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HEALTH TECHNOLOGY BRIEFING OCTOBER 2021

Estetrol for treating vasomotor symptoms

NIHRIO ID	6341	**NICE ID**	10583
Developer/Company	Mithra Pharmaceuticals	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Estetrol is currently in development for the treatment of vasomotor symptoms experienced during the menopause. Vasomotor symptoms, mainly categorised as hot flushes, are often described as a sudden feeling of heat that spreads throughout the body. They can cause intense embarrassment and inconvenience to women with reports of a reduced quality of life for women who experience them. Hormone replacement therapy (HRT) is the recognised treatment; however, current therapies have significant health risks associated with them, highlighting the need for new, safer treatments.

Estetrol is an orally administered naturally occurring oestrogen (hormone) that exerts less effect on some organs in the body, reducing some unwanted side effects when compared with other oestrogens. Increasing oestrogen reduces vasomotor symptoms. If licensed, estetrol would offer an additional treatment option for menopausal women who are currently suffering from vasomotor symptoms (hot flushes).

PROPOSED INDICATION

Treatment of moderate to severe vasomotor symptoms in postmenopausal women aged between 40 and 65 years old.[1,2]

TECHNOLOGY

DESCRIPTION

Estetrol (Donesta, E4) is an estrogenic steroid molecule produced exclusively by cooperativity between the human foetal liver and the fetoplacental unit during pregnancy.[3,4] The structure of E4 differs from the other natural oestrogens estrone (E1), oestradiol (E2) and estriol (E3), by an additional alpha-hydroxy (OH) group at position 15 of the molecule. The two additional -OH groups have a crucial impact on the oral pharmacokinetics: the half-life of estetrol is 20–28 hours, compared with only 10–20 minutes for estriol (E3), 1–2 hours for natural E2 and 10–12 hours for micronized E2. Estetrol is minimally, if at all, metabolized and not reconverted to E3 or E2. Receptor binding and target interaction studies showed estetrol to have high selectivity for the oestrogen receptors (ER), indicating a potential for low risk of side effects.[5] Estetrol acts as an oestrogen in the nucleus by activating the nuclear oestrogen receptor α (ERα) and recruiting the same coregulator activators and repressors as oestradiol (E2), or estriol (E3) in a pattern very different from the selective oestrogen receptor modulators.[6] It is not fully clear why a decline in oestrogen levels causes vasomotor symptoms in women so the mechanism of why increasing oestrogen, including estetrol, is a successful therapy, is not fully understood.[7]

In phase III clinical trials (NCT04090957, NCT04209543), estetrol is given orally at doses of 15mg or 20mg once daily for either 13 or 52 weeks.[1,2]

INNOVATION AND/OR ADVANTAGES

Other hormone replacement therapy (HRT) treatments are associated with a wide range of mild to severe risks due to the effect of oestrogen on the body; this leads to many women avoiding treatment for symptoms.[8] Estetrol has been shown to act in synergy with most of the endogenous oestrogens but exerts much less effect on the liver and breast than E2 which may reduce some unwanted side effects. Estetrol also has a high oral availability with a long enough half-life to be prescribed as a once a day drug.[6,9] In a multiple rising dose study in postmenopausal women, 2 to 40 mg estetrol once-daily improved vaginal cytology and vasomotor symptoms, and a dose-dependent oestrogenic effect was observed on endocrine parameters, bone turnover markers, lipids, and lipoproteins, together with only a small increase in triglycerides and almost neutral for haemostatic parameters.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Estetrol does not currently have Marketing Authorisation as a monotherapy for any indication in the EU/UK.

Estetrol is currently in phase II/III clinical development for the treatment of COVID-19 and as an oral contraceptive.[10]

PATIENT GROUP

DISEASE BACKGROUND

The menopause is when a woman stops having periods and is no longer able to get pregnant naturally. Periods usually start to become less frequent over a few months or years before they stop altogether. Sometimes they can stop suddenly. The menopause is a natural part of ageing that usually occurs between 45 and 55 years of age, as a woman's oestrogen levels decline. In the UK, the average age for a woman to reach the menopause is 51.[11]

Most women will experience hot flushes when going through the menopause. They are often described as a sudden feeling of heat that seems to come from nowhere and spreads throughout the body. Women may also experience sweating, palpitations and flushing of the face. Some women only have occasional hot flushes that do not really bother them, while others can have many a day and find them uncomfortable, disruptive, and embarrassing. Hot flushes can start a few months or years before a woman's periods stop and usually continue for several years after the last period.[12]

Hot flushes are thought to be caused by the decreasing levels of oestrogen and changes in hormone levels affecting temperature control.[13] They can happen without warning throughout the day and night, but can also be triggered by:[12]

- eating spicy foods
- caffeine and alcohol
- smoking
- wearing thick clothing
- a high temperature
- feeling stressed or anxious
- treatment for certain types of cancer (this can affect both men and women)
- certain medicines
- some health conditions, such as an overactive thyroid, diabetes, and tuberculosis

A woman's ethnicity, cultural, religious, sociological, and nutritional factors may modify the intensity and incidence of menopausal symptoms.[14]

Experiencing these symptoms reduces quality of life for sufferers.[15] Hot flushes and night sweats can cause social embarrassment, discomfort, sleep problems and fatigue.[16]

CLINICAL NEED AND BURDEN OF DISEASE

Hot flushes and night sweats (vasomotor symptoms) are the main physical experience reported during the menopause transition in the UK with approximately 25% of menopausal women reporting troublesome symptoms.[16-18]

In a 2013 UK study, relatively healthy mid-aged women with vasomotor symptoms reported reduced quality of life compared to age-matched norms and a general sample of menopausal women. In this study, participants reported an average of 45 hot flushes and 18 night sweats a week, for approximately 3.9 years. Average hot flush problem rating scores were 5.88 (scored 1–10, 10 being very problematic). The majority of participants (77%) had seen their GP specifically to discuss menopausal symptoms and 47% were offered possible treatments. Of the total sample, 23% were offered HRT and 8% were offered selective serotonin receptor inhibitors (SSRIs).[15]

The population likely to be eligible to receive estetrol could not be estimated from available published sources.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Postmenopausal women experiencing vasomotor symptoms are usually offered HRT. SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine should not be offered as first-line treatment for vasomotor symptoms alone.[8] Sufferers are also advised to wear light clothing, keep their bedroom cool at night, take a cool shower, use a fan or have a cold drink, reduce stress levels, avoid potential triggers, such as spicy food, caffeine, smoking and alcohol and to take regular exercise and lose weight if they are overweight.[19]

CURRENT TREATMENT OPTIONS

The only pharmacological treatments recommended are HRT.[8]

PLACE OF TECHNOLOGY

If licensed, estetrol will offer an additional treatment option as an HRT for postmenopausal women who are experiencing vasomotor symptoms.

CLINICAL TRIAL INFORMATION

Trial	**E4ComfortII;** NCT04090957; A Randomised Double-blind Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women **Phase III** - recruiting **Location(s):** US **Primary completion date:** October 2021
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo controlled
Population	N=~1000; female; 40-65 years old; Subjects seeking treatment for relief of (vasomotor symptoms) VMS associated with menopause
Intervention(s)	• 15mg estetrol orally once daily for 52 consecutive weeks • 20mg estetrol orally once daily for 52 consecutive weeks
Comparator(s)	Matched placebo
Outcome(s)	• Mean change in weekly frequency of moderate to severe VMS from Baseline to Week 4 (Efficacy part) [Time frame: Baseline and Week 4] • Mean change in weekly frequency of moderate to severe VMS from Baseline to Week 12 (Efficacy part) [Time frame: Baseline and Week 12] • Mean change in severity of moderate to severe VMS from Baseline to Week 4 (Efficacy part) [Time frame: Baseline and Week 4]

	• Mean change in severity of moderate to severe VMS from Baseline to Week 12 (Efficacy part) [Time frame: Baseline and Week 12] • Number of participants with treatment-emergent adverse events (TEAEs) (Safety part) [Time frame: From Baseline to Week 53] • Number of participants with changes in physical and gynaecological examination results (Safety part) [Time frame: Screening and Week 53] • Number of participants with changes in vital sign results (Safety part) [Time frame: Screening and Week 53] • Number of participants with changes in electrocardiogram (ECG) results (Safety part) [Time frame: Screening and Week 53] • Number of participants with changes in mammography results (Safety part) [Time frame: Screening and Week 53] • Number of participants with changes in breast examination results (Safety part) [Time frame: Screening and Week 53] • Number of participants with changes in routine clinical laboratory test (haematology and chemistry) results (Safety part) [Time frame: Screening, Baseline and Week 53] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**E4ComfortI;** NCT04209543; A Randomised Double-blind Placebo Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Estetrol for the Treatment of Moderate to Severe Vasomotor Symptoms in Postmenopausal Women **Phase III** - recruiting **Location(s):** Lithuania **Primary completion date:** August 2021
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo controlled
Population	N=~1200; female; 40-65 years old; Subjects seeking treatment for relief of vasomotor symptoms (VMS) associated with menopause
Intervention(s)	• 15mg estetrol orally once daily for up to 13 consecutive weeks • 20mg estetrol orally once daily for up to 13 consecutive weeks • 20mg estetrol + 100mg progesterone orally once daily for up to 53 weeks
Comparator(s)	Matched placebo
Outcome(s)	• Mean change in weekly frequency of moderate to severe VMS from Baseline to Week 4 (Efficacy Study Part) [Time frame: Baseline and Week 4]

	• Mean change in weekly frequency of moderate to severe VMS from Baseline to Week 12 (Efficacy Study Part) [Time frame: Baseline and Week 12] • Mean change in severity of moderate to severe VMS from Baseline to Week 4 (Efficacy Study Part) [Time frame: Baseline and Week 4] • Mean change in severity of moderate to severe VMS from Baseline to Week 12 (Efficacy Study Part) [Time frame: Baseline and Week 12] • Change from Baseline to each measured time point in endometrial thickness (Endometrial and General Safety Study Part) [Time frame: Screening, Baseline, Weeks 13, 29, and 53] • Endometrial biopsy histology at Screening and Week 53 (Endometrial and General Safety Study Part) [Time frame: Screening and Week 53] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**E4Relief;** NCT02834312; A Multicentre Dose-Finding, Randomised, Double-Blind, Placebo-Controlled Study to Select the Daily Oral Dose of Estetrol (E4) for the Treatment of Vasomotor Symptoms in Post-Menopausal Women **Phase II** - completed **Location(s):** US **Study completion date:** January 2018
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo controlled
Population	N=~260; female; 40-65 years old; Women presenting at least 7 moderate to severe hot flushes/day or at least 50 moderate to severe hot flushes/week
Intervention(s)	• Either 2.5 mg, 5mg, 10mg or 15mg estetrol orally once daily for at least 12 consecutive weeks
Comparator(s)	Matched placebo
Outcome(s)	• Change in weekly frequency of moderate to severe vasomotor symptoms (VMS) from baseline to week 4. [Time Frame: From baseline to week 4] • Change in weekly frequency of moderate to severe VMS from baseline to week 12. [Time Frame: From baseline to week 12] • Change in severity of moderate to severe VMS from baseline to week 4. [Time Frame: From baseline to week 4] • Change in severity of moderate to severe VMS from baseline to week 12. [Time Frame: From baseline to week 12] See trial record for full list of other outcomes

Results (efficacy)	• The frequency of moderate to severe hot flushes (HFs) decreased with all E4 doses. • The difference in the percentage change of weekly HF frequency was significant for 15 mg E4 versus placebo at both W4 (-66% vs -49%, P = 0.032) and W12 (-82% vs -65%, P = 0.022). • The decrease in severity of HFs was significantly more pronounced for 15 mg E4 than for placebo at both W4 (-0.59 vs -0.33, P = 0.049) and W12 (-1.04 vs -0.66, P = 0.049); the other doses failed to achieve statistical significance
Results (safety)	• In non-hysterectomized women, endometrial thickness increased during treatment and normalized following progestin treatment at study completion. No endometrial hyperplasia was observed.

ESTIMATED COST

The cost of estetrol is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline in development. Menopause: diagnosis and management. [GID-NG10241]. Expected August 2023.
- NICE clinical guideline. Menopause: diagnosis and management. [NG23]. December 2019.
- NICE Quality Standard. Menopause. [QS143]. February 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- National Institute for Health and Care Excellence. Clinical Knowledge Summary. Menopause. 2020.[14]
- British Menopause Society. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. 2020.[20]

ADDITIONAL INFORMATION

No information was received from Mithra Pharmaceuticals.

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