

Summary of Risk Management Plan for DUAVIVE

This is a summary of the risk management plan (RMP) for DUAVIVE. The RMP details important risks of DUAVIVE, how these risks can be minimised, and how more information will be obtained about DUAVIVE's risks and uncertainties (missing information).

DUAVIVE's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DUAVIVE should be used.

This summary of the RMP for DUAVIVE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DUAVIVE's RMP.

I. The Medicine and What It Is Used For

DUAVIVE is authorised for the treatment of oestrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 months since last menses) for whom treatment with progestin-containing therapy is not appropriate (see SmPC for the full indication). It contains conjugated oestrogens and bazedoxifene acetate as the active substances and it is given by orally.

Further information about the evaluation of DUAVIVE's benefits can be found in DUAVIVE's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

<https://www.ema.europa.eu/en/medicines/human/EPAR/duavive>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of DUAVIVE, together with measures to minimise such risks and the proposed studies for learning more about DUAVIVE 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of DUAVIVE is not yet available, it is listed under ‘missing information’ below.

II.A. List of Important Risks and Missing Information

Important risks of DUAVIVE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DUAVIVE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 1. List of Important Risks and Missing Information

Important identified risks	<ul style="list-style-type: none"> • Venous thromboembolism (VTE) • Hypertriglyceridaemia-induced pancreatitis
Important potential risks	<ul style="list-style-type: none"> • Arterial thromboembolic events: Cerebrovascular events and myocardial infarction (MI) • Coronary heart disease • Renal carcinoma or adenoma • Breast cancer • Ovarian cancer • Endometrial cancer • Lung, thyroid, skin, gastrointestinal and other cancers • Endometrial hyperplasia
Missing information	<ul style="list-style-type: none"> • Use in patients with malignancy • Use in patients with history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina), diabetes or obesity or long-term smoking • Long-term (>2 years) safety data on breast protection and gynaecological cancers (endometrial and ovarian in particular)

II.B. Summary of Important Risks

Table 2. Important Identified Risk: Venous thromboembolism (VTE)

Evidence for linking the risk to the medicine	In clinical trials with CE/BZA and in the post-marketing setting, cases of VTE have been reported.
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Table 2. Important Identified Risk: Venous thromboembolism (VTE)

Risk factors and risk groups	Risk factors for VTEs include age, diabetes, smoking, obesity, varicose veins, high blood pressure, immobility, trauma, surgery, cancer, cancer therapy, neurological disease with extremity paresis, and selected concomitant medications. In the BAvarian ThromboEmbolic Risk (BATER) study, a 10-year observation cohort study of 4337 women (age 18–55 years; mean age 26 ± 8.6 years), increased age, personal history of VTE, family history (of VTE, varicose veins or MI), and increased BMI ($\geq 25 \text{ kg/m}^2$) were found to be risk factors for VTE.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects</p> <p>PL Section 2 What you need to know before you take DUAVIVE PL Section 3 How to take DUAVIVE PL Section 4 Possible side effects</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 3. Important Identified Risk: Hypertriglyceridaemia-induced pancreatitis

Evidence for linking the risk to the medicine	In women with pre-existing hypertriglyceridaemia, treatment with oestrogens alone may be associated with further elevations of plasma triglycerides leading to pancreatitis and other complications.
Risk factors and risk groups	Risk factors for pancreatitis include gallstones, alcoholism, hypertriglyceridaemia, certain medications, hypercalcemia, autoimmune aetiologies, toxins, scorpion stings and congenital etiologies.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects</p> <p>PL Section 2 What you need to know before you take DUAVIVE PL Section 4 Possible side effects</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> None</p>

Table 4. Important Potential Risk: Arterial thromboembolic events: Cerebrovascular events and myocardial infarction (MI)

Evidence for linking the risk to the medicine	<p>In clinical trials of up to 2 years duration, no increased risk of stroke was observed in women treated with CE/BZA.</p> <p>Oestrogens alone have been associated with an increase in the risk of stroke. In the WHI oestrogen-alone sub-study, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE 0.625 mg-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted. Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE 0.625 mg-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).</p> <p>In clinical trials of bazedoxifene 20 mg, no increased risk of stroke was observed in postmenopausal women.</p> <p>There was no evidence of a significant increase in MI in the CE/BZA treatment groups in the Phase 3 clinical studies compared with placebo. However, an increased risk of CHD (including MI and coronary death), was observed with treatment with combined CE 0.625 mg/ MPA 2.5 mg in the WHI study.</p> <p>Myocardial infarction is listed as an ADR observed with CE monotherapy in Section 4.8 of the CE/BZA SmPC.</p>
Risk factors and risk groups	<p>The incidence of stroke increases dramatically with age. Other risk factors for stroke include elevated blood pressure, atrial fibrillation, smoking, diabetes, and TIA.</p> <p>Risk factors for MI include age (≥ 45 years for men and ≥ 55 years for women), hypertension, diabetes, metabolic syndrome, obesity, elevated total cholesterol, low HDL, smoking, high alcohol consumption, and elevated triglycerides, along with genetic and dietary factors.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects</p> <p>PL Section 2 What you need to know before you take DUAVIVE PL Section 4 Possible side effects</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 5. Important Potential Risk: Coronary heart disease

Evidence for linking the risk to the medicine	There was no evidence of a significant increase in the relative risk of CHD in the CE/BZA treatment groups in the Phase 3 clinical studies compared with placebo. An increased risk of CHD (including MI and coronary death), was observed with treatment with combined CE/MPA in the WHI study.
Risk factors and risk groups	Risk factors for these conditions include age (≥ 45 years for men and ≥ 55 years for women), hypertension, diabetes, metabolic syndrome, obesity, elevated total cholesterol, low HDL, smoking, high alcohol consumption, and elevated triglycerides, along with genetic and dietary factors.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special Warnings and Precautions <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060) [Final study report due: 31/03/2021]

Table 6. Important Potential Risk: Renal Carcinoma or Adenoma

Evidence for linking the risk to the medicine	Renal carcinoma and adenoma are included as a potential risk based on non-clinical findings of spontaneous incidental renal carcinomas in an 18 month repeat dose study in aged, ovariectomised cynomolgous monkeys with BZA, and the male rat specific finding of renal tumours resulting from bazedoxifene related corticomedullary nephrocalcinosis, in conjunction with enhanced spontaneous chronic progressive nephropathy in a 2-year repeat dose study.
Risk factors and risk groups	Risk factors include age, race (with Native Americans having the highest reported rates and those of Asian descent the lowest), smoking, obesity, family history, workplace exposures, hypertension, and advanced kidney disease requiring dialysis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 5.3 Preclinical safety data <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 7. Important Potential Risk: Breast Cancer

Evidence for linking the risk to the medicine	There was no evidence of any significant increase in the relative risk of breast cancer in the CE/BZA treatment groups compared with placebo in the CE/BZA Phase 3 clinical studies. However, breast cancer is included as a potential risk with CE/BZA due to overall evidence suggesting an increased risk of breast cancer in women taking combined oestrogen-progestin and possibly oestrogen-only HRT, that is dependent on the duration of HRT therapy. In the WHI Studies, the 95% CI for the HR for CE vs PBO included 1, but there was nominally statistically significant increase in the risk of breast cancer with CE/MPA vs PBO (HR: 1.26; 95% CI: 1.00, 1.59).
Risk factors and risk groups	Well established risk factors for breast cancer include advanced age, family history, genetic mutations of BRCA1 and BRCA2, atypia in a benign biopsy and reproductive factors (including age at menarche, parity and age at birth of first child). Other potentially important factors include mammographic density, plasma oestrogen and androgen levels, bone density, height and age at menopause. Behavioural risk factors include overweight/obesity, sedentary lifestyle, alcohol consumption and, possibly, dietary factors. Use of the SERMs, tamoxifen and raloxifene, decrease the risk of invasive breast cancer in post-menopausal women. Data from the WHI clinical study oestrogen + progestin and oestrogen alone arms suggest that new-onset breast tenderness during use of oestrogen + progestin was associated with increased subsequent breast cancer risk. The association of oestrogen + progestin therapy with increased breast cancer risk was especially pronounced in women with baseline breast tenderness.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you take DUAVIVE <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 8. Important Potential Risk: Ovarian Cancer

Evidence for linking the risk to the medicine	There was no evidence of any significant increase in the relative risk of ovarian cancer in the CE/BZA treatment groups compared with placebo in the CE/BZA Phase 3 clinical studies. However, ovarian cancer is included as a potential risk with CE/BZA due to data reported for CE, administered with or without progestin.
Risk factors and risk groups	There are numerous published reports describing a relationship between endometriosis and the development of ovarian cancer, although the specific risk factors and pathogenesis remain unclear (for example, reviewed in the following). Although endometriosis is typically diagnosed in women of reproductive age, endometriosis may persist in the abdominal cavity after menopause. Since endometriosis is an oestrogen dependent disorder, there is a theoretical possibility that use of postmenopausal hormones such as SERMs may affect the potential for malignant transformation.

Table 8. Important Potential Risk: Ovarian Cancer

Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects</p> <p>PL Section 2 What you need to know before you take DUAVIVE</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 9. Important Potential Risk: Endometrial Cancer

Evidence for linking the risk to the medicine	There was no evidence of any significant increase in the relative risk of endometrial cancer in the CE/BZA treatment groups compared with placebo in the CE/BZA Phase 3 clinical studies. However, endometrial cancer is included as a potential risk for CE/BZA due to the risk of endometrial hyperplasia and carcinoma associated with the use of unopposed oestrogens in women with an intact uterus.
Risk factors and risk groups	Risk factors for endometrial cancer include old age, Caucasian race, obesity, type II diabetes, lack of physical activity, low parity, early menarche, greater age at menopause, family history, and use of hormone therapy. The incidence of endometrial cancer is relatively low and varies somewhat by geography. Incidence is highest in North America and Northern Europe, intermediate in Eastern Europe and Latin America, and lowest in Africa and Asia.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable Effects</p> <p>PL Section 2 What you need to know before you take DUAVIVE</p> <p><u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u></p> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)

Table 10. Important Potential Risk: Lung, Thyroid, Skin, Gastrointestinal (GI) Tract and Other Cancers

Evidence for linking the risk to the medicine	There was no evidence of any significant increase in the relative risk of lung, thyroid, skin, GI or other cancers in the CE/BZA treatment groups compared with placebo in the CE/BZA Phase 3 clinical studies. Lung, thyroid, skin, GI and other cancers is included as a potential risk for CE/BZA as all cancers are considered to be a potential risk for BZA monotherapy.
Risk factors and risk groups	<p><u>Lung Cancer</u> Although tobacco smoking is known to be the major cause of lung cancer, other risk factors have also been identified, including environmental and occupational exposure to carcinogens, human papillomavirus, chronic inflammatory disease and family history. Studies have suggested that sex hormones may influence lung cancer risk and females and males show differences in lung cancer types, incidence and survival.</p> <p><u>Thyroid cancer</u> Risk factors for thyroid cancer include age, female sex, head or neck irradiation during childhood, and history of goiter.</p> <p><u>Skin Cancer</u> Exposure to ultraviolet light is a major cause of melanomas. People with certain risk factors are more likely than others to develop skin cancer. Risk factors vary for different types of skin cancer, but some general risk factors are having the following:</p> <ul style="list-style-type: none"> • A lighter natural skin color. • Family history of skin cancer. • A personal history of skin cancer. • Exposure to the sun through work and play. • A history of sunburns early in life. • A history of indoor tanning. • Skin that burns, freckles, reddens easily, or becomes painful in the sun. • Blue or green eyes. • Blond or red hair. • Certain types and a large number of moles. <p><u>GI Tract Cancer</u> A number of epidemiological studies have suggested that Helicobacter pylori infection increases the risk of some gastric cancers (distal noncardia gastric cancer). Other risk factors associated with gastrointestinal cancers are Gastrointestinal Reflux Disease and Barrett's Disease, tobacco and alcohol consumption, diet, nutrition and obesity, however, the differences in incidence rates between men and women have not been explained. It has been suggested that the female sex hormones may modulate gastric cancer risk.</p> <p><u>Other Cancers</u> Different specific risk factors apply to different cancers.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> None</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 10. Important Potential Risk: Lung, Thyroid, Skin, Gastrointestinal (GI) Tract and Other Cancers

Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060)
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Table 11. Important Potential Risk: Endometrial hyperplasia

Evidence for linking the risk to the medicine	There was no evidence of any significant increase in the risk of endometrial hyperplasia in the CE/BZA treatment groups compared with placebo in the CE/BZA Phase 3 clinical studies. However, endometrial hyperplasia is included as a potential risk for CE/BZA due to the risk of endometrial hyperplasia and endometrial carcinoma associated with the use of unopposed oestrogens in women with an intact uterus.
Risk factors and risk groups	A separate study, in the same managed care population used by Reed et al, identified two risk factors for endometrial hyperplasia: obesity and nulliparity. Both are known risk factors for endometrial carcinoma and are believed to influence the body's balance of oestrogen and progestin.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions PL Section 2 What you need to know before you take DUAVIVE <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060) [Final study report due: 31/03/2021]

Table 12. Missing Information: Use in Patients with Malignancy

Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> Drug Utilization Study in the European Union (EU) (B2311061)^a

a. Although patients with these co-morbidities may have been enrolled in study B2311061, based on the results of the study, no conclusions can be drawn about the safety of CE/BZA in patients with a history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina) diabetes, obesity, long-term smoking or malignancy. As such, these safety concerns will remain as "Missing information."

Table 13. Missing Information: Use in Patients with History of Cardiovascular Disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina) Diabetes or Obesity or Long-term Smoking

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions PL Section 2 What you need to know before you take DUAVIVE <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • Drug Utilization Study in the European Union (EU) (B2311061)^a

a. Although patients with these co-morbidities may have been enrolled in study B2311061, based on the results of the study, no conclusions can be drawn about the safety of CE/BZA in patients with a history of cardiovascular disease (including hypertension, hyperlipidaemias, arrhythmias, CHD, angina) diabetes, obesity, long-term smoking or malignancy. As such, these safety concerns will remain as “Missing information.”

Table 14. Missing Information: Long-term (>2 years) Safety data on Breast Protection and Gynaecological Cancers (endometrial and ovarian in particular)

Risk minimisation measures	<u>Routine risk minimisation measures:</u> The maximum 2-year duration of clinical studies with CE/BZA is acknowledged in: SmPC Section 4.4 Special Warnings and Precautions SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic Properties <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> <ul style="list-style-type: none"> • Post Authorization Safety Study (PASS) of CE/BZA in the United States (B2311060) [Final study report due: 31/03/2021]

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of DUAVIVE.

II.C.2. Other Studies in Post-Authorisation Development Plan

- **Post Authorization Safety Study (PASS) of DUAVIVE in the United States (B2311060).** The primary objective is to estimate and compare the incidence rates of endometrial hyperplasia and endometrial cancer among postmenopausal women initiating either DUAVIVE or oestrogen+ progestin hormone therapy. The secondary

objective is to estimate and compare the incidence rates of the selected secondary safety endpoints: (venous thromboembolism [VTE], coronary heart disease (defined as myocardial infarction [MI] and sudden death), stroke, breast cancer, ovarian cancer, thyroid cancer, renal cancer and adenoma, gastrointestinal cancer, all cancer, and all-cause mortality) among postmenopausal women initiating either DUAVIVE or oestrogen+ progestin hormone therapy.

- **Drug Utilization Study (DUS) of DUAVIVE in the European Union (B2311061). [Final Study Report Submitted on 31 March 2020]**

The study was a multi-country, drug utilization study based on secondary data analysis of existing data sources. The overall aim of the study is to describe the baseline characteristics of EU patients initiating treatment with either DUAVIVE or oestrogen + progestin hormone replacement therapy (E+P HRT), and to describe the utilization patterns of DUAVIVE.

The study objectives are:

1. Within each participating EU country, to describe and compare baseline characteristics and medical history between DUAVIVE and E+P HRT patients in EU.
2. To estimate the proportion of patients that may have been prescribed DUAVIVE outside the specifications of the authorised product information ('off-label use').

The study setting is comprised of electronic healthcare records collected in the outpatient setting from the following EU countries: Belgium, France, Italy, the Netherlands, Spain and the UK. Data from the first 3 years after DUAVIVE availability in the EU are included from 31 March 2016 through 30 March 2019.

Based on the available data, it can be concluded that the number of patients who initiated treatment with DUAVIVE in all included countries is very low. When DUAVIVE was prescribed, it was most often prescribed in an appropriate population (i.e., female patients, mostly 50 years or older, correct indication) and in the dosage recommended in the Summary of Product Characteristics (SmPC). Based on these data, overall prescribing patterns were comparable between DUAVIVE and E+P HRT. Potential off-label use ranged from 9% (France) to 29% of patients (Spain), and was primarily comprised of use in women who were \leq 45 years of age. It is very important to note that the age threshold of 45 years is a proxy measure for premenopausal status. The results of this study suggest the proportion of potential off-label use of DUAVIVE is low in clinical practice.