Yasmin
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2. Elements for a public summary

2.1 Overview of disease epidemiology

Prevention of pregnancy (contraception)

Oral contraceptives, often referred to as the birth control pill or simply 'the pill', are used by more than 80 million women worldwide, and are one of the most reliable methods of preventing an unplanned pregnancy (contraception). Oral contraceptives are among the most systematically studied and widely used medicinal products available today. DRSP/EE products are so called "combined oral contraceptives" (COCs), which contain two different hormones, an estrogen and a progestin, i.e. ethinylestradiol and drospirenone, in a low dose.

2.2 Summary of treatment benefits

Oral contraception

The single greatest benefit of the pill is their intended action: the prevention of pregnancy (contraception). The pill is a convenient and non-invasive form of contraception and its effects are completely reversible, meaning that it will not affect the ability to become pregnant once intake was stopped. Most birth-control "pills" today are low-dose combined oral contraceptives (COCs) which means that they contain two hormones, i.e. an estrogen and a progestogen (ethinylestradiol and drospirenone, respectively, in case of DRSP/EE products). The hormones in the combined pill work in three different ways to prevent pregnancy: they prevent the ovaries from releasing an egg (a process known as ovulation); they thicken the mucus in the cervix making it more difficult for sperm to enter the womb (the uterus); and they make the lining of the womb thinner, preventing implantation of a fertilized egg. The combined effects make it one of the most reliable methods of contraception. When taken COCs consistently and correctly (under conditions of perfect use), COCs have a failure rate of ≤1% per year. This means that one women (or even less) out of 100 women have become pregnant despite using a COC over a 12-month period, and is also referred to as the "Pearl Index". Only sterilization and long-acting reversible contraceptives, such as intrauterine systems and implants, demonstrate slightly better rates for prevention of pregnancy.

It is a well-recognized fact that all approved COCs reliably prevent pregnancy if taken regularly; those with 20 µg estrogen are as effective as those with higher doses.

For the DRSP/EE products the high contraceptive effectiveness has been proven in many studies specifically conducted for this purpose (Pearl Index studies). The reliable contraceptive effect was also shown in real-life studies performed with YAZ and Yasmin. In one study it was observed that shortening the pill-free interval (4 days with YAZ compared to 7 days with Yasmin) further improves contraceptive effectiveness in all age groups.

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2.3 Unknowns relating to treatment benefits

The clinical studies performed in the development of DRSP/EE products did not reveal any differences in the effectiveness in pregnancy prevention related to race, ethnic origin, or age of the patients involved in these studies. There is no evidence that there are any undetected patient groups that would not benefit from the use of DRSP/EE products.

2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Blood clots (thromboembolic events [TEE])	A thrombosis is the formation of a blood clot, which may block a blood vessel. A thrombosis sometimes occurs in the deep veins of the legs (deep venous thrombosis). Venous thromboembolism (VTE) can develop whether or not you are taking the pill. It can also happen if you become pregnant. If a blood clot breaks away from the vein where it has formed, it may reach and block the arteries of the lungs, causing a so-called “pulmonary embolism”. Blood clots can also occur very rarely in the blood vessels of the heart (causing a heart attack). Blood clots or a ruptured blood vessel in the brain may cause a stroke. Taking DRSP/EE slightly increases the risk of having a blood clot (called a thrombosis). A full recovery is not always made and in 1-2% of cases, it can be fatal.	Control for higher risk of a thrombosis due to a combination of risk factors or perhaps one very strong risk factor. In the case of a combination of factors the risk may be higher than simply adding two individual risks. The benefit-risk assessment for the respective woman has to be taken into account when considering the prescription of a YAZ family product.
Liver and bile ducts disorders (hepatobiliary disorders)	Asymptomatic elevations of transaminases are the common manifestations of liver function disturbances. Liver and bile duct disorders are considered a class effect of preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any other contraceptive pill. Severe liver damage remains rare. Studies showed that the risk of acute liver damage associated with DRSP/EE use is not substantially higher than for any contraceptive pill.	Patients who have (or have had) liver disease (symptoms of which may be yellowing of the skin or itching over the whole body) and whose liver is still not working normally should not use DRSP/EE.
Effect on hereditary angioedema	Some people inherit a tendency to develop episodes of angioedema, but it is uncommon. Women are affected more often than men. Preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill, have been associated with	

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Risk	What is known	Preventability
	an effect on hereditary angioedema. It is not known how estrogens influence the occurrence of angioedema. In patients with hereditary angioedema, the exacerbation of hereditary angioedema is potentially life-threatening.	

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Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Pancreatitis (in patients with high levels of lipids in blood)	In women on the preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill, severe hypertriglyceridemia (high levels of lipids in blood) may be a risk factor for developing acute pancreatitis. Avoiding the prescription of DRSP/EE to women with pre-existing severe high levels of lipids in blood and close monitoring of women with moderately increased blood lipids levels can be assumed to be adequate strategies to prevent the occurrence of hypertriglyceridemia-associated pancreatitis.
Breast cancer	Breast cancer is considered a class effect of preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill. Breast cancer has been observed slightly more often in women using combined pills, but it is not known whether this is caused by the treatment itself. For example, it may be that more tumors are detected in women on combined pills because they are examined by their doctor more often. In studies it has been shown that gradually less breast tumors are detected after stopping the combined hormonal contraceptive. Breast cancer may be life-threatening or may have a fatal outcome. As the risk attributable to DRSP/EE has not been completely established this is seen as a potential risk.
Benign and malignant liver tumors	Benign and malignant liver tumors are considered a class effect of preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill.In rare cases, benign liver tumors, and in even fewer cases malignant liver tumors have been reported in contraceptive pill users. In isolated cases, these tumors have led to life-threatening internal bleeding. As the risk attributable to DRSP/EE has not been completely established this is seen as a potential risk.
Cervical cancer	Cervical cancer is considered a class effect of preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill. The most important risk factor for cervical cancer is persistent Human Papilloma Virus (HPV) infection. Some studies suggest that long-term use of the pill increases a woman's risk of developing cervical cancer. However, it is not clear to what extent sexual behavior or other factors, such as Human Papilloma Virus, increase this risk. Cervical cancer may be life-threatening or may have a fatal outcome As the risk attributable to DRSP/EE has not been completely established this is seen as a potential risk.
Crohn’s disease and ulcerative colitis	Crohn's disease is a condition that causes inflammation of the wall of the gut. Any part of the gut can be affected. Ulcerative colitis is a disease where inflammation develops in the colon and the rectum (the large intestine). The cause for these conditions is not known and they could affect anyone. Among other potential causes, the preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill, have been implicated as possible factors in triggering the disease to start. To date, no evidence has shown that Crohn’s disease and ulcerative colitis are independent adverse

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Risk	What is known (including reason why it is considered a potential risk)
	reactions of DRSP/EE.
Insulin resistance/decreased glucose tolerance	Among other potential causes, the preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill, have been implicated as possible factors in triggering insulin resistance, also known as "pre-diabetes", and blood sugar tolerance disorder. Routine patient monitoring is considered a suitable and sufficient method to detect clinically relevant high blood sugar during the treatment with DRSP/EE. Diabetic women should be carefully observed while taking DRSP/EE.
Increased blood pressure	Blood pressure increase is common and may have numerous causes. Preparations which combine two different female hormones, so-called estrogens and progestogens, such as DRSP/EE or any contraceptive pill, have been associated with the risk of an increase in blood pressure. Since a causal relationship has not been fully established this is seen as potential risk.
Abnormally high blood concentration of potassium (hyperkalemia)	DRSP/ EE products combine two different female hormones; one of them, the progestogen drospirenone (DRSP) has the specific characteristic of increasing sodium and water excretion to weaken the hormone-related fluid retention (occurrence of edema) and inhibiting potassium excretion simultaneously. Normally this effect does not lead to a measurable increase in blood potassium concentration. However, there is a theoretical risk that in patients with kidney disorders, with already high blood concentration of potassium, and additionally using potassium sparing drugs YAZ family products may potentially increase the risk for abnormally high blood concentration of potassium (hyperkalemia).
Worsening of depression	Women taking combined contraceptive pills which combine two different female hormones, so-called estrogens and progestogens, such as YAZ, Yasmin, Yasminelle and YAZ Flex may be at increased risk of worsening of a pre-existing depression. Many psychiatric disorders, in particular mood and anxiety disorders but also depressions, are more common in women than in men. It is assumed that the cyclicity of menstruation and the levels of sex hormones influence mental health and the occurrence of these disorders. From recent studies it cannot be completely excluded that individual women are susceptible to worsening of mood or even depression under use of combined contraceptive pills but there is no indication of a general negative effect. On the contrary, a substantial part of the pill users may even benefit with regards to mood-related disturbances, especially if they are linked to the menstrual period. As the association of worsening of depression with use of YAZ, Yasmin, Yasminelle and YAZ Flex has not been completely established this is seen as a potential risk

Missing information

None.

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2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package leaflet for DRSP/EE products can be found in the Yasmin EPAR.

DRSP/EE products have special conditions and restrictions for its safe and effective use (additional risk minimization measures). In the CHMP decision pursuant to the article 31 EU referral procedure for CHCs specific measures were mandated with the aim to ensure safe and proper use of CHCs with respect to the increased risk of thrombosis (blood clots in veins and arteries) associated with the class of oral conatceptive pills in general and with this product in particular.

These additional risk minimization measures are for the following risk:

Blood clots (thromboembolic events {TEE})
Risk minimization measure(s): Healthcare professionals information and patients education
Objective and rationale: Healthcare professionals and patients to understand the risk of blood clots and the appropriate management of this risk to minimise its occurrence and its severity.
Additional risk minimization measure: Direct-to Healthcare Professionals-Communication, i.e. a letter directly sent to health care professionals for information • describes the outcome of the procedure of the European Medicine Agency which assessed the risk of blood clots of combined hormonal contraceptives • reminds prescribers of the risk having blood clots in the venous and arterial vessels with all combined contraceptives independent of the individual preparations, and gives information on the relative risk of having blood clots with individual preparations • reminds prescribers of conditions (e.g. diseases in the medical history/ contraindications) and risk factors which identify patients who have a higher likelihood for developing blood clots and for whom combined contraceptives should not be prescribed • reminds prescribers that it is important that patients know the risk and in addition the signs of events which are associated with blood clots in the vessels • provides room for optional text passages to be considered by national competent authorities The optional passages contain information that additional guidance documents will be developed (e.g. a prescriber checklist or a patient information card (provided with the packet or by the prescribing physician or on a website)

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2.6 Planned post-authorization development plan

List of studies in post-authorization development plan

Study/activity	Objectives	Safety concerns/efficacy issue addressed	Status	Planned date for submission of (interim and) final results
INAS-Flex	Compare incidence rates for VTE and ATE in women exposed to Flexyess® with women exposed to conventional COC regimens including DRSP/EE containing formulations. Evaluation of the incidences of cancer (including sex-hormone dependent malignancies), of pregnancy outcomes and of utilization patterns.	VTE, ATE, cancer (including sex-hormone dependent malignancies), and pregnancy outcomes)	Cancelled Not feasible (limited launch in one country only in Europe resulting in insufficient exposure)	Not applicable

Studies which are a condition of the marketing authorization

None of the above studies is a condition of the marketing authorization.

2.7 Summary of changes to the Risk Management Plan over time

The classification of safety concerns into identified and potential risks as presented in the current EU-RMP differs from the preceding EU-RMP documents for some of the DRSP-containing COC products as they were compiled in the years between 2007 and 2011. The current classification including the assignment of “effect on hereditary angioedema” to the class of important identified risk results from Bayer´s review of existing data on these risks, of which all (except hyperkalemia) are applicable for the class of combined hormonal contraceptives (CHCs). Bayer has re-evaluated the classification into identified and potential risks for the whole range of its COCs products and has come to the conclusion that this classification is adequately representing the available evidence in support of the association of these risks with the intake of COCs. For the risk, “increase of blood pressure” for

drospirenone with its unique antimineralocorticoid characteristics and the subsequent blood pressure lowering effect the MAH decided that this risk should be firmly placed in the category “important potential risks”.