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Summary of the risk management plan (RMP) for Duavive (conjugated oestrogens / bazedoxifene)

This is a summary of the risk management plan (RMP) for Duavive, which details the measures to be taken in order to ensure that Duavive is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Duavive, which can be found on Duavive's EPAR page.

Overview of disease epidemiology

Duavive (conjugated oestrogens / bazedoxifene) is used for the treatment of symptoms caused by low blood levels of the female hormone oestrogen in women who have been through the menopause. It is used in women who still have their uterus (womb) and who cannot be treated with progestogen-containing medicines (medicines derived from the hormone called progesterone).

These symptoms include vasomotor symptoms such as hot flushes and night sweats, as well as vulvovaginal atrophy (dryness, irritation and soreness around the genital area).

Vasomotor symptoms affect 60 to 85% of women who are going through the menopause. After the menopause, vasomotor symptoms become less frequent: approximately 27 to 49% of postmenopausal women in Europe and the US report hot flushes and fewer than 20% of women still experience them 10 years following menopause. Risk factors include smoking, lack of exercise, heavy alcohol consumption and a history of cancer.

Vulvovaginal atrophy is common after the menopause and unlikely to resolve without treatment. In Europe, 9 to 15% of postmenopausal women suffer from symptoms of vulvovaginal atrophy. Risk factors include lack of sexual activity, smoking, obesity, certain medications (e.g. certain hormones for cancer treatments), removal of the ovary, vaginal surgery and breast cancer.

Summary of treatment benefits

Duavive was compared with placebo (a dummy treatment) in two main studies in 996 women who have been through the menopause, investigating the effects on either hot flushes or vulvovaginal atrophy.

In the study investigating the effects on hot flushes, treatment with Duavive (conjugated oestrogen 0.45 mg and bazedoxifene 20 mg) over 12 weeks reduced the average daily number of moderate and severe hot flushes by 7.6 compared with 4.9 for placebo. Treatment with Duavive also led to a greater average fall in the daily severity score of hot flushes than placebo treatment: 0.9 versus 0.3. Similar results were seen with a higher strength of conjugated oestrogen (0.625 mg) plus bazedoxifene 20 mg when compared with placebo.

The study looking at the effects of Duavive on vulvovaginal atrophy found an improvement in some of the signs of vaginal atrophy but not in the most bothersome symptoms when compared with placebo.

Unknowns relating to treatment benefits

Women with serious medical conditions such as heart disease, stroke, liver, kidney or gallbladder disease and women with current or previous cancer were not included in the clinical studies, nor were women who had previously suffered from deep vein thrombosis (blood clot in a deep vein, usually in the leg), women with undiagnosed vaginal bleeding or women with a high amount of fats (triglycerides) in their blood.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Venous thromboembolic event (VTE)	Venous thromboembolic events (VTEs) occur when a blood clot forms within a vein, breaks off and flows with the blood to block a smaller vein. VTEs, such as clots in the legs (deep vein thrombosis), lungs (pulmonary embolism), or the eye (retinal vein thrombosis), have been reported rarely in patients treated with Duavive. VTE has also been reported with other medicines containing the active substances of Duavive, and other oestrogen-modulating medicines.	Duavive should not be given to patients who have or have had a blood clot in a vein (VTE), such as in the legs, the lungs or eyes. No specific additional preventative measures are needed for patients who do not have a history of VTE. Patients should talk to their doctor if they have any of the following risk factors: if they are seriously overweight, if they have had a blood clot before, if they or any of their close family have had blood clots, if they have had one or more miscarriages, if they have any blood-clotting problem that needs treatment with a medicine such as warfarin, if they bed rest following major surgery, injury or illness, or if they have a rare condition called SLE (systemic lupus erythematosus).
Increased blood triglycerides levels	Triglycerides are a type of fat in the blood. An increase in blood levels of triglycerides is called hypertriglyceridaemia. It is a common disorder and is often caused or made worse by untreated diabetes, obesity and lack of exercise, and it is considered a risk factor for heart disease. Increased triglycerides have been reported in patients treated with Duavive. Patients treated with Duavive	No specific preventative measures have been identified. Patients with a personal or family history of hypertriglyceridemia or who have high levels of triglycerides in their blood prior to or during treatment should be monitored by their doctor during treatment with Duavive. Yearly monitoring of levels of triglycerides in the blood is recommended in all patients.

Risk	What is known	Preventability
	experienced a bigger increase in triglycerides levels over 2 years, compared with patients who received no treatment. Increased triglycerides have also been reported with medicines containing conjugated oestrogens, one of the components of Duavive, and with other oestrogen-modulating medicines.	

Important potential risks

Risk	What is known
Cerebrovascular events (stroke and transient ischaemic attack (mini-stroke))	A stroke is caused by disruption of the blood supply to the brain, affecting brain functions such as speech and movement for more than 24 hours. A less severe form of cerebrovascular event is a transient ischaemic attack (mini-stroke) which lasts for less than 24 hours. There was no evidence of any significant increase in the risk of stroke or transient ischaemic attack in women treated with Duavive in clinical studies. Stroke has been reported with the use of conjugated oestrogens alone or in combination with another hormone medicine (progestogen). Therefore, cerebrovascular events are considered to be a potential risk with Duavive.
Coronary heart disease including myocardial infarction (heart attack)	Coronary heart disease is the term that describes what happens when the heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries (blood vessels that supply the heart muscle). Heart attack results from interruption of blood supply to a part of the heart. There was no evidence of any significant increase in the risk of coronary heart disease or myocardial infarction in women treated with Duavive in the clinical studies. An increased number of cases of coronary heart disease and heart attack have been reported with the use of conjugated oestrogens in combination with progestogen. Therefore, coronary heart disease and myocardial infarction are considered to be a potential risk with Duavive.
Atrial fibrillation	Atrial fibrillation is a heart condition that causes an irregular and often abnormally fast heart rate. There was no evidence of any significant increase in the risk of atrial fibrillation in women treated with Duavive in clinical studies. Atrial fibrillation is included as a potential risk because it is considered to be a potential risk for bazedoxifene, one of the components of Duavive. A small increase in the number of cases of atrial fibrillation in patients treated with bazedoxifene alone was found in the bazedoxifene clinical studies.
New presentation or	Kidney failure or insufficiency is a medical condition in which the kidneys fail

Risk	What is known
aggravation of pre-existing kidney failure or insufficiency (reduced kidney function)	to adequately filter waste products from the blood. There was no evidence that Duavive had an effect on kidney function in clinical studies. However, reduced kidney function or insufficiency is included as a potential risk with Duavive based on findings with bazedoxifene in pre-clinical studies conducted in monkeys and rats.
Kidney carcinoma and adenoma	Kidney adenoma is a relatively common, benign growth in the kidney while kidney carcinoma is cancer in the kidney. There was no evidence that Duavive increases the risks of kidney carcinoma or adenoma in human studies. However, kidney carcinoma and adenoma are included as a potential risk with Duavive based on findings with bazedoxifene in pre-clinical studies conducted in monkeys and rats.
Gallbladder disease	There was no evidence of any significant increase in the risk of gallbladder disease (including cholecystitis and gall stones) in women treated with Duavive in the clinical studies. In the women's health initiative (WHI) study, 2 to 4 times as many women treated with conjugated oestrogens required gallbladder surgery, compared with women who were not treated. In addition, cholecystitis is also considered to be a potential risk with bazedoxifene alone, because in clinical studies there was a small increase in the number of cases of cholecystitis in women treated with bazedoxifene 20 mg, but not with the higher dose of bazedoxifene 40 mg. An increase in the number of cases of gall stones in women at increased cardiovascular risk has also been reported with raloxifene, a medicine similar to bazedoxifene.
Breast, ovarian, and endometrial cancers	There was no evidence of any significant increase in the risk of cancer of the breast, ovaries or endometrium (lining of the womb) in women treated with Duavive in the clinical studies. Breast, ovarian and endometrial cancers are included as potential risks for Duavive based on studies of conjugated oestrogens or oestrogens when given alone or in combination with progestin. An increased risk of breast cancer was identified with the use of conjugated oestrogens in combination with progestogen in a study that was part of the women's health initiative (WHI) study. In another large study (the million women study, women who were being treated with oestrogen alone or in combination with progestin were more likely to develop and die from ovarian cancer than women who had never used these medicines. In the same study women who were being treated with oestrogen alone had an increased risk of endometrial cancer compared with women who had never used oestrogen medicines, whereas women being treated with oestrogen in combination with progestin had a decreased risk of endometrial cancer.
Lung, thyroid, skin, gastrointestinal tract and other cancers	There was no evidence of any significant increase in the risk of lung, thyroid, skin, gastrointestinal (gut) or other cancers in women treated with Duavive in clinical studies. They are included as potential risks because they are common among postmenopausal women and warrant close monitoring.

Risk	What is known
Endometrial hyperplasia	Endometrial hyperplasia is a thickening of the lining of the womb caused by overgrowth of the cells that line the womb. In women with an intact womb, the risk of endometrial hyperplasia and cancer is increased when oestrogens are administered alone for prolonged periods. The bazedoxifene component of Duavive is expected to reduce the risk of endometrial hyperplasia which may be a precursor of endometrial cancer. Women taking Duavive should not take additional oestrogens as this may increase the risk of endometrial hyperplasia and cancer.
Depression	There was no evidence of any significant increase in the risk of depression in women treated with Duavive in clinical studies. Depression is included as a potential risk for Duavive as it is considered as a potential risk for bazedoxifene.
Ocular (eye) events	Ocular events are any symptoms that affect the eye. There was no evidence of any significant increase in the risk of ocular events in women treated with Duavive in clinical studies. Ocular events are considered to be a potential risk for Duavive as they are considered to be a potential risk for bazedoxifene based on reports received from women being treated with bazedoxifene outside of clinical studies.
Gastroesophageal reflux disease (GERD)	Gastroesophageal reflux disease (GERD) is a condition in which the stomach contents (food or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach). This action can irritate the esophagus, causing heartburn and other symptoms. There was no evidence of any significant increase in the risk of GERD in women treated with Duavive in clinical studies. GERD is considered to be a potential risk for Duavive as it is considered to be a potential risk for bazedoxifene based on a study which found a possible link between GERD and the use of oestrogen-modulating medicines.
Drug-drug interactions	No data are currently available for interactions of Duavive with other medicines (drug-drug interactions). A clinical trial to investigate these interactions is currently ongoing. Information is available for the individual components of Duavive. These studies showed that there is little potential for drug-drug interactions with the bazedoxifene component of Duavive. However, the conjugated oestrogen component is broken down in the liver in a process that can be affected by other medicines. The process of breaking down conjugated oestrogen is increased by some medicines (such as St. John's wort, phenobarbital, carbamazepine, and rifampin). This may result in reduced effect of Duavive, or in a change in the pattern of vaginal bleeding experienced by the patient. The process of breaking down conjugated oestrogen is blocked by some other medicines (such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice). In this case, more conjugated oestrogens would be active in the body and may lead to side effects.
Off-label use	There is a risk that Duavive may be prescribed to patients in whom its use is not being approved. The product information provides information about the

Risk	What is known
	approved uses of Duavive.

Missing information

Risk	What is known
Use in elderly patients	Patients aged 75 years or older were not included in clinical studies with Duavive.
Use in patients with kidney impairment	Duavive has not been studied in patients with kidney disorders, and is not recommended for use in these patients.
Use in patients with liver impairment.	Duavive has not been studied in patients with liver disorders, and is not recommended for use in these patients.
Use in patients with malignancy (cancer)	Patients with cancer, or who have received treatment for cancer within the previous 5 or 10 years, were not included in the Duavive clinical studies. Similarly, patients with a history of breast cancer, melanoma or any gynaecologic cancer (cancer of the breast, ovary or womb lining) were not included in the clinical studies with Duavive.
Use in patients with history of cardiovascular disease (disease affecting the heart and blood vessels), diabetes or obesity or long-term smoking	Patients with coronary heart disease (such as heart attack or angina), high blood pressure, high levels of fats or sugar in their blood, obesity, or heavy smokers were not included in clinical studies with Duavive.
Long-term (>2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian cancers, in particular)	Only a small number of patients (341 women) received treatment with conjugated oestrogens/ bazedoxifene for over 2 years. Of these women, 67 women received the lower dose (conjugated oestrogens 0.45 mg / bazedoxifene 20 mg) and 78 women received the higher dose (0.625 mg / 20 mg). The longest duration that a woman received conjugated oestrogens/ bazedoxifene during the clinical studies was approximately 2 years and 2 months.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Duavive can be found on Duavive's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Post Authorization Safety Study (PASS) of conjugated estrogens / bazedoxifene to be conducted in the US.	Compare the incidence of safety endpoints/concern among postmenopausal women initiating Duavive or those initiating E+P (oestrogen + progestogen).	VTE, coronary heart disease, myocardial infarction, stroke, breast cancer, endometrial hyperplasia and cancer, Ovarian cancer,Thyroid cancer, Renal cancer, Renal adenoma, gastrointestinal tract cancers, and all cancers	Planned	Annual Interim Reports with 1st report submitted on 31 March 2016. Final study report to be submitted following accumulation of 4 years of post-US launch data (31 March 2019).
EU Drug Utilisation Study of conjugated oestrogens/ bazedoxifene	Describe the baseline characteristics and utilization patterns of EU patients initiating treatment with either Duavive or E+P (oestrogen + progestogen) HRT.	• Use in patients with cardiovascular risk factors or a history of cardiovascular disease • Use in patients with a history of malignancy Off-label use.	Planned	Final study report to be submitted following accumulation of 3 years of post-launch data (31 March 2019).

Studies which are a condition of the marketing authorisation

The studies above are not a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in MM-YYYY.