VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Oral contraception

Since the introduction of the first "pill" to the American market in 1960, oral contraceptives have been used for around 50 years. Oral contraception is one of the most widely used medications of our time and its safety has been investigated in thousands of epidemiological studies.[1] Nearly four million women in the UK, and 60 million women worldwide, now use the pill as a convenient and effective way to control their fertility. If taken correctly, the pill has a 99% annual effectiveness.
Between 30% and 40% of women of childbearing age use oral contraceptives and about 30% of these use the newer oral contraceptives. Current advances in oral contraception have focused on development of safer, more effective preparations with minimal side effects and without - as less as possible- metabolic disturbance. Approximately 1.5 million women were using third-generation oral contraceptives in the UK alone.[2]
A report, based on up to 25 years of follow-up, suggested that most of the mortality effects of oral contraceptives occurred in current or recent users, with few effects persisting beyond 10 years after stopping use.[3] A recent publication from the large contraception study using incident cancer data has suggested that ever users of oral contraceptives may have a reduced overall risk of cancer.[4]

VI.2.2 Summary of treatment benefits

Having almost exclusively ethinylestradiol as estrogen component, the quality of the combined oral contraceptives is determined by the progestin they are containing. The progestin in COCs is responsible for the antiovulatory action while the estrogen sustain cycle stability as it was seen earlier. Dienogest is a novel 19-nortestosterone derivative with a unique pharmacokinetic and pharmacological profile, including antiandrogenic properties. Unlike other progestins, it exerts its antiovulatory effect by acting peripherally rather than directly on gonadotropin secretion. It also decreases sperm motility, but libido, sperm volume and sperm concentration remain unaffected.[5]
A later prospective, open-label, multicenter, non-controlled Phase III clinical study was performed in Poland to investigate the efficacy and safety of the 2 mg dienogest-30µg ethinylestradiol containing COC.[6] The study design followed the recommendations of the Comission of the European Community for the clinical investigation on oral contraceptives dated 1989 January. The principal goal of the study was to obtain proof of efficacy of 2 mg dienogest-30µg ethinylestradiol as a contraceptive by determining the Pearl Index. The secondary goal was to investigate cycle stability (cycle length, frequency of dysmenorrhea, irregular bleeding), dermatological effects (hair greasiness, skin blemishes and acne vulgaris) and clinical safety (adverse events and bleeding pattern irregularities). As for the primary efficacy measure, because no women became pregnant, the unadjusted Pearl Index was 0. The global assessment of effect on hair and skin (secondary measures) was performed after Cycle 6 and 12. Only 2 from 382 subjects found the effects unsatisfactory after 6 cycles and none from 308 subjects were dissatisfied after 12 cycles. All others rated the effects as very good,

good or satisfactory. Regarding cycle control, cycle length remained at around 28 days, while the duration of the menstrual bleeding was shortened from 5.4 days to 4.0 days during treatment and showed a decreased intensity. 13% of women had excessive bleeding at baseline which dropped to 1% by Cycle 3. Increase in bleeding intensity was observed in 7% (1st Cycle) and 4% (average) compared to baseline. The frequency of dysmenorrhea decreased from 35% to 10% from Cycle 3 and onwards. Worsening of dysmenorrhea (particularly in Cycle 1) was reported in 9% of subjects. Breakthrough bleeding or spotting were observed in 10% of subjects at baseline which changed to 30% for Cycle 1 but thereafter decreased and fell below the baseline rate from Cycle 7. The adverse events documented on the checklist by 1% or more women after one or more cycles were breast tenderness, gastric complaints, headache, increased or decreased libido, edema and depressive mood. There was a clear tendency for a decreased frequency of these events over time and only 5.6% of subjects discontinued the study due to adverse events. Table 12 shows the common events for cycles 1, 3, 6, 9 and 12.

Table 12 Adverse events documented by checklist and reported by 1% or more of the women taking 2 mg dienogest-30µg ethinylestradiol for 12 cycles

Adverse event	**Cycle 1 N=431**		**Cycle 3 N=416**		**Cycle 6 N=389**		**Cycle 9 N=364**		**Cycle 12 N=350**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Breast tenderness	45	10.4	22	5.3	6	1.5	3	0.8	2	0.6
Gastric complaints	35	8.1	12	2.9	7	1.8	2	0.5	1	0.3
Headache	29	6.7	15	3.6	12	3.1	4	1.1	3	0.9
Increased libido	5	1.2	5	1.2	0	0	0	0	0	0
Reduced libido	9	2.1	7	1.7	2	0.5	1	0.3	0	0
Edema	6	1.4	0	0	1	0.3	0	0	0	0
Depressed mood	5	1.2	4	1.0	0	0	2	0.5	0	0

2 mg dienogest-30µg ethinylestradiol has an excellent contraceptive efficacy similar to other low-dose combined oral pills with an adjusted Pearl Index of 0.2. Its antiandrogenic character makes it especially applicable among women seeking for contraception with acne vulgaris and greasy skin and hair conditions. The adverse events induced by 2 mg dienogest-30µg ethinylestradiol are similar to those observable with other low-dose COCs. Although spotting or breakthrough bleeding may present especially during the initial period of treatment, these

usually decrease after the application of 2 mg dienogest-30µg ethinylestradiol preparation for several cycles affording a high compliance rate of the pill.[6-9]

VI.2.3 Unknowns relating to treatment benefits

The main indication of this combination medicinal product is oral contraception, however, other potential benefits derived from the anti-androgenic properties of CMA, such as acne and other androgen-related skin disorders (seborrhoea, alopecia and hirsutism) have been demonstrated.[6,7,9,10,11]

VI.2.4 Summary of safety concerns

Table 13 Important identified risks

Important Identified Risk	**What is known**	**Preventability**
Circulatory disorders	The use of any COC, as well as Yana, carries an increased risk of arterial thromboembolism (ATE) and venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, compared with no use. There are many risk factors which could increase this already existing risk (e.g. increasing age, smoking, obesity, family history of thromboembolism).	The risk factors for ATE and VTE are mentioned in the SmPC. Women should weigh the benefits of Yana use against the possible risks. Yana is contraindicated if a woman has one serious or multiple risk factors for ATE or if a woman has multiple risk factors for VTE. All women taking Yana should take any precautions suggested in the SmPC and in any signs of VTE or ATE stop using Yana and contact their physician. All women should be able to recognize the symptoms of VTE or ATE.
Hypertension	Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare.	If needed, blood pressure should be controlled regularly during the Yana usage.

Chloasma	Facial pigmentation known as chloasma was reported during the administration of COC. Women with history of chloasma are at higher risk of recurrent development.	Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Yana.
Interaction with active substances which may decrease the ethinylestradiol serum levels	Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure.	Additional, barrier method of contraception should be used in the case of concomitant administration of concerned medicinal products and Yana.

Table 14 Important potential risks

Important Potential Risk	**What is known (including reason why it is considered a potential risk)**
Tumours	Some epidemiological studies have suggested that long-term use of hormonal contraceptives in women infected by the human papilloma virus (HPV) is a risk factor for the development of cervical cancer. However, it is not yet clear to what extent this outcome is influenced by other factors (e.g. differences in the number of sexual partners or in the use of mechanical methods of contraception). A meta-analysis from 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of breast cancer in women who are currently using COCs. The additional risk gradually disappears 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the additional number of breast cancer diagnoses in current and recent COC users is small compared to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. In rare cases, benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases,

	these tumours have led to life-threatening intra-abdominal haemorrhages. The possibility of a hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Table 15 Important missing information

Important Potential Risk	**What is known (including reason why it is considered a potential risk)**
Safety in pregnant and nursing women	This medicinal product is a contraceptive active substance. Animal studies have shown adverse effects during pregnancy and lactation. Based on these animal data, adverse effects due to the hormonal activity of the active substances cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual adverse effect in humans.

VI.2.5 Summary of additional minimisation measures by safety concern

Not applicable.

VI.2.6 Planned post-authorisation development plan (if applicable)

Not applicable.

Studies which are a condition of the marketing authorisation (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable for initial RMP.