK Ltd	Utrogestan	100mg	In stock	
		Utrogestan	200mg	In stock	
Combined HRTs (Progestogen and oestrogen)					
Continuous combined therapy					
Oral preparations					
Estradiol hemihydrate / norethisterone acetate	Novo Nordisk	Kliofem	2mg/ 1mg	In stock	
		Kliovance	1mg/ 500mcg	In stock	
Estradiol hemihydrate / dydrogesterone	Mylan	Femoston Conti	500mcg/ 2.5mg	In stock	
			1mg/ 5mg	In stock	
Estradiol valerate/medroxyprogesterone	Orion	Indivina	1mg/2.5mg	OOS	January 2020. Unlicensed imports available; lead times vary.
			2mg/5mg	OOS	
			1mg/5mg	OOS	
Transdermal patch					
Estradiol hemihydrate/ norethisterone acetate	Janssen-Cilag	Evorel Conti**	3.2mg/11.2mg	OOS	February 2020. Unlicensed imports available; lead times vary.
Estradiol hemihydrate/ levonorgestrel	Theramex	FemSeven Conti	1.5mg/ 0.525mg	Long term OOS	Mid 2020
Sequential combined therapy					
Oral preparations					
Estradiol hemihydrate / norethisterone acetate	Mylan	Elleste Duet *	1mg/ 1mg	In stock until end of December.	Mid 2020
			2mg/ 1mg	In stock until end of December.	
Estradiol hemihydrate/ dydrogesterone		Femoston	1mg/ 10mg	In stock	
			2mg/10mg	In stock	
Estradiol hemihydrate [X,X,X]/ norethisterone acetate	Orion	Tridestra	2mg/20mg	In stock	
Transdermal patch					
a) Estradiol hemihydrate and b) estradiol hemihydrate/ norethisterone acetate	Theramex	Evorel Sequi**	a)3.2mg b) 3.2 mg /11.2 mg	OOS	February 2020. Unlicensed imports available, lead times vary
a) 1.5mg of estradiol hemihydrate b) Estradiol hemihydrate /levonorgestrel	Theramex	FemSeven Sequi	a) 1.5mg b) 1.5mg /1.5mg	Long term OOS	Mid 2020
Gonadomimetic (s)					
Tibolone 2.5mg	Advanz Pharma	Livial tablets	Tibolone 2.5mg	In stock	