EU RISK MANAGEMENT PLAN (RMP) FOR

NOMEGESTROL ACETATE + ESTRADIOL

RMP Version number: 13.0

Data lock point for this RMP: 14-Jul-2022

Date of final sign off: 11-AUG-2022

Rationale for submitting an updated RMP:

The RMP (version 13.0) was revised based on the new information following the completed referral procedure EMEA/H/A-31/1510 for chlormadinone acetate or nomegestrol acetate and meningioma risk.

Summary of significant changes in this RMP:

MP Section	UPDATE INFORMATION
PART II: MODULE SVIII Summary Of The Safety Concerns	No changes in the list of safety concerns
PART III: Pharmacovigilance Plan	Some changes deleting information about imposed, category 1 PASS which has been already finished and final report has been approved by Regulatory Authority.
PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Additional Risk Minimization Measures for meningioma risk updated with Direct Healthcare Professional Communication to be distributed in 2022. Some changes deleting information about imposed, category 1 PASS which has been already finished and final report has been approved by Regulatory Authority.
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT	Some changes deleting information about imposed, category 1 PASS which has been already finished and final report has been approved by Regulatory Authority. Additional Risk Minimization Measures for meningioma risk updated with Direct Healthcare Professional Communication to be distributed in 2022.
ANNEXES	ANNEX 3 - Some changes deleting information about imposed, category 1 PASS which has been already finished and final report has been approved by Regulatory Authority. ANNEX 4 - Meningioma Targeted Follow-up questionnaire updated based on referral outcome ANNEX 8 – list of changes in RMP updated

Other RMP versions under evaluation:

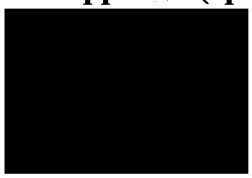
There are no previously-submitted versions of this RMP that are still under evaluation by the agency.

Details of the currently approved RMP:

Version number: 13.0

Approved with procedure: EMEA/H/A-31/1510

Date of approval (opinion date): 13-July-2022



QPPV name: Birger Fels

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
COC	Combined Oral Contraceptive
COC_{LNG}	Levonorgestrel Containing Oral Contraceptives
CT	Computed Tomography
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilization Study
E2	17β-estradiol
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NOMAC	Nomegestrol acetate
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study

PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	Nomegestrol acetate + estradiol (hereafter referred to as "NOMAC-E2")
Pharmacotherapeutic group(s) (ATC Code)	Sex hormones and modulators of the genital system, progestagens and estrogens, fixed combinations. ATC code: G03AA14.
Marketing Authorisation Holder	Theramex Ireland Limited 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1 D01 YE64 Ireland
Number of medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Zoely
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class NOMAC-E2 is a monophasic oral contraceptive containing 2.5 mg nomegestrol acetate (NOMAC), a high selective progestogen derived from the naturally occurring steroid hormone, progesterone, and 1.5 mg 17β-estradiol (E2), an estrogen identical to the endogenous human 17β-estradiol (E2), given as 24 active tablets followed by 4 placebo tablets (24/4 day regimen).
	Summary of mode of action NOMAC is a 19-norprogesterone progestogen and is designated as 17α-acetoxy-6-methyl-19-norpregna-4,6-dien-3,20-dione. E2 is synthesized as 17β-estradiol hemihydrate and is designated as estra-1,3,5(10)-triene-3,17β-diol. NOMAC has a strong affinity for the human progesterone receptor and has an anti-gonadotropic activity, a progesterone receptor-mediated anti-estrogenic activity, a moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid or mineralocorticoid activity. The contraceptive effect of NOMAC-E2 is primarily achieved by inhibition of ovulation, an effect which is already achieved by NOMAC (2.5 mg) alone, and increased viscosity of cervical mucus (which hampers sperm entry into the uterus). E2 has been added to restore suppressed estradiol levels. The effects on vaginal bleeding are considered to be the result of the combination of NOMAC and E2.
	Important information about its composition Each white active film-coated tablet contains 57.71 mg of lactose monohydrate. Each yellow placebo film-coated tablet contains 61.76 mg of lactose monohydrate.
Hyperlink to the Prescribing Information	See proposed Prescribing information in Module 1.3
Indication(s) in the EEA	Current: Oral contraception

Table Part I.1: Product Overview

Dosage in the EEA	Current: Posology: One tablet is to be taken daily for 28 consecutive days. Each pack starts with 24 white active tablets, followed by 4 yellow placebo tablets. A subsequent pack is started immediately after finishing the previous pack, without a break in daily tablet intake and irrespective of presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2-3 after intake of the last white tablet and may not have finished before the next pack is started. **Special populations** Renal impairment: Although data in renal impaired patients are not available, renal impairment is unlikely to affect the elimination of nomegestrol acetate and estradiol. Hepatic impairment: No clinical studies have been performed in patients with hepatic insufficiency. Since the metabolism of steroid hormones might be impaired in patients with severe hepatic disease, the use of Zoely in these women with hepatic impairment is not indicated as long as liver function values have not returned to normal. Method of administration: Oral use
Pharmaceutical form(s) and strengths	Current: Film-coated tablet (tablet). Active film-coated tablets: white, round and coded 'ne' on both sides. Placebo film-coated tablets: yellow, round and coded 'p' on both sides. White active film-coated tablets: Each film-coated tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate). Yellow placebo film-coated tablets: The tablet does not contain active substances.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Contraception.

Incidence: Not applicable.

Prevalence: Worldwide, 63% of females 15 to 49 years of age who were married or cohabiting used some form of contraception in 2017; contraceptive use was above 70% in Europe, Latin America, the Caribbean, and North America, and below 25% in Middle and Western Africa [Ref. 5.4: 05888W]. In 2015, female sterilization (19%) and the IUD (14%), were the most common methods used by married or in-union women worldwide followed by oral contraceptive pill (9%), male condoms (8%) and injectables (5%). The pill accounts for ≥10% of contraceptive use in over 70% of the countries contributing data to United Nations estimates; no other method is so widely used in so many countries. In 2015, the oral contraceptive pill was used by ≥20% of married or in-union women in 31 countries [Ref. 5.4: 04Z0YR].

Based on data from the Gender and Generations Program 2004-2010 survey, a multi-national study of family relationships in industrialized countries, the use of any method of contraception among women 18-44 years of age was ≥66% in all nations included in the study with the exception of Georgia where 48.7% of women reported contraceptive use. The oral contraceptive pill use was generally the most commonly reported method across countries and ranged from 10.6% in Bulgaria to 60.4% in Germany. Condom use tended to be the second most frequently reported contraceptive method ranging from 7.1% use in France to 27.6% use in Romania. Other less effective methods (emergency contraception, withdrawal, rhythm, natural family planning, foam, cream, jelly, suppository, diaphragm and cervical cap) were reported relatively frequently by women in Bulgaria (42.6%), Georgia (31.9%), Romania (27.4%), and Russia (21.7%) [Ref. 5.4: 046ZP4].

In the United States, the National Surveys of Family Growth (NSFG) collected data (in person interviews) from women 15-49 years of age on contraceptive use and choices of contraceptive methods. In the sample of 5,554 women interviewed in 2015-2017 in the United States, female sterilization, the oral contraceptive pill, long acting reversible contraception (including intrauterine devices and implants), and male condoms were the most common forms of current contraception, reported by 18.6%, 12.6%, 10.3% and 8.7%, respectively. Approximately 35% of the women age 15-44 were not currently using any form of contraception [Ref. 5.4: 058F4W].

Demographics of the population in the authorised indication: Women 15-45 are generally considered to be of childbearing potential and comprise the population commonly seeking contraceptives. In the US, among current contraceptive users 15-49 years of age, in 2015-2017, 9.2% of Hispanic women, 14.9% of non-Hispanic White women, and 8.3% of non-Hispanic Black women reported using oral contraceptive pills. Oral contraceptive pill use tended to decrease with increasing age: 16.6% of women aged 15–19 were currently

using the pill compared with 19.5% of women aged 20–29, 11.0% aged 30–39, and 5.1% aged 40–49 [Ref. 5.4: 058F4W].

Risk factors for the disease: Not applicable (N/A)

The main existing treatment options: The table below summarizes the main options available for female contraception [Ref. 5.4: 058F6G].

Table SI.1: Main Existing Treatment Options for Female Contraception

Method	Description	How it works	Effectiveness to prevent pregnancy
Combined oral contraceptives (COCs)	Contains two hormones (estrogen and progestogen)	Prevents the release of eggs from the ovaries	>99% with correct and consistent use; 92% as commonly used
Progestogen-only pills (POPs)	Contains only progestogen hormone, not estrogen	Thickens cervical mucous to block sperm and egg from meeting and prevents ovulation	99% with correct and consistent use; 90-97% as commonly used
Implants	Small, flexible rods or capsules placed under the skin of the upper arm; contains progestogen hormone only	Same mechanism as POPs	>99%
Progestogen only injectables	Injected into the muscle every 2 or 3 months, depending on product	Same mechanism as POPs	>99% with correct and consistent use; 97% as commonly used
Monthly injectables or combined injectable contraceptives (CIC)	Injected monthly into the muscle, contains estrogen and progestogen	Same mechanism as COCs	>99% with correct and consistent use; 97% as commonly used
Combined contraceptive patch and combined contraceptive vaginal ring (CVR)	Continuously releases 2 hormones-a progestin and an estrogen-directly through the skin (patch) or from the ring	Same mechanism as COCs	Effectiveness may be greater than with COCs due to lack of need for daily administration, however, data is limited.
Intrauterine device (IUD); copper containing	Small flexible plastic device containing copper sleeves or wire that is inserted into the uterus	Copper component damages sperm and prevents it from meeting the egg	>99%
Intrauterine device (IUD) levonorgestrel	A T-shaped plastic device inserted into the uterus that steadily releases small amounts of levonorgestrel each day	Thickens cervical mucous to block sperm and egg from meeting	>99%
Female condom	Sheaths, or linings, that fit loosely inside a woman's vagina, made of thin, transparent, soft plastic film	Forms a barrier to prevent sperm and egg from meeting	90% with correct and consistent use; 79% as commonly used
Female sterilization (tubal ligation)	Permanent contraception to block or cut the fallopian tubes	Eggs are blocked from meeting sperm	>99%

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Unintended pregnancies: An unintended pregnancy is a pregnancy that is either mistimed or unwanted at the time of conception [Ref. 5.4: 03KSH0]. Of the approximately 213 million pregnancies that occurred worldwide in 2012, it is estimated that 40% or 85 million were unintended. Regionally, the proportion of pregnancies that were unintended among all women 15 to 44 years of age ranged from a low of 38% in Asia to a high of 56% in Latin America/Caribbean. Proportions of unintended pregnancies in North America and Europe were 51% and 45%, respectively. The 85 million unintended pregnancies are estimated to have resulted in approximately 32 million unplanned births, 42 million abortions, and 11 million miscarriages [Ref. 5.4: 04PBT0]. Globally, unintended pregnancy is of particular concern among adolescents, with the highest rates of unintended pregnancy occurring in the youngest women. Approximately 16 million adolescents give birth each year, accounting for ~12% of all births worldwide. The proportion of all births that take place during adolescence (age 15-19 years) is approximately 15-18% in Africa, Latin America and the Caribbean, and tends to be lower in more developed countries [Ref. 5.4: 04XGBP]. In the U.S. in 2011, the percentage of pregnancies that were unintended were approximately 72% in women 15-17 years of age, 76% in 18 to 19 year old, 59% in 20 to 24 year old, 42% in 25 to 29 year old, 31% in 30 to 34 year old, and 34% in ≥ 35 year old [Ref. 5.4: 04XF4B]. Furthermore, there is a high risk of repeat unintended pregnancy in women who have had an unintended pregnancy or a previous abortion. Among adolescents who give birth, 12- 49% are pregnant again within 12 months, and 28–63% within 18 months [Ref. 5.4: 03KSH2].

There are many prenatal and perinatal consequences of unintended pregnancy including delayed initiation of prenatal care and increased risk of low weight babies, as well as longer-term consequences for the infant and mother including poor physical and mental health [Ref. 5.4: 03KSH0, 04XB3J].

Mortality in the indicated population: The target population is a healthy population. The World Health Organization (WHO) has estimated that about 830 women die from pregnancy- or childbirth-related complications around the world every day. In 2015, 303,000 women died during and following pregnancy and childbirth [Ref. 5.4: 04XB3L] including approximately 50,000 that die each year due to unsafe abortions [Ref. 5.4: 04XBG4]. Medical complications associated with pregnancy and childbirth are the major causes of death in adolescent girls in most developing countries, who face a higher risk than older women [Ref. 5.4: 04XB3L].

The European Region has made considerable progress in improving maternal health since 2000, with an average reported maternal mortality rate of 11 per 100,000 live births in 2014. However, there is substantial variation both within and between countries. The maternal mortality rate is approximately 4 per 100,000 live births in countries of the European Union, while the reported average in countries of the Commonwealth of Independent States is 16 per 100,000 live births [Ref. 5.4: 058F56].

The pregnancy-related mortality rate (including during pregnancy and within 1 year of the end of pregnancy) in the US has increased between 1987 and 2015 from 7.2 per 100,000 live

births to 17.2 per 100,000 live births. The reasons for this increase in pregnancy-related mortality are not fully understood but may be due to improved identification of pregnancy related deaths, changes in the coding of causes of death, racial and ethnic disparities and increasing frequency of chronic medical conditions in pregnant women [Ref. 5.4: 058F5P].

Important co-morbidities:

Important co-morbidity in the target population is considered to be Sexual Transmitted Diseases (STD), Human Papilloma Virus (HPV) infection, HIV, and abnormal cervical cytology.

Table SI.2: Important Comorbidity in the Target Population for Sexually Transmitted Disease

Sexually Transmitted Disease	
Incidence	Based on a meta-analysis conducted by WHO, the global incidence rates in 2016 per 1000 women 15-49 years for the curable STDs chlamydia, gonorrhea, trichomoniasis, and syphilis were 34 (95% CI: 25–45), 20 (95% CI: 14–28), 40 (95% CI: 27–58), and 1.7 (95% CI: 1.4–2.0), respectively [Ref. 5.4: 058NDH].
Prevalence	Based on a meta-analysis conducted by the WHO using prevalence data from 2009-2016, the estimated pooled global prevalence of chlamydia in 15–49-year-old women was 3.8% (95% CI: 3.3–4.5), with regional values ranging from 1.5 to 7.0%. For gonorrhea, the global estimate was 0.9% (95% CI: 0.7–1.1), with regional values ranging from 0.3 to 1.9%. The estimates for trichomoniasis were 5.3% (95% CI: 4.0–7.2), with regional values ranging from 1.6 to 11.7%. For syphilis, the global estimate was 0.5% (95% CI: 0.4–0.6) with regional values ranging from 0.1 to 1.6%. For the European region the prevalence was 3.2 (95% CI: 2.5–4.2), 0.3 (95% CI: 0.1–0.6), 1.6 (95% CI: 1.1–2.3), and 0.1 (95% CI: 0.0–0.4) for chlamydia, gonorrhea, trichomoniasis, and syphilis were, respectively [Ref. 5.4: 058NDH].
Mortality	Mother-to-child transmission of STIs can result in stillbirth, neonatal death, low-birth-weight and prematurity, sepsis, pneumonia, neonatal conjunctivitis, and congenital deformities. Approximately 1 million pregnant women had active syphilis in 2016, resulting in more than 350,000 adverse birth outcomes of which 200,000 occurred as stillbirth or neonatal death [Ref. 5.4: 058NDJ].

EU = European Union; STD = sexually transmitted disease; US = United States; WHO = World Health Organization; CI = confidence interval; STI = sexually transmitted infection

Table SI.3: Important Comorbidity in the Target Population for HPV Infection

	HPV Infection
Incidence	In several cohort studies, using polymerase chain reaction (PCR) for viral detection, incidence rates of genital HPV infections were determined in women. The studied age range differed per study. The incidence rates per 100 woman years for all HPV types varied from 14 to 36 in younger age groups (ie, age range: 15-19 and 15-20) to 18 in the age range of 17-42. [Ref. 5.4: 03KHP9] In a UK study with women ≤ 27 years, 17.7% were infected with one or more HPV genotypes. The estimated annual incidence was 12.9% (11.0% to 15.0%) for any carcinogenic HPV infection. (Annual incidence of HPV infection was estimated by dividing the number of incident cases by the total person years of follow-up; the rate per 100 person years was then expressed as the percentage annual incidence) [Ref. 5.4: 03KSHB] A Dutch prospective follow up study of 2,065 unscreened women aged 18–29 years showed an incidence rate of any-type high risk HPV to be 17 infections (14.3 for low risk HPV) per 1,000-person months [Ref. 5.4: 03KSH7].
Prevalence	A meta-analysis (one million women) of cervical HPV prevalence and age-specific prevalence distributions restricted to women with normal cytological findings, revealed a global adjusted HPV prevalence of 11.7%; and a prevalence of 4.7% for North America and between 8.8% (southern) - 21.4% (eastern) in Europe. Age specific, prevalence was highest in <25 year olds (23.2% in North America and 22.7% in Europe); and low among 35- 44 year old women (4.9% in North America and 11% in Europe). [Ref. 5.4: 03KSHR] As part of NHANES 2011 in the United States, more than 4000 females collected cervicovaginal specimens for HPV testing. The overall prevalence of 37 different types of HPV was 42.5%, which represents approximately 40 million infections. Specifically, the prevalence of high-risk HPV types was 29%. The prevalence of HPV was lowest among females 14-19 years of age (32.9%) and highest among women 20-24 years of age (53.8%) [Ref. 5.4: 03KSHV]. A meta-analysis of 21 UK studies showed a pooled prevalence for any high risk HPV to be 12%. Among age strata, prevalence estimate among women aged 20–24 years was 27%; aged 25–29 was 19% and among women aged 30–39 years was 9.5% [Ref. 5.4: 03K6M3] In a German study [Ref. 5.4: 03KSHC] with two birth cohorts, the prevalence of HR-HPV was 22.8% in the 1983/84 cohort (150/659) and 23.7% in the 1988/99 cohort (142/599); and 8.5% in low risk HPV.
Mortality	Most HPV infections are asymptomatic, and they resolve without treatment. However, some infections result in changes to the epithelium or even worse cancer. A study investigating HPV related cancers estimated that 3%, 12%, 40%, 90%, and 100% of mouth, oro-pharyngeal, vulvovaginal, anal, and cervical cancer, respectively are attributable to HPV, accounting for approximately 10% of all malignancies. [Ref. 5.4: 03KHNS]

CI = confidence interval; HPV = human Papilloma Virus; PCR = polymerase chain reaction.

Table SI.4: Important Comorbidity in the Target Population for HIV

Sexually Transmitted Disease	
Incidence	Globally, from 2010 onwards, new HIV infections among young women (aged 15-24 years) have declined by 17%, reaching 360,000 in 2016. In high HIV prevalence settings, young women remain at disproportionally high risk of HIV infection; in eastern and southern Africa young women accounted for 26% of new HIV infections in 2016 despite making up 10% of the population. Young women in western and central Africa and the Caribbean, respectively, accounted for 22% and 17% of new HIV infections in 2016 [Ref. 5.4: 04VM6P]. In 2016, in the EU/EEA the incidence of HIV among women was 2.6 per 100,000. Among women 15-49, those 30-39 years of age had the highest incidence rate of 6.8 per 100,000. Incidence rates for women 15-19, 20-24, 25-29 and 40-49 ranged from approximately 2-6 per 100,000 [Ref. 5.4: 04XRYR]. In the US in 2016 there were approximately 7,529 incident cases of HIV in women ≥ 13 years of age yielding an incidence rate of 5.4 per 100,000 [Ref. 5.4: 04XRJP]. Women 25-34 accounted for the highest proportion of newly diagnosed HIV cases in the US in 2010, comprising 29% of new cases in women. Women 13-24 and 35-44 represented 22% and 25% of new cases, respectively [Ref. 5.4: 04XRHX].
Prevalence	Based on WHO estimates, there were 36.7 million people living with HIV globally in 2016; 3.3 and 2.4 million in the Americas and European regions, respectively. Of the global adult population 15-49, 0.8% was living with HIV in 2016. The HIV prevalence in 15-49 years old was 0.4% and 0.5% in the European and Americas WHO regions, respectively [Ref. 5.4: 04XS5D]. In the US in 2014 there were an estimated 255,900 women living with HIV [Ref. 5.4: 04XRV2]. In the EU/EEA approximately 810,000 people were living with HIV in 2015 [Ref. 5.4: 04XRVP].
Mortality	Globally, AIDS-related illnesses remain the leading cause of death among women of reproductive age (15–49 years); they are the second leading cause of death for young women aged 15–24 years in Africa [Ref. 5.4: 04VM6P]. In 2016, worldwide, there were approximately 1,000,000 HIV-related deaths with 54,000 and 49,000 in the Americas and European WHO regions, respectively [Ref. 5.4: 04XS5D]. In the US in 2015 an estimated 1,667 women died of HIV [Ref. 5.4: 04XRV2].

EU/EEA = European Union/European Economic Area; US = United States; WHO = World Health Organization

Table SI.5: Important Comorbidity in the Target Population for Abnormal Cervical Cytology

	Abnormal Cervical Cytology
Incidence	In a prospective cohort study, 128,805 women were screened throughout the US for cervical cancer within 3 years of normal cytology [Ref. 5.4: 03KHP4]. The incidence of cytological abnormalities defined as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and suggestive of squamous cell cancer among different age groups were determined, over the 3 years after normal cytology results: Incidence in women < 30 years old: Normal/benign: 81.5%, Infection/reaction: 8.2%, ASCUS: 5.4%, LSIL: 2.3%, HSIL: 0.7%, Squamous cell cancer: 0.01% Incidence in women aged 30-49 years old: Normal/benign: 84.7%, Infection/reaction: 9.0%, ASCUS: 4.1%, LSIL: 1.0%, HSIL: 0.2%, Squamous cell cancer: 0.01%.
Prevalence	In an Italian study in women aged 18- 26 years an abnormal cytology was found in 11.3% (124/1,093) samples: 5.6% (62) ASCUS/AGUS; 4.7% (52) LSIL; 0.5% (6) ASCH and 0.3% (4) HSIL. [Ref. 5.4: 03KSHF] In another Italian study in women from cervical cancer region-wide screening programme aged 25-64, an abnormal cytology was found in 6.2% (210/3410) of the samples: 3.4% ASCUS; 2.1% LSIL; 0.2% HSIL and 0.3% ASCH [Ref. 5.4: 03KSHG] In a Spanish study in 2,461 samples from women aged 15-75 years, an abnormal cytology was found in 32.7% (805/2461) samples: 13.7% ASCUS; 15.7% LSIL; 3.3% HSILs. [Ref. 5.4: 03KSHF] Based on the American National Breast and Cervical Cancer Early Detection Program (NBCCEDP) the prevalence of cervical cancer screening results among women of different age groups were derived (2001-2002) [Ref. 5.4: 03KSHD]. The results are summarized below: Total prevalence: Normal/benign: 81.1%, Infection/reaction: 11.2%, ASCUS: 4.0%, LSIL: 1.5%, HSIL: 0.8%, Squamous cell cancer: 0.1% Age group 18-29: Normal/benign: 68.0%, Infection/reaction: 13.1%, ASCUS: 7.4%, LSIL: 7.7%, HSIL: 2.6%, Squamous cell cancer: 0.0% Age group 30-39: Normal/benign: 78.0%, Infection/reaction: 12.3%, ASCUS: 4.8%, LSIL: 2.2%, HSIL: 1.2%, Squamous cell cancer: 0.1% Age group 40-49: Normal/benign: 81.3%, Infection/reaction: 11.5%, ASCUS: 4.0%, LSIL: 1.2%, HSIL: 0.6%, Squamous cell cancer: 0.1% In a study of Rebolj et al (2007), evaluating the performance of the Dutch cervical cancer screening program, a comparison was made with cervical cancer screening programs in Finland, England and Sweden. [Ref. 5.4: 03KHNW] The target age groups in the programs are 30-60 years in the Netherlands and Finland, 25-64 years in England, and 20-60 years in Sweden. The percentage of positive cytology was 2.3% in the Netherlands, 7.3% in Finland, 6.4% in England and 1.5% in Sweden, of which 0.5%, 0.6%, 1.1% were highly positive cytology in the Netherlands, Finland, and England, respectively. The percentage of highly positive cytology was not available for Sweden. Classification of cytology as being positive varies between countries, ie, ≥Pap 2 in the Netherlands and Finland, ≥borderline dyskaryosis in England and ≥CIN 1 in Sweden. Pap3a2+, Pap3+ and ≥moderate dyskaryosis are considered as highly positive cytology in the Netherlands, Finland and England, respectively.
Mortality	Not applicable since abnormal cytology in itself does not directly contribute to increased mortality.

ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; US = United States.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

NOMAC-E2 and NOMAC used for supplement or replacement therapy for hormonal deficiency have been marketed for several decades without major serious adverse events that would warrant additional non-clinical investigation. The non-clinical safety data are summarized in the table below.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Repeat dose toxicity	
NOMAC only shows slight and reversible general toxic effects. The combination of NOMAC-E2 showed a toxicological profile typical of an estrogen-progestagen combination, with a predominance of estrogenic effects, particularly in the rat.	Tested dose levels were high and high systemic exposure in reference to the Anticipated Human Dose could be reached. In view of the exposure margins, general toxicity related adverse events are unlikely.
Reproductive toxicity	
In the female rat NOMAC had no effect on fertility up to the highest dose tested although this dose induced slight disturbances of the estrus cycle. NOMAC alone has no embryotoxic or teratogenic effects and does not affect the postnatal development of the offspring. The contraceptive combination induced maternal toxicity as well as fetal variations at systemic exposures are similar to that in the woman. The expected interference of the NOMAC-E2 combination with female fertility was rapidly reversible after treatment withdrawal.	Transient reduction of fertility index without toxic effect is rapidly reversible after treatment withdrawal.
Developmental toxicity	
NOMAC has no effects on early development as well as on peri- and post-natal development. NOMAC has no embryotoxic and teratogenic effects in rodents and rabbits. The combination of NOMAC-E2 induced maternal toxicity as well as fetal variations at systemic exposure similar to or slightly higher than that expected in the woman, indicating that changes observed with the combination were related to the presence of E2.	Estrogens and progestagens should not be used during pregnancy.
Nephrotoxicity	
Only incidental mild effects observed at high doses.	Tested dose levels were high and high systemic exposure in reference to the Anticipated Human Dose could be reached. In view of the exposure margins, general toxicity related adverse events are unlikely.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Hepatotoxicity	
Only incidental mild effects observed at high doses.	Tested dose levels were high and high systemic exposure in reference to the Anticipated Human Dose could be reached. In view of the exposure margins, general toxicity related adverse events are unlikely.
Genotoxicity	
NOMAC has no genotoxic properties.	No special reasons for concern.
Carcinogenicity	
NOMAC had no carcinogenic effect in the rat and only induced mammary and pituitary tumors in mice, findings which are known for this class of compounds in rodents. E2 is known for its carcinogenic effects in rodents.	No special reasons for concern.
Cardiovascular Safety Pharmacology (including QT interval prolongation)	
NOMAC at high concentrations can inhibit hERG tail current. Single dose administration to Cynomolgus monkeys did not result in effects on cardiovascular or ECG parameters.	In view of the wide safety margins NOMAC is unlikely to cause any relevant cardiovascular adverse events.
Mechanism for Drug Interactions	
No relevant interactions with P-gp, no CYP-induction or CYP-inhibition. Metabolism mainly by CYP3A4/5, with possible contribution of CYP2C19, and CYP2C8.	Co-administered drugs that induce CYP3A4/5, CYP2C19, and/or CYP2C8 may decrease NOMAC exposure and consequently its efficacy.
Other Toxicity-Related Information or Data	
Not applicable.	Not applicable.

CYP = Cytochrome P450; E2 = 17β-estradiol; ECG = electrocardiogram; hERG = human Ether-à-go-go Related Gene; NOMAC = Nomegestrol acetate; P-gp = P-glycoprotein.

Need for Additional Nonclinical Data for Use in Special Populations

NOMAC-E2 is intended as a contraceptive for all fertile women who have a fully functioning reproductive system. No toxicology studies in juvenile animals have been performed, or are planned. Thus, the applicant has developed no separate strategy in relation to nonclinical development aspects for the adolescent population. In addition, it should be noted that non-clinical safety studies are generally performed in young adult rats and, therefore, the collected data are also relevant for the adolescent population.

There is no need for toxicity studies for neurotoxicity, immunotoxicity, or nephrotoxicity endpoints, since steroids are not immunotoxic at clinically relevant doses and in the preclinical pharmacological safety studies no indication for neurotoxicity or nephrotoxicity was found.

Conclusions on Non-clinical Data

Table SII.2: Summary of Important Safety Concerns from Non-clinical Data

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

NOMAC-E2 is a monophasic oral contraceptive containing a fixed dose nomegestrol acetate (NOMAC, 2.5 mg) and 17β-estradiol (E2, 1.5 mg), given in a 24 (active tablets) / 4 (placebo) regimen. NOMAC-E2 is indicated for oral contraception.

Approximately 6,434 women were exposed to the NOMAC-E2 tablet formulation during development including 478 in Phase 1 studies, 85 in Phase II, and 5871 in Phase III.

Phase I clinical pharmacology studies (Total N = 478)

- Study 292006, Single and multiple dose pharmacokinetics of the tablet formulation used in the clinical Phase III program (N= 25)
- Study 292007, A study to compare the pharmacokinetics of NOMAC after single dose oral administration of different NOMAC-E2 batches (N=18)
- Study 292008, A study to compare the pharmacokinetics of NOMAC after single dose administration of NOMAC-E2 between healthy female adolescents and female adults (N=30)
- Study 292011, A study to investigate the effect of multiple oral therapeutic and supratherapeutic doses of NOMAC-E2 on QT/QTc interval in healthy women (N=189)
- Study 06328, A bio-equivalence study comparing the batches used in the pivotal studies with the batch prepared using the commercial production process (N=156).
- Study 06456, A food effect study with the commercial film-coated NOMAC-E2 tablet formulation was performed to complete the characterization of the commercial tablet formulation (N=60).

Phase II studies (Total N = 85)

- Study 02-ESC/NOM-1-RD investigated dose finding, regimen validation and efficacy and clinical safety parameters (N=40).
- Study 02-ESC/NOM-2-RD investigated the effects of NOMAC-E2 on markers of coagulation and fibrinolysis (N=45).

The Phase III studies (N listed for subjects in NOMAC-E2 groups only; total N=5871)

- Studies 292001 (N=1591) and 292002 (N=1666) pivotal efficacy and safety studies
- Study 292004 (N=60) a metabolic safety study versus levonorgestrel plus ethinylestradiol (LNG-EE) including effects on hemostasis, lipid metabolism, carbohydrate metabolism, adrenal function, thyroid function and androgens

- Study 292003 (N=32), a pharmacodynamic study into the contraceptive mechanism of action versus drospirenone plus ethinylestradiol (DRSP-EE)

- Study 292005 (N=56), a bone mineral density study

- Study 022-01 (N=2466) a randomized, open-label, multicenter trial to assess the contraceptive efficacy and safety of NOMAC-E2. The study included a comparator agent, norethisterone acetate plus ethinylestradiol (NETA-EE). This study was discontinued based upon difficulties encountered with data collection (related to incomplete eDiary entries) in concert with business considerations. This decision was not related to any new or unexpected safety or efficacy findings with MK-8175A.

This RMP is based upon safety data from a total of seven trials (two Phase II and five Phase III) that were pooled for an integrated analysis (Integrated Safety Data Set, ISDS) and one Phase III trial (P022-01) which was not possible to be pooled due to differences in database platforms.

The Phase I trials were not included in the ISDS because the treatment durations were relatively short (24, 1, and 14 day(s), respectively). The 21/7 regimen data set of the 02-ESC/NOM-1-RD trial was also excluded from the ISDS as the treatment regimen differs from the marketed product which has a 24/4 regimen.

The Integrated Safety Data Set (ISDS) includes all trials that were conducted with the 'to be marketed' formulation (NOMAC-E2; 2.5 mg - 1.5 mg) administered in the 'to be marketed' regimen (a cyclic 28-day regimen of 24 active and 4 placebo tablets) to healthy female volunteers at risk for pregnancy.

The two Phase II trials (02-ESC/NOM-1-RD (24/4 data only) and 02-ESC/NOM-2-RD) were included in the ISDS because they were conducted with the same dose regimen; however, uncoated tablet were used instead of coated tablets as in the other trials. Data from the Phase III trial (P022-01) are presented separately.

Trials included in the Integrated Safety Data Set are shown in Table SIII.1

Table SIII.1: Trials with the Investigational Drug Product Formulation and Dose Regimen Included in the Integrated Safety Data Set

Report Number	Number of Subjects Exposed	Treatment Duration	Report Title
02- ESC/NOM-1-RD Phase II	40	3 cycles	Estradiol/NOMAC contraceptive combination: Double-blind, randomized, comparative study of 2 regimens (21 days out of 28 versus 24 days out of 28) on follicle like structure maturation during the treatment free period.
02- ESC/NOM -2-RD Phase II	45	3 cycles	A double-blind, randomized study to compare the effects of a new contraceptive pill (estradiol/NOMAC) on blood coagulation and fibrinolysis versus Miranova® during a 3-month treatment period.
292001 Phase III	1591	13 cycles	A randomized, open-label, comparative, multi-center trial to evaluate contraceptive efficacy, cycle control, safety and acceptability of a monophasic combined oral contraceptive (COC) containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg estradiol (E2), compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinyl-estradiol (EE).
292002 Phase III	1666	13 cycles	A randomized, open-label, comparative, multi-center trial to evaluate contraceptive efficacy, cycle control, safety and acceptability of a monophasic combined oral contraceptive (COC) containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg estradiol (E2), compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinyl estradiol (EE).
292003 Phase III	32	6 cycles	A randomized, open-label, comparative trial to evaluate the effects on ovarian function of a monophasic combined oral contraceptive (COC) containing 2.5 mg nomegestrol acetate (NOMAC) and 1.5 mg estradiol (E2), compared to a monophasic COC containing 3 mg drospirenone (DRSP) and 30 µg ethinyl estradiol (EE).
292004 Phase III	60	6 cycles	A randomized, open-label, comparative trial to evaluate the effects on hemostasis, lipids and carbohydrate metabolism, and on adrenal and thyroid function of a monophasic COC containing 2.5 mg NOMAC and 1.5 mg E2, compared to a monophasic COC containing 150 µg levonorgestrel (LNG) and 30 µg EE.
292005 Phase III	56	26 cycles	An open-label, randomized, single center trial in healthy young women, to evaluate the effects of a monophasic combined oral contraceptive (COC) containing 2.5 mg NOMAC and 1.5 mg E2 on bone mineral density (BMD) compared to a monophasic COC containing 0.150 mg levonorgestrel and 0.030 mg ethinylestradiol.

BMD = bone mineral density; COC = combined oral contraceptive; DRSP = drospirenone; E2 = 17β-estradiol; EE = ethinyl estradiol; LNG = levonorgestrel; NOMAC = nomegestrol acetate.

Within the ISDS, a total of 3,490 subjects were exposed to NOMAC-E2 for a total of 35,028.0 cycles (2,694.5 woman years) as summarized below in Table SIII.2. The mean and median extent of exposure (in 28-day cycles) was 10.0 and 13.0 cycles, respectively. A total of 85 subjects were exposed to NOMAC-E2 in randomized, double-blind trials included in the ISDS. These trials are the 2 Phase II trials as listed in Table SIII.2.

Table SIII.2: Summary of Clinical Trial Exposure with NOMAC-E2 in Contraception for Pooled Studies – All Subjects Treated

		All ISDS Clinical Trials N=3490	Randomized, Blinded Trials N=85
Extent of exposure (in 28-days cycles)	Mean (SD)	10.0 (4.8)	2.9 (0.3)
	Median (Min – Max)	13.0 (0, 27)	3.0 (1, 3)
Number of woman years		2694.5	19.2
Number of 28-day cycles		35028.0	249.5

ISDS = Integrated safety data set ; SD = standard deviation; Min = minimum; Max = maximum

Note: if the extent of exposure could not be determined, it was set to zero.

The exposure by duration in clinical trials included in the Integrated Safety Data Set (ISDS) is summarized in Table SIII.3.

Table SIII.3: Summary of Clinical Trial Exposure with NOMAC-E2 in Contraception for Pooled Studies by Duration – All Subjects Treated

	All Clinical Trials		**Randomized, Blinded Trials**	
	(N=3490)		(N=85)	
	Number of Subjects	Women Years	Number of Subjects	Women Years
Completing 3 cycles	3097	714.7	82	18.9
Completing 6 cycles	2678	1235.8		
Completing 13 cycles	2122	2120.0		
Completing 26 cycles	42	83.6		

Note that the women years do not add up to the total number of women years presented in Table 10.

Exposure data broken down by clinical Trials 292001 and 292002, as well as exposure data broken down by different geographical regions in these two trials is provided in Table SIII.4.

Table SIII.4: Summary of Exposure to NOMAC-E2 in Trials 292001 and 292002, per Trial and Region – All Subjects Treated

		P292001				P292002		
		Asia	Australia	Europe	Overall	North America (a)	Latin America (b)	Overall
Extent of exposure (in 28-days cycles)	n (%)	66 (4.1)	80 (5.0)	1445 (90.8)	1591	1247 (74.8)	419 (25.2)	1666
	Mean (SD)	12.3 (2.4)	9.4 (4.7)	10.9 (3.8)	10.9 (3.8)	8.9 (4.9)	11.1 (3.7)	9.5 (4.7)
	Median (Min - Max)	13.0 (1, 14)	12.9 (0, 14)	13.0 (0, 15)	13.0 (0, 15)	12.8 (0, 15)	13.0 (0, 15)	13.0 (0, 15)
Number of women years		62.2	58.0	1208.9	1329.1	857.3	358.7	1216.0
Number of 28-day cycles		809.2	753.9	15715.1	17278.3	11144.7	4663.3	15808.0

n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum
a) Including Canada
b) Including Mexico

Exposure by age within the ISDS is summarized in Table SIII.5. The majority of subjects were aged 18-35 years.

Table SIII.5: Summary of Clinical Trial Exposure with NOMAC -E2 in the Integrated Safety Data Set by Age Category – All Subjects Treated

		All Clinical Trials (N=3490)			Randomized, Blinded Trials (N=85)		
		Age (years)			Age (years)		
		18-24	25-35	36-50	18-24	25-35	36-50
Extent of exposure (in 28-days cycles)	n (%)	1445 (41.4)	1494 (42.8)	551 (15.8)	33 (38.8)	47 (55.3)	5 (5.9)
	Mean (SD)	9.8 (5.3)	10.1 (4.5)	10.7 (4.0)	3.0 (0.3)	3.0 (0.2)	2.6 (1.0)
	Median (Min - Max)	13.0 (0, 27)	13.0 (0, 26)	13.0 (0, 15)	3.0 (1, 3)	3.0 (1, 3)	3.0 (1, 3)
Number of women years		1084.4	1155.1	454.9	7.5	10.7	1.0
Number of 28-day cycles		14097.0	15016.7	5914.2	97.4	139.4	12.8

n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum

Exposure by ethnic origin within the ISDS is summarized in Table SIII.6. The majority of the subjects were white Caucasian women.

Table SIII.6: Summary of Clinical Trial Exposure with NOMAC -E2 in the Integrated Safety Data Set by Race – All Subjects Treated

		All Clinical Trials (N=3490)				Randomized, Blinded Trials (N=85)			
		Race				Race			
		Asian	Black/African American	White	Other	Asian	Black/African American	White	Other
Extent of exposure (in 28-days cycles)	n (%)	117 (3.4)	153 (4.4)	3128 (89.6)	92 (2.6)	4 (4.7)	9 (10.6)	67 (78.8)	5 (5.9)
	Mean (SD)	11.0 (4.2)	6.8 (5.2)	10.2 (4.7)	9.5 (5.1)	3.0 (0.0)	3.0 (0.0)	2.9 (0.4)	3.0 (0.0)
	Median (Min - Max)	13.0 (0, 26)	5.5 (0, 14)	13.0 (0, 27)	13.0 (0, 15)	3.0 (3, 3)	3.0 (3, 3)	3.0 (1, 3)	3.0 (3, 3)
Number of women years		99.2	80.6	2447.7	67.0	0.9	2.1	15.0	1.2
Number of 28-day cycles		1289.5	1047.5	31820.3	870.7	12.0	27.0	195.5	15.0

n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum

Exposure by Body Mass Index (BMI) is summarized in Table SIII.7. The majority of subjects had normal BMI (≥18.5 - <25 kg/m^2).

Table SIII.7: Summary of Clinical Trial Exposure with NOMAC-E2 in Contraception for Pooled Studies by BMI Category – All Subjects Treated

		All Clinical Trials (N=3490)				Randomized, Blinded Trials (N=85)		
		BMI (kg/m2))				BMI (kg/m2))		
		<18.5	>=18.5 to <25	>=25 to <30	>=30	<18.5	>=18.5 to <25	>=25 to <30
Extent of exposure (in 28-days cycles)	n (%)	121 (3.5)	2300 (65.9)	779 (22.3)	290 (8.3)	2 (2.4)	68 (80.0)	15 (17.6)
	Mean (SD)	10.0 (4.8)	10.2 (4.7)	9.7 (5.0)	9.8 (5.0)	3.0 (0.0)	3.0 (0.3)	2.8 (0.6)
	Median (Min - Max)	13.0 (0, 26)	13.0 (0, 27)	13.0 (0, 26)	13.0 (0, 26)	3.0 (3, 3)	3.0 (1, 3)	3.0 (1, 3)
Number of women years		93.0	1802.9	580.4	218.2	0.5	15.5	3.2
Number of 28-day cycles		1209.6	23437.1	7544.8	2836.4	6.0	201.8	41.8

n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum

Exposure from study protocol 022-01 (P022-01) is provided separately (Tables SIII.8-10). As previously noted, a difference in the platforms used for collecting the data prevents integration of exposure data from P022-01 with the ISDS. This study, which was being conducted for registration within the United States, began in November 2012 and enrollment

completed in May 2013. The study was discontinued in November 2013 due to difficulties encountered with data collection (related to incomplete eDiary entries) in concert with business considerations. The decision to discontinue the study was not related to any new or unexpected safety or efficacy findings with NOMAC-E2. In P022-01 a total of 2,466 subjects were exposed to NOMAC-E2 for a total of 20,238.0 cycles (1,556.8 woman years). The mean and median extent of exposure (in 28-day cycles) was 8.2 and 9.0 cycles, respectively. These data represent the All-Subjects-Treated (AST) dataset, included in the final abbreviated clinical study report (aCSR; 10-Oct-2014). One hundred and three subjects were randomized but did not take any trial medication. Table SIII.9 below provides the exposure for P022-01 by age and Table SIII.10 provides exposure by race/ ethnicity.

Table SIII.8: P022-01 Extent of Exposure by Treatment Group – All Subjects as Treated

Parameter	Statistics	Treatment group as treated		
		MK-8175A	NETA-EE	Total
Extent of exposure (in 28-days cycles)	N	2466	604	3070
	Mean	8.2	8.7	8.3
	SD	3.9	4.1	3.9
	Min	0.0	0.0	0.0
	Median	9.0	10.0	9.1
	Max	13.6	13.7	13.7
Cumulative exposure in woman years		1556.8	403.8	1960.6
Cumulative exposure in 28-day cycles		20238.0	5249.6	25487.6

Note: if the extent of exposure could not be determined, it was set to zero.

Table SIII.9: P022-01 Extent of Exposure by Treatment Group All Subjects as Treated by Age

	NOMAC-E2		NETA-EE		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,466		604		3,070	
Age (Years)						
<=35	1,976	(80.1)	476	(78.8)	2,452	(79.9)
> 35	490	(19.9)	128	(21.2)	618	(20.1)
Mean	29.2		29.5		29.3	
SD	7.6		7.7		7.6	
Median	28.0		28.0		28.0	
Range	18 to 50		18 to 49		18 to 50	

Table SIII.10: P022-01 Extent of Exposure by Treatment Group All Subjects as Treated by Racial Group/ Ethnicity

	NOMAC-E2		NETA-EE		Total	
	n	(%)	n	(%)	n	(%)
Race						
American Indian Or Alaska Native	33	(1.3)	7	(1.2)	40	(1.3)
Asian	45	(1.8)	10	(1.7)	55	(1.8)
Black Or African American	482	(19.5)	131	(21.7)	613	(20.0)
Multiple	166	(6.7)	35	(5.8)	201	(6.5)
Native Hawaiian Or Other Pacific Islander	12	(0.5)	3	(0.5)	15	(0.5)
White	1,728	(70.1)	418	(69.2)	2,146	(69.9)
Ethnicity						
Hispanic Or Latino	510	(20.7)	108	(17.9)	618	(20.1)
Not Hispanic Or Latino	1,949	(79.0)	495	(82.0)	2,444	(79.6)
Not Reported	3	(0.1)	1	(0.2)	4	(0.1)
Unknown	4	(0.2)	0	(0.0)	4	(0.1)

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patients with hypersensitivity to the active substances or to any of the excipients of NOMAC-E2.	Alternate treatments must be considered for such patients.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with the presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism) or presence of a severe or multiple risk factor(s) for venous thrombosis, including severe hypertension.	Epidemiological studies have associated the use of CHCs with an increased risk for venous thromboembolism. Alternate treatments must be considered for such patients.	**Yes**	**N/A**
Patients with the presence or history of arterial thrombosis (e.g. myocardial infarction), prodromal conditions (e.g. transient ischaemic attack, angina pectoris) or presence of a severe or multiple risk factor(s) for arterial thrombosis, including severe hypertension.	Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism. Alternate treatments must be considered for such patients.	**Yes**	**N/A**
Patients with a history of migraine with focal neurological symptoms.	The risk of cerebrovascular accident increases with migraine with focal neurological symptoms. Alternate treatments must be considered for such patients.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.	Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using CHCs. Alternate treatments must be considered for such patients.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with Presence or history of severe hepatic disease as long as liver function values have not returned to normal.	Impaired liver function may increase the bioavailability of steroids, which may result in increased incidence of adverse effects.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patients with Presence or history of liver tumours (benign or malignant).	In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of CHCs. Alternate treatments must be considered for such patients.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts).	Epidemiological studies have indicated that long-term use of ethinylestradiol-containing CHCs may contribute to an increased risk of breast cancer. Alternate treatments must be considered for such patients.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with Undiagnosed vaginal bleeding	Changes in vaginal bleeding patterns may mask an underlying gynecological condition that may be contraindicated in the use of CHCs. If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated.	**No**	**Listed as a contraindication in the NOMAC-E2 SmPC.**
Patients with a known or suspected pregnancy	NOMAC-E2 is indicated for contraception and is not indicated during pregnancy. If pregnancy occurs while taking NOMAC-E2, further intake should be stopped.	**Yes**	**NA**
Patients with jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.	These conditions have been reported to occur or deteriorate with both pregnancy and CHC use and were excluded in order to minimize confounding in the assessment of safety in clinical trials.	**No**	**Listed in the Special Warning and Precautions Section of the NOMAC-E2 SmPC.**
Patients with abnormal cervical smear	Condition was a potentially confounding baseline characteristic in the assessment of safety in clinical trials.	**No**	**Clinical research over time has demonstrated that abnormal pap testing is related to HPV viral infection and is not secondary to hormonal contraception.**

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Patients who are breastfeeding	Condition was a potential confounding baseline characteristic in the assessment of efficacy data in clinical trials.	**No**	**Listed as not recommended in the NOMAC-E2 SmPC.**
Patients using medications known to induce liver enzymes	The use of medications that induce liver enzymes were prohibited in clinical trials since these medications may affect the bioavailability of steroids and may have resulted in potential confounding of efficacy data in pivotal efficacy trials.	**No**	**Listed as medications which could potentially interact with NOMAC-E2 in the SmPC.**

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Table SIV.2.1: Limitations of Clinical Trial Programme

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare (it may be appropriate to choose other ADR frequencies)	In the integrated safety data set, a total of 3,490 subjects were exposed to NOMAC-E2 within the clinical development program for a total of 2,694.5 woman years (35,028.0 cycles). The mean and median extent of exposure (in 28-day cycles) was 10.0 and 13.0 cycles, respectively. In P022, a total of 2,466 subjects were exposed to NOMAC-E2 for a total of 20238.0 cycles (1,556.8 woman years). The mean and median extent of exposure (in 28-day cycles) was 8.2 and 9.0 cycles, respectively	This sample size allows for the detection with >95% probability of 1 of more adverse experiences per 899 women years.
Due to prolonged exposure	The maximum duration of exposure to NOMAC-E2 during the clinical development program was 2 years (26 28-day cycles).	Exposure to NOMAC-E2 was investigated for up to 2 years in clinical trials. Novel effects are not anticipated based upon what is known about the use of CHCs over time.
Due to cumulative effects	Exposure up to 2 years in clinical trials.	Exposure to NOMAC-E2 was investigated for up to 2 years in clinical trials. Novel effects are not anticipated based upon what is known about the use of CHCs over time.
Which have a long latency	Exposure up to 2 years in clinical trials.	Exposure to NOMAC-E2 was investigated for up to 2 years in clinical trials. Novel effects are not anticipated based upon what is known about the use of use of CHCs over time.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

The population studied during clinical trials is similar to the intended population for marketed use, ie, healthy fertile women, who would like to use NOMAC-E2 for contraception.

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	The use of NOMAC-E2 in pregnancy and lactation has not been studied. Before starting treatment with NOMAC-E2, pregnancy must be excluded. Small amounts of NOMAC-E2 may be excreted in human milk, but there is no evidence that this adversely affects infant health.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment	Safety or pharmacokinetics of NOMAC-E2 in patients with hepatic impairment have not been studied. However, the metabolism of NOMAC-E2 might be impaired in patients with severe hepatic disease. Safety or pharmacokinetics of NOMAC-E2 in patients with renal insufficiency have not been studied. However, the excretion of NOMAC-E2 might be impaired in these patients.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not included in the preauthorization clinical development program.
Immunocompromised patients	No clinical studies were performed in immunocompromised
Patients with disease severity different from inclusion criteria in clinical trials	Patients. The MAH is not aware of any publications regarding the use of NOMAC-E2 in immunocompromised patients however, the post-registration clinical literature describes hormonal contraceptive studies performed in HIV-positive women and includes information of drug-drug interactions with anti-viral medication. Not applicable for the indication of contraception.
Population with relevant different ethnic origins	Development program was global and had a wide range of races and ethnicities.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations carrying relevant genetic polymorphisms were not assessed in the pre-authorization clinical development program as there are no known relevant genetic polymorphisms.

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Other	
• Post-menarcheal adolescents	Post-menarcheal adolescents, specifically those 12-17 years of age, were not included in NOMAC-E2 clinical efficacy and safety trials, which limited enrollment to women 18-50 years of age. It is unknown whether the amount of estradiol in NOMAC-E2 is sufficient to maintain adequate levels of estradiol in adolescents, especially for bone mass accrual. Safety in post-menarcheal adolescents is considered missing information for NOMAC-E2.
• Age	The age of women included in the NOMAC-E2 clinical trials ranged from 18-50 years old. Women greater than 50 years of age are not represented in the exposed population because it is generally acknowledged that the proposed therapeutic indication for NOMAC-E2, ie, contraception, is not applicable for these women. Although not studied, no specific safety concerns are expected with NOMAC-E2 when used in healthy patients older than 50 years.
• Women with Metabolic Dysfunction	NOMAC-E2 is not indicated for women with metabolic dysfunctions such as severe hepatic disease, liver tumors, and diabetes mellitus with vascular involvement. Women belonging to this special subject group were excluded from the clinical trials.
• Safety in Women with a History of or Risk Factors for VTE and ATE	The use of NOMAC-E2 in women with an increased risk for venous and arterial thromboembolism has not been studied. Epidemiological studies have associated the use of CHCs with an increased risk for venous and arterial thromboembolism. Alternate treatments must be considered for such patients.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide patient exposure for Estradiol+Nomegestrol Acetate (Zoely) for the cumulative reporting period of 27-Jul-2011 to 26-Jan-2021 was estimated from quarterly unit sales data provided by the IQVIA MIDAS Quantum database. The data from IQVIA market research database are based on an estimate of the number of prescriptions in an individual country (i.e., sales data reported by pharmacies and wholesalers to IQVIA). The MIDAS database is the most comprehensive source of global pharmaceutical information in the world, providing information for over 70 countries in the world.

For time periods not currently captured in the Quantum database, it is standard practice for IQVIA to obtain the unit distribution exposure per day from a known time period and apply that exposure rate to the unknown period. If current exposure is considerably more (or less) than the actual exposure in the unknown periods the estimates could be skewed high (or low).

- Due to a divesture in 2018, full history from Q3 2011 to Q3 2020 was pulled from MIDAS Quantum and used to estimate the patient exposure for the full request period

- A calendar year of data was used to extrapolate the Jan 27 to Jan 26 yearly time periods (ex: Q1 to Q4 2018 was used to extrapolate 27-Jan-2018 to 26-Jan-2019)

- Q1 2020 to Q3 2020 was used to extrapolate the period 27-Jan-2020 to 26-Jan-2021

Theramex Ireland Limited is the MAH in the EEA (European Economic Area); MSD was the distributor in all EEA countries, except for France, Italy, Spain, Luxembourg, Belgium, Croatia, Romania, Bulgaria, Greece, Cyprus and Slovenia, where Theramex is marketing the product. The MSD transferred over the responsibilities for distribution of Zoely in EU markets in June 2020 to Theramex Ireland. At the time these sales data were collected, NOMAC-E2 was approved in 65 countries. It should be noted that since not all countries are represented within the IQVIA database, the actual sales might differ from the estimation presented below.

The estimated patient exposure is presented in woman-years (WY). Thirteen sold blisters are considered to be equivalent to one WY.

SV.1.2 Exposure

Worldwide sales for NOMAC-E2 were estimated to be approximately **44,830,380** blisters of NOMAC-E2 during the cumulative reporting period. The patient exposure of NOMAC-E2 was estimated to be **3,448,491** WY during the cumulative period. Thirteen sold blisters are considered to be equivalent to one WY.

Distribution of Exposed Patients by Age (<20, 20-35, 36-45, >45 years old)

Demographic breakouts for age were derived from prescription data pulled from the Prescribing Insights database. Prescribing Insights is limited to fewer years of history and contains only a subset of the Quantum country panels.

- Insights data is almost exclusively retail based

- Worldwide age splits were derived from MATs (12 months of data) ending Sep for 2018, 2019 and 2020 and applied to respective yearly periods of data.

WORLDWIDE										
Age	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
0-19	12%	12%	11%	10%	13%	15%	13%	14%	12%	11%
20-35	52%	51%	50%	48%	54%	55%	57%	50%	60%	55%
36-45	24%	24%	25%	26%	26%	22%	22%	25%	20%	24%
46+	11%	13%	14%	16%	7%	8%	8%	11%	8%	11%

Table SV 1.2.1 : Patient Exposure NOMAC-E2 27-JUL-2011 to 26-JAN-2021

	Cumulative Period	
	27-Jul-2011 to 26-Jan-2021	
Age Group	**Blister Packs**	**WY**
Total	44,830,380	3,448,491
0-19	5,631,508	433,193
20-35	24,141,337	1,857,026
36-45	10,553,109	811,778
46+	4,504,427	346,494

	27-Jul-2011 to 26-Jan-2012	
Age Group	**Blister Packs**	**WY**
Total	8,423	648
0-19	1,052	81
20-35	4,412	339
36-45	2,004	154
46+	954	73

	27-Jan-2012 to 26-Jan-2013	
Age Group	**Blister Packs**	**WY**
Total	1,688,508	129,885
0-19	201,180	15,475
20-35	867,988	66,768
36-45	408,248	31,404

46+	211,091	16,238

	27-Jan-2013 to 26-Jan-2014	
Age Group	**Blister Packs**	**WY**
Total	3,455,530	265,810
0-19	391,284	30,099
20-35	1,734,058	133,389
36-45	853,794	65,676
46+	476,395	36,646

	27-Jan-2014 to 26-Jan-2015	
Age Group	**Blister Packs**	**WY**
Total	4,265,385	328,107
0-19	429,914	33,070
20-35	2,059,117	158,394
36-45	1,101,906	84,762
46+	674,448	51,881

	27-Jan-2015 to 26-Jan-2016	
Age Group	**Blister Packs**	**WY**
Total	5,359,612	412,278
0-19	695,930	53,533
20-35	2,868,173	220,629
36-45	1,406,415	108,186
46+	389,094	29,930

	27-Jan-2016 to 26-Jan-2017	
Age Group	**Blister Packs**	**WY**
Total	6,226,496	478,961
0-19	904,827	69,602
20-35	3,448,673	265,283
36-45	1,360,327	104,641
46+	512,669	39,436

27-Jan-2017 to 26-Jan-2018

Age Group	Blister Packs	WY
Total	6,813,356	524,104
0-19	885,878	68,144
20-35	3,853,848	296,450
36-45	1,523,127	117,164
46+	550,503	42,346

	27-Jan-2018 to 26-Jan-2019	
Age Group	**Blister Packs**	**WY**
Total	6,806,460	523,574
0-19	939,310	72,255
20-35	3,409,578	262,275
36-45	1,700,464	130,805
46+	757,109	58,239

	27-Jan-2019 to 26-Jan-2020	
Age Group	**Blister Packs**	**WY**
Total	5,665,878	435,837
0-19	703,974	54,152
20-35	3,382,937	260,226
36-45	1,125,540	86,580
46+	453,428	34,879

	27-Jan-2020 to 26-Jan-2021	
Age Group	**Blister Packs**	**WY**
Total	4,540,732	349,287
0-19	478,158	36,781
20-35	2,512,553	193,273
36-45	1,071,285	82,407
46+	478,737	36,826

* Due to rounding the sum of the individual formulations may not match the Total provided in the table.
Patient-Treatment Years = Patient-Treatment Days / 365.25.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Oral contraceptives in general are not known to have a potential for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

The list of important safety concerns in the NOMAC-E2 EU RMP has been revised, in accordance with GVP Module V (revision 2 Updates to the NOMAC-E2 important identified risks, important potential risks and missing information are described below.

Important Identified risk:

Acne

Acne previously classified as important identified risk is proposed to be removed from the list of safety concerns.

Reasons for the removal to the list of safety concerns:

Changes in the level of scientific evidence for the impact on risk-benefit ratio. The PASS study provides evidence that acne is in fact ameliorated during therapy with Zoely.

Acne is described in the current label for Zoely and is adequately managed by the current routine risk minimization measures (RMMs), including language in section 4.8 of the SmPC.

Important Potential Risks:

Inflammatory bowel disease

Inflammatory bowel disease previously classified as important potential risk is proposed to be removed from the list of safety concerns.

Reasons for the removal to the list of safety concerns:

Changes in the level of scientific evidence for the causal association or risk-benefit impact.

There is no reasonable expectation that any additional pharmacovigilance activity can further characterise the risk. Data from the PASS provided very few cases and the analysis showed no increase in risk than with other contraceptives.

Inflammatory bowel disease is described in the current label for Zoely and is adequately managed by the current routine RMMs, including language in section 4.4 of the SmPC.

Missing information:

Safety in women with a history of or risk factors for VTE and ATE

Safety in women with a history of or risk factors for VTE and ATE previously classified as missing information is proposed to be removed from the list of missing information safety concerns.

Reasons for the removal from the list of safety concerns:

VTE and ATE are important identified risks of Zoely. The PASS study extensively described these risks, including in women with a history of risk factors for VTE and ATE.

Risk factors for VTE and ATE are described in the current label for Zoely and are adequately managed by the current routine RMMs, including language in sections 4.3 and 4.4 of the SmPC. Moreover, they are consistent and considered within the important identified risks of VTE and ATE.

Routine PV and PASS activities have revealed the benefit-risk profile of Zoely to be favorable. All risks and missing information that are being removed from this EU RMP will continue to be monitored through routine pharmacovigilance activities.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Three important identified risks (depression/depressed mood, venous thromboembolic events, arterial thromboembolic events) and two important potential risks (cholelithiasis/cholecystitis/elevated hepatic enzymes, , and meningioma) are discussed.

DEPRESSION/DEPRESSED MOOD

Depressive states are psychiatric disorders consisting of pervasive, prolonged, and disabling changes of mood, associated with behavioral, physiological, cognitive, neurochemical, and psychomotor dysfunctions. Depressive states are often chronic in nature, with a marked tendency to remissions and exacerbations throughout lifetime.

The female preponderance of depression suggests the involvement of sex hormones. There is some evidence that depression is associated with an altered mechanism of neurotransmitters.

Table SVII.3.1.1: Details of Important Identified Risk: Depression/Depressed Mood

Frequency with 95% CI	A total of 131 cases for NOMAC-E2 users were reported in the Integrated Safety Data Set, consisting of the following PTs: Depression (89 occasions), Depressed mood (37), Depressive symptom (1), Decreased interest (1), Tearfulness (1), Major depression (1), Post-partum depression (1). From these 131 cases the following relatedness according to the investigator was reported: • Related: 78 • Not related: 52 • Missing: 1 (1) Clinical data with NOMAC-E2 With 131 reported cases and an exposure of 2694.5 woman years, the incidence for NOMAC- E2 is 48.6 (95% CI 40.6-57.7) cases per 1000 woman years. For the comparator DRSP/EE (3mg-30µg) 28 cases have been reported with an exposure of 881.8 woman years, corresponding to an incidence of 31.8 (95% CI 21.1-45.9) cases per 1000 woman years. The incidence for NOMAC-E2 is slightly higher than the incidence for DRSP/EE. (2) Epidemiological studies There are no published epidemiological studies investigating the relative risk of depression among NOMAC-E2 users versus non-users. For OC users in general, in an Australian survey among young women (18-23 years) the odds of a nonuser experiencing depressive symptoms is not statistically significantly different from that of an OC user [Ref. 5.4: 03KHMM].
Seriousness / Outcomes	A total of 131 cases were reported of which two were classified as serious. From these 131 cases the following outcomes were reported: • Not recovered: 30 • Recovered: 85 • Recovering: 10 • Unknown: 5 • Missing: 1
Severity and Nature of the Risk	From the 131 cases reported the following severities were reported: • Mild: 41 • Moderate: 72 • Severe: 17 • Missing: 1

Table SVII.3.1.1: Details of Important Identified Risk: Depression/Depressed Mood

Background Incidence / Prevalence

Incidence

Incidence of major depression

Description of the Study Country, Year of Study (reference)	Number of Women	Age Group	Incidence (% per Year, 95% CI)
National Health Survey	11,859[a]	12-24	7.1 (5.1-9.1)
Canada, 1996-1997		25-44	4.5 (3.4-5.7)
[Patten 2000] [Ref. 5.4: 03KHNT]		45-64	4.1 (2.5-5.7)
Birth cohort Study	319	13	2.2
New Zealand, 1972-1993		15	6.89
[Hankin et al 1998] [Ref. 5.4: 03KHMX]		18	20.69
		21	15.05
			Incidence (per 1000 woman years, 95% CI)
Prospective longitudinal study	1,402	15-39	4.1 (2.3-5.8)
Sweden, 1947-1997		40-69	3.9 (2.8-5.0)
[Mattison et al 2005] [Ref. 5.4: 03QQCC]			

a: Total number of people included in the study, no age and/or gender stratification.

The incidence of major depression can vary among studies partly due to different methods of diagnostic assessment, eg, Composite International Diagnostic Interview (CIDI) [Patten 2000], Diagnostic Interview Schedule (DIS), Diagnostic Interview Schedule for Children- Child Version (DISC-C), or an interview. [Ref. 5.4: 03KHMX, 03QQCC] The taxonomy that was used differed also which was major depressive episode (MDE) and dysthymia (DD) (DSM-III and DSM-III-R), Major Depressive Disorder (DSM-IV) and in Mattison et al [2005] the analysis was restricted to subjects diagnosed with Major depressive disorder, Mood disorder NOS, Depressive disorder NOS, Adjustment disorder with depressed mood, Dysthymic disorder, Mood disorder due to a medical condition corresponding to DSM-IV. [Ref. 5.4: 03KHMX, 03KHNT, 03QQCC]

Table SVII.3.1.1: Details of Important Identified Risk: Depression/Depressed Mood

Background Incidence / Prevalence

Prevalence

Prevalence of Major Depression

Description of the Study Country, Year of Study (reference)	Number of Women	Period of Prevalence	Age Group	Prevalence %
Health Omnibus Survey	797[a]	Last 2 weeks	15-29	14.4
Australia, 2004 [Ref. 5.4: 03KHMY]			30-49	10.7
			50-69	8.1
National Health Survey	11,859[a]	1 year	12-24	9.6
Canada, 1996-1997 [Ref. 5.4: 03KHNT]			25-44	8.6
			45-64	6.3
Ontario Health Survey	697,289	1 year	15-24	6.5
Canada, 1990 [Ref. 5.4: 03KHNP]			25-44	5.6
			45-64	4.2
Student screening Sweden [Ref. 5.4: 03KHNR]	1,228	Lifetime	16-17	11.5
Birth cohort Study	319	Lifetime	13	2.51
New Zealand, 1983-1993 [Ref. 5.4: 03KHMX]		Lifetime	15	6.89
		Lifetime	18	27.51
		Lifetime	21	42.63
National representative survey	900	1 year	15-16	21.5
USA, 1990-1992 [Ref. 5.4: 03KHN7]		1 year	17-18	14.0
		1 year	19.20	16.7
		1 year	21-22	17.9
		1 year	23-24	9.8
		Lifetime	15-16	23.4
		Lifetime	17-18	15.6
		Lifetime	19-20	20.4
		Lifetime	21-22	26.3
		Lifetime	23-24	17.6

a: Total number of people included in the study, no age and/or gender stratification.

The prevalence of major depression can vary among studies partly due to different method of diagnostic assessment for the studies, eg, Primary Care Evaluation of Mental Disorders (PRIME-MD), Composite International Diagnostic Interview (CIDI), Diagnostic Interview for Children and Adolescents (DICA-R-A), Diagnostic Interview Schedule (DIS), [Diagnostic Interview Schedule for Children- Child Version (DISC-C). [Ref. 5.4: 03KHMY, 03KHNT, 03KHNP, 03KHN7, 03KHNR, 03KHMX] The taxonomy that was used differed also which was Major depressive episode and dysthymia (DSM-III and DSM-III-R) Major depressive disorder (DSM-III-R) Unipolar major depression (DSM-III-R), and Major depressive disorder (DSM-IV). [Ref. 5.4: 03KHMX, 03KHNP, 03KHNR, 03KHN7] [Ref. 5.4: 03KHNT, 03KHMY]

Table SVII.3.1.1: Details of Important Identified Risk: Depression/Depressed Mood

Risk Groups or Risk Factors	The following factors predispose certain women to OC-related negative changes in mood/affect: A history of depression, other symptoms of psychological distress (eg, anxiety, stress, neuroticism), dysmenorrheal and premenstrual mood symptoms prior to OC use, a history of pregnancy-related mood symptoms, a family history of OC-related mood complaints, being in the postpartum period and age. [Ref. 5.4: 03KTP2] A number of OC-related variables also mediate mood/affect changes for certain individuals: For women with a history of premenstrual emotional symptoms prior to OC use, OC formulations with higher progesterone to estrogen dosage ratios are associated with less negative mood changes, as are the use of monophasic versus triphasic OCs. For women without a history of premenstrual irritability, formulations with lower ratios of progesterone to estrogen decrease the risk of negative mood change. Finally, monophasic OCs have a greater stabilizing effect than triphasic OCs. [Ref. 5.4: 03KTP2]
Potential Mechanisms	Several potential mechanisms for a link between exogenous steroid use and mood disturbance have been proposed: i) Vitamin B_6 deficiency is associated with a decrease in serotonin and GABA. [Ref. 5.4: 03KTP0] ii) Progesterone and estrogen-mediated augmentation of GABA-induced inhibition of glutamate transmission. [Ref. 5.4: 03KTPL] iii) Progesterone-mediated increase in monoamine oxidase activity, resulting in lower serotonin levels. [Ref. 5.4: 03KTNH] iv) Potentiation of progesterone mood effect by estrogen. [Ref. 5.4: 03KTPK]
Preventability	The risk of depressive states can be (partially) reduced by improving one's physical, social, and psychological status.
Impact on the Risk-Benefit Balance of the Product	The important identified risk of depression/depressed mood is a known adverse effect which can occur with hormonal contraceptives. This risk is described in the product labeling. There is no information on the effect of NOMAC-E2 on quality of life in the event a woman suffers from depression. This risk was evaluated with the PASS and NOMAC-E2 continues to have a positive benefit-risk balance.
Potential Public Health Impact of Safety Concern	Depressive states are psychiatric disorders consisting of pervasive, prolonged, and disabling changes of mood, associated with behavioral, physiological, cognitive, neurochemical, and psychomotor dysfunctions. Depressive states are often chronic in nature, with a marked tendency to remissions and exacerbations throughout lifetime. The female preponderance of depression suggests the involvement of sex hormones. The safety profile of NOMAC-E2 related to depression is well characterized and therefore, the expected public health impact is minimal given the data above.
Evidence Source	Clinical trial data Published literature
MedDRA Terms	MedDRA PTs reported in clinical trials: 'Depression', 'Major depression', 'Post-partum depression', 'Depressed mood', 'Depressive symptom', 'Decreased interest' and 'Tearfulness'

Table SVII.3.1.1: Details of Important Identified Risk: Depression/Depressed Mood

CI = confidence interval; CTD = common technical document; DRSP/EE = Drospirenone and ethinyl estradiol; GABA = Gamma-aminobutyric acid; MedDRA = Medical Dictionary for Regulatory Activities; NOS = not otherwise specified; PT = preferred term; OC = oral contraceptive

Post Marketing data

From the final study report for the PASS study (P08291):

Results from this study show that there were no statistically significant differences in the risk of depressive disorders between women in the NOMAC-E2 cohort and women in the COC_{LNG} cohort. Overall, there were 46 events in NOMAC-E2 users (9.4 per 10,000 WY; 95% CI, 6.9 - 12.6), 80 events in COC_{LNG} users (14.8 per 10,000 WY; 95% CI, 11.7 – 18.4), 13 events in COC Other users (15.7 per 10,000 WY; 95% CI, 8.3 – 26.8), 8 events in OHC users (33.8 per 10,000 WY; 95% CI, 14.6 – 66.6) and 41 events in ex-users (13.1 per 10,000 WY; 95% CI, 9.4 – 17.7). Additional analysis performed by stratifying women under the age of 25 years and women aged 25 years and older showed that there were no statistically significant differences in the incidence of depressive disorders between the user cohorts.

Regarding mood changes, the results suggest that there may be an improvement in mood from baseline to each follow-up time point for NOMAC-E2 and COC_{LNG} users. Also, an additional analysis performed to determine the mean change in mood when only women who switched or stopped hormonal contraceptive use showed a trend toward positive change in mood was observed in relation to both user cohorts.

VENOUS THROMBOEMBOLISM

Epidemiological studies have shown an association between the use of CHCs containing *ethinylestradiol* and an increased risk of venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely. It should be noted that the epidemiological studies were conducted with CHCs containing ethinylestradiol, while NOMAC-E2 contains 17β-estradiol.

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

Frequency with 95%CI	In addition to adverse event reporting, the effect of NOMAC-E2 on hemostasis was investigated in Trial 292004 and Trial 02-ESC/NOM-2-RD. Parameters of hemostasis that were investigated included: Prothrombin fragment 1+2, D-Dimer, APC resistance ratio, Factors VIIa, Factor VIIc, Factor VIII, Factor II, Antithrombin III, Protein S (free and total), Protein C, and CRP. The changes compared to baseline at Cycle 3 and 6 for surrogate markers of coagulation in NOMAC-E2 treated subjects were consistent in these trials. NOMAC-E2 induced smaller changes in hemostasis parameters as compared to Levonorgestrel-EE 150/30 and 100/20µg. In addition, NOMAC-E2 had a lower impact on CRP. (1) Clinical data with NOMAC-E2 No in-treatment deep vein thromboses on NOMAC-E2 have occurred during the clinical trials. For the comparator DRSP/EE (3mg-30µg) one case of in-treatment deep vein thrombosis was reported with an exposure of 881.8 woman years, corresponding to an incidence of 1.1 (95% CI 0.0 – 6.3) cases per 1000 woman years. (2) Epidemiological studies There are no cases of VTE in published epidemiological studies among NOMAC-E2 users. A retrospective cohort study of 1,296,120 Danish women 15-49 years contributing 8,010,290 women years of observation, investigated whether use of OCs was associated with VTE risk. Compared with users of oral contraceptives with levonorgestrel, the relative risk of VTE for users of oral contraceptives with desogestrel was 2.2 (95% CI 1.7-3.0), with gestodene was 2.1 (95% CI 1.6-2.8), and with drospirenone was 2.1 (95% CI 1.6-2.8) [Ref. 5.4: 00WDGS].
Seriousness / Outcomes	The one case of deep vein thrombosis (discussed above) was classified as moderate and the subject's outcome was reported as recovering.
Severity and Nature of the Risk	The case of in-treatment deep vein thrombosis was classified as moderate.

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

Background Incidence / Prevalence

Incidence

Non-users of CHCs

Estimating the incidence of VTEs is complicated due to variations in definitions used. The incidence in healthy women of fertile age who do not use a CHC has been estimated to be in the range of 0.4-4.7 per 10,000 woman years (see table below). These studies did not stratify by age-group except for one [Ref. 5.4: 03KHNV]. In the latter, two age groups were defined, ie, 15-29 years and 30-44 years. The VTE incidence was 0.3 and 0.4 per 10,000 woman years in the age group 15-29 and 30-44 years, respectively (based on two and four VTE cases).

VTE incidence per 10,000 woman years in non-CHC users in cohort studies

Study	Age Years	No CHC		
		N	Women Years	Incidence /10000 wy
Royal College of General Practitioners, 1978 [Ref. 5.4: 03KHNX]	15-49	13	47,084	2.8
Porter et al, 1985 [Ref. 5.4: 03KHNV] (Puget Sound database)	15-44	6	167,901	0.4
Vessey, 1988 [Ref. 5.4: 03KHPC] Oxford Family Planning Association	<40	13	118,000	1.1
Farmer et al, 1995 [Ref. 5.4: 03NLRR]	14-45	62	542,906	1.1
Jick et al, 1995 [Ref. 5.4: 00W4PX]	<40	5	130,590	0.40.4
Samuelsson et al, 2004 [Ref. 5.4: 03KHP2]	15-44	32	171,206	1.9
Dinger et al, 2007 [Ref. 5.4: 00WDJG]	25.9	12	25,767	4.7
Lidegaard et al, 2012 [Ref. 5.4: 03M27V]	15-49	1209	5892182	2.1
a: As calculated from values provided in Vessey 1988. b: mean age				

Studies stratifying VTE incidence by age but where no distinction was made between users and non-users of CHCs

Several studies do not distinguish by use or non-use of CHCs and provide incidence data per 100,000 women (not woman years). Data from these studies are presented in the table below.

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

Background Incidence / Prevalence

1st Author Year of Publication Country	Study Period	Population	Diagnosis	Age Group	Cases N	Annual Incidence/ 100,000 Women
Silverstein et al 1998 [Ref. 5.4: 03RJM7] USA	1986-1990[a]	Census data from Olmsted County 1990 106,470 (men and women)	DVT only	0-14	0	0
				15-19	2	11
				20-24	6	30
				25-29	8	31
				30-34	9	34
				35-39	4	19
				40-44	6	34
				45-49	6	41
			PE ± DVT	0-14	0	0
				15-19	0	0
				20-24	1	5
				25-29	5	19
				30-34	0	0
				35-39	1	5
				40-44	2	11
				45-49	3	20
			VTE	0-14	0	0
				15-19	2	11
				20-24	7	35
				25-29	13	50
				30-34	9	34
				35-39	5	24
				40-44	8	45
				45-49	9	61
Worcester DVT study USA [Ref. 5.4: 03KHM9]	Jul '85-Dec '86	Census data from Worcester Standard Metropolitan Statistical Area 379,953 (men and women)	DVT	0-9	n.r.	0
				10-19	n.r.	0
				20-29	n.r.	11
				30-39	n.r.	14
				40-49	n.r.	10
			PE	0-9	n.r.	0
				10-19	n.r.	2
				20-29	n.r.	6
				30-39	n.r.	7
				40-49	n.r.	12

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

Background Incidence / Prevalence

Oger 2000 [Ref. 5.4: 03RJM6] France	1 Apr '98-31 Mar '99	46,988 [b]	DVT	0-19	1	2
		51,661 [b]		20-39	15	29
		38,198 [b]		40-59	21	55
		46,988 [b]	PE	0-19	0	0
		51,661 [b]		20-39	7	13
		38,198 [b]		40-59	6	16
		46,988 [b]	VTE	0-19	1	2
		51,661 [b]		20-39	22	42
		38,198 [b]		40-59	27	71

a: Incidence data are available for the whole period (1966-1990) and for the last 5 years (1986-1990). Because incidence data are not separately presented for CHC users and non-CHC users, and the estrogen dose in CHCs has significantly decreased over time, only the last 5 years are presented in this table.

b: Census data from Brest District 1990.

Studies stratifying VTE incidence by age in CHC users

The total VTE incidence in CHC users found in a retrospective cohort study was 5.2, 9.7, 11.0 per 10,000 woman years in the age groups 15-24, 25-34, and 35-44, respectively. In the group of CHC users without other acquired risk factors such as surgery trauma, immobilization, BMI ≥35 or disease in combination with CHC use, the incidence of VTE was 1.9, 4.2 and 9 per 10,000 woman years in the age groups 15-24, 25-34. and 35-44, respectively. [Ref. 5.4: 03KHP2]

A study in the UK GPRD and MediPlus database in users of CHCs (January 1992-June 1997) aged 15-49 years gave an idiopathic VTE incidence of 3 per 10,000 woman years in 15-19 year old women rising to 17.5 per 10,000 woman years in women aged 45-49 years. Idiopathic VTE was defined as cases of deep venous thrombosis (DVT) or pulmonary embolism (PE) unrelated to trauma, surgery, pregnancy or the puerperium, malignancy, congenital heart disease or drug-overdose.
[Ref. 5.4: 03KHNN]

CHC users

In the EURAS study [Dinger et al 2007] including 58,674 women followed for 142,475 woman years of observation, the VTE incidence in CHC-users was approximately 9 per 10,000 woman years.[Ref. 5.4: 00WDJG]

In a historical national registry based cohort study in Denmark, the VTE incidence for women using NuvaRing was 7.8 per 10,000 WY, for women using CHC with norgestimate a VTE incidence of 4.5 per 10,000 WY, for women using a transdermal contraceptive patch a VTE incidence of 9.7 per 10,000 WY and for women using Levonorgestrel (LNG)-containing CHCs the VTE incidence was 6.2 per 10,000 WY[Ref. 5.4: 03M27V]

A retrospective cohort study using data from 4 health plans in USA showed a VTE incidence for women using drospirenone-containing CHCs of 13.7 events per 10,000 WY, for women using norelgestromin-containing CHCs a VTE incidence of 12.3 events per 10,000 WY, for women using NuvaRing a VTE incidence of 11.3 events per 10,000 WY and for women using Levonorgestrel (LNG) 10-20, LNG 15-30, norethindrone, norgestimate containing CHCs a VTE incidence of 8.2 events per 10,000 WY[Ref. 5.4: 03M335].

Prevalence

There are no data available on the prevalence of VTE in healthy women of fertile age who do not use a CHC.

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

Risk Groups or Risk Factors	Risk factors for VTE are: [Ref. 5.4: 03RJLS, 03KHN8] Hereditary risk factors: • Antithrombin III deficiency • Protein C deficiency • Protein S deficiency • Activated protein C resistance (Factor V Leiden gene mutation) • Prothrombin gene mutation (G20210A) • Hyperhomocysteinemia Acquired risk factors: • Obesity • Varicose veins • Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) • Postpartum period • Pregnancy • Surgery • Trauma • Stasis (eg, due to prolonged immobility) • Increasing age • Positive (family) history • Other diseases (eg, hemolytic uremic syndrome, inflammatory bowel disease, auto-immune states such as systemic lupus erythematosus, HBsAg, hypothyroidism, malignancy, renal disease) • Smoking
Potential Mechanisms	The risk of VTE in women using CHCs is attributed to changes in coagulation and fibrinolysis. [Ref. 5.4: 03KHPB] However, in healthy women, hemostatic variables remain within their normal ranges and their significance in relation to VTE risk in healthy women remains to be established.[Ref. 5.4: 03KTP3]
Preventability	To prevent VTE among users of CHCs, a complete medical history (including a family medical history) should be taken prior to the initiation or reinstitution of CHC use. CHCs should not be used in the presence of any of the contraindications listed in the labeling. If any of the conditions/risk factors mentioned in the section "special warnings and precautions for use" of the labeling is present, the benefits of the use of CHCs should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using CHCs.
Impact on the Risk-Benefit Balance of the Product	The important identified risk of VTE is a known adverse effect which can occur with combined hormonal contraceptives. This risk is described in the product labeling. There is no information on the effect of NOMAC-E2 on quality of life in the event a woman suffers from VTE. This risk was evaluated with the PASS and NOMAC-E2 continues to have a positive benefit-risk balance.
Potential Public Health Impact of Safety Concern	VTE have been reported in association with all CHCs above. VTE risk has not been established in post marketing studies but based on clinical trials, VTE risk is not expected to be higher than other CHCs, including CHCs containing LNG.
Evidence Source	Clinical trial data Published literature
MedDRA Terms	MedDRA PTs reported in clinical trials: 'Portal vein thrombosis', 'Mesenteric vein thrombosis' and 'Deep Vein Thrombosis',

Table SVII.3.1.2: Details of Important Identified Risk: Venous Thromboembolism

APC = activated protein C; BMI = body mass index; CI = confidence interval; CHC = combined hormonal contraception; CRP = C-reactive protein; CTD = common technical document; DRSP/EE = Drospirenone and ethinyl estradiol; DVT = Deep Venous Thrombosis; FPA = Family Planning Association; GPRD = General Practice Research Database; HBsAg = hepatitis B virus surface antigen; MedDRA = Medical Dictionary for Regulatory Activities; n.a. = not available; n.r. = Not reported; PE = Pulmonary Embolism; PE±DVT = Pulmonary Embolism with or without Deep Venous Thrombosis; PT = preferred term; RCGP = Royal College of General Practitioners; VTE = venous thromboembolic events; wy = woman years.

Post Marketing data

From the final study report for the PASS study (P08291):

Baseline characteristics and cardiovascular risk factors at study entry were similar between the user cohorts, although NOMAC-E2 users had a higher mean age compared to COC_{LNG} users and reported a higher level of education. A 1.5-fold risk of VTE (DVT of the lower extremities and pulmonary embolism) in NOMAC-E2 users compared with COC_{LNG} users was excluded. Overall, there were 34 VTEs in the main analysis of the primary outcome (DVT of the lower extremities and PE): 9 NOMAC-E2 (2.0 per 10,000 WY; 95% CI, 0.9 – 3.7), 15 COC_{LNG} (3.0 per 10,000 WY; 95% CI, 1.7 – 5.0), 4 COC Other (5.2 per 10,000 WY; 95% CI, 1.4 – 13.4), 1 OHC (4.8 per 10,000 WY; 95% CI, 0.1 – 26.8) and 5 ex-users (1.8 per 10,000 WY; 95% CI, 0.6 – 4.1). The Cox proportional hazards a priori expert model (complete case analysis) resulted in a crude hazard ratio (HRcrude) for NOMAC-E2 versus COC_{LNG} of 0.65 (95% CI, 0.28 – 1.48). After adjusting for age, BMI, family history of VTE and current duration of HC use, the adjusted hazard ratio (HRadj) was 0.59 (95% CI, 0.25 – 1.35). Several additional sensitivity analyses supported this conclusion.

Also, an analysis was conducted in which women with pre-defined risk factors at study entry were included. The inclusion of 4 VTEs in women who had pre-defined risk factors at study entry resulted in a dataset containing 38 VTEs: 10 in NOMAC-E2 users (2.0 per 10,000 WY; 95% CI, 1.0 – 3.8), 17 in COC_{LNG} users (3.1 per 10,000 WY; 95% CI, 1.8 – 5.0), 4 in COCOther users (4.8 per 10,000 WY; 95% CI, 1.3 – 12.3), 1 in an OHC user (4.2 per 10,000 WY; 95% CI, 0.1 – 23.5) and 6 in ex-users (1.9 per 10,000 WY; 95% CI, 0.7 – 4.2)

In total, 46 VTEs were included in the analysis of the secondary outcome of all VTE (i.e. not restricted to DVT of the lower extremities and PE): 12 NOMAC-E2 (2.5 per 10,000 WY; 95% CI, 1.3 – 4.3), 20 COC_{LNG} (3.7 per 10,000 WY; 95% CI, 2.3 – 5.7), 5 COC Other (6.0 per 10,000 WY; 95% CI, 2.0 – 14.1), 1 OHC (4.2 per 10,000 WY; 95% CI 0.1 – 23.5) and 8 ex-users (2.6 per 10,000 WY; 95% CI, 1.1 – 5.0).

Overall, 35 of the 46 confirmed VTEs were considered idiopathic VTEs. The numbers and incidence rates for each (sub-)cohort were as follows: NOMAC-E2 10 VTEs (2.0 per 10,000 WY; 95% CI, 1.0 3.8), COC_{LNG} 15 VTEs (2.8 per 10,000 WY; 95% CI, 1.6 – 4.6), COC Other 5 VTEs (6.0 per 10,000 WY; 95% CI, 2.0 – 14.1), OHC 1 VTE (4.2 per 10,000 WY. 95% CI, 0.1 – 23.5) and ex-users 4 VTEs (1.3 per 10,000 WY; 95% CI, 0.35 – 3.3).

ARTERIAL THROMBOEMBOLISM

Epidemiological studies have shown an association between the use of CHCs containing *ethinylestradiol* and an increased risk of arterial thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely. It should be noted that the epidemiological studies were conducted with CHCs containing ethinylestradiol, while NOMAC-E2 contains 17β-estradiol.

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

<table>
<tr><td>Frequency with 95%CI</td><td>1) Clinical data
No cases for NOMAC-E2 users were reported.
2) Epidemiological studies
There are no cases of ATE in published epidemiological studies among NOMAC-E2 users.</td></tr>
<tr><td>Seriousness / Outcomes</td><td>Not applicable</td></tr>
<tr><td>Severity and Nature of the Risk</td><td>Not applicable</td></tr>
<tr><td>Background Incidence / Prevalence</td><td><u>Incidence</u>
Studies stratifying ATE incidence by age and risk factor but where no distinction was made between users and non-users of CHCs

Incidence of Thrombotic Stroke per 100,000 woman years in non-pregnant women aged 15-49 from Danish cohort studies, by age and risk factor(no distinction made between users and non-users of CHCs)
<table>
<tr><th>Study</th><th>Age
Age years</th><th>N</th><th>Women Years</th><th>Incidence /100000 wy</th></tr>
<tr><td>Lidegaard, 2012, NEJM [Ref. 5.4: 023WB3]</td><td>15-19</td><td>70</td><td>2,075,087</td><td>3.4</td></tr>
<tr><td></td><td>20-24</td><td>110</td><td>1,961,954</td><td>5.6</td></tr>
<tr><td></td><td>25-29</td><td>201</td><td>1,906,954</td><td>10.5</td></tr>
<tr><td></td><td>30-34</td><td>317</td><td>2,053,357</td><td>15.4</td></tr>
<tr><td></td><td>35-39</td><td>501</td><td>2,149,752</td><td>23.3</td></tr>
<tr><td></td><td>40-44</td><td>825</td><td>2,104,119</td><td>39.2</td></tr>
<tr><td></td><td>45-49</td><td>1287</td><td>2,000,033</td><td>64.4</td></tr>
<tr><td></td><td>Risk factors</td><td></td><td></td><td></td></tr>
<tr><td></td><td>Diabetes</td><td>186</td><td>123,264</td><td>150.9</td></tr>
<tr><td></td><td>Hypertension</td><td>1039</td><td>1,343,081</td><td>77.4</td></tr>
<tr><td></td><td>Hyperlipidemia</td><td>139</td><td>63,111</td><td>220.3</td></tr>
<tr><td></td><td>Arrythmia</td><td>68</td><td>69,752</td><td>97.5</td></tr>
<tr><td></td><td>Smoking</td><td>204</td><td>1,195,490</td><td>17.1</td></tr>
</table></td></tr>
</table>

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

Background Incidence / Prevalence

Incidence of Myocardial Infarction per 100,000 woman years in among Nonpregnant women aged 15-49 from Danish cohort studies, by age and risk factor (no distinction made between users and non-users of CHCs)

Lidegaard, 2012, NEJM Study	Age Age years	N	Women Years	Incidence /100000 wy
Lidegaard,2012 [Ref. 5.4: 023WB3]	15-19	9	2,075,087	0.4
	20-24	13	1,961,954	0.7
	25-29	41	1,906,954	2.2
	30-34	102	2,053,357	5.0
	35-39	262	2,149,752	12.2
	40-44	534	2,104,119	25.4
	45-49	764	2,000,033	38.2
	Risk Factors			
	Diabetes	159	123,264	129
	Hypertension	581	1,343,081	43.3
	Hyperlipidemia	85	63,111	134.7
	Arrhythmia	54	69,752	77.4
	Smoking	112	1,195,490	9.37

Summary: The rates of thrombotic stroke and myocardial infarction increased by factors of 20 and 100, respectively, with increasing age. Arterial thrombosis after the age of 30 years is more frequent and has more serious consequences than venous thrombosis.

Study comparing ATE risk among users of CHCs versus non-users of CHCs

Incidence of ATE among Users of CHCs compared to non-users, by type of CHC

Lidegaard, 2012, NEJM Incidence rates and adjusted relative risks of thrombotic stroke and myocardial infarction among users of different types of Hormonal Contraception, as compared to Non-users [Ref. 5.4: 023WB3].

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

Background Incidence / Prevalence

Type of CHC	Person Years	Thrombotic Stroke N	Incidence Rate	Adj RR	Myocardial Infarction N	Incidence Rate	Adj RR
None	9,336,662	2,260	24.2	1.00	1,228	13.2	1.00
Ethinyl Estradiol, 50 mcg							
Norethindrone	43,234	9	20.8	1.27 (0.66-2.45)	11	25.4	2.74 (1.51-4.97)
levonorgestrel	54,474	32	58.7	2.26 (1.59-3.2)	36	66.1	4.31 (3.09-6.0)
Ethinyl estradiol, 30-40 mcg							
Norethindrone	126,984	28	22.1	2.17 (1.49-3.15)	14	11.0	2.28 (1.34-3.87)
Levonorgestrel	460,559	144	31.3	1.65 (1.39-1.95)	91	19.8	2.02 (1.63-2.5)
Norgestimate	453,536	78	17.2	1.52 (1.21-1.91)	28	6.2	1.33 (0.91-1.94)
Desogestrel	313,560	99	31.6	2.20 (1.79-2.69	43	13.7	2.09 (1.54-2.84)
Gestodene	1,318,962	285	21.6	1.80 (1.58-2.04)	133	10.1	1.94 (1.62-2.33)
Drospirenone	286,770	52	18.1	1.64 (1.24-2.18)	18	6.3	1.65 (1.03-2.63)
Cyproterone acetate	187,145	29	15.5	1.40 (0.97-2.03)	12	6.4	1.47 (0.83-2.61)
Ethinyl Estradiol, 20 mcg							
Desogestrel	695,603	105	15.1	1.53 (1.26-1.87)	40	5.8	1.55 (1.13-2.13)
Gestodene	564,268	88	15.6	1.70 (1.37-2.12)	21	3.7	1.20 (0.77-1.85)
Drospirenone	23,056	2	8.7	0.88 (0.22-3.53)	0	0	0 (0-12.99)
Progestin Only							
Norethindrone	85,874	28	32.6	1.35 (0.93-1.96)	9	10.5	0.81 (0.42-1.56)
Levonorgestrel	8,556	1	11.7	0.44 (0.06-3.12)	0	0	0 (0-35.01)
Desogestrel	29,185	9	30.8	1.37 (0.71-2.63)	4	13.7	1.46 (0.55-3.90)
Implant	24,954	3	12.0	0.88 (0.28-2.72)	3	12.0	2.14 (0.69-6.65)
Other							
Patch	4,748	2	42.1	3.15 (0.79-12.60)	0	0	0 (0-63.1)
Vaginal Ring	38,246	12	31.4	2.49(1.41-4.41)	3	7.8	2.08 (0.67-6.48

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

Background Incidence / Prevalence

Poulter, Lancet 1999

In a multicenter World Health Organization study, it was reported that women who used second-generation oral contraceptive pills with levonorgestrel, as compared with nonusers, had a relative risk of thrombotic stroke of 2.7 (95% CI, 1.8-4.1) and users of third-generation pills had a relative risk of 1.8 (95% CI, 0.6-5.2). These estimates were reduced to 2.0 (95% CI1.1-3.6) and 1.6 (95% CI 0.4-6.6), respectively when adjusted for blood pressure.

Studies showing incidence of ATE by type of CHC and by age

Sidney, Contraception, 2013 [Ref. 5.4: 03M335]

Age specific incidence rates and age- and site-adjusted rates for hospitalized Arterial thromboembolism (ATE) by type of contraception

CHC/Age	Person Years	Events (N)	Rate per 10,000 PY(95% CI)
Drospirenone/Age			
10-24	39,452	0	0
25-34	27,362	3	1.1 (0.2-3.2)
35-44	10,672	5	4.7 (1.5-10.9)
45-55	2,684	6	22.4 (8.2-48.7)
total	80,171	14	2.5 (1.3-5.2)
NGNM Patch/Age			
10-24	17,680	1	0.6 (0.01-3.2)
25-34	9,424	2	2.1 (0.3-7.7)
35-44	2,651	1	3.8 (0.1-21.0)
45-55	397	0	0
Total	3,0152	4	1.8 (0.4-15.1)
Etonogestrel /Age			
10-24	3,913	0	0
25-34	3,497	0	0
35-44	1,073	2	18.6 (2.3-67.3)
45-55	301	0	0
Total	8,784	2	2.2 (0.3-21.2)
Levonorgestrel containing OCs/Age			
10-24	103,683	5	0.5 (0.2-1.1)
25-34	77,191	9	1.2 (0.5-2.2)
35-44	42,631	13	3.0 (1.6-5.2)
45-55	24,526	18	7.3 (4.4-11.6)
total	248,031	45	1.8 (1.3-2.5)

Studies showing incidence of ATE by type of CHC

Dinger, Contraception, 2014 [Ref. 5.4: 03XZ7K]

In a prospective cohort study of 85,109 women investigating the risks of short and long term use of drospirenone compared to established oral contraceptives, the following incidence rates for arterial thromboembolism were reported:

Drospirenone 24 day regimen: 1.5/10,000 WY
Drospirenone 21 day regimen: 1.8/10,000 WY
Non-Drospirenone containing OCs: 2.8/10,000WY
Levonorgestrel containing OCs: 3.6/10,000WY

Non-oral hormonal contraceptives: 2.5/10,000WY

No Contraceptive use: 1.4/10,000WY

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

Background Incidence / Prevalence

Though not reported, the authors state that the 95% Confidence intervals overlap widely.

TASC study[Ref. 5.4: 03MX4D]

In a large multinational controlled prospective observational active surveillance study of 33,295 women designed to characterize and compare the risks of short and long term use of NuvaRing with those of other marketed COCs, the risk of arterial thromboembolism was evaluated. Results are summarized as follows:

Arterial Thromboembolic events: Number, incidence, and 95% CI by exposure group

Category	NuvaRing (22,927 WY)		COC (28,252 WY)		No Use (13,695 WY)	
	N	Incidence (95 % CI)	N	Incidence (95 % CI)	N	Incidence (95 % CI)
All ATE	5	2.2 (0.7-5.1)	8	2.8 (1.2-5.6)	3	2.2 (0.5-6.4)
-MI	2	0.9 (0.1-3.2)	3	1.1 (0.2-3.1)	1	0.7 (0.0-4.1)
-Ischemic stroke	2	0.9 (0.1-3.2)	3	1.1 (0.2-3.1)	0	0 (0-2.2)
-TIA	1	0.4(0.0-2.4)	2	0.7 (0.1-2.6)	1	0.7(0.0-4.1
-peripheral ATE	0	0 (0.0-1.3)	0	0(0.0-1.1)	1	0.7 (0.0-4.1)

Chan, Risk of Stroke in Women exposed to low dose OC, Arch Int Med 2004 [Ref. 5.4: 02CG84]

In a meta-analysis of observational studies examining the risk of stroke with low does OC use, the authors found no increased stroke risk with OC use among all the cohort studies (pooled OR: 0.95, 95%CI 0.51-1.78). In contrast, they found a significant association between OC use and thrombotic stroke (but not hemorrhagic) when the case-control studies were pooled (pooled OR: 2.13, 95% CI 1.59-2.86). The authors note that there was significant heterogeneity among studies and potential biases and confounders were not adequately addressed. They further conclude that these results cast doubt on a true association between low dose OC use and stroke because of the low absolute magnitude of the ORs, the severe methodological limitations and the ORs of less than 1 in the cohort studies.

Prevalence

There are no studies describing the prevalence of ATE

Risk Groups or Risk Factors

Risk factors for ATE are:

- Increasing age, particularly above 35 years.
- Smoking.
- Hypertension
- Obesity (body mass index over 30kg/m^2)
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g., below 50)
- Migraine
- Other medical conditions associated with adverse vascular events (e.g., diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinemia and systemic lupus erythematosus).

Potential Mechanisms

The risk of ATE in women using CHCs is attributed to changes in coagulation and fibrinolysis. [Ref. 5.4: 03KHPB] Age and smoking are considered to be the key risk factors for arterial thromboembolic events

Table SVII.3.1.3: Details of Important Identified Risk: Arterial Thromboembolism

Preventability	To prevent ATE among users of CHCs, a complete medical history (including a family medical history) should be taken prior to the initiation or reinstitution of CHC use. CHCs should not be used in the presence of any of the contraindications listed in the labeling. If any of the conditions/risk factors mentioned in the section "special warnings and precautions for use" of the labeling is present, the benefits of the use of CHCs should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using CHCs.
Impact on the Risk-Benefit Balance of the Product	The important identified risk of ATE is a known adverse effect which can occur with combined hormonal contraceptives. This risk is described in the product labeling. There is no information on the effect of NOMAC-E2 on quality of life in the event a woman suffers from ATE. This risk was evaluated with the PASS and NOMAC-E2 continues to have a positive benefit-risk balance.
Potential Public Health Impact of Safety Concern	ATE have been reported in association with all CHCs above. ATE risk has not been established in post marketing studies but based on clinical trials, ATE risk is not expected to be higher than other CHCs, including CHCs containing LNG.
Evidence Source	Clinical trial data Published literature
MedDRA Terms	MedDRA PTs reported in clinical trials: Not applicable.

Post Marketing data

From the final study report for the PASS study (P08291):

There were no substantial differences between the NOMAC-E2 cohort and the COC_{LNG} cohort with regard to their risk of ATE. In this study, a total of 16 ATEs were confirmed: 4 ATEs (2 ischemic strokes, 1 TIA and 1 myocardial infarction) in NOMAC-E2 users (0.8 per 10,000 WY; 95% CI, 0.2 – 2.1), 7 ATEs (4 ischemic strokes and 3 AMI) in COC_{LNG} users (1.3 per 10,000 WY; 95% CI, 0.5 – 2.7), 1 ATE (an AMI) in a COC Other user (1.2 per 10,000 WY; 95% CI, 0.0 – 6.7) and 4 ATEs (3 ischemic strokes and 1 AMI) in ex-users (1.3 per 10,000 WY; 95% CI, 0.35 – 3.3). According to the statistical analysis plan of the study, a minimum of 5 events in each of the comparison groups was necessary to carry out a Cox regression analysis. The COC_{LNG} cohort was the only group with the minimum required number of events and the Cox regression analysis was therefore not conducted.

CHOLELITHIASIS/CHOLECYSTITIS/ELEVATED HEPATIC ENZYMES

Cholelithiasis is a disorder characterized by the presence or formation of gallstones in the biliary tract, usually in the gallbladder. About 20% of the subjects who suffer from cholelithiasis have symptoms. Most prominent symptoms are jaundice (icterus), pruritus, and pain. Cholecystitis is a disorder characterized by inflammation of the gallbladder; the disease can be acute or chronic. Acute cholecystitis is characterized by inflammation of the gallbladder that develops over hours, usually because a gallstone obstructs the cystic duct. Symptoms may include right upper quadrant pain and tenderness, sometimes accompanied by fever, chills, nausea, and vomiting. Chronic cholecystitis is characterized by longstanding

gallbladder inflammation, almost always due to gallstones. A possible role of OCs is feasible on the basis of an involvement of female sex hormones, as indicated by the female preponderance of gallstones, notably in women between menarche and menopause.

Table SVII.3.1.4: Details of Important Potential Risk: Cholelithiasis/Cholecystitis/Elevated Hepatic Enzymes

Frequency with 95%CI	A total of 8 cases of cholelithiasis and 2 cases of cholecystitis for NOMAC-E2 users have been reported in the Integrated Safety Data Set. From these 10 cases the following relatedness according to the investigator was reported: • Related: 4 • Not related: 6 For NOMAC-E2, 35 subjects experienced one or more PTs of Elevated hepatic enzymes. In these 35 cases, a total of 46 occasions of 'Elevated hepatic enzymes' were reported, concerning the following PTs: Hepatic enzyme increased (9), Alanine aminotransferase increased (16), Aspartate aminotransferase increased (9), Gamma-glutamyltransferase increased (5), Liver function test abnormal (3), Blood bilirubin increased (1), Blood lactate dehydrogenase increased (1), Hepatic enzyme abnormal (1), and Transaminase increased (1). From the 46 occasions the following relatedness according to the investigator was reported: • Related: 33 • Not related:10 • Missing: 3 (1) Clinical trials with NOMAC-E2 <u>Cholelithiasis/cholecystitis</u> With 10 reported cases and an exposure of 2694.5 woman-years, the incidence for NOMAC-E2 is 3.7 (95% CI 1.8-6.8) cases per 1000 woman-years. For the comparator DRSP/EE (3mg-30µg) 2 cases have been reported with an exposure of 881.8 woman-years, corresponding to an incidence of 2.3 (95% CI 0.3-8.2) cases per 1000 woman-years. The cholelithiasis incidence for NOMAC-E2 is slightly higher than the incidence for DRSP/EE <u>Elevated Hepatic Enzymes</u> With 35 reported cases and an exposure of 2,694.5 woman-years, the incidence for NOMAC-E2 is 13.0 (95% CI 9.0-18.1) cases per 1,000 woman-years. For the comparator DRSP/EE (3mg-30µg) 2 cases have been reported with an exposure of 881.8 woman-years, corresponding to an incidence of 2.3 (95% CI 0.3-8.2) cases per 1000 woman-years.
Frequency with 95%CI	(2) Epidemiological studies <u>Cholelithiasis/Cholecystitis</u> There are no published epidemiological studies investigating the relative risk of cholelithiasis among NOMAC-E2 users versus non-users. For OC users in general, 25 epidemiological studies on the association of CHC use and gallbladder disease were evaluated in a meta-analysis by Thijs and Knipschild (1993). [Ref. 5.4: 03KTPR] The results varied considerably. Odds ratios ranged from 0.3 to 6.0. The authors selected six studies in which asymptomatic women were screened for gallstones. Pooling of the very similar results of these six case-control studies yielded a relative risk of 1.36 (95% CI, 1.15 to 1.62). In the studies reported after 1982, no relative risk above 1.4 was observed, which could be attributable to an increased use of CHCs with a low estrogen dose. A systematic review and meta-analysis of the association of exogenous estrogen (OC and hormonal replacement therapy [HRT]) and incidence of gallstones was conducted by Wang *et al.* including literature through October 2016. Wang *et al.* found no significant association between OC use and gallbladder disease (RR: 1.19 (95% CI: 0.97-1.45); with removal of studies of low quality RR:1.10 (95% CI: 0.92-1.3) [Ref. 5.4: 052MK7].

Table SVII.3.1.4: Details of Important Potential Risk: Cholelithiasis/Cholecystitis/Elevated Hepatic Enzymes

	In a prospective study a relative risk of 1.2 (95% CI 0.9-1.6) for gallstones development among ever-use of OC was found compared to non-users. Furthermore, current and long-term users had somewhat elevated risks (current users total relative risk (RR) 1.6, 95% CI 1.1-2.4; current users long term (15+ years) RR 1.5, 95% CI 0.8-2.9). The risk of symptomatic gallstones increased with increasing body mass index and weight gain since age 18. [Ref. 5.4: 03KTNP] A case control study showed a transient increase in the occurrence of gallstones following the administration of CHCs that did not accumulate beyond 10 years of use. [Ref. 5.4: 03KTPS] A follow-up analysis of the Oxford/FPA Contraceptive Study revealed that there was no significant association between CHC use and gallbladder disease and no indication for any interaction between CHC use and age or obesity in the development of the disease. [Ref. 5.4: 03KTPX] Elevated hepatic enzymes There are no data on epidemiological studies investigating the relative risk of elevated hepatic enzymes among NOMAC-E2 users versus women not taking combined oral contraceptives.
Seriousness / Outcomes	Cholelithiasis/Cholecystitis From the 10 cases which were reported with the PTs 'Cholelithiasis' and 'Cholecystitis', 9 were classified as serious. From these 10 cases the following outcomes were reported: Not recovered: 1 Recovered: 9 Elevatedhepaticenzymes All 35 cases of Elevated hepatic enzymes were classified as non-serious. From the 46 occasions the following outcomes were reported: • Not recovered: 11 • Recovered: 22 • Recovering: 3 • Unknown: 8 • Missing: 2
Severity and Nature of the Risk	Cholelithiasis/cholecystitis From the 10 cases which were reported with the PTs Cholelithiasis' and 'Cholecystitis' the following severities were reported: • Moderate: 4 • Severe: 6 Elevated hepatic enzymes From the 46 occasions of Elevated hepatic enzymes the following severities were reported: • Mild: 25 • Moderate: 18 • Severe:2 • Missing: 1

Table SVII.3.1.4: Details of Important Potential Risk: Cholelithiasis/Cholecystitis/Elevated Hepatic Enzymes

Background Incidence / Prevalence

Incidence

Incidence in Europe

The few prospective ultrasound surveys in Europe that have assessed gallstone incidence show an incidence <1/100 persons per year (0.34-0.97% in Italy, 0.93% in Denmark). Incidence rates increase with age and are higher in women than in men. [Ref. 5.4: 03KHMT]

An estimation of age-specific incidence rates was made from published gallstone prevalence data in seven populations. [Ref. 5.4: 03KKHM]

Estimated average annual incidence (and SE) of gallstones per 1,000 women by age group. [Ref. 5.4: 03KKHM]

Country	Age group				
	20-29	30-39	40-49	50-59	60-69
Denmark	-	2.7 (1.3)	5.1 (1.8)	9.4 (2.6)	-
Germany	3.8 (4.2)	5.7 (5.4)	8.2 (6.2)	11.2 (7.8)	15.1 (9.2)
India, Kashmir	2.3 (2.5)	4.2 (3.8)	7.2 (8.0)	11.9 (11.9)	-
Italy, Rome	2.0 (1.6)	3.6 (1.9)	6.2 (3.3)	10.3 (8.1)	15.9 (12.1)
Italy, Sirmione	3.0 (2.1)	5.2 (2.7)	8.8 (3.3)	13.9 (4.1)	-
Norway	4.4 (3.4)	6.8 (4.4)	10.2 (5.5)	14.5 (6.7)	19.5 (8.3)
UK, Bristol	1.7 (1.5)	2.8 (2.2)	4.4 (3.4)	6.6 (5.4)	9.8 (7.2)

There are no data on the incidence of elevated hepatic enzymes in women not taking combined oral contraceptives.

Prevalence

Prevalence in Europe

A recent review on the burden of gallstone disease in Europe presented median prevalence of gallstone disease from the largest population surveys in Europe, ranging from 6.7 to 24.5% in females. [Ref. 5.4: 03KHMT]
Most surveys showed that the prevalence of gallstones increases with age and is higher in women than in men. [Ref. 5.4: 03KHMT]

There are no data on the prevalence of elevated hepatic enzymes in women not taking combined oral contraceptives.

Prevalence in the United States

Most gallstones stay asymptomatic; therefore clinically diagnosed cases of gallstones represent less than half of the overall prevalence. [Ref. 5.4: 03KHMT]

The third National Health and Nutrition Examination Survey (NHANES III) conducted gallbladder ultrasonography among a representative US sample of 14,238 persons. [Ref. 5.4: 03QJD4] From these participants 1,149 had gallstones and 886 had undergone cholecystectomies. A total of 20.5 million aged 20-74 years, from which 14.2 million women, were estimated to have gallbladder disease.

There are no data on the prevalence of elevated hepatic enzymes in women not taking combined oral contraceptives.

Risk Groups or Risk Factors

Some risk factors for gallstones are unalterable, such as advancing age, being female, and genes/ethnicity. [Ref. 5.4: 03KHMT] Ethnic differences vary from a high prevalence of 60-70% in American Indians to prevalences of 20% in Northern Europe and 6-17% overall in Europe and North American white adults. Very low rates occur in Black Africans. [Ref. 5.4: 03KTPJ] Other factors can be modified such as obesity, rapid weight loss, diet, drugs, and activity. [Ref. 5.4: 03KTPJ] Detrimental are diets with a high caloric intake and refined carbohydrates. Beneficial are diets high in fiber, vegetable protein, nuts, calcium, vitamin C, caffeinated coffee, and alcohol in moderation. [Ref. 5.4: 03KTPJ] Physical activity appears protective, decreasing the possibility of developing cholelithiasis. [Ref. 5.4: 03KTNT] Reduced physical activity increased the risk. [Ref. 5.4: 03KKJ2]

Ceftriaxone is avidly secreted into bile and can precipitate with calcium to form biliary sludge and stones. [Ref. 5.4: 03MVV0] Estrogen is also thought to promote the formation of gallstones. [Ref. 5.4: 03KTPT]

Table SVII.3.1.4: Details of Important Potential Risk: Cholelithiasis/Cholecystitis/Elevated Hepatic Enzymes

Potential Mechanisms	Gallstone formation is thought to rely on three factors: supersaturation of biliary cholesterol due to hepatic hypersecretion, nucleation of cholesterol monohydrate crystals, and gallbladder hypomotility. [Ref. 5.4: 03KTNB] Estrogens have been shown to increase cholesterol saturation of bile, alter bile acid composition, and decrease bile flow. [Ref. 5.4: 03KTNV]
Preventability	The risk of gallstones could be reduced (partly) by controlling diet and physical activity.
Impact on the Risk-Benefit Balance of the Product	Gallstone formation is a condition which has been reported to occur or deteriorate with both pregnancy and combined oral contraceptive (COC) use, however the evidence of an association with COC use is inconclusive. Additionally, hepatic enzyme increased is a known adverse effect which can occur with NOMAC-E2. These adverse events are noted in the product labeling. There is no information on the effect of NOMAC-E2 on quality of life in the event a woman suffers from cholelithiasis, cholecystitis, or elevated hepatic enzymes. This risk is being further evaluated in the PASS and NOMAC-E2 continues to have a positive benefit-risk balance.
Potential Public Health Impact of Safety Concern	The safety profile of NOMAC-E2 related to cholelithiasis, cholecystitis, and elevated hepatic enzymes is well characterized and therefore, the expected public health impact is minimal given the data above.
Evidence Source	Clinical trial data Published literature
MedDRA Terms	Cholelithiasis/Cholecystitis MedDRA PTs for Cholelithiasis reported in clinical trials: 'Cholelithiasis' and 'Cholecystitis'. Elevated hepatic enzymes MedDRA PTs for Elevated hepatic enzymes reported in clinical trials: 'Hepatic enzyme increased', 'Alanine aminotransferase increased', 'Aspartate aminotransferase increased', 'Gamma-glutamyltransferase increased', 'Liver function test abnormal', 'Blood bilirubin increased', 'Blood lactate dehydrogenase increased', 'Hepatic enzyme abnormal', and Transaminase increased'.
CI = confidence interval; CHC = combined hormonal contraceptive; CTD = common technical document; DRSP/EE = Drospirenone and ethinyl estradiol; GBD = gall bladder disease; MedDRA = Medical Dictionary for Regulatory Activities; NHANES = National Health and Nutrition Examination Survey; PT = preferred term; RR = relative risk; SE = standard error; UK = United Kingdom.	

Post Marketing data

From the final study report for the PASS study (P08291):

There were no statistically significant differences in the risk of **cholelithiasis** between the user (sub-)cohorts. Out of 261 cases of cholelithiasis (18.0 per 10,000 WY; 95% CI, 15.9 – 20.3), 84 were in NOMAC-E2 users (17.2 per 10,000 WY; 95% CI, 13.7- 21.3), 92 were in COC_{LNG} users (17.0 per 10,000 WY; 95% CI, 13.7 – 20.9), 21 were in COC Other users (25.3 per 10,000 WY; 95% CI, 15.7 – 38.6), 8 in OHC users (33.8 per 10,000 WY; 95% CI, 14.6 – 66.6) and 56 in ex-users (17.9 per 10,000 WY; 95% CI, 13.5 – 23.2)

MENINGIOMA

Meningiomas are the most common primary brain tumor [Ref. 5.4: 0534KN]. They are more common in women and their incidence increases progressively with age and varies by race. Most meningiomas are benign and often asymptomatic or present with subtle symptoms [Ref. 5.4: 05DQQ5] [Ref. 5.4: 05DQQ3] [Ref. 5.4: 05DQQ2]. In patients who are symptomatic from their meningioma, neurologic symptoms are determined by the location of the mass. Seizures are a common presenting symptom in patients with intracranial meningioma [Ref. 5.4: 05DQQ4].

Table SVII.3.1.5: Details of Important Potential Risk: Meningioma

Frequency with 95% CI	Epidemiological studies There are no published epidemiological studies investigating the relative risk of meningioma among NOMAC-E2 users versus non-users. A comprehensive literature review was conducted including literature through December 31, 2019 to identify published epidemiologic literature on the association of oral hormonal contraceptive (OC) use and the risk of meningioma. The literature review resulted in 56 potentially relevant articles. After abstract and full text review as well as review of the reference list of identified articles, 15 articles (1 review, 1 meta-analysis, 3 prospective cohort studies, 10 case-control studies) that provided relevant risk estimates for the association of OCs and meningioma were identified. Cowppli-Bony *et al.* reviewed the published epidemiologic literature through September 2010 concerning exogenous and endogenous hormonal exposures and brain tumors (meningioma and gliomas). Thirteen articles were identified that provided information on meningiomas, and 7 of these examined the use of OCs. None of these 7 articles reported information specific to NOMAC-E2. The risk estimates were not consistent across studies and ranged from 0.2 (95% CI: 0.1,0.7) [Ref. 5.4: 05398V] to 1.5 (95% CI: 0.8,3.0) [Ref. 5.4: 0538ML]. Three of the studies found no association between meningioma risk and OC use as well as duration of OC use. In contrast, a significant reduced risk with OC use was found in the studies of Lee et al. and in Preston-Martin *et al.* for ≥ 3 years of OC use. The remaining 2 studies found non-significant increased risks of meningioma [Ref. 5.4: 053NHX]. Qi *et al.* conducted a systematic literature review through 2013 and meta-analysis of studies assessing the association between OCs, hormone replacement therapy (HRT), and reproductive factors and meningioma risk. A total of twelve studies including seven retrospective studies and five prospective studies reported risk estimates for ever versus never use of OCs. None of these studies provided risk estimates specifically for NOMAC-E2. The cumulative risk associated with ever OC use was 0.93, 95% CI: 0.83,1.03. Of the 12 studies included, none had statistically significant risk estimates and only 4 of the 12 risk estimates were > 1.0 ranging from 1.02-1.33 [Ref. 5.4: 053999]. One prospective cohort study was identified in the published literature that reported a statistically significant increased risk of meningioma in current users of OCs compared to never users. The European Prospective Investigation into Cancer and Nutrition (EPIC) followed 276,451 women from 9 European countries for an average of 8.4 years;194 cases of meningioma were diagnosed. The average age (SD) age at recruitment and meningioma diagnosis was 50.4 (10.5) years and 53.9 (8.0) years, respectively. Women who reported being current users of OCs at the time of recruitment into the cohort had a higher risk of meningioma than women who never used OCs: Hazard ratio (HR) 3.61, 95% CI: 1.75,7.46, whereas former users did not have an elevated risk HR 1.20, 95% CI: 0.86,1.68. There was no clear trend of increased risk with duration of ever OC use and meningioma risk overall, but there was a statistically significant trend for increased risk by duration of exposure among premenopausal women: HR (95% CI) of 1.21 (0.36,4.06), 1.55 (0.53,4.56), 2.97 (1.08,8.15), 3.22 (1.04,10.0), and 3.60 (1.00,13.0) for ≤1, >1-<5, ≥5-<10, ≥10-≤15, and >15 years of use, respectively, P trend = 0.01 [Ref. 5.4: 053935]. In contrast to the findings from the EPIC study, Jhawar *et al.* conducted an analysis of the Nurses' Health Study, a prospective cohort study including nurses from 11 US states who were between 30 and 55 years of age at enrollment and did not find a significant association

Table SVII.3.1.5: Details of Important Potential Risk: Meningioma

	between current OC use and the risk of meningioma. During 1,213,522 person-years of follow-up, 125 cases of meningioma were confirmed. The mean age at diagnosis was 54.2± 8.0 years. The relative risk (RR) for past vs never use of OCs was 0.76, 95% CI: 0.51–1.14, and for current vs never use 1.34, 95% CI: 0.18–9.96 [Ref. 5.4: 0538MY]. The majority of the remaining cohort (1/1) and case-control studies (8/10) identified as part of the literature review did not find significant risk estimates for meningioma comparing OC users versus non-users. In the remaining 2 case-control studies the odds ratios were 1.8, 95% CI: 1.1,2.9 [Ref. 5.4: 0538M7] among premenopausal women currently using OCs, and 1.24, 95% CI: 1.01,1.51 in ever users of OC versus never users [Ref. 5.4: 05B337], respectively.
Background Incidence / Prevalence	The Central Brain Tumor Registry of the United States (CBTRUS) contains the most currently available data on all newly diagnosed primary brain and central nervous system tumors from the Centers for Disease Control and Prevention (CDC), the National Program of Cancer Registries (NPCR), and the National Cancer Institute (NCI), Surveillance, Epidemiology and End Results (SEER) program. Based on these nationally representative data from 2011-2015, meningioma was the most frequently reported brain and other central nervous system tumor, accounting for 37.1% of newly diagnosed brain and other CNS tumors overall. Most meningiomas (79.8%) were located in the cerebral meninges, 4.2% were located in the spinal meninges, and approximately 15.2% did not have a specific meningeal site listed. Non-malignant meningioma accounted for 98.8% of the meningiomas reported to CBTRUS [Ref. 5.4: 0534JW]. The incidence of meningioma per 100,000 United States (US) population increases with age, and is 1.41, 95% CI: 1.37,1.46 for those 20-34 years, 5.24, 95% CI: 5.14,5.34 for those 35-44 years, 9.71, 95% CI: 9.58,9.84 for those 45-54 years, 15.64, 95% CI: 15.47,15.82 for those 55-64 years, 27.66, 95% CI: 27.36,27.96 for those 65-74 years, 40.78, 95% CI: 40.30, 41.27 for those 75-84 years, and 52.53, 95% CI: 51.72,53.36 for those 85+ years. Meningiomas are more than twice as common in females as in males. The estimated incidence of meningioma is 4.97, 95% CI: 4.92,5.02 and 11.28, 95% CI: 11.21,11.35, in males and females, respectively. Incidence rate ratios by age group and gender are lowest in those <20 years old, where incidence rates for males and females are approximately equal, and highest from 35–54, where incidence rates are 3 times higher in females [Ref. 5.4: 0534JW]. There are several population-based registries in Europe that collect information on brain and CNS malignant neoplasms as well as benign and intermediate tumors [Ref. 5.4: 0534H9]. The Austrian Brain Tumor Registry (ABTR) found meningioma to be the most common brain tumor type in 2005 and showed similar or slightly higher incidence rates in Austria compared with findings from the US-based CBTRUS registry [Ref. 5.4: 0534L4]. The Swedish Brain Tumor Registry (SBTR) of adult patients with CNS tumors found the age-standardized incidence per 100,000 population in 2012 in those ≥20 years of age at diagnosis to be approximately 3.0 and 8.0 in men and women, respectively [Ref. 5.4: 0534H9]. Findings from the Gironde registry in France are consistent with the US and other European countries in that women were more likely to experience meningioma; the age-standardized incidence rate overall was 6.1 per 100,000 population and 3.5 and 8.4 per 100,000 population for males and females, respectively. Incidence rate ratios by age group and gender were lowest in those ≤24 years old (where incidence rates for males and females are approximately equal), and highest from 25–49, where incidence rates were approximately 3 times higher in females [Ref. 5.4: 0534KD]. The prevalence of meningioma represents the combined effects of disease incidence and survival and can be estimated using data from the CBTRUS. Incidence data for 2004 and survival data from 1985–2005 for non-malignant meningioma were obtained by Porter *et al.* from CBTRUS and used to model prevalence. In 2004, the prevalence of non-malignant meningioma was estimated to be approximately 70.7/100,000 with over 200,000 individuals living with this condition in the US [Ref. 5.4: 0406W7].
Risk Groups or Risk Factors	Established risk factors for meningioma include mutations in the neurofibromatosis gene (NF2) as well as exposure of the brain to high dose ionizing radiation.

Table SVII.3.1.5: Details of Important Potential Risk: Meningioma

Potential Mechanisms	An etiologic role for hormones (both endogenous and exogenous) has been hypothesized based on the presence of hormone receptors on these tumors and the fact that women are more likely than men to develop meningiomas [Ref. 5.4: 0534KN]. However, the etiology of meningioma is unknown, therefore it is difficult to postulate potential mechanisms regarding the role of oral contraceptives in the pathogenesis of meningioma.
Preventability	Because the etiology of meningioma is still largely unknown, there is no data on the preventability of meningioma.
Impact on the Risk-Benefit Balance of the Product	Symptoms from a meningioma and the impact on the patient´s quality of life are determined by the size, the time course over which the tumor develops and the location. 80 to 90 percent of meningiomas are World Health Organization (WHO) grade I [Ref. 5.4: 0534JW]. There is no information on the effect of NOMAC-E2 on quality of life in the event a woman suffers from meningioma. This risk will continue to be monitored and NOMAC-E2 continues to have a positive benefit-risk balance.
Potential Public Health Impact of Safety Concern	The public health impact of the risk of meningioma in NOMAC-E2 users is unknown.
Evidence Source	Published literature

SVII.3.2 Presentation of the Missing Information

Missing information: Safety in post-menarcheal adolescents

Evidence Source:

There are no adequate and well-controlled studies of NOMAC-E2 use in post-menarcheal adolescents.

Population in Need of Further Characterisation:

Post-menarcheal adolescents, specifically those 12-17 years of age, were not included in NOMAC-E2 clinical efficacy and safety trials, which limited enrollment to women 18-50 years of age. It is unknown whether the amount of estradiol in NOMAC-E2 is sufficient to maintain adequate levels of estradiol in adolescents, especially for bone mass accrual.

Post Marketing data

From the final study report for the PASS study (P08291):

There were 3 VTEs in adolescents (i.e. study participants under the age of 18 years): 2 in COC_{LNG} users (5.9 per 10,000 WY; 95% CI, 0.7 – 21.4) and 1 in a COC Other user (17.4 per 10,000 WY; 95% CI, 0.4 – 96.7). No case of VTE was recorded in NOMAC-E2 adolescent users.

Missing information: Safety in women during pregnancy

Evidence Source:

There are no adequate and well-controlled studies of NOMAC-E2 use in pregnancy.

Population in Need of Further Characterisation:

NOMAC-E2 must not be used by women who are pregnant or think they might be pregnant. Women who had a known or suspected pregnancy were not included in clinical trials. If a women gets pregnant while using NOMAC-E2, she should stop using NOMAC-E2 and contact her doctor. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used ethinylestradiol-containing COCs prior to pregnancy, nor an increased risk of deformity in the unborn baby when ethinylestradiol-containing COCs were taken by mistake during early pregnancy. In animal studies, abnormalities in the offspring have been observed with the NOMAC-E2 combination which is related to high exposure of estradiol during pregnancy. Clinical data on a limited number

of pregnant women who took NOMAC-E2 indicate no side effect of NOMAC-E2 on the unborn baby or newborn infant.

Post Marketing data

From the final study report for the PASS study (P08291):

In this study, there were 289 unintended pregnancies: 64 in NOMAC-E2 users (0.15 per 100 WY; 95% CI, 0.11 – 0.19), 200 in COC_{LNG} users (0.41 per 100 WY; 95% CI, 0.35 – 0.47), 19 in COC Other users (0.26 per 100 WY; 95% CI, 0.16 – 0.40) and 6 in OHC users (0.28 per 100 WY; 95% CI, 0.10 – 0.61). Out of the 64 pregancies in NOMAC-E2 users: 22 reported healthy child, 21 induced abortion, 9 spontaneous abortion, 3 missed abortion, 1 ectopic pregnancy, 3 malformation and in 5 cases the outcome was unknown. In the 200 COC_{LNG} users with unexpected pregnancies, 98 reported healthy child, 59 induced abortion, 16 spontaneous abortion, 3 missed abortion, 4 ectopic pregnancies, 4 malformation, 2 anomalies/ disoders in newborn, and in 13 cases the outcome was unknown.

Overall, among study participants, there were 2,604 deliveries (resulting from both intended and unintended pregnancies). Among these, there were 31 malformations (1.2% of all deliveries). There were similar proportions of malformations among deliveries by NOMAC-E2 users (1.3%) and those who had last used COC_{LNG} (1.2%). Women were allocated to a user cohort based upon their last hormonal contraceptive use prior to delivery. The malformations were analyzed further on in accordance to the temporal proximity of last hormonal contraceptive exposure. Congenital malformations that occurred in the sub-group exposed to hormonal contraceptice at time of conception could reflect a teratogenic potential for a specific study treatment. This sub-group is therefore particularly relevant for the assessment of potential teratogenic effects. From NOMAC-E2 subgroup, 3 malformation was reported (0.3% of deliveries), and from COC_{LNG}, 5 malformation was reported (0.4% of deliveries).

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	▪ Depression/Depressed mood ▪ Venous thromboembolic events ▪ Arterial thromboembolic events
Important potential risks	▪ Cholelithiasis/Cholecystitis/Elevated hepatic enzymes ▪ Meningioma
Missing information	▪ Safety in post-menarcheal adolescents ▪ Safety in women during pregnancy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-Up Questionnaires for and Meningioma:

- Routine PV is planned, including event-specific questionnaires sent to reporters of meningioma, VTE and ATE to collect details to closely monitor reported cases of these events and to quantify possible risk factors.

III.2 Additional Pharmacovigilance Activities

The additional pharmacovigilance activity of imposed PASS study (P08291- Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5 mg) and 17β-estradiol (1.5 mg)) has been completed.

There are no planned or ongoing additional pharmacovigilance activities for any risk.

III.3 Summary Table of Additional Pharmacovigilance Activities

N/A

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for NOMAC-E2.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Depression/ depressed mood	Routine risk communication: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects No other routine risk minimization measures are proposed.
Venous thromboembolic events	Routine risk communication: • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: • Symptoms of VTE in the SmPC • Signs and symptoms of blood clots in a vein in the Package Leaflet (PL)
Arterial thromboembolic events	Routine risk communication: • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: • Symptoms of ATE in the SmPC • Signs and symptoms of blood clots in an artery in the Package Leaflet (PL)
Cholelithiasis/ Cholecystitis/ Elevated hepatic enzymes	Routine risk communication: • Section 4.3 Contraindications • Section 4.8 Undesirable effects No other routine risk minimization measures are proposed.

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Meningioma	Routine risk communication: • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use No other routine risk minimization measures are proposed.
Safety in post-menarcheal adolescents	Routine risk communication: • Section 4.4 Special warnings and precautions for use • Section 5.1 Pharmacodynamic properties • Section 5.2 Pharmacokinetic properties No other routine risk minimization measures are proposed.
Safety in women during pregnancy	Routine risk communication: • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.6 Fertility, pregnancy and lactation No other routine risk minimization measures are proposed.

V.2 Additional Risk Minimization Measures

1.1. Direct Healthcare Professional Communication distributed in 2014

Objectives:

When prescribing a CHC, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE and ATE. Information to communicate this risk and to highlight the risk of VTE and ATE has been provided to prescribers in the first quarter of 2014 via a one-time distribution of a Direct Healthcare Professional Communication (DHPC).

Rationale for the Additional Risk Minimisation Activity:

In February 2013, EMA has started a Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data to review the risk of VTE and ATE of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate. The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed all available data on the risk of VTE and ATE with these contraceptives and the European Commission made its final decision on 16 January 2014, concluding the Article 31 review of CHCs. Following an extensive review of data related to CHCs; the PRAC and CHMP concluded that the benefits of all CHCs continue to outweigh the risks, and there is no reason for women who have been using CHCs without any problem to stop taking them on the basis of its review. The product information of CHCs has been updated in the Indications, Contraindications, Warnings and Precautions, Fertility, Pregnancy and Lactation as well as the Undesirable Effects sections related to the risk of VTE and ATE. When prescribing a CHC, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE, and the difference in risk of VTE between products. A new contraindication (major surgery with prolonged immobilization) was added and the warnings and precautions strengthened.

Target audience and Planned Distribution Path:

Information to communicate the outcome of the review and to highlight the risk of the thromboembolic events through a one-time distributed DHPC, which was sent in collaboration with other MAHs of CHCs and National Competent Authorities in the first quarter of 2014. Also, educational materials were implemented at the time of DHPC distribution and are being maintained and distributed on a country-specific level according to local Health Authority requirements.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

Effectiveness is measured through routine PV and routine ADR collection.

1.2. Direct Healthcare Professional Communication to be distributed in 2022

Objectives:

When prescribing low dose nomegestrol containing product, careful consideration should be given to the individual woman's current risk factors, as this product must not be used by patients who have, or have had, meningioma. Information to communicate this risk will be provided to prescribers after finalization of the referral procedure (EMEA/H/A-31/1510).

Rationale for the Additional Risk Minimisation Activity:

In September 2021, EMA has started a Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data to review the risk of meningioma. Recently, results from two French epidemiological cohort studies observed a cumulative dose-dependent

association between chlormadinone acetate or nomegestrol acetate and meningioma [Nguyen P et al. (2021) CMA] [Nguyen P et al. (2021) NOMAC]. These studies were based on data from the French health insurance (CNAM) and included a population of 828,499 patients for chlormadinone acetate and 1,060,779 for nomegestrol acetate. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose chlormadinone acetate (cumulative dose > 360 mg) or high dose nomegestrol acetate (cumulative dose > 150 mg) and women who were slightly exposed to chlormadinone acetate (cumulative dose ≤ 360 mg) or nomegestrol acetate (cumulative dose ≤ 150 mg). Literature review and EudraVigilance analysis have also been performed.

No new safety concern regarding a risk of meningioma associated with the use of low dose (2 mg) chlormadinone acetate containing medicinal products or low dose (2.5 mg) nomegestrol acetate containing contraceptives could be identified. However, as the risk of meningioma increases with increasing cumulative doses of products containing chlormadinone acetate or nomegestrol acetate, low dose products are contraindicated in patients with meningioma or history of meningioma and treatment should be permanently stopped in case of signs and symptoms of meningioma.

Target audience and Planned Distribution Path:

DHPC to inform about the outcome of the review regarding products containing chlormadinone acetate or nomegestrol acetate and the risk of meningioma will be distributed in collaboration with other MAHs and National Competent Authorities after finalization of the referral procedure.

DHPC recipients as agreed by PRAC: Endocrinologists, gynaecologists, general practitioners, learned societies and any other relevant target groups as agreed at national level.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

Effectiveness will be measured in the upcoming PSUR.

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Depression/ Depressed Mood	**Routine risk minimisation measures:** The risk of depression/ depressed mood is described in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Venous thromboembolic events	**Routine risk minimisation measures:** The risk of VTEs are described in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC. **Additional risk minimization measures:** A DHPC has been sent in collaboration with other MAHs of CHCs and National Competent Authorities. Also, educational materials distributed on a country-specific level according to local Health Authority requirements.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific follow-up questionnaire
Arterial thromboembolic events	**Routine risk minimisation measures:** The risk of ATEs are described in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC. **Additional risk minimization measures:** A DHPC has been sent in collaboration with other MAHs of CHCs and National Competent Authorities. Also, educational materials distributed on a country-specific level according to local Health Authority requirements.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific follow-up questionnaire
Cholelithiasis/ Cholecystitis/ Elevated hepatic enzymes	**Routine risk minimisation measures:** The risks of cholelithiasis/ cholecystitis/ elevated hepatic enzymes are described in sections 4.3 Contraindications and 4.8 Undesirable effects of the SmPC.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Meningioma	**Routine risk minimisation measures:** The risk of meningioma is described in sections 4.3 Contraindications and 4.4 Special warnings and precautions for use of the SmPC. **Additional risk minimization measures:** A DHPC will be send in collaboration with other MAHs of chlormadinone and nomegestrol containing products and National Competent Authorities as an	Routine pharmacovigilance activities Additional pharmacovigilance activities: None Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event-specific follow-up questionnaire

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
	obligation of the referral procedure (EMEA/H/A-31/1510).	
Safety in post-menarcheal adolescents	**Routine risk minimisation measures:** The missing information regarding safety in post-menarcheal adolescents is described in sections 4.4 Special warnings and precautions for use, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Safety in women during pregnancy	**Routine risk minimisation measures:** The missing information regarding safety in women during pregnancy is described in sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.6 Fertility, pregnancy and lactation.	Routine pharmacovigilance activities Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for Zoely

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

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

This summary of the RMP for Zoely 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 Zoely 's RMP.

I. The Medicine and What it is Used For

Zoely is authorised for oral contraception (see SmPC for the full indication). It contains nomegestrol acetate + 17β-estradiol as the active substances and it is given as a film-coated oral tablet.

Further information about the evaluation of Zoely's benefits can be found in Zoely's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/zoely#assessment-history-section

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

Important risks of Zoely, together with measures to minimise such risks and the proposed studies for learning more about Zoely '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 the case of NOMAC-E2, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions 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 Zoely is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Zoely are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Zoely. 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 II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	▪ Depression/Depressed mood ▪ Venous thromboembolic events ▪ Arterial thromboembolic events
Important potential risks	▪ Cholelithiasis/Cholecystitis/Elevated hepatic enzymes ▪ Meningioma
Missing information	▪ Safety in post-menarcheal adolescents ▪ Safety in women during pregnancy

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Depression/ Depressed Mood

Evidence for linking the risk to the medicine	Clinical trial data Published literature
Risk factors and risk groups	The following factors predispose certain women to OC-related negative changes in mood/affect: A history of depression, other symptoms of psychological distress (eg, anxiety, stress, neuroticism), dysmenorrheal and premenstrual mood symptoms prior to OC use, a history of pregnancy-related mood symptoms, a family history of OC-related mood complaints, being in the postpartum period and age. A number of OC-related variables also mediate mood/affect changes for certain individuals: For women with a history of premenstrual emotional symptoms prior to OC use, OC formulations with higher progesterone to estrogen dosage ratios are associated with less negative mood changes, as are the use of monophasic versus triphasic OCs. For women without a history of premenstrual irritability, formulations with lower ratios of progesterone to estrogen decrease the risk of negative mood change. Finally, monophasic OCs have a greater stabilizing effect than triphasic OCs.
Risk minimisation measures	**Routine risk minimisation measures:** The risk of depression/ depressed mood is described in sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table II.B.2: Important Identified Risk: Venous Thromboembolic Events

Evidence for linking the risk to the medicine	Clinical trial data Published literature
Risk factors and risk groups	Risk factors for VTE are: Hereditary risk factors: • Antithrombin III deficiency • Protein C deficiency • Protein S deficiency • Activated protein C resistance (Factor V Leiden gene mutation) • Prothrombin gene mutation (G20210A) • Hyperhomocysteinemia Acquired risk factors: • Obesity • Varicose veins • Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) • Postpartum period • Pregnancy • Surgery • Trauma • Stasis (eg, due to prolonged immobility) • Increasing age • Positive (family) history • Other diseases (eg, hemolytic uremic syndrome, inflammatory bowel disease, auto-immune states such as systemic lupus erythematosus, HBsAg, hypothyroidism, malignancy, renal disease) • Smoking
Risk minimisation measures	**Routine risk minimisation measures:** The risk of VTEs are described in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC. **Additional risk minimization measures:** A one-time distributed DHPC was sent in collaboration with other MAHs of CHCs and National Competent Authorities in the first quarter of 2014. Also, educational materials were implemented at the time of DHPC distribution and maintained and distributed on a country-specific level according to local Health Authority requirements.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table II.B.3: Important Identified Risk: Arterial Thromboembolic Events

Evidence for linking the risk to the medicine	Clinical trial data Published literature
Risk factors and risk groups	Risk factors for ATE are: • Increasing age, particularly above 35 years. • Smoking. • Hypertension • Obesity (body mass index over 30kg/m^2) • Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g., below 50) • Migraine • Other medical conditions associated with adverse vascular events (e.g., diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinemia and systemic lupus erythematosus)
Risk minimisation measures	**Routine risk minimisation measures:** The risk of ATEs are described in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC. **Additional risk minimization measures:** A one-time distributed DHPC was sent in collaboration with other MAHs of CHCs and National Competent Authorities in the first quarter of 2014. Also, educational materials were implemented at the time of DHPC distribution and maintained and distributed on a country-specific level according to local Health Authority requirements.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table II.B.4: Important Potential Risk: Cholelithiasis/ Cholecystitis/ Elevated Hepatic Enzymes

Evidence for linking the risk to the medicine	Clinical trial data Published literature
Risk factors and risk groups	Some risk factors for gallstones are unalterable, such as advancing age, being female, and genes/ethnicity. Ethnic differences vary from a high prevalence of 60-70% in American Indians to prevalences of 20% in Northern Europe and 6-17% overall in Europe and North American white adults. Very low rates occur in Black Africans. Other factors can be modified such as obesity, rapid weight loss, diet, drugs, and activity. Detrimental are diets with a high caloric intake and refined carbohydrates. Beneficial are diets high in fibre, vegetable protein, nuts, calcium, vitamin C, caffeinated coffee, and alcohol in moderation. Physical activity appears protective, decreasing the possibility of developing cholelithiasis. Reduced physical activity increased the risk. Ceftriaxone is avidly secreted into bile and can precipitate with calcium to form biliary sludge and stones. Estrogen is also thought to promote the formation of gallstones.
Risk minimisation measures	**Routine risk minimisation measures:** The risks of cholelithiasis/ cholecystitis/ elevated hepatic enzymes are described in sections 4.3 Contraindications and 4.8 Undesirable effects of the SmPC.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table II.B.5: Important Potential Risk: Meningioma

Evidence for linking the risk to the medicine	Published literature
Risk factors and risk groups	Established risk factors for meningioma include mutations in the neurofibromatosis gene (NF2) as well as exposure of the brain to high does ionizing radiation.
Risk minimisation measures	**Routine risk minimisation measures:** The risk of meningioma is described in sections 4.3 Contraindications and 4.4 Special warnings and precautions for use of the SmPC. **Additional risk minimization measures:** DHPC will be send in collaboration with other MAHs of chlormadinone and nomegestrol containing products and National Competent Authorities as an obligation of the referral procedure (EMEA/H/A-31/1510).

Table II.B.6: Missing Information: Safety in Post-menarcheal Adolescents

Risk minimisation measures	**Routine risk minimisation measures:** The missing information regarding safety in post-menarcheal adolescents is described in sections 4.4 Special warnings and precautions for use, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table II.B.7: Missing Information: Safety in Women During Pregnancy

Risk minimisation measures	**Routine risk minimisation measures:** The missing information regarding safety in women during pregnancy is described in sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.6 Fertility, pregnancy and lactation.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C Post-Authorisation Development Plan

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

There are no studies which are conditions to the marketing authorisation or specific obligation for Zoely at the time of updating the RMP.

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

There are no studies required for NOMAC-E2.

REFERENCES

[Ref. 5.4: 05888W] Department of Economic and Social Affairs. World family planning 2017, highlights. New York (NY): United Nations; 2017. 37 p. Report No.: ST/ESA/SER.A/414.

[Ref. 5.4: 04Z0YR] Department of Economic and Social Affairs. Trends in contraceptive use worldwide 2015. New York (NY): United Nations; 2015. 70 p. Report No.: ST/ESA/SER.A/349.

[Ref. 5.4: 046ZP4] Eeckhaut MC, Sweeney MM, Gipson JD. Who is using long-acting reversible contraceptive methods? Findings from nine low-fertility countries. Perspect Sex Reprod Health. 2014 Sep;46(3):149-55.

[Ref. 5.4: 058F4W] Daniels K, Abma JC. Current contraceptive status among women aged 15–49: United States, 2015–2017. NCHS Data Brief. 2018 Dec;327:1-8.

[Ref. 5.4: 058F6G] World Health Organization [Internet]. Geneva (Switzerland): World Health Organization (WHO); c2019. Family planning/contraception; 2018 Feb 8; [cited 2019 Jun 17]; [about 12 screens]. Available from: https://www.who.int/news-room/fact-sheets/detail/family-planning-contraception.

[Ref. 5.4: 03KSH0] Logan C, Holcombe E, Manlove J, Ryan S. The consequences of unintended childbearing: A white paper, 2007.

[Ref. 5.4: 04PBT0] Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. Stud Fam Plann. 2014 Sep;45(3):301-14.

[Ref. 5.4: 04XGBP] Department of Economic and Social Affairs. World population monitoring adolescents and youth. New York (NY): United Nations; 2012. Chapter 3, Childbearing and sexual activity among adolescents and youth. 13 p. Report No.: ST/ESA/SER.A/330.

[Ref. 5.4: 04XF4B] Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. N Engl J Med. 2016 Mar 3;374(9):843-52.

[Ref. 5.4: 03KSH2] Meade CS, Ickovics JR. Systematic review of sexual risk among pregnant and mothering teens in the USA: pregnancy as an opportunity for integrated prevention of STD and repeat pregnancy. Social Science & Medicine 2005;60:661-78.

[Ref. 5.4: 04XB3J] Tsui AO, McDonald-Mosley R, Burke AE. Family planning and the burden of unintended pregnancies. Epidemiol Rev. 2010;32:152-74.

[Ref. 5.4: 04XB3L] Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016 Jan 30;387:462-74.

[Ref. 5.4: 04XBG4] Department of Reproductive Health and Research, World Health Organization. Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2008. 6th ed. Geneva (Switzerland): World Health Organization; 2011. 64 p.

[Ref. 5.4: 058F56] World Health Organization. Fact sheets on sustainable development goals: health targets. Copenhagen (Denmark): World Health Organization (WHO) Regional Office for Europe; 2017. 8 p.

[Ref. 5.4: 058F5P] Reproductive Health [Internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC). Pregnancy mortality surveillance system; [updated 2019 Jun 4; cited 2019 Jun 19]; [about 8 screens]; Available from: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-mortality-surveillance-system.htm.

[Ref. 5.4: 058NDH] Rowley J, Hoorn SV, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016 [manuscript]. 2019. 43 p.

[Ref. 5.4: 058NDJ] Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiane SG, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes - estimates for 2016 and progress since 2012. PLoS One. 2019 Feb 27;14(2):e0211720.

[Ref. 5.4: 03KHP9] Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine 2006;24SI:SI/4-SI/15.

[Ref. 5.4: 03KSHB] Oakeshott P, Aghaizu A, Reid F, Howell-Jones R, Hay PE, Sadiq ST, et al. Frequency and risk factors for prevalent, incident, and persistent genital carcinogenic human papillomavirus infection in sexually active women: Community based cohort study. BMJ 2012;344:1-10.

[Ref. 5.4: 03KSH7] Schmeink CE, Massuger LFAG, Lenselink CH, Quint WGV, Witte BI, Berkhof J, et al. Prospective follow-up of 2,065 young unscreened women to study human papillomavirus incidence and clearance. Int J Cancer 2013;133:172-81.

[Ref. 5.4: 03KSHR] Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010;202(12):1789-99.

[Ref. 5.4: 03KSHV] Erickson BK, Alvarez RD, Huh WK. Human papillomavirus: what every provider should know. Am J Obstet Gynecol 2013:169-75.

[Ref. 5.4: 03K6M3] Anderson L, O'Rorke M, Jamison J, Wilson R, Gavin A, on behalf of the HPV Working Group members. Prevalence of human papillomavirus in women attending cervical screening in the UK and Ireland: New data from northern Ireland and a systematic review and meta-analysis. J Med Virol 2013;85(2):295-308.

[Ref. 5.4: 03KSHC] Petry KU, Luyten A, Justus A, Iftner A, Strehlke S, Reinecke-lüthge A, et al. Prevalence of high-risk HPV types and associated genital diseases in women born in 1988/89 or 1983/84- results of wolves, a population-based epidemiological study in Wolfsburg, Germany. BMC Infectious Diseases 2013;13(135):1-11.

[Ref. 5.4: 03KHNS] Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine 2006:S3-11-S3/25.

[Ref. 5.4: 04VM6P] Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS: data 2017 [Internet]. Geneva: UNAIDS; 2017. 242 p. Available from: http://www.unaids.org/en/resources/documents/2017/2017_data_book.

[Ref. 5.4: 04XRYR] European Centre for Disease Prevention and Control, World Health Organization Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 - 2016 data. Stockholm (Sweden): European Centre for Disease Prevention and Control (ECDC); 2017. 115 p.

[Ref. 5.4: 04XRJP] Centers for Disease Control and Prevention. HIV surveillance report: diagnoses of HIV infection in the United States and dependent areas, 2016. Vol 28. Atlanta (GA): U.S. Department of Health and Human Services (DHHS); 2017. 125 p.

[Ref. 5.4: 04XRHX] Centers for Disease Control and Prevention. HIV surveillance report: estimated HIV incidence in the United States, 2007-2010. Vol. 17, no. 4. Atlanta (GA): U.S. Department of Health and Human Services (DHHS); 2012 Dec. 26 p.

[Ref. 5.4: 04XS5D] World Health Organization. HIV/AIDS data and statistics [Internet]. Geneva (Switzerland): World Health Organization; 2018. 3 p. Available from: http://www.who.int/hiv/data/en/.

[Ref. 5.4: 04XRV2] Centers for Disease Control and Prevention. HIV and women. Atlanta (GA): U.S. Department of Health and Human Services (DHHS); 2018 Mar; 2 p. Available from: https://www.cdc.gov/hiv/pdf/group/gender/women/cdc-hiv-women.pdf.

[Ref. 5.4: 04XRVP] Pharris A, Quinten C, Noori T, Amato-Gauci AJ, van Sighem A. Estimating HIV incidence and number of undiagnosed individuals living with HIV in the European Union/European Economic Area, 2015. Euro Surveill. 2016 ;21(48):30417.

[Ref. 5.4: 03KHP4] Sawaya GF, Kerilkowske K, Lee NC, Gildengorin G, Washington E. Frequency of cervical smear abnormalities within 3 years of normal cytology. Am Coll Obstet Gynecol 2000;96:219-23.

[Ref. 5.4: 03KSHF] Giambi C, Donati S, Carozzi F, Salmaso S, Declich S, Ciofi degli Atti Ml, et al. A cross-sectional study to estimate high-risk human papillomavirus prevalence and type distribution in Italian women aged 18-26 years. BMC Infectious Diseases 2013;13(74):1-10.

[Ref. 5.4: 03KSHG] Rossi PG, Chini F, Bisanzi S, Burroni E, Carillo G, Lattanzi A, et al. Distribution of high and low risk HPV types by cytological status: a population based study from Italy. Infectious Agents and Cancer 2011;6(2):1-8.

[Ref. 5.4: 03KSHD] Ryerson AB, Benard VB, Major AC. National breast and cervical cancer early detection program summarizing the first 12 years of partnerships and progress against breast and cervical cancer, 1991-2002 National Report [Internet]. Atlanta: Centers for Disease Control and Prevention; 2016. Available from: https://www.cdc.gov/cancer/nbccedp/pdf/national_report.pdf .

[Ref. 5.4: 03KHNW] Rebolj M, van Ballegooijen M, Berkers LM, Habbema D. Monitoring a national cancer prevention program: successful changes in cervical cancer screening in the Netherlands. Int J Cancer 2006;120:806-12.

[Ref. 5.4: 03KHMM] Duke JM, Sibbritt DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women? Contraception 2007;75:27-31.

[Ref. 5.4: 03KHNT] Patten SB. Incidence of major depression in Canada. JAMC 2000;163(6):714-5.

[Ref. 5.4: 03KHMX] Hankin BL, Moffitt TE, Silva PA, McGee R. Development of depression from preadolesecence to young adulthood: emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 1998;107(1):128-40.

[Ref. 5.4: 03QQCC] Mattisson C, Bogren M, Nettelbladt P, Munk-Jörgensen P, Bhugra D. First incidence depression in the Lundby Study: A comparison of the two time periods 1947-1972 and 1972-1997. J Affect Disord 2005;87:151-60.

[Ref. 5.4: 03KHMY] Hawthorne G, Goldney R, Taylor AW. Depression prevalence: is it really increasing? Aust N Z J Psychiatry 2008;42:606-16.

[Ref. 5.4: 03KHNP] Offord DR, Boyle MH, Campbell D, Goering P, Lin E, Wong M, et al. One-year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. Can J Psychiatry 1996;41:559-63.

[Ref. 5.4: 03KHNR] Olsson GI, vonKnorring A-L. Adolescent depression: prevalence in Swedish high-school students. Acta Psychiatr Scand 1999;99:324-31.

[Ref. 5.4: 03KHN7] Kessler RC, Walters EE. Epidemiology of DSM-III-R major depression and minor depression among adolescents and young adults in the national comorbidity survey. Depress Anxiety 1998;7:3-14.

[Ref. 5.4: 03KTP2] Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? J Affect Disord 2002;70:229-40.

[Ref. 5.4: 03KTP0] McCarty MF. High-dose pyridoxine as an 'anti stress' strategy. Med Hypotheses 2000;54(5):803-7.

[Ref. 5.4: 03KTPL] Smith SS, Waterhouse BD, Chapin JK, Woodward DJ. Progesterone alters GABA and glutamate responsiveness: A possible mechanism for its anxiolytic action. Brain Res 1987;400:353-9.

[Ref. 5.4: 03KTNH] Fink G, Sumner BEH, McQueen JK, Wilson H, Rosie R. Sex steroid control of mood, mental state and memory. Clin Exp Pharmacol Physiol 1998;25:764-75.

[Ref. 5.4: 03KTPK] Sherwin BB. Hormones, mood, and cognitive postmenopausal women functioning in postmenopausal women. Obstet Gynecol 1996;87(Suppl 2):20S-6S.

[Ref. 5.4: 00WDGS] Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423:1-15.

[Ref. 5.4: 03KHNV] Porter JB, Hunter JR, Jick H, Stergachis A. Oral contraceptives and nonfatal vascular disease. J Am Coll Obstet Gynecol 1985;66(1):1-4.

[Ref. 5.4: 03KHNX] Kay CR. Oral contraceptives, venous thrombosis, and varicose veins. J Royal College Gen Pract 1978;28:393-9.

[Ref. 5.4: 03KHPC] Vessy MP. Epidemiological studies of lower dose oral contraceptives. Report on the presentation by M.P. Vessey, M.B. at the XII World Congress of Gynecology and Obstetrics, Rio de Janeiro, October 26, 1988.

[Ref. 5.4: 03NLRR] Farmer RDT, Preston TD. The risk of venous thromboembolism associated with low oestrogen oral contraceptives. J Obstet Gynaecol 1995;15:195-200.

[Ref. 5.4: 00W4PX] Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995;346:1589-93.

[Ref. 5.4: 03KHP2] Samuelsson E, Hagg S. Incidence of venous thromboembolism in young Swedish women and possibly preventable cases among combined oral contraceptive users. Acta Obstet Gynecol Scand 2004;83:674-81.

[Ref. 5.4: 00WDJG] Dinger JC, Heinemann LAJ, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: Final results from the European active surveillance study on oral contraceptives based on 142,475 women-years of observation. Contraception 2007;75:344-54.

[Ref. 5.4: 03M27V] Lidegaard O, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 201-2010. BMJ 2012:1-9.

[Ref. 5.4: 03RJM7] Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton III LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93.

[Ref. 5.4: 03KHM9] Anderson FA, Wheeler B, Goldberg RJ, Hosmer DW, Patwardhan NA, Joranovic B, et al. A population-based perspective of the hosptial incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. Arch Intern Med 1991;151:933-9.

[Ref. 5.4: 03RJM6] Oger E. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost 2000;83:657-60.

[Ref. 5.4: 03KHNN] Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD, Farmer RDT. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. Eur J Contracept Reprod Health Care 2000;5:265-74.

[Ref. 5.4: 03M335] Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, et al. Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. Contraception 2013;87:93-100.

[Ref. 5.4: 03RJLS] Ageno W, Squizzato A, Garcia D, Imberti D. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost 2006;32(7):651-8.

[Ref. 5.4: 03KHN8] Kniff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Summary of contraindication to oral contraceptives. Parthenon 1999:135-203.

[Ref. 5.4: 03KHPB] Van Vlijmen EFW, Brouwer JLP, Veeger NJGM, Eskes TKAB, de Graeff PA, van der Meer J. Oral contraceptives and the absolute risk of venous thromboembolism in women with single or multiple thrombophilic defects. Arch Intern Med 2007;167:282-9.

[Ref. 5.4: 03KTP3] The Oral Contraceptive and Hemostasis Study Group. The effects of seven monophasic oral contraceptive regimens on hemostatic variables: Conclusions from a large randomized multicenter study. Contraception 2003;67:173-85.

[Ref. 5.4: 023WB3] Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366:2257-66.

[Ref. 5.4: 03XZ7K] Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives. Contraception 2014;89:253-63.

[Ref. 5.4: 03MX4D] Dinger J, Möhner S, Heinemann K. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstet Gynecol 2013;122(4):800-8.

[Ref. 5.4: 02CG84] Chan W-S, Ray J, Wai EK, Ginsburg S, Hannah ME, Corey PN, et al. Risk of stroke in women exposed to low-dose oral contraceptives: A critical evaluation of the evidence. Arch Intern Med 2004;164:741-7.

[Ref. 5.4: 03KTPP] Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007;56(4):651-63.

[Ref. 5.4: 03KTPR] Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: A meta-analysis. Am J Public Health 1993;83(8):1113-20.

[Ref. 5.4: 052MK7] Wang S, Wang Y, Xu J, Chen Y. Is the oral contraceptive or hormone replacement therapy a risk factor for cholelithiasis: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96(14):e6556.

[Ref. 5.4: 03KTNP] Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ. A prospective study of symptomatic gallstones in women: Relation with oral contraceptives and other risk factors. Obstet Gynecol 1994;84(2):207-14.

[Ref. 5.4: 03KTPS] Thijs C, Leffers P, Knipschild P. Oral contraceptive use and the occurrence of gallstone disease - A case-control study. Prev Med 1993;22:122-31.

[Ref. 5.4: 03KTPX] Vessey M, Painter R. Oral contraceptive use and benign gallbladder disease; revisited. Contraception 1994;50:167-73.

[Ref. 5.4: 03KHMT] Fendrich K, Vennemann M, Pfaffenrath V, Evers S, Berger K, Hoffman W. Headache prevalence among adolescents-the German DMKG headache study. Cephalalgia 2007;27:347-54.

[Ref. 5.4: 03KKHM] Lowenfels AB, Velema JP. Estimating gallstone incidence from prevalence data. Scand J Gastroenterol 1992;27:984-6.

[Ref. 5.4: 03QJD4] Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999;117(3):632-9.

[Ref. 5.4: 03KTPJ] Shaffer EA. Epidemiology of gallbladder stone disease. Best Pract Res Cl Ga 2006;20(6):981-96.

[Ref. 5.4: 03KTNT] Leitzmann MF, Rimm EB, Willett WC, Spiegelman D, Grodstein F, Stampfer MJ, et al. Recreational physical activity and the risk of cholecystectomy in women. N Engl J Med 1999;341(11):777-84.

[Ref. 5.4: 03KKJ2] Leitzmann MF, Giovannucci EL, Rimm EB, Stampfer MJ, Spiegelman D. The relation of physical activity to risk for symptomatic gallstone disease in men. Ann Intern Med 1998;128(6):417-25.

[Ref. 5.4: 03MVV0] Lopez AJ, O'Keefe P, Morrissey M, Pickleman J. Ceftriaxone-induced cholelit. Ann Intern Med 1991;115:712-4.

[Ref. 5.4: 03KTPT] Uhler ML, Marks JW, Voigt BJ, Judd HL. Comparison of the impact of transdermal versus oral estrogens on biliary markers of gallstone formation in postmenopausal women. J Clin Endocrinol Metab 1998;83(2):410-4.

[Ref. 5.4: 03KTNB] Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, et al. Effect of estrogen therapy on gallbladder disease. JAMA 2005;293(3):330-9.

[Ref. 5.4: 03KTNV] Lynn J, Williams L, O'Brien J, Wittenberg J, Egdahl RH. Effects of estrogen upon bile: Implications with respect to gallstone formation. Ann Surg 1973;178(4):514-22.

[Ref. 5.4: 0534KN] Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neurooncol. 2010;99:307-14.

[Ref. 5.4: 05DQQ5] Vernooij MW, Ikram MA, Tanghe HL, Vincent AJPE, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. N Engl J Med. 2007 Nov 1;357(18):1821-8.

[Ref. 5.4: 05DQQ3] Nakasu S, Hirano A, Shimura T, Llena JF. Incidental meningiomas in autopsy study. Surg Neurol. 1987;27:319-22.

[Ref. 5.4: 05DQQ2] Islim AI, Mohan M, Moon RDC, Srikandarajah N, Mills SJ, Brodbelt AR, et al. Incidental intracranial meningiomas: a systematic review and meta-analysis of prognostic factors and outcomes. J Neurooncol. 2019;142:211-21. Erratum in: J Neurooncol. 2019;144:427-9.

[Ref. 5.4: 05DQQ4] Englot DJ, Magill ST, Han SJ, Chang EF, Berger MS, McDermott MW. Seizures in supratentorial meningioma: a systematic review and meta-analysis. J Neurosurg. 2016 Jun;124:1552-61.

[Ref. 5.4: 05398V] Preston-Martin S, Monroe K, Lee PJ, Bernstein L, Kelsey J, Henderson S, et al. Spinal meningiomas in women in Los Angeles county: investigation of an etiological hypothesis. Cancer Epidemiol Biomarkers Prev. 1995 Jun;4:333-9.

[Ref. 5.4: 0538ML] Custer B, Longstreth WT Jr, Phillips LE, Koepsell TD, Van Belle G. Hormonal exposures and the risk of intracranial meningioma in women: a population-based case-control study. BMC Cancer. 2006 Jun 7;6:152.

[Ref. 5.4: 053NHX] Cowppli-Bony A, Bouvier G, Rue M, Loiseau H, Vital A, Lebailly P, et al. Brain tumors and hormonal factors: review of the epidemiological literature. Cancer Causes Control. 2011;22:697-714.

[Ref. 5.4: 053999] Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. PLoS One. 2013 Dec;8(12):e83261.

[Ref. 5.4: 053935] Michaud DS, Gallo V, Schlehofer B, Tjonneland A, Olsen A, Overvad K, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiol Biomarkers Prev. 2010 Oct;19(10):2562-9.

[Ref. 5.4: 0538MY] Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Sex steroid hormone exposures and risk for meningioma. J Neurosurg. 2003 Nov;99:848-53.

[Ref. 5.4: 0538M7] Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM. Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females [manuscript]. J Neurosurg. 2013. 15 p.

[Ref. 5.4: 05B337] Muskens IS, Wu AH, Porcel J, Cheng I, Le Marchand L, Wiemels JL, et al. Body mass index, comorbidities, and hormonal factors in relation to meningioma in an ethnically diverse population: the multiethnic cohort. Neuro Oncol. 2019;21(4):498-507.

[Ref. 5.4: 0534JW] Ostrom TQ, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro-Oncol. 2018;20(suppl 4):iv1-86.

[Ref. 5.4: 0534H9] Asklund T, Malmstrom A, Bergqvist M, Bjor O, Henriksson R. Brain tumors in Sweden: data from a population-based registry 1999-2012. Acta Oncol. 2015;54:377-84.

[Ref. 5.4: 0534L4] Woehrer A. Brain tumor epidemiology in Austria and the Austrian brain tumor registry. Clin Neuropathol. 2013;32(4):269-85.

[Ref. 5.4: 0534KD] Pouchieu C, Gruber A, Berteaud E, Menegon P, Monteil P, Huchet A, et al. Increasing incidence of central nervous system (CNS) tumors (2000-2012): findings from a population based registry in Gironde (France). BMC Cancer. 2018;18:653.

[Ref. 5.4: 0406W7] Porter KR, McCarthy BJ, Freels S, Kim Y, Davis FG. Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. Neuro Oncol. 2010 Jun;12(6):520-7.

[Nguyen P et al. (2021) CMA] Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien: une étude de cohorte à partir des données du SND". Available at: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_chlormadinone_avril-2021-1.pdf

[Nguyen P et al. (2021) NOMAC] Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de nomégestrol et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS" . Available at: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_nomegetrol_avril-2021.pdf

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

VENOUS THROMBOEMBOLIC-VTE

[Letter Date]

Name

Address

Address2
City, State, Zip Code

Dear ;

We have been notified of a report concerning an experience following exposure to a Theramex product.

Patient Name / Initial	
Age	
Gender	
Product (All Theramexsuspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities, Theramex subsidiaries worldwide, and business partners with whom we have contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

We would like to inform you that your inquiry is being documented with the aim to process it appropriately. Any personal data provided by you will be used to keep track of the inquiry with you and treated by Theramex with full respect of your privacy.

Enclosed is a form for you to complete and return to us at your earliest convenience. Your assistance in this matter is greatly appreciated.

Sincerely,

Theramex Pharmacovigilance

REPORTER INFORMATION:

Name and Title: _____

Affiliation: _____

Address: _____

_____

_____

Daytime Telephone Number: _____

Signature and Date: _____

PATIENT INFORMATION:

Patient Name / Initials		
Age:	DOB:	Gender:

UNDERLYING ETIOLOGY:	
Type of venous thromboembolism (VTE)?	☐ Deep vein thrombosis (DVT) ☐ Pulmonary embolism (PE) Other: ☐ specify:
What is the underlying etiology of the VTE?	☐ hypercoagulable state (specify): ☐ Other (specify): ☐ Unknown:

HISTORY	
Does the patient have a history of VTE other than the event reported)? *If yes, specify onset, type of event ond outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a history of any of the following procedures? *If yes, specify dote of procedure, indicotion for the procedure ond outcome?*	☐ Doppler Ultrasound ☐ Inferior vena cava filter insertion
Are there any family members with VTE? *If yes, specify relotion to potient, type of event ond age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a known clotting or fibrinolytic system disorder? *If yes, specify type of disorder ond age ot onset.*	☐ Yes, specify: ☐ No ☐ Unknown

Does the patient have (a history of) other relevant medical conditions (e.g. Sickle cell anemia, myeloproliferative disease (hyperviscosity), nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, cancer)? *If yes, specify condition and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient taken any hormonal contraceptives/estrogen therapy in the past? *If yes, specify which contraceptive/treatment, dose and duration of exposure (start and stop dates, last date taken prior to the event).*	☐Yes, specify: ☐No ☐Unknown
Were there (earlier) pregnancy(s)? *Provide number and indicate if "0". Do not leave these fields blank.*	Gravida (No. of pregnancies): Para (Number of deliveries): Elective Abortions: Spontaneous Abortions:

RISK FACTORS:	
Does the patient smoke or have a smoking history? *If yes, specify age, duration and extent of smoking If ex-smoker indicate how long since cessation*	☐Yes, specify: ☐No ☐Unknown
Is the patient a passive smoker (exposed to second-hand smoke)? *If yes, specify age, duration and extent of exposure*	☐Yes, specify: ☐No ☐Unknown
Is there (a history of) excessive alcohol consumption? *If yes, specify (include duration and extent).*	☐Yes, specify: ☐No ☐Unknown
Is the patient obese?	☐Yes, specify: ☐No ☐ Unknown
Did the patient have a history of trauma? *If Yes, specify dates and nature and anatomical location of trauma.*	☐Yes, specify: ☐No ☐Unknown
Has the patient undergone surgery recently (in the past 3 months)? *If yes, specify dates and type of surgery.*	☐Yes, specify: ☐No ☐Unknown
Has the patient had a history of an indwelling venous catheter? *If yes, specify dates and reason for catheter.*	☐Yes, specify: ☐No ☐Unknown
Has the patient been immobilized recently? *If yes, specify dates, duration and degree of immobilization.*	☐Yes, specify: ☐ No ☐ Unknown
Has the patient recently taken a long journey by air/car/bus/train? *If yes, specify dates, nature and duration of travel.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have varicose veins? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

RISK FACTORS:	
Has the patient had recent intravenous injections/infusions? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient been diagnosed with cancer? *If yes, specify type, dates of diagnosis, treatment and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any other relevant information about the patient? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

RELEVANT DIAGNOSTIC TESTS	
What was the method of diagnosis of the VTE?	
Have the following tests been performed? If yes, specify the dates and results	**Results**
Ultrasound (i.e. Doppler, Duplex) ☐ Yes (specify type below) Type: ☐ No ☐ Unknown	
Venography (i.e. Contrast venography , MRI venography, Computed axial tomography venography) ☐ Yes (specify type below) No ☐ ☐ Unknown Type:	
Computed tomographic pulmonary angiography (CTPA) ☐ Yes ☐ No ☐ Unknown	
Ventilation-perfusion scan ☐ Yes ☐ No ☐ Unknown	
Pulmonary angiography ☐ Yes ☐ No ☐ Unknown	
CT scan ☐ Yes ☐ No ☐ Unknown	
MRI scan ☐ Yes ☐ No ☐ Unknown	
Have the following parameters been determined? *If yes, specify and provide values.*	**Values**
PT/APTT ☐ Yes ☐ No ☐ Unknown	
AT III level/activity ☐ Yes ☐ No ☐ Unknown	
Protein S level/activity ☐ Yes ☐ No ☐ Unknown	
Protein C level/activity ☐ Yes ☐ No ☐ Unknown	

RELEVANT DIAGNOSTIC TESTS	
Factor VII ☐ Yes ☐ No ☐ Unknown	
Factor VIII ☐ Yes ☐ No ☐ Unknown	
Factor XI ☐ Yes ☐ No ☐ Unknown	
Prothrombin mutation G20210 ☐ Yes ☐ No ☐ Unknown	
APC resistance (factor V Leiden) Yes ☐ ☐ No Unknown ☐	☐ Homozygous ☐ Heterozygous ☐ Unknown whether it is homozygous - or heterozygous
Antiphospholipid antibodies (SLE/lupus) ☐ Yes ☐ No ☐ Unknown	
D-dimer ☐ Yes ☐ No ☐ Unknown	☐ Normal ☐ Increased Decreased ☐
Homocysteine blood levels ☐ Yes ☐ No ☐ Unknown	
Other (specify)	
PROVIDE ADDITIONAL DETAILS/OUTCOME OF EVENT(s):	

PLEASE RETURN VIA E—MAIL to
TO: safety.global@theramex.con

ARTERIAL THROMBOEMBOLISM

[Letter Date]

Name

Address

Address2
City, State, Zip Code

Dear ;

We have been notified of a report concerning an experience following exposure to a Theramex product.

Patient Name / Initial	
Age	
Gender	
Product (All Theramex suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities, Theramex subsidiaries worldwide, and business partners with whom we have contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will behandled confidentially.

We would like to inform you that your inquiry is being documented with the aim to process it appropriately. Any personal data provided by you will be used to keep track of the inquiry with you and treated by Theramex with full respect of your privacy

Enclosed is a form for you to complete and return to us at your earliest convenience. Your assistance in this matter is greatly appreciated.

Theramex Pharmacovigilance

REPORTER INFORMATION

Name and title: _____

Affiliation: _____

Address: _____

_____

_____

Daytime Telephone Number: _____ Signature and Date: _____

PATIENT INFORMATION

Age:	DOB:	Gender:
Patient Name / Initial		

UNDERLYING ETIOLOGY

Type of Arterial Thromboembolism (ATE)	☐ CVA ☐ TIA ☐ Unknown ☐ MI ☐ Peripheral arterial Thromboembolism ☐ Other (specify below) Please explain: _____ _____ _____
What is the underlying etiology of the ATE?	☐ Athero-thromboembolism (specify artery if known):
	☐ Emboli from heart (specify): ☐ Originating from heart valves (specify): ☐ Mural thrombus (specify):
	☐ Vasculitis (specify):
	☐ Hypercoagulable state (specify):
	☐ Other (specify):
	☐ Unknown

HISTORY/PATIENT CHARACTERISTICS

Does the patient have a history of ATE (other than the event reported)? *If yes, specify date of onset, type of event, duration and outcome.*	☐Yes, specify: ☐No ☐Unknown
Does the patient have a history of any of the following procedures? *If yes, specify date of procedure, indication for the procedure and outcome.*	☐Cardiac endarterectomy (specify): ☐Percutaneous coronary intervention (PCI) (specify): ☐Coronary Artery Bypass Graft (CABG) (specify): Other ☐(specify): ☐None
Are there any family members with a history of ATE? *If yes, specify relation to patient, type of event and age at onset.*	☐Yes, specify: ☐No ☐Unknown
Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).* *If ex-smoker indicate how long since cessation.*	☐Yes, specify: ☐No ☐Unknown
Is the patient a passive smoker (exposed to second-hand smoke)? *If yes, specify age, duration and extent of exposure.*	☐Yes, specify: ☐No ☐Unknown
Is there (a history of) excessive alcohol consumption? *If yes, specify (include duration and extent).*	☐Yes, specify: ☐No ☐Unknown
Is there (a history of) drug/substance abuse? *If yes, specify (include duration and extent).*	☐Yes, specify: ☐No ☐Unknown
Has the patient taken any hormonal treatment in the past? *If yes, specify product, dose and duration of exposure.*	☐Yes, specify: ☐No ☐ Unknown

RISK FACTORS

Presence/ absence of (risk factors for) atherosclerosis	
Does the patient have hypertension? *If yes, specify age at onset, type of hypertension, most recent blood pressure readings prior to the event, medications.*	☐Yes, specify: ☐No ☐ Unknown
Does the patient have dyslipidemia? *If yes, specify age at onset, most recent cholesterol and lipid levels prior to the event or outcome of other investigations, medications.*	☐Yes, specify: ☐No ☐Unknown
Does the patient have diabetes? *If yes, specify age at onset, type of diabetes and level of diabetic control,most recent HbA1C prior to the event, medications.*	☐Yes, specify: ☐No ☐Unknown
Have symptoms of atherosclerosis been detected before?	☐Yes, specify: ☐Unstable angina ☐Claudication ☐Other ☐No ☐ Unknown

Have signs of atherosclerosis been detected before? *If yes, specify by which investigation and provide results.*	☐Yes (specify below) ☐No ☐Unknown
Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).*	☐Yes, specify: ☐No ☐Unknown
Is the patient exposed to second-hand smoke? *If yes, specify age, duration and extent of exposure.*	☐Yes, specify: ☐No ☐Unknown
Has the patient taken any hormonal treatment in the past? *If yes, specify product, dose and duration of exposure.*	☐Yes, specify: ☐No ☐Unknown
Presence or absence of cardiac diseases	
Does the patient have any past or present cardiac diseases? (E.g. Atrial fibrillation, Other arrhythmias, Myocardial infarction, Valvular diseases, Infective endocarditis, cerebrovascular disease, peripheral vascular disease)? *If yes, specify which cardiac disease, give date of onset and other relevant details.*	☐Yes, specify: ☐No ☐Unknown
Presence or absence of any (risk factors for) other possible causes of ATE	
Does the patient have any hematological abnormalities? *If yes, specify which abnormality.*	☐Yes, specify: ☐No ☐Unknown
Does the patient have increased homocysteine levels? *If yes, specify.*	☐Yes, specify: ☐No ☐Unknown
Does the patient have any inflammatory diseases, e.g. vasculitis, arteritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis? *If yes, specify disease and date of onset.*	☐Yes, specify: ☐No ☐Unknown
Does the patient consume or is there a history of alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) drug/substance abuse? *If yes, specify (include duration and extent).*	☐Yes, specify: ☐No ☐Unknown

RELEVANT DIAGNOSTIC TESTS

What was the method of diagnosis of the ATE?	
Have the following tests been performed? *If yes, specify the dates and the results of the tests, in particular in relation to valvular diseases, arrhythmias and ischemic heart disease.*	**Results**
MRI ☐ Yes ☐No ☐Unknown	
ECG ☐ Yes ☐No ☐Unknown	
CT-scan ☐ Yes ☐No ☐Unknown	
Echocardiography ☐ Yes ☐No ☐Unknown	
PET ☐Yes ☐No ☐Unknown	
Arteriography ☐Yes ☐No ☐Unknown	
Ultrasound ☐ Yes *(specify type below)* ☐No ☐Unknown Type	

EEG ☐ Yes ☐ No ☐ Unknown	
Stress Test ☐ Yes ☐ No ☐ Unknown	
Ankle-Brachial Index (ABI) Yes ☐ No ☐ Unknown	
Cardiac Catheterization ☐ Yes ☐ No ☐ Unknown	
Coronary Angiogram ☐ Yes ☐ No ☐ Unknown	
Other	
Have the following tests been performed? *If yes, specify the dates and the results of the tests...*	**Values (Units)**
PT/APTT ☐ Yes ☐ No ☐ Unknown	
AT III level/activity ☐ Yes ☐ No ☐ Unknown	
Protein S level/activity ☐ Yes ☐ No ☐ Unknown	
Protein C level/activity ☐ Yes ☐ No ☐ Unknown	
Factor VII ☐ Yes ☐ No ☐ Unknown	
Factor VIII ☐ Yes ☐ No ☐ Unknown	
Prothrombin mutation G20210 ☐ Yes ☐ No ☐ Unknown	
Platelet Count ☐ Yes ☐ No ☐ Unknown	
APC resistance (factor V Leiden) Yes ☐ No ☐ Unknown	☐ Homozygous ☐ Heterozygous ☐ Unknown whether it is homozygous - or heterozygous
Antiphospholipid antibodies (SLE/lupus) ☐ Yes ☐ No ☐ Unknown	
Homocysteine blood levels ☐ Yes ☐ No ☐ Unknown	
Other (specify)	
PROVIDE ADDITIONAL DETAILS/OUTCOME OF EVENT(s):	

PLEASE RETURN VIA e-mail TO safety.global@theramex.com

Meningioma Questionaire

[Letter Date]

Name
Address
Address2
Country

Dear ;

We have been notified of a report concerning an experience following exposure to a nomegestrol containing product.

Patient Initials	
Age	
Gender	
Product	
Event(s) – All events	

The information will be provided to regulatory authorities, Theramex subsidiaries worldwide, and business partners with whom we have contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

We would like to inform you that your inquiry is being documented with the aim to process it appropriately. Any personal data provided by you will be used to keep track of the inquiry with you and treated by Theramex with full respect of your privacy.

Enclosed is a form for you to complete and return to us at your earliest convenience. Your assistance in this matter is greatly appreciated.

Sincerely,

Theramex Pharmacovigilance

REPORTER INFORMATION:

Name and Title: _____

Affiliation: _____

Address: _____

_____

_____

Daytime Telephone Number: _____

Signature and Date: _____

Patient Initials:		
Age:	DOB:	Gender:
BMI:	Weight:	Height:

Gynecological History		
Age at menarche: Click or tap here to enter text.		
Age at menopause: Click or tap here to enter text. N/A ☐		
Is the patient pregnant? ☐ Yes ☐ No ☐ Unknown	Weeks of gestation: Date of LMP:	Gravida: Para:

If the patient has a history of more than one gestation, please indicate all gestational outcomes utilizing the checkboxes and date field below:

☐ Live birth
Date: (DD/MM/YY)

☐ Elective Termination/Induced Abortion
Date: (DD/MM/YY)

☐ Spontaneous Abortion (<20 weeks)
termination Date: (DD/MM/YY) Trimester ☐1st ☐2nd

☐ Ectopic pregnancy
Date: (DD/MM/YY)

☐ Stillbirth/Fetal Death (>20 weeks)
Date (DD/MM/YY):

Comments:

Previous Hormonal Therapy

Has the patient previously been treated with hormonal therapy? ☐ No ☐ Yes, specify below

Drug Name	Indication	Start Date	Stop Date	Route	Dose	Total Daily Dosage	Reason for discontinuation

Other Concomitant Hormonal Therapies (If applicable, specify below)

Is the patient currently being treated with hormonal therapy in addition to NOMAC-E2? ☐ No ☐ Yes, specify below

Drug Name	Indication	Start Date	Stop Date	Route	Dose	Total Daily Dosage

Personal and Family History

Does the patient have a history of meningioma? ☐ Yes ☐ No ☐ Unknown	Date of diagnosis: (DD/MM/YY) Treatment: Click or tap here to enter text.
Does the patient have a history of cerebrospinal irradiation? ☐ Yes ☐ No ☐ Unknown	Date of treatment: (DD/MM/YY) Indication: Click or tap here to enter text.

Does the patient have a history of neurofibromatosis? ☐ Yes ☐ No ☐ Unknown If yes, indicate type: ☐ Type 1 ☐ Type 2 ☐ Type 3	Date of diagnosis: (DD/MM/YY) Treatment: Click or tap here to enter text.
Does the patient have a history of cancer? ☐ Yes ☐ No ☐ Unknown Type of cancer: Click or tap here to enter text.	Date of diagnosis: (DD/MM/YY) Treatment: Click or tap here to enter text.
Does the patient have a family history of meningioma? ☐ Yes ☐ No ☐ Unknown *Please specify if first degree relative or other* ☐ 1st degree relative ☐ Other, specify: Click or tap here to enter text.	

Does the patient have a family history of neurofibromatosis? ☐ Yes ☐ No ☐ Unknown If yes, indicate type: ☐ Type 1 ☐ Type 2 ☐ Type 3 *Please specify if first degree relative or other* ☐ 1st degree relative ☐ Other, specify: Click or tap here to enter text.
Does the patient have a personal history of any other genetic disease? ☐ Yes ☐ No ☐ Unknown *If yes, provide details:* Click or tap here to enter text.
Meningioma / Meningiomatosis Clinical Details
Select all the clinical symptoms that apply below: ☐ Asymptomatic ☐ Headache ☐ Vertigo ☐ Visual disturbances If ophthalmological consultation, provide diagnostic conclusion Click or text. tap here to enter text. ☐ Personality/mental status changes Loss of ☐ hearing or ☐ smell ☐ Speech disorder ☐Extremity weakness ☐ Seizures ☐ Other, specify: Click or tap here to enter
Imaging
Imaging before diagnosis of meningioma: ☐ Brain CT Scan ☐ Brain MRI ☐ N/A *If brain imaging performed before diagnosis, fill out the corresponding information below:* Reason for scan: Click or tap here to enter text. Date of scan: (DD/MM/YY) Result of scan: Click or tap here to enter text.
Brain imaging for the diagnosis of meningioma: ☐ Brain CT Scan ☐ Brain MRI ☐ N/A Date of scan: (DD/MM/YY) Result of scan: Click or tap here to enter text. Location of meningioma(s): Click or tap here to enter text. Number of meningioma(s): Click or tap here to enter text. Size (or volume) of meningioma: Click or tap here to enter text. Grading of meningioma: Click or tap here to enter text.
Management of Meningioma
Medical ☐ No ☐ Yes *If yes, provide details below:* ☐ ZOELY discontinuation + monitoring ☐ ZOELY discontinuation + switch to a different treatment (Specify treatment: Click or tap here to enter text.) ☐ Continuation of ZOELY + monitoring ☐ Other, specify: Click or tap here to enter text. Date of discontinuation: (DD/MM/YY) Date of switch: (DD/MM/YY)

Outcome after medical intervention on meningioma: ☐ Regression ☐ Stabilization ☐ Progression ☐ Other ☐ Unknown
Surgical ☐ No ☐ Yes ☐ Total or ☐ Partial resection? *Provide details in the section below:* Operative report: Summary: Click or tap here to enter text. Outcome after the surgery: ☐ Recovered ☐ Recovered with sequelae ☐ Not recovered ☐ Unknown

Pathology Report	
Histological type: Click or tap here to enter text. **WHO classification:** Click or tap here to enter text. **Proliferation index:** Click or tap here to enter text. **Receptor (type and presence):** ☐ Androgen ☐ Progestogen ☐ Estrogen Click or tap here to enter text. **Other:** Click or tap here to enter text.	
Monitoring/Evolution	
Outcomes of clinical symptoms:	
☐ Headache	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ Vertigo	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ Visual disturbances recovered If ophthalmological consultation, provide diagnostic conclusion: Click or tap here to enter text.	☐ Recovered ☐ Recovered with sequelae ☐ Not
☐ Personality/mental status changes	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
Loss of ☐ hearing or ☐ smell	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ Speech disorder	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ Extremity weakness	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ Seizures	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
☐ **Other, specify:** Click or tap here to enter text.	☐ Recovered ☐ Recovered with sequelae ☐ Not recovered
Follow-Up Brain Imaging	
Follow-up brain imaging for meningioma: ☐ Brain CT Scan ☐ Brain MRI ☐ N/A Date of scan: (DD/MM/YY) **Result of scan:** Click or tap here to enter text. **Location of meningioma(s):** Click or tap here to enter text. **Number of meningioma(s):** Click or tap here to enter text. **Size of meningioma:** Click or tap here to enter text. **Grading of meningioma:** Click or tap here to enter text.	
Follow-up brain imaging for meningioma: ☐ Brain CT Scan ☐ Brain MRI ☐ N/A Date of scan: (DD/MM/YY) **Result of scan:** Click or tap here to enter text. **Location of meningioma(s):** Click or tap here to enter text. **Number of meningioma(s):** Click or tap here to enter text. **Size of meningioma:** Click or tap here to enter text. **Grading of meningioma:** Click or tap here to enter text.	
Follow-up brain imaging for meningioma: ☐ Brain CT Scan ☐ Brain MRI ☐ N/A Date of scan: (DD/MM/YY) **Result of scan:** Click or tap here to enter text. **Location of meningioma(s):** Click or tap here to enter text. **Number of meningioma(s):** Click or tap here to enter text. **Size of meningioma:** Click or tap here to enter text. **Grading of meningioma:** Click or tap here to enter text.	
Additional Information	
Additional comments : Click or tap here to enter text.	

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

1.1. Approved key messages of the additional risk minimisation measures – distributed in 2014

In February 2013, EMA has started a Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data to review the risk of VTE and ATE of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate. The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed all available data on the risk of VTE and ATE with these contraceptives and the European Commission made its final decision on 16 January 2014, concluding the Article 31 review of CHCs. Information to communicate the outcome of the review and to highlight the risk of the thromboembolic events was sent through a one-time distribution of a direct healthcare professional communication (DHPC) in collaboration with other MAHs of CHCs and National Competent Authorities. Also, educational materials were implemented at the time of DHPC distribution and are being maintained and distributed on a country-specific level according to local Health Authority requirements.

1.2. Direct Healthcare Professional Communication distributed in 2014

- This review confirmed previous understanding that the level of VTE risk with all low dose CHCs (ethinylestradiol <50μg) is small.
- There is good evidence for differences between CHCs in their risk of venous thromboembolism (VTE), depending on the type of progestogen they contain.
- Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE among combined hormonal contraceptives (see table 1 below).
- When prescribing CHCs, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE, and the difference in risk of VTE between products.
- A woman who has been using her combined contraceptive without any problems does not need to stop using it.
- There is no evidence for differences between low dose CHCs (ethinylestradiol <50μg) in their risk of arterial thromboembolism (ATE).
- The benefits associated with using a CHC far outweigh the risk of serious side

effects in most women. The focus is now on emphasising the importance of an individual woman's risk factors and the need to regularly reassess them, and raising awareness of the signs and symptoms of VTE and ATE which should be described to women when a CHC is prescribed.

- Always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.

Additional guidance documents have been developed to help facilitate consultations, including: a checklist that prescribers may go through with the woman to ensure a CHC is suitable. A user card and information sheet that provides the important signs and symptoms of VTE and ATE for women to be aware of has also been developed.

2.1 Approved key messages of the additional risk minimisation measures to be distributed in 2022

In September 2021, EMA has started a Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data to review the risk of meningioma (EMEA/H/A-31/1510). Recently, results from two French epidemiological cohort studies observed a cumulative dose-dependent association between chlormadinone acetate or nomegestrol acetate and meningioma [Nguyen P et al. (2021) CMA] [Nguyen P et al. (2021) NOMAC]. These studies were based on data from the French health insurance (CNAM) and included a population of 828,499 patients for chlormadinone acetate and 1,060,779 for nomegestrol acetate. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose chlormadinone acetate (cumulative dose > 360 mg) or high dose nomegestrol acetate (cumulative dose > 150 mg) and women who were slightly exposed to chlormadinone acetate (cumulative dose ≤ 360 mg) or nomegestrol acetate (cumulative dose ≤ 150 mg). Literature review and EudraVigilance analysis have also been performed.

As a result of this referral a DHPC is to be distributed for Zoely in collaboration with other MAHs of chlormadinone and nomegestrol containing products and National Competent Authorities. Key messages approved within the referral procedure are presented below in section 2.2.

2.2 Direct Healthcare Professional Communication to be distributed in 2022

- Medicinal products containing chlormadinone acetate (5-10 mg/tablet) or nomegestrol acetate (3.75 -5 mg/tablet) are only indicated when other interventions are considered inappropriate. Treatment should be restricted to the lowest effective dose and shortest duration.
- There is an increased risk for developing meningioma (single or multiple) after use of chlormadinone acetate or nomegestrol acetate, primarily at high doses over prolonged time. The risk increases with cumulative doses.

- Products containing chlormadinone acetate or nomegestrol acetate are contraindicated in patients with a meningioma or a history of meningioma.
- Patients should be monitored for meningiomas in accordance with clinical practice.
- If a patient treated with chlormadinone acetate or nomegestrol acetate is diagnosed with meningioma, treatment must be permanently stopped.

No new safety concern regarding a risk of meningioma associated with the use of low dose (2 mg) chlormadinone acetate containing medicinal products or low dose (2.5 mg) nomegestrol acetate containing contraceptives could be identified. However, as the risk of meningioma increases with increasing cumulative doses of products containing chlormadinone acetate or nomegestrol acetate, low dose products are contraindicated in patients with meningioma or history of meningioma and treatment should be permanently stopped in case of signs and symptoms of meningioma.