Medicines Adverse Reactions Committee

Meeting date	7/12/2023	Agenda item	3.2.2
Title	**Potential drug interaction between estrogen-based hormone replacement therapy and lamotrigine.**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Estradiol	Estradiol transdermal patch	Viatris Limited
	Estradot transdermal patch	Sandoz New Zealand Limited
	Estrofem	Novo Nordisk Pharmaceuticals
Estradiol valerate	Progynova	Bayer New Zealand Limited
Estradiol + norethisterone	Kliovance, Kliogest, Trisequens	Novo Nordisk Pharmaceuticals
Estriol	Ovestin (cream, tablet, pessaries)	Pharmacy Retailing NZ Limited
Conjugated estrogen	Premarin	Pfizer New Zealand
Ethinylestradiol	Ethinylestradiol	New Zealand Medical & Scientific Ltd

PHARMAC funding	Estradiol patches, estradiol valerate tablets, estriol cream, pessaries, and tablets are fully funded. Estradiol tablets +/- norethisterone, and conjugated estrogen products are not fully funded.
Previous MARC meetings	HRT- PHARMAC proposal to restrict prescribing 10 March 2004 HRT and cancer/stroke/heart disease 11 September 2002 HRT and cardiovascular and cerebrovascular disease 11 December 2001
International action	The European Medicines Agency has requested the SmPCs of oral HRT products be updated with a warning about a potential interaction with lamotrigine.
Prescriber Update	Hormone replacement therapy HRT reminder March 2020 HRT- new advice from the Medicines Adverse Reactions Committee November 2003 Hormone replacement therapy- Rapid Review November 2002 Letter to health professionals about HRT September 2002 Updated HRT guideline released June 2001
Classification	Prescription medicine
Advice sought	**The Committee is asked to advise:** • If the data sheets for estrogen containing HRT medicines require updating with information on a drug interaction with lamotrigine? ○ If yes, does this apply to all formulations of HRT? • Whether further communication is required other than in MARC's remarks?

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1 PURPOSE

In May 2023, the European Medicines Agency (EMA) agreed that the Summary of Product Characteristics (SmPCs) of oral hormonal replacement therapy (HRT) products be updated to include information about a drug interaction with lamotrigine [1].

Information on a drug interaction between lamotrigine and hormonal contraception is currently included in the lamotrigine and combined oral contraceptive (COC) data sheets. However, there is no information about this interaction in the data sheets of products indicated for HRT.

The purpose of this paper is to review the information on a drug interaction between HRT and lamotrigine, and to consider if updates to the data sheets of HRT products are required.

2 BACKGROUND

2.1 Source of the safety concern

In September 2022, the Netherlands Pharmacovigilance Centre Lareb received a report about an interaction between lamotrigine and Femoston (estradiol/dydrogesterone). The report describes a patient taking lamotrigine for the treatment of depressive episodes, who was started on Femoston to manage menopausal symptoms. After five months of taking Femoston, the patient noticed worsening depressive symptoms and her serum lamotrigine level measured 2.9mg/L. Femoston was stopped, and her lamotrigine dose tapered. Approximately four and a half weeks after stopping Femoston, her lamotrigine serum level had increased to 5.3mg/L. The patient indicated that she was recovering from her depressive symptoms [2].

Lareb alerted their Medicines Evaluation Board (MEB) to this report. The MEB discussed the report with the EMA, who agreed that the SmPCs of HRT products should be updated with information on this possible drug interaction [1, 3]. The proposed wording for HRT SmPCs is as follows:

> *SmPC Section 4.5 Interactions*
>
> *Effect of HRT with oestrogens on other medicinal products*
>
> *Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.*

Novo Nordisk and Bayer Pharmaceuticals are sponsors for several HRT products available in New Zealand. [redacted]

Comment:

It is interesting that the proposed EMA wording only mentions a reduction in seizure control, given the ADR report was for a person with worsening symptoms of bipolar depression. If changes are warranted for the New Zealand HRT data sheets, should the wording be reflective of a reduction in seizure control and/or worsening symptoms of bipolar disorder. Refer to section 2.3 of this paper to find the information currently included in the lamotrigine data sheets.

2.1.1 Proposed mechanism behind the drug interaction

A drug interaction between estrogen and lamotrigine is thought to be related to activation of UDP-glucuronosyltransferase (UGT) enzymes. 17β-Estradiol (E2) is a naturally produced estrogen which has been linked to the upregulation of UGT1A4 expression [4].

Lamotrigine is metabolised by UGT1A4 and UGT2B7 [5]. Upregulation of UGT1A4 by estrogen can increase lamotrigine glucuronidation and therefore decrease lamotrigine serum levels [4]. The interaction between estrogen in COCs and lamotrigine is well documented in the literature, product data sheets, and clinical guidelines [6,7].

Comment:

Although estrogens should be considered as potential inducers of UGT enzymes, HRT is not commonly known to cause drug interactions. There is some information about lamotrigine clearance in postmenopausal women, however the information is conflicting with studies suggesting decreased, increased, and unaltered clearance.

It is also important to note that HRT-treated women with epilepsy may experience an increase in seizure frequency. This could be related to the proconvulsant effects of estrogens [8]. The reported worsening in seizure activity may be a direct estrogen effect, but it may also be due to a drug interaction leading to lower serum concentrations of antiepileptic medications that are metabolised via glucuronidation.

2.2 Hormonal replacement therapy

Estrogen therapy is indicated for the treatment of signs and symptoms of estrogen deficiency due to menopause, and prevention of postmenopausal osteoporosis. Combination therapy with a progestogen should be considered in women with an intact uterus [9]. Unapproved indications of estradiol valerate include feminisation in transgender therapy, and control of problematic break-through bleeding in patients with endometriosis [10].

Estradiol, estrone, and estriol are naturally occurring forms of estrogen, they have a more appropriate profile for menopausal HRT compared to synthetic estrogens (ethinylestradiol) [11]. Estrogen products available in New Zealand consist of oral tablets, vaginal creams, pessaries, and transdermal patches. Section 2.5 of this paper discusses usage data and prescribing trends; transdermal patches of estradiol are the most common form of HRT prescribed. Given that transdermal application of estradiol leads to systemic absorption, an interaction with lamotrigine could theoretically occur.

The pharmacokinetic parameters differ depending on the product formulation and route of administration. A summary of the serum concentration levels for various HRT products is provided on Table 1. The serum estrogen concentration associated with upregulation of UGT1A4 is unknown.

Table 1: Information on serum concentrations for HRT products

Product	Pharmacokinetic properties: information on serum concentrations
Progynova (estradiol valerate) oral tablet	Estradiol valerate is rapidly and completely absorbed. After multiple administrations, serum levels of estradiol are about twice as high as those obtained after a single dose. On average, the concentration of estradiol varies between 15-30pg/mL for Progynova 1mg strength and between 30-60pg/mL for Progynova 2mg tablets.

Kilogest (estradiol + norethisterone acetate) oral tablet	Following oral administration of 17β-estradiol in micronised form, rapid absorption from the gastrointestinal tract occurs. Peak plasma concentrations are approximately 44pg/mL (range of 30-55pg/mL) occurring within 6 hours after ingestion.
Estradot (estradiol) transdermal patch	Transdermal administration of estradiol achieves therapeutic plasma concentrations using a lower total dose of estradiol than required with oral administration. Average C_{max} levels range from 25-105pg/mL depending on the patch size.
Ovestin (estriol) vaginal cream and pessary	Intravaginal absorption of estriol ensures optimal availability at the site of action. It is also absorbed into the general circulation. Peak plasma levels are reached 1-2 hours after application. After vaginal application of 0.5mg estriol, C_{max} is approximately 100pg/mL, C_{min} is approximately 25pg/mL and $C_{average}$ is approximately 70pg/mL. After 3 weeks of daily administration $C_{average}$ decreases to 40pg/mL.

Source: Medicine data sheet available at: https://www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 3 November 2023)

Comment:

The EMA has specified that only oral HRT SmPCs require updating, no information relating to the EMA decision was available at the time of preparing this report. However, it is possible that different formulations/route of administration of estrogen could also be linked with a drug interaction with lamotrigine.

The exact levels of estrogen linked to UGT upregulation are not specified in the studies that identified an interaction. However in the studies available, most participants are exposed to estrogen through COC use, this would give higher concentrations of estrogen compared to medicines used for HRT. In the cell study by Chen et al (reference 4), the authors used higher concentrations of estradiol to mimic levels associated with pregnancy and COC use. This cell study identified that higher levels of estrogen was linked to upregulation of UGT enzymes.

In theory, HRT should restore serum estrogen concentrations to physiological premenopausal levels an interaction is unexpected. This may be a reason as to why information on a drug interaction is only listed in lamotrigine and COC data sheets and not for HRT products.

However, if the committee believe a warning should be available in the data sheet for oral HRT products (as per the EMA request), it may also be worth considering if this should be extended to other formulations of HRT.

2.3 Lamotrigine: risks associated with a drug interaction

Lamotrigine is indicated as an adjunctive therapy in the treatment of epilepsy, for partial and generalised seizures including those associated with Lennox-Gastaut syndrome. It is also indicated for the prevention of mood episodes in patients with bipolar disorder [5].

The use of ethinylestradiol/levonorgestrel has been shown to increase the clearance of lamotrigine by approximately two-fold, resulting in decreased lamotrigine levels [5, 13]. If not managed appropriately, this

drug interaction may lead to subtherapeutic lamotrigine levels resulting in reduced seizure control, or reduced effectiveness of lamotrigine when used for other indications [7].

The lamotrigine data sheet contains information on this interaction and provides guidance on the management of it. The information is located in the data sheet sections 4.2 dose and administration, 4.4 special warnings and precautions for use, and 4.5 interactions with other medicines and other forms of interactions.

Section 4.4 includes a warning statement reminding prescribers to exercise appropriate clinical management of women who start or stop hormonal contraceptives during lamotrigine therapy, as dosing adjustments may be needed. The data sheet also states that an interaction with other formulations of oral contraceptives and HRT treatments has not been studied. However, it's possible that a similar effect on lamotrigine pharmacokinetic parameters may occur [5].

> *Lamictal data sheet section 4.4 special warnings and precautions for use*
>
> *Hormonal contraceptives*
>
> *Effects of hormonal contraceptives on lamotrigine efficacy: An ethinylestradiol/levonorgestrel (30 micrograms/150 micrograms) combination has been demonstrated to increase the clearance of lamotrigine by approximately twofold resulting in decreased lamotrigine levels (see section 4.5 Interaction with other medicines and other forms of interaction). Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive medication. For dosing instructions see section 4.2 Dose and method of administration - General dosing recommendations for lamotrigine in special patient populations: Women taking hormonal contraceptives.*
>
> *Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during lamotrigine therapy and lamotrigine dosing adjustments will be needed in most cases.*
>
> *Other oral contraceptive and hormone replacement therapy (HRT) treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters (see section 4.2 Dose and method of administration - General Dosing Recommendations for lamotrigine in special patient populations (for dosing instructions for women taking hormonal contraceptives) and section 4.4 Special warnings and precautions for use).*

Comments:

In New Zealand there are three Lamotrigine products with published data sheets (Lamictal, Arrow-Lamotrigine, and Logem). All three data sheets contain information on the drug interaction with COCs and includes how to manage this interaction.

2.4 Data sheets

2.4.1 New Zealand

A review of New Zealand HRT product data sheets was conducted. None of these data sheets contained information about a drug interaction with lamotrigine (Table 2). This is consistent with information in the UK SmPC, Australian Product Information, and Irish SPC.

The Progynova data sheet refers healthcare professionals to other resources 'The Data Sheet of concomitant medicines should be consulted to identify potential interactions.' No other HRT products contain this warning.

Table 2: Review of HRT data sheets Section 4.5 Interactions.

Product	Interaction with lamotrigine stated?
Kliogest (estradiol/norethisterone acetate)	No
Kliovance (estradiol/norethisterone acetate)	No
Trisequens (estradiol/norethisterone acetate)	No
Estrofem (estradiol)	No
Ethinyloestradiol (ethinylestradiol)	No
Estradot Patch (estradiol)	No
Climara Patch (estradiol)	No
Progynova (estradiol valerate)	No
Estradiol Mylan Patch (estradiol)	No
Ovestin Cream/Pessary (estriol)	No
Premarin (conjugated estrogens)	No

Source: Medicine data sheet available at: https://www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 3 November 2023)

Section 4.4 (warnings and precautions) of the lamotrigine data sheet contains information about the effects of hormonal contraceptives of lamotrigine efficacy, see section 2.3 above.

Comment:

The New Zealand HRT data sheets are consistent with current international prescribing information. The sponsors of oral HRT products in Europe are in the process of updating their SmPC's which are expected to be submitted for review by December 2023.

The New Zealand data sheets of all COCs contains a short warning about an interaction with lamotrigine. The wording available in Section 4.5 is 'Oral contraceptives may affect the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine).

2.5 Usage

Usage data of medicines is captured via the Te Whatu Ora Pharmaceutical data web tool. Table 3 and 4 highlight the number of initial dispensings, and number of people dispensed a funded prescription for an estradiol, or lamotrigine product. In terms of estrogen dispensing for HRT, the most common chemical dispensed was estriol (Ovestin). Estriol products are fully funded. The web tool does not collect dispensing information for non-funded medicines, for which there are several HRT products available.

The web tool does not capture dispensing information relating to concomitant use of medicines. The number of people who take HRT and lamotrigine, and therefore could be affected by this drug interaction is unknown.

In terms of prescribing trends in New Zealand, a Bpac review of HRT prescribing in 2018-2019 identified that women of European ethnicity were approximately 1.5 times more likely to be dispensed HRT compared to Māori women, and twice as likely as Pacific and Asian women. Transdermal estradiol was dispensed at a rate of five to seven times higher than oral estradiol irrespective of ethnicity [12].

Table 3: Number of initial dispensings for estradiol (including combination products[a]), 2018-2022.

Year of dispensing	Number of dispensings	Number of people
2018	234,556	106,857
2019	257,379	114,914
2020	284,400	122,238
2021	321,941	136,782
2022	381.561	158.467

[a] Products include estradiol, estradiol valerate, estriol, and estradiol plus norethisterone.

Table 4: Number of initial dispensings for Lamotrigine, 2018-2022.

Year of dispensing	Number of dispensings	Number of people
2018	60,414	12,550
2019	65,404	13,433
2020	68,842	14,135
2021	74,835	15,054
2022	79,479	16,211

3 SCIENTIFIC INFORMATION

3.1 Published literature

Most of the literature around this interaction is related to COCs and lamotrigine. In these articles serum lamotrigine levels were found to have decreased, and patients experienced adverse reactions as a result of the interaction [6, 14, 15]. Given that patients on COCs will have a higher level of estrogen compared to HRT users, the clinical significance of an interaction with HRT and lamotrigine is unknown.

The literature evaluating a drug interaction between HRT products and lamotrigine is very limited. There are no formal studies investigating the clinical significance of an interaction when HRT and lamotrigine are co-administered. The number of participants included in the studies that have been conducted is small, there is missing information on concomitant medicines and, medical history. There is also no information relating to possible differences associated with the type and formulation of HRT products.

3.1.1 Reimers, 2017. Hormone replacement therapy with estrogens may reduce lamotrigine serum concentrations: a matched case-control study [13].

The aim of this study was to explore the possibility of a drug interaction between lamotrigine and estrogens used for HRT. The study used datasets from the routine therapeutic drug monitoring database of the St. Olav University Hospital Department of Clinical Pharmacology in Trondheim, Norway from October 1999 to May 2007.

Patients on lamotrigine and HRT (either transdermal or oral) were matched with patients not taking estrogen therapy. Patients using hormonal contraception (ethinylestradiol) and lamotrigine were included in as a group for validation, with its own control (no hormonal contraception). Each patient was matched for age, and dose. Lamotrigine serum dose levels were measured and divided by the total daily dose to give a concentration-to-dose ratio (CDR).

In the analysis, there were 79 patients exposed to HRT and lamotrigine, and 200 patients who took hormonal contraception and lamotrigine. The clinical characteristics and results of the CDR of the participants is presented on Table 5.

Table 5: Clinical characteristics and results of case groups and controls. Reimers 2017.

HRT intends to restore serum estradiol concentrations to premenopausal levels. Therefore, authors expected the lamotrigine CDR in women who received HRT to be similar to the control group and that of premenopausal women.

The study found that patients on ethinylestradiol for hormonal contraception had significantly lower lamotrigine CDR ($p<0.001$). In the HRT group, the mean serum lamotrigine concentrations and CDR were also lower than the control.

The author note several limitations to this study particularly as this was a historical study based on routine data, the results should be interpreted with caution. A prospective, cross-over study would be desirable to further explore this possible drug interaction.

Comment:

The author of this matched case control study concluded that estrogen exposure from hormonal contraception or HRT in women taking lamotrigine may reduce LTG serum concentrations, However, as it was a historical study based on routine data, the results should be interpreted with caution.

Information on clinical outcomes, patient medical history, use of concomitant medicines, lamotrigine dose were not provided or analysed. It is unknown whether any participants experienced adverse effects as a result of altered lamotrigine levels.

The study participants used various types of estrogen, the study did not differentiate on the type of estrogen exposure and reduction in lamotrigine levels. This would be an area of interest given the differences in estrogen potencies however, this was not the purpose of the study.

3.1.2 Harden et al, 2006. Hormone replacement therapy in women with epilepsy: a randomised, double-blind, placebo-controlled study [16].

Authors sought to determine whether adding HRT to the medicine regimen of postmenopausal women with epilepsy was associated with an increase in seizure frequency. This study was a randomised, placebo-controlled, double-blind, clinical trial. Participants were postmenopausal women with epilepsy taking stable doses of an antiepileptic medicine and within 10 years of their last menses.

Participants were exposed to a placebo or standard or double dose of Prempro (0.625mg conjugated equine estrogen/2.5mg medroxyprogesterone). Participants were randomised and stratified into groups by seizure severity. The primary end point of the study was to evaluate increased seizure activity during HRT treatment. Change in seizure frequency was determined by comparing the daily seizure rate during baseline with the daily seizure rate while the study drug was taken. The baseline participant characteristics are summarised on Table 6. Antiepileptic medicines taken by participants included carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, phenobarbital, primidone, topiramate, tiagabine, and sodium valproate.

Table 6: Characteristics of subjects in each treatment arm with number of seizures during the 84-day baseline period.

[redacted]

A total of 21 participants underwent randomisation, and during the study period eight subjects had simple partial seizures, nine subjects had complex partial seizures and three had secondary generalised seizures. Five subjects in the double dose HRT group discontinued the study due to an increase in seizure activity or due to HRT-related adverse effects. The study associated an increase in seizure frequency (of any seizure type) with increasing HRT dose (p =0.05), the results of the study are outline on Table 7.

[redacted]

There were two subjects exposed to HRT concomitantly taking lamotrigine, these patients had a decline in lamotrigine levels by 25-50%. One of these participants experienced an increase in seizure frequency. The findings from this study provides evidence that HRT is associated with dose-related increases in seizure

frequency. However, as the number of participants in this study is small (n=21) these results are not generalisable to the wider population.

Comment:

This study investigated the association with HRT and increase in seizure frequency. The authors found that double dose HRT was associated with an increase in seizure frequency. However, the number of participants was small, and several participants exited the study due to adverse events. Therefore, the generalisability of the results is limited. There were only two patients on lamotrigine exposed to HRT with one experiencing an increase in seizure frequency.

3.1.3 Mostacci et al, 2018. Estrogen-related seizure exacerbation following hormone therapy for assisted reproduction in women with epilepsy [17]

The authors describe two cases of seizure exacerbation following hormone therapy in women with epilepsy. One of the cases occurred in a female taking lamotrigine.

The case summary is as follows: at 36 years, after a diagnosis of infertility, the patient underwent four assisted reproduction attempts preceded by ovarian stimulation and endometrial preparation. Therapy included ganirelix, alpha-follitropin, choriogonadotropin alpha and estradiol valerate. Concomitant clobazam 10mg was added to her regular antiepileptic therapy (lamotrigine 450mg/day) during the hormone cycles.

Lamotrigine blood levels decreased from 11mg/l to 9.3mg/l while on follitropin. Afterwards lamotrigine was reduced to 350mg/day (blood level 7.1mg/l). At 38 years she underwent a new attempt at embryo transfer during which she took estradiol valerate 4mg for 10 days for endometrial preparation. This time she did not take concomitant clobazam and had a seizure relapse after 40 months of freedom.

After that episode her usual therapy remained unchanged and during a further cycle with follitropin alpha and estradiol valerate she took clobazam as recommended and did not experience a seizure.

Comment:

This report highlights an association between worsening seizures in a woman on lamotrigine and hormone therapy. Very limited information was provided in the case report.

3.1.4 Kirkpatrick et al, 2023. Lamotrigine and exogenous estrogen among females with epilepsy: a retrospective analysis of administrative claims data [18].

An interaction between estrogen and lamotrigine is well characterised, there is sufficient information about the need to titrate lamotrigine dose in patients exposed to estrogen. The authors of this study investigated the incidence of lamotrigine dose adjustments in women exposed to exogenous estrogen. The authors conducted their analysis using the Clinformatics prescription database in the United States.

There were 643 females prescribed a stable dose of lamotrigine, who had an overlapping prescription with estrogen from 2011 to 2021. The median age of participants was 31 years, and most people were prescribed estrogen for contraception (76%) not HRT (24%). Authors calculated the cumulative incidence of a dose increase in lamotrigine following estrogen prescribing and used Cox proportional hazard models for subsequent analysis.

The cumulative incidence of any lamotrigine dose increase was 28% [95%CI 25-32%], the median number of days after the first estrogen prescription until the first lamotrigine dose adjustment was 118. In unadjusted Cox models, older age, use of estrogen in hormone replacement therapy as opposed to contraception, and annual household income of $50,000-$99,999 (compared with <$50,000) were significant negative predictors of a dose adjustment in lamotrigine with hazard ratios (HRs) of 0.82 [95%CI 0.72–0.92], 0.63 [95%CI 0.42–0.95], and 0.62 [95%CI 0.40–0.95]. In the adjusted Cox model, age and income remained significant predictors with HRs of 0.79 [95%CI 0.66–0.94] and 0.59 [95%CI 0.36–0.95]. This study found that dose increases of lamotrigine

following prescribing of exogenous estrogen is rare, there is potential disparities based on patient age and income level, prescribers may need further guidance on this topic.

Comment:

This article provided an interesting review of prescribing practices in the United States and notes that lamotrigine dose changes due to concurrent use of estrogen is rare. However, this study does not provide any information on lamotrigine levels (whether they are subtherapeutic for the indication), what prompted the dose change (did the patient experience a seizure or other ADR), or the proportion of patients who experienced reduced lamotrigine levels but no clinically significant signs or symptoms that warranted a dose change. The review did not include patients who did not have insurance or those using HRT for gender affirming care.

Overall, the authors suggested that physicians in the United States may require additional information about monitoring and potential changes in lamotrigine dosing.

3.1.5 Carvalho et al, 2023. Sex steroid hormones and epilepsy: effects of hormonal replacement therapy on seizure frequency of postmenopausal women with epilepsy- a systematic review [19].

The authors conducted a systematic review on the impact of HRT on seizure frequency in women with epilepsy. Authors searched PubMed and Scopus for articles published up until August 2022. Critical appraisal was performed using the revised Cochrane risk-of-bias tool for randomized trials and ROBINS-E tool.

There were 497 articles screened and 13 studies included. However, only three of the 13 studies were conducted in humans. One cross-sectional study showed a decrease in seizure frequency in women with epilepsy using combined HRT, a case–control study showed an increase in comparison with controls, and a randomised clinical trial found a dose-dependent increase in seizure frequency in women with focal epilepsy taking combined HRT (Harden et al). Ten studies addressing the impact of HRT in rat models were also included, showing conflicting results. A summary of the data related to the human studies is presented on Table 8 below.

Table 8. Summary of data from human studies selected in the Carvalho review.

[redacted]

In the cross-sectional and case-control studies completed in humans, the authors of this systematic review noted a high risk of bias in the studies, mainly driven by the study designs. Variables that may have influenced the results included type of epilepsy, HRT formulation, years of menopause and concomitant medicines were not considered in the study design or reported in the results.

Overall, the authors concluded that the information about the effects of HRT on seizure control is scarce and contradictory. There is very little data from human studies which all have significant limitations including small sample size and several methodological flaws which may reduce the validity of the study findings. The results of the review suggest a potential increased risk of seizure frequency with HRT in women with epilepsy, however this topic requires further assessment.

Comment:

The authors found little information on the risk of seizures associated with HRT. There were only three studies conducted in humans researching this topic and all studies had several limitations. Therefore it is difficult to generalise the results to the wider population. One of the RCT studies included in the review (Harden et al) has been discussed in this paper in section 3.1.2.

The remaining two human studies and preclinical studies did not look at the relationship of lamotrigine dosing and seizure frequency and therefore was not relevant to this paper.

3.2 Company reports

3.2.1 [redacted]

[redacted]

3.2.2 [redacted]

[redacted]

3.3 CARM data

Up to 30 October 2023, there were 17 cases reported where lamotrigine is a suspect/interacting medicine, and the reported adverse reaction is 'drug interaction'. There is one report for 'drug interaction' where lamotrigine and estradiol are suspect medicines.

There is a second report for lamotrigine where the person was also taking a COC and the ADR reported was 'suicidal tendency'. In this report, the reporter comments that there may be a potential drug interaction. However, the term 'drug interaction' was not coded. These two cases are summarised in Table 9.

Table 9: New Zealand case reports

Case number	Patient details	ADR reported	Comments
138464	26-year-old female Suspect: lamotrigine, venlafaxine, estradiol, cyproterone acetate	Consciousness decreased, depersonalisation, drug interaction	[redacted]
98759	31-year-old female Suspect: lamotrigine [redacted] Concomitant medicines: monofeme 28, Symbicort, amitriptyline, melatonin	Suicidal tendency	[redacted]

Comment:

There were several other reports for lamotrigine suggestive of a decreased therapeutic effect/flare of symptoms where an estrogen product was reported as a concomitant medicine. However, as these reports did not specify the term 'drug interaction' as an ADR or noted in the comment section of the reports, they were not included in this paper. This is a limitation relating to the coding of adverse reaction reports and was also noted when trying to identify case reports in VigiLyze and other international databases (DAEN, FAERS).

4 DISCUSSION AND CONCLUSIONS

The interaction between HRT and lamotrigine is suspected to be linked to upregulation of UGT enzymes by estrogen. A case report in a patient with worsening depression on HRT and lamotrigine was identified by Lareb Pharmacovigilance Centre in the Netherlands. This ultimately led to the EMA request to update the SmPCs of oral HRT products to include a warning about a potential interaction.

Currently no interaction between HRT and lamotrigine is listed in the data sheets for HRT products. However, the lamotrigine data sheet contains a summary paragraph about the interaction with COC products and does mention that the effect of HRT has not been studied but a similar interaction could occur.

The literature surrounding this topic is very scarce and all studies identified have issues with study designs making it difficult to generalise the results. These issues included small sample size, use of concomitant medicines, lack of patient information and dose levels, lack of analysis by HRT formulation, some studies did not specifically focus on lamotrigine, ones showing a reduction in lamotrigine levels often did not elaborate on the clinical significance of this decrease. With these caveats in mind, the authors of these studies have identified that HRT exposure has been associated with a decrease in lamotrigine levels. An additional article by Kirkpatrick et al was included to highlight prescribing practices in the United States and found that most women did not have a change in lamotrigine dose following HRT exposure whether or not this is related to a lack of clinically significant issues is unknown.

It may also be worth mentioning that HRT is used off label in gender affirming care and very little/no information about this interaction or other safety issues have been identified in this population. Given the possible interaction is listed in the lamotrigine data sheet, the committee are asked to consider if the potential interaction should be included in the data sheets for HRT products. Additionally should this apply to HRT products administered via other routes (transdermal, vaginal) where systemic exposure to estrogen may be less than oral, and noting that the evidence is severely limited and [redacted]

5 ADVICE SOUGHT

The Committee is asked to advise:

- If the data sheets for estrogen containing HRT medicines require updating with information on a drug interaction with lamotrigine?
    - If yes, does this apply to all formulations of HRT?
- Whether further communication is required other than in MARC's remarks?

6 ANNEXES

- Annex 1: [redacted]

7 REFERENCES

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